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Benzodiazepines: Use, Abuse, and Consequences*

JAMES H. WOODS,† JONATHAN L. KATZ, AND GAIL WINGER

Department of Pharmacology, University of Michigan Medical School, Ann Arbor, Michigan, and Psychobiology Laboratory, National Institute on Drug Abuse Addiction Research Center, Baltimore, Maryland

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† Reprint requests to: Department of Pharmacology, University of Michigan Medical School, M6322 Med. Sci. I, Ann Arbor, MI 48109.

I. Introduction

VIRTUALLY since their introduction, benzodiazepines have occupied a prominent place in medicine. They have largely displaced drugs, such as the barbiturates, that were previously used for similar purposes and, in doing so, have substantially improved the therapeutic index in pharmacological management of anxiety, insomnia, and an array of physical diseases.

As clinical experience with these compounds begins its fourth decade, refinements in their use continue to be considered. Indeed, benzodiazepines remain the subject of considerable research interest and the focus of much attention among clinicians and policy makers.

In 1986, we concluded a review of one aspect of the pharmacology of these drugs, i.e., their liability for abuse (Woods et al., 1987); we found that more than 1500 relevant publications of some importance had appeared as of 1985, when our systematic coverage of the literature effectively ended. We undertook this second review for a number of reasons, not the least of which was the significant increment of relevant publications appearing in the last several years, reflecting the sustained interest in the benzodiazepines, and in their liability for abuse and dependence.

The frequency of these publications has increased over time to the extent that the total literature relevant to aspects of the abuse liability of benzodiazepines almost doubled between 1985 and 1990. Fig. 1 shows the cumulative numbers of citations during the last 25 yr, in MEDLINE alone, relevant to these matters (left) and to benzodiazepine tranquilizers in general (right).

A. Recent Reviews

A number of general reviews have been published since our previous review. We wish to make note especially of the reports of two major committees, one edited by DuPont (1988) and another by Salzman (American Psychiatric Association, 1990), the latter chairing an American Psychiatric Association task force on benzodiazepine dependency. In addition, three other reviews were general in intent and worthy of note, namely, those by Griffiths and Sannerud (1987), Hayward et al. (1989), and Uhlenhuth et al. (1988).

Special mention should be made of important reviews that have addressed specific aspects of the abuse liability of benzodiazepines, namely, critiques of the procedures used for abuse liability assessment by Roache and Griffiths (1989b) and De Wit and Griffiths (1991) and a more theoretical paper, describing a set of pharmacokinetic hypotheses that might be applied to abuse liability assessment, by Busto and Sellers (1986).

Miller et al. (1990) published an innovative review of the relation of benzodiazepines' biochemical actions in vitro to their in vivo effects.

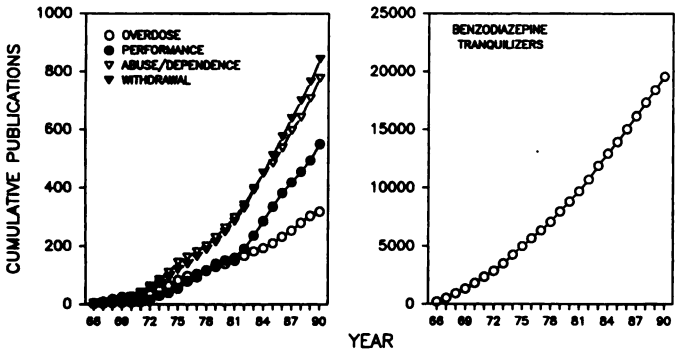

FIG. 1. Cumulative numbers of publications relevant to benzodiazepine tranquilizers and to aspects of their abuse liability, cited in MEDLINE from 1966 through 1990.

An especially useful review of the use of benzodiazepines in elderly patients, and of the problems associated with this use, was contributed by Kruse (1990).

Finally, a particular point of view about the abuse liability of benzodiazepines that has gained great currency in the United Kingdom is well described in opinion pieces by Lader (1987b, 1991). The evolution of this point of view and its ramifications in the United Kingdom have been considered in a broad and interesting sociological perspective by Gabe (1990, 1991) and Gabe and Bury (1991).

B. Approach of the Present Review

We believe the present review is self-contained and can be read independently of the review we conducted several years ago, although the strength of the evidence can best be appreciated by reading both reviews consecutively.

Our current approach makes use of the previous review in two important ways. The present review has taken the general and specific conclusions of the previous review as hypotheses to be evaluated in the light of the more recent evidence on these matters. In addition, we continue to favor the structure of the previous review as a means of organizing the information pertinent to the abuse liability of benzodiazepines, and therefore, we have retained the major demarcations of this structure.

C. Definition of Abuse Liability and Organization of the Review

We continue to find in our previous definition of abuse liability a very useful basis for addressing the relevant issues and restate it here as an introduction to the organization of the review. We define the abuse liability of a compound as its capacity to produce psychological dependence (which we prefer to address in terms of objective measures of drug taking), or physiological dependence, in conjunction with the capacity to alter behavior in a manner that is detrimental to the individual or his or her social environment. This definition is consistent with the broad conception of abuse liability under which psychotropic substances are reviewed by the World Health Organization (World Health Organization, 1971). In accord with this definition, in this review, we include consideration of the areas of research which will be described in the following sections.

In section II, we consider studies of drug taking and drug seeking by animals and humans—the essential aspects of what is commonly referred to as "psychological dependence." We consider the analysis of these behaviors to be of fundamental importance to abuse liability assessment.

Physiological dependence is sometimes associated with the chronic administration of drugs, in the context of therapeutic use or of misuse. In section III, therefore, we consider research in animals and humans pertaining to the potential of the benzodiazepines to produce physiological dependence, in that this information might bear on their liability for abuse.

In section IV, we review evidence pertaining to the ability of the benzodiazepines to alter behavior in ways detrimental to the individual and/or to those around him or her. In this section, we consider experimental research into effects on human cognition and performance (but excluding, perhaps arbitrarily, evidence from animal research that could be construed as relevant to behavioral toxicity) and epidemiological data bearing on the contribution of these effects to accidents.

In section V, we consider epidemiological research pertaining to the use and misuse of the benzodiazepines. This information should ultimately provide the primary context in which to evaluate the significance of other forms of evidence of their abuse liability. In fact, the available epidemiological information concerning the actual use of these drugs, and on the prevalence and consequences of their misuse, is now impressive in extent and serves this purpose extraordinarily well. A new focus of this section is the evaluation of the effects of restrictions on benzodiazepine use.

In section VI, we present a general summary and discussion of the review findings.

D. New Concerns

In the six sections of the review, we consider recent evidence bearing on the various continuing concerns entailed in assessment of the abuse liability of benzodiazepines. However, we would like to point out some new concerns that have emerged in large part since our last review that are addressed in the following pages.

In most of the countries where benzodiazepines are used in large volume, there have been major shifts in prescribing practices, in favor of the compounds with short half-lives. The importance of this change is illuminated by many studies in which various effects of benzodiazepines of shorter and longer half-lives have been compared, which are discussed in the appropriate sections of the review. For purposes of reference in interpreting these studies, the data in table 1 may prove

TABLE 1
*Elimination half-lives of benzodiazepines**

Drug	Elimination half-life (h)		
	Single value	Lower estimate	Upper estimate
Alphabetical order			
Alprazolam	11.01	7.31	17.18
Bromazepam		14.55	23.65
Brotizolam	5.37	3.30	7.10
Camazepam	21.00		
Chlordiazepoxide		12.62	23.26
Clobazam		9.70	30.30
Clonazepam	32.37	21.40	49.40
Clorazepate		1.65	2.66
Desmethyldiazepam (clorazepate)	42.67	52.40	65.00
Clotiazepam		6.50	17.00
Delorazepam, chlordesmethyldiazepam	97.30	60.80	173.20
Diazepam	54.00	24.73	65.30
Desmethyldiazepam (diazepam)	92.00	45.00	139.40
Estazolam	1.00	11.05	22.55
Ethyl loflazepate	97.00		
Flumazenil, RO 15-1788		42.00	71.00
Flunitrazepam		14.97	25.43
Flurazepam		1.60	5.30
N-1-hydroxyethylflurazepam (flurazepam)	2.00	2.05	4.05
N-desalkylflurazepam (flurazepam)	19.00	39.50	71.00
Halazepam	34.74		
Ketazolam	2.00		
Loprazolam	6.30	5.48	17.28
N-oxide loprazolam		4.12	24.50
Lorazepam	12.90	10.13	23.30
Lormetazepam	10.00		
Midazolam	1.98		
Nitrazepam	19.99	17.90	38.28
Oxazepam	6.18	6.67	17.53
Oxazolam		34.00	100.40
Pinazepam	15.72		
Prazepam	1.24		
Desmethyldiazepam (prazepam)	117.50		
Quazepam	30.97		
2-Oxoquazepam (quazepam)	32.23		
N-desalkyl-2-oxoquazepam (quazepam)	75.00		
Temazepam	12.35	5.36	18.44
Tetrazepam	15.10	17.20	39.55
Nortetrazepam (tetrazepam)	37.40		
Triazolam	2.90	1.61	3.48

Drug	Elimination half-life (h)		
	Single value	Lower estimate	Upper estimate
Sorted by half-life duration			
Estazolam	1.00	11.05	22.55
Prazepam	1.24		
Flurazepam		1.60	5.30
Clorazepate		1.65	2.66
Midazolam	1.98		
Ketazolam	2.00		
N-1-hydroxyethylflurazepam (flurazepam)	2.00	2.05	4.05
Triazolam	2.90	1.61	3.48
N-oxide loprazolam		4.12	24.50
Brotizolam	5.37	3.30	7.10
Oxazepam	6.18	6.67	17.53
Loprazolam	6.30	5.48	17.28
Clotiazepam		6.50	17.00
Clobazam		9.70	30.30
Lormetazepam	10.00		
Alprazolam	11.01	7.31	17.18
Temazepam	12.35	5.36	18.44
Chlordiazepoxide		12.62	23.26
Lorazepam	12.90	10.13	23.30
Bromazepam		14.55	23.65
Flunitrazepam		14.97	25.43
Tetrazepam	15.10	17.20	39.55
Pinazepam	15.72		
N-desalkylflurazepam (flurazepam)	19.00	39.50	71.00
Camazepam	21.00		
Nitrazepam	26.50	17.93	41.85
Quazepam	30.97		
2-Oxoquazepam (quazepam)	32.23		
Clonazepam	32.37	21.40	49.40
Oxazolam		34.00	100.40
Halazepam	34.74		
Nortetrazepam (tetrazepam)	37.40		
Flumazenil, RO 15-1788		42.00	71.00
Desmethyldiazepam (clorazepate)	42.67	52.40	65.00
Diazepam	54.00	24.73	65.30
N-desalkyl-2-oxoquazepam (quazepam)	75.00		
Desmethyldiazepam (diazepam)	92.00	45.00	139.40
Ethyl loflazepate	97.00		
Delorazepam, chlordesmethyldiazepam	97.30	60.80	173.20
Desmethyldiazepam (prazepam)	117.50		

* Values were obtained from Schütz (1982, 1989), which provides a comprehensive summary of the published literature concerning benzodiazepine pharmacokinetics, as well as other information. All values for oral administration were averaged. For single values, an average of all single values is given; for ranges, the lower and upper bounds of the ranges were averaged separately. The values represent averages of one to 12 values given in individual studies. Values from blood and plasma were pooled. Drug names that are followed by another in parentheses are metabolites of the parent drug which is the name in parentheses. See Schütz (1982, 1989) for the original citations. In one case (estazolam), the average of the ranges does not agree with the single value, which was obtained in a single study.

helpful as a guide to the variation among the compounds with respect to half-life.

Prescribing practices in some countries have also been influenced by various forms of response to the risks of abuse and dependence on benzodiazepines. For example, in the United States, there has been increased regulatory control of benzodiazepine prescribing. In the United Kingdom, benzodiazepine prescribing has been significantly altered by both formal and informal pressure on practitioners to limit such prescriptions, as well as by fear of legal action associated with allegations of iatrogenic dependence.

Finally, we note the emergence of new compounds in the class that have partial agonist properties or novel action at the benzodiazepine receptor complex. The future of clinical pharmacology in this area will certainly be marked by a major effort to evaluate new compounds of this kind.

II. Studies of Drug Taking and Drug Seeking

A. Introduction

When a subject takes a drug, the pharmacological effects of the drug occur as a consequence of this behavior. If this behavior subsequently increases in frequency or if it is maintained at a high frequency, the behavior is considered to have been reinforced by the drug, and the drug can be called a reinforcer. This psychological process is an essential determinant of the abuse liability of a drug, and studies of behaviors reinforced by drug administration have largely supplanted traditional studies of "psychological dependence." In this section, we will review studies in which the reinforcing effects of drugs have been examined. As in our previous review, when we refer to psychological dependence, we are referring solely to the reinforcing effects of drugs, i.e., their potential to increase or maintain the frequency of behaviors of drug seeking or drug taking.

In many of these studies, reinforcing effects were directly examined by studying behaviors maintained by drug administration. Relatively simple procedures, such as measuring the drinking of drug solutions as the reinforced response, were used in some studies. Others were more demanding in experimental methods, such as studies in which some response of a subject—either a press on a lever by a laboratory animal or a verbal response of a human subject—is followed by drug administration. There have also been less direct assessments of reinforcing effects, such as the studies of place-preference learning.

B. Studies in Animals

Because most uses of benzodiazepines in humans entail oral administration, in animal studies, the reinforcing effects of these drugs when delivered orally have been frequently examined. As we found in our previous review (Woods et al., 1987), when subjects (usually rodents) are given unrestricted access to both benzodiazepine and placebo solutions, preference for a benzodiazepine solution generally does not develop. Thus, in several studies, preference for the drug compared with placebo have been examined after imposition of some setting condition that induces exposure to the effects of the drug, such as mixing the drug with the only supply of drinking water or food. In our previous review, we concluded that studies of oral drug ingestion have failed to find substantial preference for benzodiazepines over placebo using these procedures.

1. Studies of oral drug ingestion. The intermittent delivery of small amounts of food can induce subjects to consume large amounts of fluid (schedule-induced polydipsia); this technique has been used to establish consumption of large amounts of drug solutions. In one study previously reviewed (Falk and Tang, 1985), food pellets were delivered to subjects at a rate of once per minute during daily 3-h experimental sessions, inducing polydipsic consumption of water and drug. During single-probe sessions, the schedule of pellet delivery was altered so that pellets were delivered less frequently. Although intakes of midazolam and water were comparable when pellets were delivered once per minute, a greater intake of midazolam compared with water was found at the lower rates of pellet delivery.

In a further study in which similar methods were used (Falk and Tang, 1989a), schedule-induced intake of several drug solutions was compared with water intake. As had been found with midazolam, an increase in drug intake compared with water intake was obtained with ethanol and cocaine but not with flurazepam or chlordiazepoxide. The investigators suggested that drugs for which consumption was greater than that of water (such as cocaine, ethanol, and midazolam) might be regarded as those with some liability for abuse; whereas those for which consumption was not greater than that of water (such as chlordiazepoxide and flurazepam) might be regarded as having relatively low abuse liability.

In another study (Falk and Tang, 1989b) chlordiazepoxide was examined using the same procedure. In this study, the effects of chlordiazepoxide were examined in subjects in which polydipsic consumption of water, cocaine, or ethanol had been induced. As in the previous study, subjects previously exposed either to water alone or to cocaine did not show a significantly increased intake of chlordiazepoxide at the lower rate of pellet delivery compared with a water intake group. However, previous induction of ethanol polydipsia did result in marginally greater consumption of chlordiazepoxide solutions at the lower rate of pellet delivery. The authors suggested that this response parallels results of behavioral studies of i.v. self-administration, in which a history of exposure to sedative-hypnotic drugs has been shown to increase the

likelihood that benzodiazepines will function as reinforcers (e.g., Bergman and Johanson, 1985).

Results of another study (Wolffgramm and Heyne, 1991) did not confirm that a history of ethanol consumption increases reinforcing effects of oral benzodiazepine intake. Rats in different social conditions were allowed access to ethanol solutions; those in social isolation drank more ethanol solution than group-housed rats. When exposed to diazepam solutions, rats showed a preference for these solutions; however, that preference was less than the preference for diazepam vehicle. With 2 wk of exposure, the preference for diazepam decreased further in ethanol-experienced subjects, whereas the control subjects maintained a preference for diazepam vehicle.

Ator and Griffiths (1992) examined drinking of diazepam, triazolam, and ethanol solutions in four baboons, three of which had a history of oral ethanol or methohexital ingestion. Drinking of drug solutions was induced by delivering the daily food ration at one time, when only the drug solution was available for drinking. Following induction of drinking, food was delivered at times other than those in which drinking of drug solutions was assessed. Only one of four subjects consumed more triazolam or diazepam than vehicle. Subsequently, subjects were given concurrent access to drug and vehicle, and the drug concentrations were varied across a greater than ten-fold range. Two subjects showed a preference for triazolam, each at one of approximately seven concentrations studied; the other two subjects showed no preference for triazolam at any concentration. One of four subjects showed consistent preferences for diazepam across a range of concentrations, whereas the other three subjects showed no preference at any concentration. In contrast, all of the subjects showed significant preference for ethanol. Subjects were then trained to press a lever which allowed access to the drug solution. At various numbers of required responses, ethanol maintained rates of responding significantly greater than those maintained by vehicle. Neither triazolam nor diazepam maintained rates of responding above those maintained by their vehicles. The fact that this study did not yield clear evidence of reinforcing effects of benzodiazepines is especially intriguing, because physiological dependence was demonstrated by injection of the benzodiazepine antagonist, flumazenil.

To summarize, in our previous review, we concluded that studies of oral ingestion had failed to find substantial preferences for benzodiazepines over placebo. One recent study of oral intake of drug solutions in rats supported that conclusion, because it indicated a preference for ethanol that did not transfer to diazepam. Likewise, the more extensive studies of preference for diazepam and triazolam in baboons did not demonstrate significant preference for benzodiazepines under conditions in which clear preferences for ethanol were observed. In addition, results of these studies indicate that a history of sedative exposure is not sufficient to induce a significant preference for benzodiazepines. Although preference was not examined in studies of schedule-induced drug ingestion, the studies described do offer evidence that oral intake of midazolam can be increased above intake of water under certain conditions. These conditions do not, however, increase the intake of either chlordiazepoxide or flurazepam. On the other hand, a history of schedule-induced ethanol polydipsia does appear to increase intake of chlordiazepoxide.

These studies illustrate the importance of further research concerning oral benzodiazepine consumption under these conditions. One objective of this research should be to establish levels of placebo consumption in subjects exposed to polydipsic drug consumption. Also, these studies showed increased drug intake during single-probe sessions; it would be of interest to determine whether this increased intake is a transient phenomenon or whether it might be sustained during continued exposure to schedules of infrequent pellet delivery. Finally, results of studies in baboons indicate minimal reinforcing effects of both diazepam and triazolam, even in subjects with a history of exposure to ethanol; however, at least one finding suggests that a history of oral ethanol ingestion can increase oral ingestion of chlordiazepoxide. Thus, further studies are needed to clarify the conditions under which a history of ethanol exposure increases oral intake of benzodiazepines. Histories of exposure to other drugs of abuse, such as barbiturates, would also be of interest.

2. *Studies of place preference.* These are among the few studies purported to assess reinforcing effects without observations of actual drug-taking behavior. In these studies, the subject is placed in a chamber with two distinct compartments. During training conditions, the subject is placed in one compartment after injection of drug and the other compartment after injection of vehicle, with no opportunity to move between compartments. After some exposure to both drug and vehicle, the subject is then placed in the chamber with free access to either compartment. Because it is hypothesized that the compartment associated with a reinforcing drug acquires conditioned reinforcing effects, it has been suggested that the time that the subject spends in this compartment might serve as a measure of the drug's reinforcing effects. However, it should be noted that reinforcing effects are assessed only indirectly, at best, by these studies.

Only one study of place preference was discussed in our previous review. In that study, diazepam produced a place preference that was antagonized by the benzilate antagonist, CGS 8216 (Spyraki et al., 1985). That finding has been replicated by Spyraki and Fibiger (1988). There has been only one report of the effects of another benzodiazepine in this procedure, namely, triazolam. Pettit

et al. (1989) reported neither reinforcing nor aversive effects of triazolam; however, triazolam attenuated the place preference induced by *d*-amphetamine but not that induced by morphine.

In a number of recent place-preference studies, the mechanisms underlying the effects of diazepam were examined. Results of several studies have suggested that effects of the traditionally recognized drugs of abuse, such as cocaine and amphetamines, are mediated by dopaminergic activity in the nucleus accumbens (Koob and Bloom, 1988). Therefore, some investigators have examined the effects of lesions of this brain region or the effects of dopamine antagonists.

Place preferences produced by diazepam were attenuated by 5,7-dihydroxytryptamine-induced serotonergic lesions of the nucleus accumbens, suggesting a role of this transmitter in the effects of diazepam. In contrast, place preferences produced by *d*-amphetamine were not attenuated by the serotonergic lesion, suggesting differences in the mechanisms underlying the place preferences produced by these two drugs (Spyraki et al., 1988). In contrast to the effects of the serotonergic lesion, the 5-HT_2‡ antagonist, ritanserin, did not affect place preferences produced by diazepam (Nomikos and Spyraki, 1988). More complete pharmacological studies are necessary to interpret the role of serotonin in these effects of diazepam.

Results of other studies of place preference support a role of dopamine in mediating these effects. For example, conditioned place preferences induced by diazepam have reportedly been attenuated by the dopamine D_1 antagonist, SCH 23390 (Acquas et al., 1989), the D_2 antagonist, haloperidol (Spyraki and Fibiger, 1988), and by 6-hydroxydopamine lesions of the nucleus accumbens. These results are consistent in suggesting that dopamine plays a role in mediating the effects of diazepam in place-preference procedures.

The place-preference procedure has some advantages. Because it does not require elaborate motor behavior, this procedure can document effects at doses that might interfere with responding in other procedures. In addition, the results of some neuroanatomical studies suggest that structures (e.g., the nucleus accumbens) proposed to be important in more conventional assessments of abuse liability are also important in place-preference procedures. However, it has yet to be determined whether or to what extent the results of place-preference studies among the benzodiazepines can be assumed to correspond with the findings of more conventional experimental procedures. Preliminary results (Carr et al., 1989) suggest that the correspondence may be quite good across drug classes.

Although the results of the one study of place preference with diazepam that was discussed in our previous review have since been replicated, other results reviewed above suggest that triazolam did not produce a place preference; this finding contrasts with studies of i.v. drug self-administration that indicate some reinforcing effects of this drug (Griffiths et al., 1985). Thus, at this time, results of these procedures should be interpreted with caution.

3. Drug infusion studies. Reinforcing effects of drugs have been assessed by several different procedures involving delivery by infusion in laboratory animals. In the simplest of these, each time the subject presses a lever, a dose of the drug is injected. This procedure is referred to as an FR 1 schedule (also referred to as continuous reinforcement). Often the FR 1 schedule is used in procedures in which the subject may respond at any time of day (unlimited access conditions). More often, availability of the drug is confined to daily experimental sessions lasting anytime from a few minutes to a few hours. In other procedures, the drug is available only according to a more complex set of contingencies between responses and reinforcers.

a. CONTINUOUS ACCESS AND FR 1 RESPONSE STUDIES. Results of previous studies suggested that diazepam, chlordiazepoxide, and midazolam functioned as reinforcers in rats responding under FR 1 schedules. More limited evidence for reinforcing effects was obtained with flurazepam and medazepam. The results of earlier studies with primates under FR 1 continuous access schedules of diazepam administration tended to be equivocal. For example, Yanagita and colleagues found marginal self-administration of diazepam under FR 1 schedules of continuous access to i.g. injections of diazepam. Studies of other benzodiazepines delivered i.g. have indicated some reinforcing effects with triazolam, clobazam, and flutoprazepam. A wide variety of other benzodiazepines has failed to maintain responding unequivocally under these conditions (Yanagita, 1981; Yanagita, 1985; Woods et al., 1987). These results are complicated by the finding, discussed in our previous review, that the rates of responding maintained by vehicle after drug exposure were higher than those prior to drug exposure. As we noted, this hysteresis in the vehicle baseline complicates interpretation of the results of many studies in which the

‡ Abbreviations: 5-HT, 5-hydroxytryptamine; FR, fixed ratio; i.g., intragastric; GABA, γ-aminobutyric acid; POMS, Profile of Mood States; VAS, visual analog scale(s); MBG, Morphine-Benzedrine Group; ARCI, Addiction Research Center Inventory; CNS, central nervous system; [^{35}S]TBPS, *t*-[^{35}S]butylbicyclophosphorothionate; BPAS, Benzodiazepine-Precipitated Abstinence Score; NPAS, Nordiazepam-Precipitated Abstinence Score; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Rating Scale for Depression; GAD, generalized anxiety disorder; MMPI, Minnesota Multiphasic Personality Inventory; DSM-III, Diagnosis and Statistical Manual of Mental Disorders, edition III; EEG, electroencephalography(ic); DSST, digit symbol substitution test; DDD, defined daily dose(s); NHS, National Health Service; NPA, National Prescription Audit; NDTI, National Disease and Therapeutic Index; NIDA, National Institute on Drug Abuse; GHQ, General Health Questionnaire; DAWN, Drug Abuse Warning Network; ER, emergency room; HCL, Hopkins Checklist.

investigators attempted to establish benzodiazepine self-administration.

The phenomenon of changing vehicle baselines has been examined more closely in a recent study in which diazepam and cocaine self-administration were compared (Grant and Johanson, 1987). Rhesus monkeys were trained using schedules of i.v. saline or diazepam administration. Following the establishment of stable performances using an FR 1 schedule (the schedule was FR 10 for one subject), blocks of sessions in which diazepam was available were alternated with blocks in which saline was available. Subsequently, a period of cocaine availability was followed by a period of saline availability. The investigators compared the change in rate of responding upon transition to saline following diazepam with that following cocaine. The transition from diazepam to saline was associated with only a small decrease in response rate, whereas rates of responding typically decreased substantially upon transition from cocaine to saline. The authors suggested that the relatively small changes in response rates upon change from diazepam to saline may have been due to the relatively low reinforcing efficacy of diazepam.

These findings confirm previous study results that showed modest increases in response rates when diazepam was available compared with vehicle. However, although these results confirm previous findings that diazepam has only marginal reinforcing effects and document differences between diazepam and cocaine, it remains unclear why rates of responding maintained by vehicle should be greater following exposure to a drug with a relatively modest reinforcing effect compared with those following exposure to a drug with a relatively greater reinforcing effect.

A recent study has confirmed results of previous studies indicating some maintenance of responding by i.g. administration of a benzodiazepine (Yanagita, 1981; Woolverton and Schuster, 1983). Davis et al. (1987) demonstrated in rats that chlordiazepoxide could maintain responding when delivered by either the i.v. or i.g. route. Responding was maintained across a range of doses from 0.1 to 1.0 mg/kg per injection; the lowest dose maintained maximal rates when the drug was administered i.v., whereas the 0.5 mg/kg per injection dose maintained maximal rates when the i.g. route was used. The authors stated that chlordiazepoxide maintained responding in 60 to 70% of the subjects by both routes and at all doses but presented data only for the subjects that responded.

The mechanisms underlying the effects of midazolam were examined in one recent study in which an i.v. self-administration procedure was used. As mentioned before, previous studies had suggested that the reinforcing effects of traditionally recognized drugs of abuse are mediated by dopaminergic activity in the nucleus accumbens (Koob and Bloom, 1988). Studies of in vivo brain dialysis have shown that cocaine produces increases in dopamine levels in the accumbens (Hurd and Ungerstedt, 1989). Finlay et al. (1987) found that doses of midazolam that were self-administered i.v. were associated with a decrease in dopamine levels in the nucleus accumbens. Thus, preliminary study results of the neurochemical substrates of reinforcing effects of midazolam suggest differences between these drugs and traditionally accepted drugs of abuse.

b. INTERMITTENT DRUG AVAILABILITY. Studies of responding maintained by intermittent injections of drugs have shown that diazepam can maintain responding at a level greater than that of vehicle; however, those rates are well below those maintained by reference drugs such as cocaine and several barbiturates. Only midazolam and triazolam maintained rates that approached those of the reference compounds (Woods et al., 1987).

These findings have been replicated in several recent studies. Grant and Johanson (1988), in a study in which they focused primarily on schedule-induced water consumption, found that i.v. diazepam maintained responding above vehicle levels in one of two rhesus monkeys using a 5-min fixed interval schedule. The subjects were initially trained to respond to a fixed-interval schedule of food reinforcement; after responding had been maintained for some time and the effects of changes in fixed-interval duration on concurrent water consumption were assessed, diazepam injections replaced food presentations. The subject that showed some reinforcing effects of diazepam across doses had been trained previously with a schedule of drug injection, but details of that history were not specified. Rates of responding maintained by cocaine injection were higher than those maintained by diazepam in both subjects.

In another study (de la Garza and Johanson, 1987), responding of one of two subjects was maintained with an FR 10 response schedule with diazepam. The rates were uniformly lower than those maintained by psychomotor stimulant drugs such as cocaine and amphetamine, although they were not appreciably lower than those maintained by nicotine in the one subject in which diazepam maintained responding. Both flurazepam and pentobarbital, but not the novel anxiolytic enciprazine, were reported to maintain responding in rhesus monkeys using an FR 10 schedule (Engel et al., 1990). Few details of this study were provided, although the report indicated that the method was similar to that described previously (Bergman and Johanson, 1985); presumably, responding was established and maintained with pentobarbital, and doses of flurazepam or enciprazine were substituted for several sessions.

Nader et al. (1991) compared responding maintained by diazepam, pentobarbital, and brotizolam, a triazolobenzodiazepine, in rhesus monkeys trained to self-administer the ultrashort-acting barbiturate, methohexital, using an FR 10 schedule. Both methohexital and pentobar-

bital maintained relatively high rates of responding in this study. Diazepam also maintained rates of responding that approached those maintained by the barbiturates. This finding is consistent with previous results suggesting that diazepam maintains higher rates of responding in subjects trained to self-administer barbiturates (Bergman and Johanson, 1985). Brotizolam maintained lower rates of responding than did diazepam or either of the barbiturates.

Griffiths et al. (1991) compared effects of substitutions of several benzodiazepines, barbiturates, and other sedative or antianxiety agents in baboons trained to self-administer cocaine using an FR 160 schedule. Alprazolam, bromazepam, chlordiazepoxide, lorazepam, and triazolam (as reported previously by Griffiths et al., 1985) each maintained responding to a greater extent than did vehicle. On average, triazolam was taken in greater amounts than the other benzodiazepines. In addition, methohexital, but not hexobarbital or phenobarbital, maintained responding. Casual observations of the subjects indicated that sedative effects were sometimes obtained when hexobarbital was substituted, indicating that the lack of reinforcing effects of hexobarbital was not for lack of pharmacological activity. Of the other compounds, chloral hydrate and methyprylon were effective in maintaining behavior. Unreliable results were obtained with the GABA agonist baclofen, as has been reported previously (Swain et al., 1980). Of the benzodiazepines, triazolam maintained the most responding, which approached that maintained by methohexital, chloral hydrate, and methyprylon. As reported previously (Balster and Woolverton, 1982), buspirone did not maintain responding.

This confirms results of several previous self-administration experiments with alprazolam, chlordiazepoxide, lorazepam, and triazolam (Yanagita et al., 1981, 1975, 1977; Yanagita, 1981; Kubota et al., 1986) and extends the evaluation to bromazepam, which had not been studied previously. As in the previous study of self-administration of several other benzodiazepines by this group of investigators (Griffiths et al., 1981), the benzodiazepines maintained responding at a level between that maintained by vehicle and that maintained by cocaine, the standard used for training. In addition, the benzodiazepine with the fastest onset of action and the most rapid elimination, triazolam, maintained the highest rates of responding.

This study also provided interesting data concerning a number of barbiturates that had not previously been directly compared. The ultrashort-acting methohexital maintained greater responding than did either of the other barbiturates. Interestingly, although it is tempting to attribute the effectiveness of methohexital to its fast onset and rapid elimination, hexobarbital, which is also rapidly eliminated in man, did not maintain responding. These results indicate that, with respect to the relative effectiveness of drugs in self-administration procedures, explanations that refer simply to kinetics may not be sufficient.

In a study reported in abstract form, Martin et al. (1990a) reported that the benzodiazepine partial agonist bretazenil (Ro 16–6028) did not maintain responding in cynomolgus monkeys trained to self-administer pentobarbital. Bretazenil was examined over a range of doses, from 0.001 to 0.06 mg/kg per injection, which encompassed the range active in other behavioral procedures.

In another abbreviated report, Ator et al. (1991) described self-administration of abecarnil, a β-carboline with agonist actions at benzodiazepine receptors, with that of triazolam. Baboons were trained to self-administer cocaine, after which injections of abecarnil (0.03 to 1.0 mg/kg per injection) were substituted for periods of 15 d. Although values were not specified, rates of drug intake after substitution of abecarnil were described as similar to or marginally above the vehicle mean. In contrast, triazolam maintained rates of responding above that maintained by vehicle.

The question of whether physiological dependence increases the reinforcing effects of diazepam has been addressed in a study of progressive-ratio performances maintained by diazepam in rhesus monkeys; these studies were presented within a methodological review, which did not provide precise details (Yanagita, 1987). Under the progressive ratio schedule, the number of responses required for each successive drug injection increases. The number of responses at which the subject stops responding is defined as the break point; higher values for break point suggest a greater reinforcing effect. Subjects were exposed to 4 wk of diazepam (12 mg/kg/d, i.v.) or saline injections. Subsequently, self-administration of diazepam (1.0 mg/kg per injection, i.v.) was examined. Break points obtained with diazepam did not differ between subjects that had been exposed to diazepam and those exposed to saline. In contrast, 7 d of treatment with codeine (72 mg/kg/d) tended to increase the break points obtained in subjects self-administering codeine (1.0 mg/kg per injection) as compared with subjects that had been treated with saline.

4. Summary and conclusions. Results of recent studies are consistent with previous findings that benzodiazepines are marginally effective as reinforcers under a wide variety of conditions. We previously concluded that studies of oral intake showed little evidence of preference for benzodiazepines; more recent findings are consistent with that conclusion. Recent study findings of i.v. self-administration are also consistent with conclusions of our previous review. These studies have shown that benzodiazepines will on occasion maintain responding at a level greater than that maintained by saline; however, these drugs do not reinforce self-administration behavior as effectively as most drugs of abuse, such as cocaine or many barbiturates.

Earlier study results suggested that diazepam might maintain higher rates of responding in subjects trained to self-administer barbiturates than in subjects trained to self-administer stimulants; there has been no further systematic study assessing the mechanism of that effect. However, because a similar result has been reported for self-administration of amphetamine (Woolverton et al., 1980), a complete pharmacological and behavioral analysis of this effect is needed.

Significant questions remain with regard to the reinforcing effects of benzodiazepines. It has been suggested that drugs with relatively faster onsets of action are more effective as reinforcers. Direct examination of this possibility, for example by varying the duration of infusion of a single, rapidly acting benzodiazepine, has not been done. However, a recent study of barbiturates (Griffiths et al., 1991) suggests that kinetics alone (at least those in man) do not predict which drugs will function as reinforcers. It has also been suggested that benzodiazepines with longer durations of action are generally less effective in maintaining responding than those with shorter durations of action. This possibility deserves closer attention, including quantitative studies of elimination kinetics in the species actually tested, as well as studies utilizing techniques that can limit the behavior-disrupting effects of drug levels accumulating throughout these experimental sessions.

Whether physiological dependence on benzodiazepines might influence the drugs' ability to maintain self-administration behavior is an important question that can be addressed experimentally but has received little attention. Results of two studies have indicated that dependence does not increase the reinforcing effects of benzodiazepine agonists. These studies provide preliminary evidence that reinforcing effects are not enhanced when subjects are in the dependent state. Findings from one clinical study suggest that reinforcing effects may be enhanced during withdrawal (see section III.C). Clearly, further studies should be conducted to determine the potential changes in reinforcing effects during the course of dependence and withdrawal to reconcile these preliminary findings in animals and humans and to better document the effects of physiological dependence on reinforcing effects of benzodiazepines.

A significant number of new compounds have been introduced that differ in actions from those of many of the older benzodiazepines. Effects of two of these compounds have been described only in brief reports. The possibility that these compounds may be less effective as reinforcers than previously studied benzodiazepines is another important question for further study.

C. Studies in Humans

Subjective liking or choice of benzodiazepines over placebo or over other sedative-hypnotic drugs has been evaluated in several different human subject populations, which are considered here in three groups: normal subjects, anxious subjects, and sedative abusers. Normal and anxious subjects were typically recruited by poster or local newspaper advertising or by word of mouth, usually within a university community. Sedative abusers were recruited in a similar manner or were individuals receiving treatment for sedative or other drug abuse; their drug abuse history typically consisted of either occasional, recreational use of a variety of psychoactive drugs, including sedative-hypnotics, or fairly extensive use of sedative-hypnotics in combination with i.v. opioids and/or other drugs of abuse.

1. Studies in normal subjects. Much of the research involving normal subjects, i.e., those with no history of psychiatric disorder or drug abuse, has been conducted at the University of Chicago by De Wit and colleagues. As described in our previous review (Woods et al., 1987), in the original procedure used by this group to evaluate drug preference, subjects were given one of two color-coded capsules during each of four sessions. During sessions 1 and 3, they took a capsule of one color, and during sessions 2 and 4, they took a capsule of the other color. They were asked to note the color of the capsule they took during each session and to associate any effects of the capsule with that color. An evaluation of mood (POMS) was made at 1, 3, and 6 h following capsule ingestion, at the same times subjects rated their "liking" of the effects of the capsule. During sessions 5 through 9, the subjects were given the opportunity to choose to take either of the two color-coded capsules. In our previous review, we reported that investigators using this procedure found that, in the doses evaluated, diazepam, lorazepam, and flurazepam produced changes in POMS scores but were not chosen over placebo in the five-choice tests by normal college students or by subjects who reported high levels of anxiety.

These investigators in more recent studies have used a different procedure, in which subjects were given the opportunity to regulate the dose of the drug they chose (De Wit et al., 1989a). In this procedure, groups of three or four acquainted volunteers were given color-coded capsules of either diazepam (4 mg) or placebo every 30 min during the first four of seven weekly sessions (the sampling sessions). During the final three sessions, subjects selected the color capsule they wished to take; every 30 min thereafter, they could take a capsule of the same type (color) or take no capsule. As many as six additional capsules could be taken after the first one, for a maximum dose of 28 mg of diazepam. During all sessions, subjects filled out an abbreviated version of the POMS before drug ingestion and after each capsule was taken. At the end of each session, they were asked to try to identify the class of the drug that they had taken and to indicate how much they liked the drug's effects on a VAS.

Subjects had no history of alcohol or drug-related

problems but were divided into groups of light drinkers (less than five drinks/wk) and moderate drinkers (average of 11 drinks/wk). Of the light drinkers, 61% selected diazepam during all three of the choice sessions and administered an average of 3.9 capsules or 15.6 mg diazepam per session. All of the moderate drinkers selected diazepam during all three of the choice sessions, ingesting an average of 25.2 mg (6.3 capsules) per session.

This proportion of subjects selecting diazepam is markedly higher than that found in previous studies in which single doses of diazepam were available for ingestion. In the group of light drinkers, subjects who consistently selected the diazepam capsules were those who reported greater drug liking in the VAS questionnaire given after the sampling sessions. These subjects also showed less intoxication than the subjects who rarely selected diazepam but did not differ from them on measures of prior drug use, personality characteristics, or ability to identify the drug. The moderate drinkers showed drug-induced increments in the "friendliness" and "positive mood" measures of the POMS. This did not occur among the light drinkers, even among those who consistently selected diazepam. The moderate drinkers were somewhat older than the light drinkers and had used marijuana, tobacco, hallucinogens, and opioids more than had the light drinkers. It would be interesting to know whether the moderate drinkers would show a greater choice of ethanol or other drugs than the light drinkers in a similar choice-test protocol.

The authors speculated that the most likely reason why drug choice was greater in the multiple-dose regimen than in the single-dose studies was the opportunity for the subjects to regulate the dose of the drug they took. The subjects were also tested in small groups of acquaintances, and the test environment was designed to encourage comfortable social interaction; these factors might also have contributed to the increased selection of diazepam. Interestingly, this same procedure also increased the selection of alcohol in other studies (De Wit et al., 1989b) but did not alter the selection of pentobarbital (De Wit et al., 1989c).

It may also be worth noting that, as reported in our previous review, investigators in earlier studies had given subjects with histories of drug abuse the opportunity to regulate their dose. In these studies, subjects could choose to administer as many as ten tablets of 10 or 20 mg of diazepam, with doses spaced at intervals of at least 15 min. Subjects were required to ride a stationary bicycle during each 15-min period before receiving their next dose. Diazepam maintained some behavior in these subjects, although it was less than that maintained by pentobarbital, and it declined across the 10-d period of drug access (Griffiths et al., 1979). It is not clear what aspects of the regulated dosing procedures in these more recent studies (De Wit et al., 1989a) led to benzodiazepine selection or whether this self-administration, once established, would be maintained across several days.

The regulated-dose paradigm was used by De Wit (1991) to evaluate the effect of family history of alcohol abuse on choice of diazepam over placebo. The study was based on findings reported by Ciraulo et al. (1989). In this latter open study, 1 mg of alprazolam produced feelings of euphoria, as measured by the MBG scale of the ARCI, in nine of 12 sons of alcoholics, but in only two of 12 subjects without a family history of alcoholism. De Wit (1991) studied 27 normal, nonalcoholic subjects, 14 of whom had a parent or sibling with alcoholism; 13 had no history of alcoholism in their first- or second-degree relatives. Fifteen percent of subjects with no family history of alcoholism selected diazepam during all three choice sessions; 21% of those with a family history of alcoholism selected diazepam during all three choice sessions. The difference was not statistically significant and was due primarily to the fact that three of the family history-positive subjects selected diazepam during every available occasion. None of those with a negative family history of alcoholism selected diazepam on every occasion. There was, therefore, a trend toward a greater selection of diazepam by those with a family history of alcoholism that warrants further evaluation. As was mentioned with regard to the study described before, it would be interesting to know whether there is a difference in the selection of ethanol or other drugs by these groups of subjects.

2. *Studies in anxious subjects.* As described in our earlier review, De Wit and her colleagues, using the single-dose procedure described before, found little difference in the selection of diazepam between subjects who were anxious and those who were not anxious. Because some of the anxious subjects indicated that they found their anxiety to be helpful in their daily activities, the authors surmised that these subjects might not have been distressed by their anxiety and, thus, might not be representative of subjects who seek treatment for anxiety.

To determine whether greater diazepam selection might occur in such subjects, McCracken et al. (1990) recruited anxious subjects who were promised treatment for anxiety in return for participating in the study. In the single-dose choice procedure, diazepam was chosen over placebo during all five choice sessions by 21.4% of the 14 anxious subjects. The proportion of subjects choosing diazepam was considerably higher than had been found in earlier studies.

Diazepam increased POMS measures of confusion in subjects who subsequently chose diazepam during two or fewer of the five opportunities. The drug decreased measures of confusion in those who selected diazepam during each of the five opportunities, and it produced an unusual increase in stimulant-like effects in these subjects.

The more recent study findings suggest that subjects

who are distressed by their anxiety are more likely to choose diazepam than subjects who are not anxious or subjects who are not seeking treatment for their anxiety. These experiments also raise the question of whether subjects seeking treatment for anxiety would choose diazepam even more frequently under conditions in which they could regulate their dose more closely.

3. Subjects undergoing benzodiazepine withdrawal. There have been a few studies of benzodiazepine self-administration under conditions in which the subjects were undergoing benzodiazepine withdrawal, with presumed but unmeasured increases in anxiety, either as part of a withdrawal syndrome or because of return of symptoms, or both. Apelt et al. (1990) studied preference for alprazolam (0.5 or 0.37 mg) over diazepam (5 mg) in 14 patients admitted to hospital for benzodiazepine withdrawal. The patients were initially given diazepam in a dose equivalent to that of the benzodiazepine they had been taking. In those taking more than the equivalent of 15 mg of diazepam per day, their doses were gradually reduced to this dose. A very mild withdrawal reaction was reported during this dose reduction. During a 4-d study period when withdrawal was in evidence, diazepam (5 mg) was given three times daily on days 1 and 4. On day 2, alprazolam replaced the morning dose, and on day 3, alprazolam replaced the noon dose of diazepam. Patients self-rated their withdrawal signs each day. They completed a number of tests designed to measure liking of the drug they had taken several hours earlier. They were also asked whether they would like to take the morning medication or the noon medication they had received that day. In subjects receiving 0.5 mg of alprazolam, preference for alprazolam over diazepam was significant. A nonsignificant choice of 0.37 mg of alprazolam over 5 mg of diazepam was found. Reports of drug liking were also greater for the larger dose of alprazolam than for diazepam. The authors suggested that the larger dose of alprazolam might have a slightly higher abuse liability in drug-dependent patients undergoing withdrawal.

This issue was studied more thoroughly by Cappell et al. (1987) using data from the study reported by Busto et al. (1986). Subjects in this study were self-referred or referred by a physician because they had reportedly been unsuccessful in their attempts to terminate their prescribed benzodiazepine medication. Subjects took their usual medication for 3 wk and were then given a dose of diazepam corresponding to the dose of the medication they had been using. They were told that this medication would be gradually tapered; they were not told that, for half of them, the diazepam would be abruptly discontinued. This procedure was done with 24-h access to support personnel; in addition, subjects were allowed to retain their original medication and, although they were discouraged from using it, they were given permission to take it if they were sufficiently distressed.

Subjects were asked to report any use of supplemental medication during withdrawal, and weekly blood samples were obtained to check these reports, which usually proved accurate. The group that was abruptly withdrawn supplemented their study "medication" with their own medication much more frequently than did those in the group receiving tapered doses. The authors hypothesized that the abruptly withdrawn subjects were self-medicating to reduce the discomfort of benzodiazepine withdrawal. Withdrawal was more intense in this group, despite the fact that these subjects tended to supplement their benzodiazepine intake (Busto et al., 1986). Thus, the study demonstrated that benzodiazepine self-administration appears to increase in dependent subjects who are undergoing withdrawal.

The question of whether benzodiazepine withdrawal actually increases "craving" for benzodiazepines was pursued by Lucki et al. (1991). These investigators asked a group of 25 recovering alcoholics and a group of 43 patients under treatment for discontinuation of chronic use of therapeutic doses of benzodiazepines to indicate their "urge" for alcohol or tranquilizers during the previous week. They found that abstinent alcoholics reported a much greater craving for alcohol at this time (at least 3 mo following their last drink) than did benzodiazepine users for their medication. Alcoholics reported more intense and more frequent urges to drink, thought about drinking more, and reported missing drinking more than benzodiazepine users reported with respect to their medication. Former alcohol abusers indicated that it would be somewhat difficult for them to resist a drink if one were offered; benzodiazepine users anticipated no difficulty in refusing an available benzodiazepine.

Results of these studies suggest that benzodiazepine withdrawal may lead to increased consumption of benzodiazepines but that, after the withdrawal syndrome has dissipated, patients are not likely to report urges to resume benzodiazepine consumption. They appear to be taking the drugs specifically to attenuate their withdrawal symptoms.

4. Studies in subjects with histories of sedative abuse. The suggestion that a history of drug use might increase the reinforcing effects of benzodiazepines in humans has been supported in studies of the subjective effects of these drugs in individuals who use sedative drugs recreationally (Woods et al., 1987). In some of these studies, measures of drug taking indicated the actual reinforcing effects of benzodiazepines in sedative abusers. These subjects typically showed more self-administration of barbiturates such as pentobarbital than of benzodiazepines such as diazepam, but benzodiazepines were self-administered more regularly than was placebo. Other studies, in which subjective measures of "drug liking" were used, also indicated that barbiturates and some nonbarbiturate sedative-hypnotics, such as methaqualone, had a greater abuse liability than benzodiazepines

but that benzodiazepines, particularly in high doses, were associated with greater "liking" than were some other drugs, such as chlorpromazine, zopiclone, or buspirone.

In more recent studies, direct measures of self-administration of benzodiazepines in sedative abusers have rarely been included. Rather, subjects have typically been exposed to the drugs being studied, and a battery of tests of drug effects have been taken, including measures of whether or how much the subjects "liked" the drug. Measures of drug liking have involved simple VAS ratings, direct questions of drug liking, questions of whether the subjects would take the drug again if it were provided, an estimate of how much they thought the drug would cost "on the street," or more complex measures of drug effects such as the ARCI scales that measure subjective effects such as euphoria.

a. STUDIES COMPARING BENZODIAZEPINES AND NONBENZODIAZEPINES. Nonbenzodiazepine sedative-hypnotics have been compared to benzodiazepines by a number of investigators. Methaqualone (300 mg) produced larger and longer lasting measures of euphoria on the ARCI scale and less effects on the sedation scale than did alprazolam (2 mg), lorazepam (4 mg), or diazepam (20 mg). Methaqualone was also rated as having a significantly greater street value and as significantly more likely to be used again than were the benzodiazepines. A higher street value was placed on diazepam than on placebo or the other two benzodiazepines, although the subjects, who had fairly extensive histories of sedative and stimulant use, indicated that they would use all of the benzodiazepines again (Orzack et al., 1988).

Buspirone (10 and 20 mg) did not differ from placebo in measures of drug liking; both lorazepam (2 mg) and secobarbital (100 mg) produced higher measures of drug liking than did placebo (Schneiderman et al., 1989).

Lorazepam (1.5 to 9.0 mg) and meprobamate (600 to 3600 mg) produced similar reports of drug liking in subjects with prolonged histories of drug abuse. When asked the day following drug ingestion whether they would choose to take the drug again and to estimate a street price for the drug, the subjects gave a slightly higher ranking to meprobamate than to lorazepam (Roache and Griffiths, 1987a).

Methocarbamol, a skeletal muscle relaxant, was compared in a range of doses (2.25, 4.5, and 9 mg) to lorazepam (1, 2, and 4 mg) (Preston et al., 1989b). Both drugs produced reports of drug liking following drug administration and on the next day. The effects of the two drugs were similar immediately following drug administration; reports the next day of drug liking were greater with methocarbamol than with lorazepam administration. Interestingly, methocarbamol produced greater increases in dysphoria and greater decreases in euphoria measures on the ARCI scales than did lorazepam. Lorazepam produced increases in the euphoria scale.

Zolpidem, a hypnotic that is thought to act on the GABA complex, as do classical benzodiazepines, was compared with triazolam in 15 volunteers with histories of sedative abuse (Evans et al., 1990). Several doses of each drug were compared; the two largest doses of both drugs produced a greater rating of "liking" than did placebo. Nevertheless, neither drug increased scores on the MBG ("euphoria") scale of the ARCI. Zolpidem produced several negative effects that were not shared by triazolam, among them an increase in the dysphoria scale of the ARCI. The authors concluded that zolpidem had a different profile of drug action than triazolam.

In sedative abusers, both flupirtine, a novel nonopioid analgesic with sedative effects, and lorazepam increased measures of drug liking and "high," compared with placebo, but were not different from each other. Both produced increases in the euphoria scale of the ARCI; only flupirtine also increased scores on the sedation and dysphoria scale (Preston et al., 1991).

b. STUDIES COMPARING DIFFERENT BENZODIAZEPINES. People with histories of sedative abuse have been used as subjects in experimental studies of the subjective and psychomotor effects of various benzodiazepines. The procedures are generally quite similar to those used to compare benzodiazepines with other sedative-hypnotics in this subject population. Funderburk et al. (1988) evaluated 10, 20, and 40 mg of diazepam in comparison with 1.5, 3, and 6 mg of lorazepam on measures of drug liking. Larger doses of both drugs produced higher drug-liking scores, and there was no significant difference between the two drugs. Drug-liking scores increased across the first 90 min after drug administration, and the time to peak liking score was the same for the two drugs. The effects of lorazepam lasted longer than those of diazepam.

A single-dose comparison of small doses of diazepam (5 mg), clorazepate (7.5 mg), and lorazepam (1 mg), each tested in both the presence and absence of 0.54 or 1.08 g/kg of ethanol, was carried out by Funderburk et al. (1989). Clorazepate alone appeared to produce no effects on any of the measures evaluated, including drug liking, subjective or observer ratings, and measures of psychomotor effects. Diazepam's effects appeared limited to increases in drug liking, and in both subjective and observer ratings of drug effect, it was found to be similar to lorazepam. Lorazepam also altered some psychomotor measures but had no other effects. Ethanol produced dose-related increases in drug liking when it was combined with each of the benzodiazepines. It is not clear what effects ethanol alone had on reports of drug liking.

Bird et al. (1988) used a "mental unpleasantness" scale to indicate the potential abuse liability of lorazepam (2 and 4 mg), diazepam (20 mg), and adinazolam (30 and 50 mg). Adinazolam produced more mental unpleasantness than placebo either 3 h after drug administration (30-mg dose) or at 1, 2, and 3 h after drug administration

(50-mg dose). The mental unpleasantness effects of diazepam and lorazepam were not described.

Roache and Griffiths (1986) evaluated the possibility that tolerance developed rapidly to effects of diazepam. The authors theorized that the appearance of tolerance was due to accumulation of the diazepam metabolite, *N*-desmethyldiazepam; therefore, they compared repeated dosing of diazepam with repeated dosing of triazolam, which has no active metabolites. Diazepam (80 mg) was given every third day to three subjects and every sixth day to three subjects for a total of three to six doses. Triazolam (2 or 3 mg) was administered every other day to four subjects and every third day to two subjects. Placebo was administered, under double-blind conditions, on the intervening days for both drug conditions. Subjects' reports of drug liking were evaluated, using a simple questionnaire, prior to and 1, 2, 3, 4, 6, 8, and 12 h after drug administration.

The two benzodiazepines produced nearly equal drug-liking reports when initially administered. The peak effect and duration of liking of diazepam, but not of triazolam, decreased across repeated drug administration. This suggests tolerance to the drug liking produced by diazepam but not to that produced by triazolam. The small number of subjects and the relatively small differences between the drugs with respect to possible development of tolerance make the significance of the findings uncertain without further investigation.

Roache and Griffiths (1989a) compared triazolam (1 or 2 mg), diazepam (40 or 80 mg), and placebo self-administration and drug liking. Subjects were given one of the drugs or placebo on day 1 and could ride a stationary bicycle to obtain drug on subsequent days. Tolerance to reports of drug liking were observed with both drugs across the first 2 d of drug administration. The fact that tolerance to triazolam developed in this study, whereas it did not develop in the 1986 study, was attributed to the difference between the 48-h interdrug interval in the previous investigation as opposed to the 24-h interdrug interval in the current investigation.

The drug self-administration and liking scores described by Roache and Griffiths (1989a) are particularly interesting. Following a drug-sampling trial on the first day, the subjects rode a stationary bicycle for 30 min to earn drug on day 2. On subsequent days, the time requirement on the bicycle was progressively increased by 30 min to a maximum of 180 min on day 7. The number of subjects self-administering the benzodiazepine declined over the study days, from a maximum of eight on day 2 to a minimum of four on day 7. Unfortunately, this decline could be ascribed either to the increased work requirement or to a decline in the reinforcing effects of the drug due to exposure or to a combination of these effects. There was a positive correlation of 0.73 for diazepam and 0.72 for triazolam between next-day reports of drug liking after days 1 and 2 and number of occasions on which these drugs were self-administered. The next-day reports of drug liking were most consistently correlated with self-administration, suggesting, perhaps, that more immediate ratings of drug liking were not as consistently correlated with self-administration.

Roache et al. (1988) published an interesting short report of the effects of yohimbine on self-administration of triazolam in three subjects with histories of sedative abuse. Yohimbine alone produced increases in heart rate and blood pressure and produced increases in subjective reports of "anxiety/tension" and decreases in subjective reports of "calm/relaxed" in two of the three subjects.

The schedule of triazolam delivery permitted the subjects to select one of two colored capsules—placebo or triazolam (0.125 mg)—whenever a desk lamp was illuminated. The lamp was turned off for 10 min after each capsule ingestion. A maximum of 18 capsules could be taken in each daily 3-h session. In the absence of yohimbine, subjects showed a stable preference for triazolam over placebo. Increasing the amount of triazolam in the capsules to 0.25 mg resulted in a decrease in triazolam selection, whereas decreasing the amount of triazolam in the capsules to 0.031 mg resulted in an increase in triazolam selection. Administration of yohimbine (20 to 40 mg) produced an increase in the number of triazolam capsules taken by all subjects, although the increased selection was not related to the dose of yohimbine. The interesting possibility that the increased selection of triazolam was due to increased anxiety produced by yohimbine needs to be investigated further with a larger number of subjects.

5. Studies in alcoholics. The results of experiments described in earlier sections suggest that alcoholic subjects might be particularly susceptible to the reinforcing effects of benzodiazepines. There have been a limited number of studies of the subjective effects of benzodiazepines in abstinent alcoholics, although no recent reports have indicated the propensity of abstinent alcoholics to self-administer benzodiazepines.

Ciraulo et al. (1988a) compared 17 recently discharged alcoholic men with a group of 12 normal control subjects on variables that included certain subscales of the ARCI and VAS of sedation, current mood, drug liking, and intensity of drug effect. Tests were given and blood samples obtained periodically following oral administration of 1 mg of alprazolam. There was no difference between the groups with respect to peak alprazolam plasma concentration or to the time to reach that peak. The elimination half-life of alprazolam was longer and alprazolam clearance was slower in the alcoholic subjects. Although neither of these differences reached significance, together they produced a significantly greater total plasma level over time in the alcoholic subjects.

The baseline measures on the MBG ("euphoria") subscale of the ARCI were lower in alcoholic than in normal subjects. The control subjects changed very little from

their baseline values on the MBG subscale following alprazolam administration, whereas there was a dramatic increase in MBG subscale responses on the part of the alcoholic subjects. Similarly, the control subjects showed a slight decrease in drug-liking reports during the 6-h period following alprazolam administration, whereas the alcoholic subjects showed a marked increase in drug-liking scores compared with baseline measures. Measures of sedation or intensity of drug effect were not different in the two groups of subjects. The data suggest that persons who have abused alcohol in the past may be at greater risk for abusing benzodiazepines than are subjects without a history of alcohol abuse.

The possibility that a predisposition to alcohol abuse may be inherited has received a good deal of attention in recent years. McCaul et al. (1988) reported a study of 888 respondents to a questionnaire sent to 5000 male college students. The questionnaire requested information concerning family history of alcohol use and abuse as well as information about current and past drug use. Those with a positive family history of alcohol abuse reported drinking nearly twice as much alcohol as did those with a negative family history of alcohol abuse. Of more significance for this review, 23% of those with a positive alcohol use history reported using benzodiazepines (perhaps illicitly, although this was not clear), whereas only 0.9% of those with no family history of alcohol abuse reported use of benzodiazepines. The authors suggested that male offspring of alcoholics may be more likely to use a variety of psychotropic drugs than those of nonalcoholic parents. These survey data are supported by the study of Ciraulo et al. (1989) but not by the study of De Wit (1991) described in section II.C.1.

6. Summary and discussion. In general, results of recent experimental studies of benzodiazepine abuse in humans support the conclusions drawn in our previous review. Normal volunteers clearly do not choose to take diazepam, preferring instead to take placebo. Even anxious subjects tend to choose placebo over diazepam, particularly if they are not clearly seeking treatment for their anxiety. Anxious subjects seeking treatment are more likely to choose diazepam over placebo, although, even in this group of subjects, only a minority always selected the active drug.

Self-administration of benzodiazepines appears increased in subjects in whom diazepam is abruptly withdrawn. This interesting finding lends support to the suggestion that physiological dependence on benzodiazepines, and the withdrawal signs resulting from their discontinuation, may lead to maintained ingestion of these drugs.

Perhaps the most interesting new finding is that normal subjects with a history of moderate alcohol consumption appear to respond to diazepam as a reinforcer more often than do those with a history of little alcohol consumption. It remains to be determined whether the consistent selection of diazepam would be sustained throughout several sessions and whether the reinforcing effects of diazepam are enhanced in the paradigm of dose regulation used in these experiments; these questions will almost certainly be pursued in the near future.

An attempt to demonstrate greater euphoric effects of alprazolam in alcoholic subjects than in normal subjects suggested that this benzodiazepine, at least, might be liable to abuse in this subject population.

Benzodiazepines continue to produce "drug-liking" scores above those elicited by placebo in populations that abuse sedative-hypnotics. Some nonbenzodiazepine anxiolytics, such as meprobamate, tend to produce greater drug-liking scores than do benzodiazepines, as was shown by research considered in our earlier review. Other nonbenzodiazepine anxiolytics, such as buspirone, tend to produce less drug liking than do benzodiazepines.

As we have pointed out previously, it is important to study several doses of test drugs in research concerning drug liking in humans, and, even though there appears to be a reasonably good correlation between drug liking and drug taking in subjects with histories of drug abuse, it remains important to observe actual selection and ingestion of the drugs in question to determine their reinforcing effects. In addition, because results of studies of reinforcing effects have indicated decreasing trends over time, it appears to be important to conduct studies of subjective and reinforcing effects for at least several days. Given the overriding significance of studies of the reinforcing effects of benzodiazepines in human populations, we are encouraged by the recent work in this area and look forward to further research concerning relative abuse liability of various benzodiazepines, as well as relative abuse liability of benzodiazepines in various populations of human subjects.

D. Summary and Discussion

The results of recent studies in animals do not appreciably alter the findings of our previous review, namely, that, across a wide range of conditions, benzodiazepines generally do not maintain appreciable self-administration behavior. Studies in which more than one response is required for each injection are generally considered relatively stringent assessments of the reinforcing effects of drugs. Such studies of benzodiazepines have demonstrated rates of responding above those maintained by vehicle; however, these rates have typically been lower than those maintained by reference drugs such as cocaine or several barbiturates. Factors that may predispose to benzodiazepine self-administration, such as a history of sedative self-administration or physiological dependence, have not been fully studied. Reinforcing effects of the benzodiazepines introduced in recent years have not been extensively characterized.

As we commented in our previous review, it is unfortunate that research concerning the reinforcing effects

of drugs in humans remains in its foundling stages. In these circumstances, it is premature to assume that one measure of these effects should take precedence over others. In particular, the most recent studies have tended to neglect direct measures of self-administration in favor of indirect measures of subjective effects and/or measures of psychometric performance. With respect to the latter, some investigators have attempted to establish the bioequivalence of doses of test compounds by examining the effects of various doses on an array of measures of psychomotor performance. As will be discussed in section IV, the results of such tests vary widely with a number of factors; more important, it is unlikely that any particular psychometric measure, or indeed any particular battery of such measures, will serve as a universal standard for assaying the relative potency of various benzodiazepines. Thus, the diverse results obtained from such tests often raise more questions than may be appropriate in studies directed primarily toward measurement of reinforcing effects. We submit that the purpose of comparing drugs for assessing their abuse liability would be better served by examining a variety of complementary measures more directly relevant to abuse liability per se, in particular, rates of self-administration and drug preference. Measures of subjective effects should be used as a complement to these direct assessments of reinforcing effects. Such an approach would advance the purpose of establishing the degree of covariance among all of these imperfect measures of abuse liability.

The conditions under which the reinforcing effects of benzodiazepines might be enhanced have not been fully delineated. Results of some animal studies discussed in our previous review suggested that a history of sedative self-administration appears to increase the reinforcing effects of benzodiazepines; however, this suggestion has not been extensively pursued in recent research. Similarly, in some human studies, benzodiazepines have been found to have greater reinforcing effects in subjects with histories of alcohol or sedative abuse.

Among the recent studies of reinforcing effects in humans, one of the most important findings is that a history of moderate alcohol consumption can enhance preference for diazepam. If this finding can be replicated, it would indeed be pivotal, because it would suggest a segment of the population at risk of psychological dependence that is far greater in number than the frequently studied population of sedative abusers. In fact, given the large proportion of the population that would qualify as "moderate drinkers," if preference for benzodiazepines is enhanced in these individuals, one wonders why there are apparently not a great many more who abuse these drugs.

Thus, this study raises a number of intriguing questions for further research. For example, can it be shown that preference for benzodiazepines other than diazepam might be similarly enhanced in these subjects? What characteristics of these individuals make them different from others with respect to this preference? Are these characteristics comparable to those that make sedative abusers more likely to prefer some benzodiazepines? Exploration of the reinforcing effects of benzodiazepines in the population of moderate drinkers might help to clarify the significance of such research in sedative abusers and might shed a good deal of light overall on the abuse liability of these drugs.

Several observations suggest that reinforcing effects of benzodiazepines are increased in humans undergoing withdrawal. This suggestion is not supported by the few studies in animals that have directly addressed this important issue. Results of studies of oral self-administration of triazolam in baboons, or studies of progressive ratio schedules of diazepam self-administration in monkeys, have not indicated that reinforcing effects of these drugs are increased in dependent subjects. However, none of these studies has been explicitly designed to assess reinforcing effects of benzodiazepines during withdrawal in animal subjects; such studies are clearly needed to pursue the suggestions from studies in humans.

Few investigators have examined reinforcing effects, drug preferences, or even subjective effects of benzodiazepines throughout extensive periods of time. It is important to recall that the investigators who first assessed the reinforcing effects of diazepam in sedative abusers found that the rate of behavior maintained by the drug consistently decreased during the course of the study and never stabilized. The single recent study in which reinforcing effects were examined over a period of several days also demonstrated a similar decreasing trend. It continues to be important to submit the benzodiazepines to stringent examination of their reinforcing effects. The evidence to date pertains largely to brief observations in sedative abusers, such as those described above, and may convey a sense of the pharmacological activity of these drugs that is inconsistent with the vast majority of experience outside the laboratory.

III. Studies of Physiological Dependence

A. Introduction

As defined in our previous review (Woods et al., 1987), physiological dependence is a state of an organism during drug treatment such that discontinuation of that treatment is followed by the development of a time-limited withdrawal reaction that can be reversed by the resumption of treatment. We concluded that high doses of all of the benzodiazepines studied produced dependence in animals. Dependence occurring after treatment with low doses had been examined in few studies. Differences among benzodiazepines with respect to their potential to produce dependence had been suggested but not substantiated, in part due to a lack of studies in which pharmacologically equivalent doses were compared. Only a few benzodiazepines had been studied for their potential to

produce dependence in humans. These studies demonstrated that physiological dependence can develop to high doses and that a mild dependence can develop to therapeutic doses. However, the proportion of patients receiving therapeutic doses at risk for developing dependence was not clear. There were suggestions that predisposing factors for physiological dependence might include a history of prior or current exposure to other CNS depressants, including ethanol.

Since our previous review, there has been some interest in refining definitions of terms used in discussion of the effects of chronic drug treatment, particularly with benzodiazepines (Miller, 1988). Recently, the American Psychiatric Association convened a Task Force on Benzodiazepine Dependency (American Psychiatric Association, 1990), which defined three categories of symptoms that can occur when benzodiazepine treatment is discontinued and that can characterize a "benzodiazepine discontinuance syndrome." "Rebound symptoms" were described as qualitatively the same as the symptoms existing before treatment but of greater intensity or frequency; the Task Force further posited that these symptoms had a rapid onset and were temporary. "Recurrence symptoms" (relapse or recrudescence of symptoms) were also characterized as similar to those that existed before treatment; it was suggested that these symptoms had a more gradual onset and tended to persist over time. The third category, "withdrawal symptoms," was comprised of two types of symptoms. The first type consisted of symptoms that did not exist before treatment. The second included those that existed prior to treatment and that became more severe after treatment stopped; withdrawal symptoms of this type were distinguished from rebound symptoms in that they were not part of the disorder for which the drugs were originally prescribed. The Task Force further proposed that these symptoms define a "true" abstinence syndrome. These withdrawal symptoms were considered to have a variable intensity and were proposed to occur early or late, lasting 2 to 4 wk or occasionally longer following the cessation of treatment.

There is some rationale for some of the above definitions. As we noted previously, rebound symptoms are appropriately considered as indicative of physiological dependence if they are time limited and can be reversed by the resumption of treatment. Certainly, symptoms present before treatment that reappear following treatment and persist (are not time limited) should not be considered a withdrawal reaction or indicative of physiological dependence. However, in our view, the value of other distinctions made by the Task Force is unclear.

For example, the distinction between the exacerbation of one set of symptoms related to the initial condition of the patient ("rebound") and the exacerbation of another set of symptoms unrelated to the original condition ("withdrawal" reactions) is of questionable utility at best. Furthermore, it is not clear that anything is gained from distinguishing rebound and withdrawal symptoms in general or from considering only new symptomatology or exacerbation of unrelated symptoms as defining a "true abstinence syndrome." None of these distinctions appear important to a scientific understanding of the dependence process. We argued previously that rebound symptoms are withdrawal symptoms in their own right and are indicative of physiological dependence on the basis of their functional similarity to other withdrawal signs and symptoms; it is by no means clear that rebound symptoms are distinct from withdrawal symptoms. It also seems inappropriate to regard the recurrence of the initial condition as a discontinuance syndrome or as any kind of syndrome.

The attempt by the American Psychiatric Association Task Force to distinguish rebound and withdrawal symptoms according to their different time courses could be of some empirical merit. However, the period indicated for withdrawal symptoms ("early or late; lasts 2 to 4 wk, occasionally longer") is too vague to be useful. The references cited by the Task Force do not support any distinctions among these categories of symptoms on the basis of their relative durations. It has been well established with opioid and ethanol withdrawal, and to a lesser extent with benzodiazepine withdrawal (e.g., see studies by H. H. Swain cited in our previous review), that several signs characteristic of the withdrawal syndrome appear at different times as the syndrome unfolds. This may indicate that various signs of withdrawal are expressed at different thresholds of receptor uncovering; it is unclear that it represents a significant functional difference among these signs. Therefore, in the absence of more compelling arguments, we will continue to consider rebound anxiety and insomnia as examples of withdrawal symptoms that may be found following termination of benzodiazepine treatment.

Results from other recent studies (Ashton, 1991) suggested that a benzodiazepine "protracted withdrawal" syndrome can be defined. A protracted withdrawal syndrome has been best documented, although not extensively studied, with opioids (Himmelsbach, 1942). This syndrome is difficult to study, due largely to the high degree of variability in the signs and symptoms of which it is thought to be comprised (Martin and Sloan, 1977); moreover, it is not clear that it is appropriate to apply the criteria by which withdrawal is conventionally defined (including the criterion that the withdrawal symptoms should be time limited) to a putative syndrome of protracted withdrawal. In any case, such a syndrome has not been well documented with benzodiazepines.

B. Studies in Animals

1. Cross-dependence studies. In studies of cross-dependence, the subject is rendered dependent on a prototype drug, and treatment is subsequently withheld until

the subject is in a state of withdrawal. Test compounds are then administered for assessment of their ability to reverse this withdrawal syndrome. It is assumed that drugs that completely reverse the withdrawal that follows discontinuation of a given compound will themselves produce a similar type of dependence (Himmelsbach, 1941). In our previous review (Woods et al., 1987), we discussed a number of studies showing that withdrawal reactions obtained after treatment with barbiturates and with alcohol could be reversed by administration of benzodiazepines. However, findings from several studies had suggested that the dependence states that develop upon treatment with benzodiazepines may not be equivalent to those that develop with barbiturate treatment. For example, Yanagita (1981) reviewed studies of the ability of a series of benzodiazepines to suppress signs of barbital withdrawal; although most of the compounds suppressed all signs of withdrawal, several of the drugs did so only incompletely. Similarly, Martin et al. (1982) showed incomplete cross-substitution of diazepam and pentobarbital in rodents.

a. ABILITY OF BENZODIAZEPINES TO SUPPRESS WITHDRAWAL FROM OTHER DRUGS. In several recent studies, investigators have examined further the cross-dependence among benzodiazepines and other drugs. Some have demonstrated that cross-dependence can occur (Bourn and Reigel, 1987; Bone et al., 1989; Chan et al., 1986; Chan, 1987; Chan et al., 1990; Dolin et al., 1990) but provide little other information. Others have compared several drugs with regard to their ability to suppress withdrawal signs. Studies of this kind run the risk of drawing conclusions that are inappropriate because of the selection of doses tested. A simple illustration of such an error would be the comparison of one drug, at a single dose below the active range, with another drug at an active dose; it would be inappropriate to derive from this comparison the conclusion that the first drug was ineffective. Obviously, it is preferable to examine a range of doses of each drug. In addition, in a comparison of the ability of two drugs to suppress withdrawal, the potency of each drug in achieving this effect might be related to its potency in achieving some other effect that the two drugs share; in the absence of this information, the doses compared should be equated on the basis of some other pharmacologically relevant effect of each drug.

For example, Suzuki et al. (1988a) established equivalence of doses of test drugs on the basis of their effects on motor coordination. Rats were rendered dependent on methaqualone by mixing the drug with the only source of food; the daily dose ingested was not reported but, based on a previous publication (Suzuki et al., 1988b), was approximately 730 mg/kg/d. Barbital (156 mg/kg), ethanol (3.7 g/kg), and diazepam (65 mg/kg) each suppressed methaqualone withdrawal signs and either reversed or attenuated the loss of weight that followed the cessation of methaqualone treatment. Pentobarbital (at doses up to 43 mg/kg) only slightly attenuated the weight loss and had no effects on the withdrawal syndrome. These effects suggest that the dependence produced by methaqualone is similar to that produced by ethanol and diazepam but may differ from that produced by pentobarbital.

Kaneto et al. (1986) compared cross-dependence among several drugs in mice that were chronically exposed to ethanol vapor (12 mg/liter) or given repeated injections of barbital (100 mg/kg/12 h, p.o.). Ethanol, barbital, diazepam, ethosuximide, and morphine, but not naloxone, suppressed the signs associated with both ethanol and barbital withdrawal. The suppression by morphine was characterized as transient.

Gilbert-Rahola et al. (1988) showed that flunitrazepam and diazepam both produced some suppression of naloxone-precipitated jumping, tremor, and teeth chattering in morphine-dependent rats. However, the frequency of another sign, "wet dog shakes," was increased by flurazepam but not diazepam. The same group (Maldonado et al., 1990) in another study replicated the effects with flunitrazepam and found some similar effects with the benzodiazepine partial agonist, bretazenil. However, the inconsistency of the effects of these drugs on specific behaviors that are components of the opioid withdrawal syndrome suggest that these observations are not indicative of a robust attenuation of opioid withdrawal by benzodiazepines.

Quantitative effects of several benzodiazepines in the suppression of barbiturate withdrawal were reported in two recent papers. Rats were treated with a continuous i.v. infusion of pentobarbital at doses that increased throughout the course of 12 d to 950 mg/kg/d. Intravenous infusions of several doses of either temazepam (32.5 to 130 mg/kg/d) or midazolam (60 to 120 mg/kg/d) were substituted for pentobarbital treatment on the 13th d. Both drugs produced a dose-dependent suppression of pentobarbital withdrawal (Yutrzenka et al., 1989). In a subsequent study using the same techniques, Yutrzenka et al. (1990) found that bromazepam (14 to 28 mg/kg/d), diazepam (20 to 40 mg/kg/d), and methaqualone (100 to 200 mg/kg/d) suppressed withdrawal. Drugs that did not suppress withdrawal included nortriptyline and mazindol (doses not reported). Bupropion at 150 mg/kg/d unexpectedly suppressed pentobarbital withdrawal, although a higher dose (300 mg/kg/d) did not. These findings, like those reviewed previously by Yanagita (1981), reflect the value of a standard technique that can be used to assess large numbers of drugs under comparable conditions. Assessments of this kind will contribute to a better understanding of similarities and differences among mechanisms of dependence for different classes of drugs.

b. ABILITY OF OTHER DRUGS TO SUPPRESS WITHDRAWAL FROM BENZODIAZEPINES. Several recent studies have focused on whether drugs from other pharmacological classes might alter the intensity of benzodiazepine

withdrawal. For example, Chan et al. (1990) recently demonstrated suppression of chlordiazepoxide withdrawal by ethanol. In addition to answering basic research questions, these studies may also provide information that can be applied to treatment issues.

Costall et al. (1989) examined several behavioral effects claimed to be indicative of a withdrawal-induced anxiety reaction. These procedures purport to represent in animal subjects behavior that is analogous to the anxiety often reported in human patients undergoing benzodiazepine withdrawal (see section III.B.3 for a description of these procedures and primary dependence studies using them). Following treatment for 7 d with diazepam in two doses of 10 mg/kg, rats spent less time in social interactions with other rats. After the same dosing regimen, mice spent less time in the brightly illuminated section of a box that was divided into brightly and dimly illuminated sections. The 5-HT_3 antagonist, ondansetron, but not the 5-HT_{1A} agonist, buspirone, attenuated the decreases in time spent in the brightly illuminated sections and increased the amount of time spent in social interactions. The authors suggested that these results indicate that the anxiety produced by withdrawal from diazepam was alleviated by ondansetron but not by buspirone.

Goudie and Leathly (1990) also examined the effects of ondansetron. Rats were rendered dependent on chlordiazepoxide by twice-daily injections of escalating doses that reached 80 mg/kg/d. After 21 d of chlordiazepoxide administration, ondansetron was substituted for chlordiazepoxide. A dose of 0.1 mg/kg twice daily attenuated the weight loss and suppression in feeding behavior accompanying withdrawal, supporting the results of Costall et al. However, doses both ten times higher and ten times lower were without significant effects on these withdrawal signs. In a similar experiment (Goudie and Leathly, 1991), the 5-HT_{1A} agonist, ipsapirone, at doses from 3 to 10 mg/kg twice daily, was without effects; a higher dose exacerbated chlordiazepoxide withdrawal signs.

The mechanism and pharmacological specificity of these effects of ondansetron are not clear. The effects of other 5-HT_3 antagonists on benzodiazepine withdrawal have not been characterized. Therefore, whether the effect is due to antagonist actions at 5-HT_3 receptors has not been determined. The pharmacological specificity of the effects of ondansetron is, however, suggested by the observations that, at least at some doses, other signs such as weight loss were suppressed. To date, however, the effects of ondansetron have been assessed on relatively few benzodiazepine withdrawal signs. Specificity of an effect on withdrawal is suggested by a reversal of the entire constellation of signs associated with withdrawal (Martin and Sloan, 1977). Therefore, it would be of particular interest to examine the effects of ondansetron on the spectrum of withdrawal signs as characterized by Boisse et al. (1986a), Martin and colleagues (1982, 1986), or Griffiths and colleagues (Lukas and Griffiths, 1984). Other studies by Costall and colleagues (1988) suggest that ondansetron suppresses similar signs associated with withdrawal from several other drugs. These findings indicate that the effect of ondansetron on withdrawal is not specific to the drug on which the subject is dependent but may be a result of some more generalized behavioral action.

c. SUMMARY. Studies of cross-dependence with benzodiazepines appear to have become less frequent as studies of direct dependence on these compounds have increased. This is unfortunate for several reasons. Cross-dependence studies can reveal differences in potency and efficacy among drugs, which can help to elucidate the mechanisms of dependence that are peculiar to drugs of a given class and the mechanisms shared across classes. In contrast, primary dependence studies entail treatment parameters (such as frequency of injection, duration of drug action, or duration of treatment) that can complicate direct comparison among drugs. In addition, more cross-dependence studies are needed to advance our understanding of the extent to which benzodiazepines suppress withdrawal from ethanol or barbiturates and the extent to which other drugs suppress withdrawal from benzodiazepines. Results of recent studies have substantiated earlier suggestions of incomplete substitution between benzodiazepines and other sedative-hypnotics. Information of this kind could help in the development of treatments for individuals dependent on these drugs.

2. Primary dependence studies. In primary dependence studies, dependence on benzodiazepine agonists is directly assessed by examining withdrawal phenomena following either discontinuation of chronic benzodiazepine treatment or administration of a benzodiazepine antagonist during chronic treatment. Various signs are examined as indicators of a withdrawal state. Studies we reviewed previously indicated that withdrawal signs are more frequent or of greater magnitude (*a*) following administration of higher doses or doses with greater effects (although there was some evidence of possible exceptions), (*b*) following longer durations of treatment, or (*c*) following continuous rather than intermittent drug administration. We noted some preliminary evidence of differences in dependence produced by different benzodiazepines; however, rigorous comparisons among different drugs had not been conducted under conditions that allowed unambiguous conclusions.

Many recent studies have demonstrated the development of dependence on benzodiazepines that had previously received little experimental study. In a number of these studies, only single doses of a select compound were examined; although other issues were frequently examined in these studies, we will consider here only the findings relevant to the development of dependence following chronic administration. Dependence has been

reported to develop to alprazolam (Gallaher and Crabbe, 1987; Sloan et al., 1990), halazepam (Sloan et al., 1991c), lorazepam (Petersen and Jensen, 1987; Nutt and Costello, 1988), flurazepam (Little et al., 1988), and tetrazepam (Bachy et al., 1987). Sannerud and Griffiths (1990) found a lesser degree of dependence development to abecarnil, a β-carboline derivative that has partial or unique agonist actions at benzodiazepine receptors (Stephens et al., 1990), whereas Löscher and Rundfeldt (1990) found no dependence following chronic administration of this compound.

a. NEUROCHEMICAL SUBSTRATES OF DEPENDENCE. Scherkl et al. (1989) examined changes in sensitivity to pentylenetetrazol-induced convulsions in all surviving dogs during withdrawal from 2 mg/kg clorazepate, which was administered orally three times per day for 5 to 6 wk. Only two of the six subjects showed clear indications of tolerance to clorazepate, whereas increased sensitivity to pentylenetetrazol developed in all of the subjects. The authors suggested that these findings reflected differences in the mechanisms for tolerance and dependence to these drugs, because severe withdrawal seizures occurred in subjects in which tolerance had not developed.

Neurochemical mechanisms presumably underlying dependence and the withdrawal syndrome have been examined in several recent studies. Chronic administration of lorazepam to mice (1, 2, 4, and 10 mg/kg/d delivered s.c. via continuous infusion) produced dependence as evidenced by rebound increases in locomotor behavior. During treatment, there were correlated decreases in in vivo and in vitro binding of [^{3}H]flumazenil. This change in binding was likely due to changes in number of receptors, because the apparent affinity of clonazepam was not changed in vivo. In vitro studies of [^{3}H]flunitrazepam binding to the benzodiazepine receptor and [^{35}S]TBPS binding to the chloride channel also indicated a change in number of receptors, primarily in cortex. Thus, chronic lorazepam treatment produced a general downregulation of benzodiazepine and $GABA_A$ receptor function (Miller et al., 1988a,b).

Discontinuation of lorazepam treatment increased the number, but not affinity, of benzodiazepine receptors 4 d after the last dose, the time at which there were rebound increases in locomotor behavior (Miller et al., 1988b). In addition, increases in in vivo [^{3}H]flumazenil binding occurred 4 d after the last dose. This increase did not appear to be due to an increase in receptor affinity. In vitro studies of [^{3}H]flunitrazepam and [^{35}S] TBPS binding also indicated increases in numbers of binding sites 4 d after the last dose; results of other studies indicated increases in the stimulation of chloride channel function by the GABA agonist, muscimol. Thus, during withdrawal, there was a general upregulation of benzodiazepine and $GABA_A$ receptor function. This upregulation was opposite that seen during the chronic administration of the agonist. The correlation of the observed changes with the behavioral hyperactivity is suggestive of a mechanism underlying the changes that occur during benzodiazepine withdrawal.

b. EFFECTS OF DOSE OF AGONIST. We previously concluded that there was a direct relation between dose of agonist and intensity or frequency of withdrawal signs. However, several exceptions to this relation were noted. Guarino et al. (1988) had reported that withdrawal intensity increased with dose of chlordiazepoxide; however, the function relating withdrawal intensity to dose of chlordiazepoxide had a greater slope at the higher doses, suggesting a different mechanism for the high-dose dependence. In other studies of effects on individual withdrawal signs, frequencies of some signs increased with increasing agonist dose, whereas others increased and then decreased as dose was further increased (Lukas and Griffiths, 1984). Finally, withdrawal intensity appeared to reach a plateau with increasing agonist doses when some composite scales were used (Rosenberg et al., 1983; Rosenberg and Chiu, 1985).

Boisse et al. (1988) also examined twice-daily oral administration of chlordiazepoxide at doses of 2.5, 5, 20, 75, or 150 mg/kg in rats. Thresholds for induction of seizures were assessed by infusing flurothyl (0.11 ml/min of a 10% or 25% solution of flurothyl in 95% ethanol) into a chamber. The subject was observed continuously until the occurrence of the first myoclonic jerk or clonic seizure. Acute administration of each dose produced an increase in seizure threshold, and tolerance to this effect was observed with chronic dosing. The group treated with 75 mg/kg also showed a more intense spontaneous withdrawal syndrome of a constellation of signs than the other groups. Another group of subjects, given a single 450-mg/kg dose of chlordiazepoxide followed 76 h later by an injection of 25 mg/kg of flumazenil (acute dependence), also showed a lower seizure threshold during precipitated withdrawal. The report of this study is interesting but is brief and ambiguous.

Gallaher et al. (1988) reported in an abstract the effects of incorporation of diazepam in the food (0%, 0.01%, 0.03%, and 0.1%) of mice for a period of 4 wk. The actual milligrams per kilogram of drug intake was not specified for any of the groups. The subjects exhibited unspecified withdrawal signs that were characterized as "minimal" on a single day of discontinuation from the lowest concentration (0.01%). The withdrawal syndrome was described as dose dependent.

The effects of dose of midazolam on flumazenil-precipitated withdrawal were examined in baboons (Sannerud et al., 1989). Injection of 5.0 mg/kg of flumazenil followed 5 d of treatment with daily doses of 5.6 (one injection per day), 11.2, or 20 (two injections per day) mg/kg of midazolam. The duration of three of the four signs examined following flumazenil injection was directly related to midazolam dose.

Nutt and Costello (1988) reported the incidence of

seizures induced by the inverse agonist, FG 7142, following various 3-d treatment regimens of lorazepam. Doses of 1, 2, or 4 mg/kg were given i.p. to mice either once or twice daily (at 9 AM and 4 PM). The incidence of seizures was not significantly elevated in mice given lorazepam once per day at any of the doses. When it was administered twice per day, however, the incidence of seizures was greater than in controls at doses of 2 and 8 mg/kg/d.

Thus, recent data support the conclusion that withdrawal intensity is a function of agonist dose. However, possibly because of the difficulty of such studies, there have been few that have adequately followed the suggestion by Guarino et al. (1988) that withdrawal intensity may vary as a biphasic function of dose. Further studies of this phenomenon are needed to determine its pharmacodynamic basis and possible clinical implications.

c. EFFECTS OF DURATION OF TREATMENT. We previously concluded that there was also a direct relation between duration of treatment and intensity or frequency of withdrawal signs. Lukas and Griffiths (1984) had noted that some signs increased in frequency or intensity with continued treatment, whereas other signs first increased and then decreased in frequency or intensity.

Gallaher et al. (1988) reported in abstract form the effects of duration of exposure to diazepam. The drug was mixed with the only source of food (at 0.1%) for groups of mice exposed to the food for 2, 4, or 16 wk. The actual milligram per kilogram intake of drug was not specified. At the 2-wk exposure, the withdrawal was characterized as "mild," lacking convulsions, and lasting 2 d. The group exposed for 4 wk also exhibited withdrawal signs for 2 d; however, convulsions were observed in 73% of the subjects. The group exposed for 16 wk exhibited withdrawal signs for 11 d; all of the subjects experienced convulsions. Thus, the duration of treatment clearly affected the types of withdrawal signs observed, as well as the duration of the syndrome.

Similar results were reported by Zharkovskii and Zharkovskaya (1987). Rats were injected with diazepam in doses of 5 to 10 mg/kg once daily for 5 to 30 d. Withdrawal was precipitated with 2.5 mg/kg of the antagonist, CGS 8216 (administered 48 h after the last dose of diazepam), following 10 d of treatment. The intensity of the withdrawal increased when treatment was extended to 30 d.

Falk and Tang (1987) examined audiogenic seizures induced by flumazenil in rats made dependent on midazolam by inducing drinking of midazolam solutions; during daily 3-h sessions, subjects were exposed to a schedule of intermittent presentations of small pellets of food which induced drinking of large amounts of fluid. During an initial 2-mo period of exposure, concentrations of midazolam were increased from 0.025 to 0.05 mg/ml. After this exposure, subjects drank approximately 17 mg/kg of midazolam within the session. At several points during 26 wk of exposure to midazolam, flumazenil was administered, and subjects were examined for the induction of audiogenic seizures at an unspecified time after the drinking session. Seizures increased in intensity and duration during the course of 26 wk; the number of subjects exhibiting seizures appeared to stabilize at four of nine rats. These results are of particular interest, because blood levels of midazolam and its metabolites were found to be virtually eliminated within 3 h of exposure. The authors concluded that episodic exposure to midazolam was sufficient to produce dependence.

Sloan et al. (1991a) studied effects of the duration of diazepam treatment on precipitated withdrawal in dogs. During 5 wk, the dose was increased and stabilized at 12 mg/kg given three times per day. Withdrawal precipitated by oral flumazenil (18 mg/kg) was assessed with the BPAS scoring system. During the latter 3 of the first 5 wk of treatment, there was no significant change in withdrawal scores. Across the entire 14 wk of treatment, however, there was a linear increase in withdrawal scores.

Wilson and Gallager (1988) examined flumazenil-precipitated seizures in rats with diazepam-filled s.c. implanted capsules that produced relatively constant exposure of the brain to low levels of the drug. Flumazenil was continuously infused i.v. until death or until delivery of 20 to 25 mg/kg. The proportion of subjects showing various types of seizure activity increased as a function of duration of exposure to diazepam. No seizure activity was evident after 1 d of exposure; seizure activity increased up to 4 wk of exposure but decreased in weeks 5 and 6. No further exposure to diazepam was examined. One day after removal of the capsule, seizure activity was markedly reduced.

Thus, results of more recent studies have generally substantiated the conclusion that intensities or frequencies of withdrawal signs are related to the duration of agonist treatment. However, specific relations have not been systematically studied. In particular, it is important to pursue the possibility that dependence may vary qualitatively as a function of duration of treatment. In addition, the study of midazolam drinking has suggested that dependence can develop with episodic exposures to the drug. Thus, the duration of the episodic exposures becomes an important parameter of dependence studies and suggests that some measure of cumulative benzodiazepine exposure may be necessary to evaluate both frequency and episodic duration of exposure. Because the relation between intensity of withdrawal and duration of treatment has important clinical implications, these relations should be thoroughly investigated for all of the clinically important benzodiazepines.

d. ACUTE DEPENDENCE. Several studies have offered some support of earlier findings (Boisse et al., 1986b) that dependence on benzodiazepines can develop after a single dose (acute dependence). For example, Wilks and File (1988) noticed an increase in locomotor activity 48

h after a single dose of lorazepam. Because this effect could not be antagonized by flumazenil, it was apparently not a delayed effect of the agonist. Concurrent biochemical studies indicated that, at the time that this effect was observed, there was virtually no remaining displacement of tritiated flunitrazepam by lorazepam. These findings suggest that the locomotor activity was due to an uncovering of receptor sites by the elimination of the agonist, i.e., withdrawal.

In another study (Spealman, 1986), squirrel monkeys were trained with food reinforcement to press a response key. After daily performances were stable, the effects of 3.0 mg/kg flumazenil on rates of responding were assessed. Effects of flumazenil were assessed 24 h after administration of a single dose of diazepam (3.0 or 5.6 mg/kg), chlordiazepoxide (10.0 mg/kg), or *N*-desmethyldiazepam (5.6 mg/kg). Flumazenil, which was inactive when administered alone, disrupted rates of lever pressing 24 h after treatment with any of the benzodiazepines. The disruption in performance after flumazenil appears functionally similar to precipitated withdrawal.

Further studies of this phenomenon are necessary to establish that it is indeed related to the dependence-producing effects of benzodiazepine agonists. For example, it should be shown that flumazenil does not have similar effects after administration of sedative drugs, such as barbiturates, that do not act at the benzodiazepine receptor. Furthermore, it should be shown whether and how the effects of flumazenil are related to its dose, as well as to the dose of the agonist. The use of disruptions in operant behavior could be quite useful in examining quantitative aspects of the pharmacology of dependence, such as duration of benzodiazepine exposure, as well as for carefully examining differences between types of benzodiazepine agonists.

Boisse et al. (1990) determined whether acute dependence could be observed after a single dose of the short-acting agonist, midazolam. Single doses of 120 mg/kg of midazolam were administered to rats, which were then observed for withdrawal signs at 8 through 72 h after the injection. This dose of midazolam produced signs of CNS depression comparable to those produced by a dose of chlordiazepoxide (450 mg/kg) that had previously been demonstrated to produce acute dependence (Boisse et al., 1986b). In contrast to these results with chlordiazepoxide, this dose of midazolam did not produce obvious signs of withdrawal. The duration of action of this dose of midazolam was at most 8 to 10 h, whereas the duration of action of the equipotent dose of chlordiazepoxide was as long as 3 d. Because it was found that dependence could be produced with longer durations of midazolam treatment, the authors suggested that the observation that acute dependence did not develop could be attributed to the short duration of action of midazolam.

Thus, more recent studies have generally substantiated earlier findings of acute dependence on benzodiazepines. These findings suggest a means of quantitating differences among benzodiazepines without potential confounding variables such as duration of exposure and frequency of injection. However, with the relatively short-acting drugs, such as midazolam, a single injection may not have a duration of action sufficient to produce dependence. This finding has important implications for mechanistic studies of dependence and should be pursued further with other benzodiazepines. Results of a previous study (Boisse et al., 1986a) suggested pharmacodynamic differences between acute and chronic dependence on the basis of differences in the constellation of signs observed. Such differences could have important mechanistic or clinical implications but have not been further pursued.

e. COMPARISONS OF DIFFERENT BENZODIAZEPINES. We previously concluded that there was some preliminary evidence of differences in the potentials of different benzodiazepines to produce dependence. However, the evidence came from several studies in which single doses of different agonists were compared; such comparisons are inadequate, because drugs may appear different at one set of doses and similar at another.

A study by Martin et al. (1988) illustrates the difficulties inherent in comparing different agonists. Withdrawal was precipitated by flumazenil in squirrel monkeys that received once-daily oral doses of alprazolam, diazepam, flunitrazepam, oxazepam, or vehicle. The doses were chosen as equieffective in producing loss of the righting reflex. Withdrawal was precipitated by i.v. flumazenil 5 h after the ninth treatment. Precipitated withdrawal consisting of convulsions, tremor, or vomiting was observed in 25% of subjects receiving alprazolam, 100% receiving diazepam, 25% receiving flunitrazepam, 80% receiving oxazepam, and 0% receiving vehicle. After an additional 9 d of treatment, withdrawal was again precipitated, and withdrawal signs were observed in 100%, 100%, 75%, 60%, or 0% of the subjects, respectively. Thus, when administered for sufficiently long periods at relatively high doses, each of the drugs produced physiological dependence in the majority of subjects. It is important to note that, had the assessment been limited to the earlier time point, the results would have suggested much greater differences among these drugs with regard to their capacity to produce dependence.

i. Agonists with comparable durations of action. Feely et al. (1989) compared convulsive thresholds in mice receiving 0.5 mg/kg of lorazepam or 0.25 mg/kg of clonazepam twice daily for 3 d. These doses were chosen on the basis of equivalence of acute dose effects and duration of action. Threshold of pentylenetetrazol-induced convulsions served as an indication of tolerance development as well as of withdrawal. Tolerance developed to the effects of both drugs but was greater for lorazepam. In addition, a sensitivity to pentylenetetrazol

was observed during withdrawal from lorazepam but not clonazepam.

Piot et al. (1990) compared the effects of FG 7142-precipitated seizures in mice treated with various daily doses of lorazepam and triazolam (2, 4, 8, 16 mg/kg), diazepam and flunitrazepam (4, 8, 16, 40 mg/kg), and the nonbenzodiazepines, zopiclone and suriclone (4, 8, 16, 40, 80, 400 mg/kg). Drugs were administered i.p. four times daily for 3 d. The inverse agonist FG 7142 (40 mg/kg) was administered 2 d after the last injection, and seizures were recorded for the following 45 min. Seizures were observed after treatment with both diazepam and lorazepam and to a lesser extent after triazolam and flunitrazepam; the incidence of seizures appeared to depend on the dose of the agonist. In contrast to the other drugs, neither zopiclone nor suriclone produced seizures across the range of doses studied. The authors concluded that these cyclopyrrolones may be less likely to produce dependence than the benzodiazepines. However, this conclusion appears premature; although the drugs were administered over a wide range of doses, it was not shown that either of these drugs had activity within these dose ranges. In addition, previous studies with zopiclone in primates (Yanagita, 1983) demonstrated dependence following chronic treatment.

The most extensive series of comparisons among benzodiazepines are studies by W. R. Martin and colleagues in which precipitated withdrawal was compared after treatment with several agonists. Oral doses of the drugs were administered every 6 h to dogs. Doses were increased over time, typically to the point that the subjects began to lose weight. The dose was then stabilized or decreased slightly and stabilized. Blood and brain levels of the parent drugs and metabolites were assessed in many of these studies. The results of these studies have recently been summarized (Martin et al., 1990b). Most but not all of the results were reported previously. The following discussion refers to the original publications where possible.

In efforts to quantify the degree of withdrawal observed, several investigators have devised scales that measure frequency or incidence of particular signs, assign weights to these values, and arithmetically combine them to arrive at an overall score. In initial comparisons of diazepam and nordiazepam, McNicholas et al. (1988) devised a NPAS, comprised of four weighted signs common to both diazepam and nordiazepam withdrawal: gross tremor, twitches/jerks, hot-foot walking, and respiration rate change. This scale was later modified to weigh the four signs differently (Modified NPAS; Sloan et al., 1990) and then was modified again to include additional signs (BPAS; Martin et al., 1990b). With the BPAS scale, equal weights were assigned to each sign except status epilepticus. Because status epilepticus is typically fatal, withdrawal was terminated by administration of pentobarbital when this sign was observed; status epilepticus was accordingly assigned a larger weight to compensate for the shorter observation period. Because of the evolution of this method of measurement, comparisons of withdrawal scores across these studies can be inappropriate, necessitating the reanalysis of withdrawal in the summary paper (Martin et al., 1990b).

In the first of these comparisons, McNicholas et al. (1988) examined withdrawal precipitated by either flumazenil or CGS 8216 in dogs dependent on p.o. diazepam (24 or 36 mg/kg/d) or its primary metabolite, nordiazepam (*N*-desmethyldiazepam; 18 mg/kg/d). The half-lives of diazepam and nordiazepam are similar in humans and are 4.4 and 5.0 h, respectively, in dogs. Flumazenil precipitated a dose-dependent elevation in the NPAS score which appeared greater among diazepam-dependent subjects. In addition, CGS 8216 appeared more effective in precipitating seizures in diazepam- than in nordiazepam-dependent subjects.

Results of a previous study had suggested that the intensity of flumazenil-precipitated withdrawal was greater in dogs treated with nordiazepam than with diazepam; thus, dependence on diazepam could be due largely to the effects of its metabolite, nordiazepam (McNicholas et al., 1985). The more recent study by McNicholas et al. (1988) failed to replicate the greater intensity of withdrawal in nordiazepam-treated subjects. Nonetheless, the finding of some precipitated withdrawal after treatment with nordiazepam indicates that this metabolite may contribute to the dependence produced by diazepam.

Similarly, both spontaneous and flumazenil-precipitated withdrawal were demonstrated after 3 to 4 wk of exposure to chlordiazepoxide mixed with food (Chan et al., 1989). Circulating plasma levels of the chlordiazepoxide metabolite *N*-desmethylchlordiazepoxide were greater than those for the parent drug. Although these results suggest an important role for the metabolite, the relative roles of the parent drug and metabolite in producing dependence must be established by direct comparisons, such as those conducted by McNicholas et al. (1985). Absolute levels of the parent drug and metabolite alone are insufficient for conclusions regarding which is responsible for the dependence; the pharmacological activity of the metabolite must be assessed as well.

In several of the more recent studies, Martin and colleagues have compared dependence-producing effects of agonists that are used therapeutically. For example, Sloan et al. (1991b) compared the withdrawal syndrome (as measured by the BPAS) precipitated by flumazenil in groups of dogs treated chronically with oral flunitrazepam (7.6 mg/kg/d) or diazepam (24 to 36 mg/kg/d). The half-life of flunitrazepam was estimated as 1.7 h, compared with 4.4 h for diazepam. Withdrawal scores increased as a function of flumazenil dose and were comparable in the two groups of subjects despite lower plasma levels of flunitrazepam. Although the withdrawal

reactions were similar for the two agonists, there were some differences that the authors suggested were due to differences in the pharmacology of the drugs' metabolites.

In a similar experiment, dogs were treated chronically with halazepam (half-life of 3.4 h), diazepam, or nordiazepam, given orally four times per day (Sloan et al., 1991c). Doses of diazepam (20 to 26 mg/kg/d) and nordiazepam (18 to 36 mg/kg/d) were increased until the subjects started to lose weight; they were then stabilized at this dose or a lower dose at which body weights were maintained. Because subjects treated with halazepam did not lose weight, they were initially stabilized at 450 mg/kg/d. In the course of studies of flumazenil-precipitated withdrawal, four of seven subjects died. An additional four subjects were then studied at a dose of 180 mg/kg/d. Following precipitation studies at this dose, the dose was increased to 450 mg/kg/d; two of these subjects also died during studies with flumazenil. Withdrawal was assessed (using the modified NPAS) at weekly intervals 2 to 5 wk after achieving the stabilization dose. Withdrawal scores were higher at the higher halazepam dose. These scores were similar to those in diazepam-dependent subjects and higher than those obtained in nordiazepam-dependent subjects. There were also differences among drugs with respect to the signs making up the withdrawal syndrome, their intensity and duration, and the time following flumazenil injection at which they appeared. In particular, seizure activity was much less marked with halazepam-dependent subjects. The plasma and brain levels of each of the parent drugs and their metabolites were compared to assess their contributions to the different spectra of withdrawal signs obtained. The authors concluded that the drugs produced different types of dependence due to interactions of the parent compounds and their metabolites.

Martin et al. (1990b) directly compared results of several flumazenil-precipitated withdrawal studies of dogs dependent on different benzodiazepine agonists by reanalyzing earlier results, as well as some additional results, using the BPAS. The agonists studied included diazepam (20 to 36 mg/kg/d), nordiazepam (18 to 36 mg/kg/d), flunitrazepam (7.6 mg/kg/d), alprazolam (48 mg/kg/d), oxazepam (270 mg/kg/d), halazepam (180 or 450 mg/kg/d), and lorazepam (140 mg/kg/d). The dosing procedure to induce dependence was as described before. Flumazenil produced an increased BPAS score in all groups of subjects except those maintained on lorazepam; the effects of flumazenil were dose related in subjects dependent on diazepam, nordiazepam, and flunitrazepam. Diazepam-dependent subjects had the highest scores, followed by subjects maintained on flunitrazepam or halazepam (450 mg/kg/d). Lower scores were obtained in nordiazepam- and alprazolam-treated subjects (in a study described more fully in the next subsection), and still lower scores were obtained with oxazepam-treated subjects. The highest frequencies of flumazenil-precipitated seizures were obtained with alprazolam, diazepam, flunitrazepam, and, to a lesser extent, nordiazepam; the lowest frequencies were with the high doses of halazepam and lorazepam. Interestingly, the low frequency of seizures occurred while the halazepam-dependent group exhibited one of the highest BPAS scores. Conversely, alprazolam-dependent subjects exhibited the highest frequency of seizures with a modest BPAS score.

Plasma levels of the benzodiazepines and their metabolites indicated accumulation of some metabolites, particularly nordiazepam in diazepam- and nordiazepam-treated subjects. Halazepam-treated subjects showed a lower accumulation of nordiazepam as well as some accumulation of oxazepam conjugates (see also Wala et al., 1991). Alprazolam-treated subjects showed an accumulation of α-hydroxyalprazolam. Subjects treated with the other drugs did not show appreciable accumulation of parent drugs or metabolites. The authors suggested that plasma accumulation of drugs or metabolites may play an important role in the development of dependence. However, they also noted that it is not appropriate to attribute dependence to any particular metabolite on the basis of its accumulation. They further suggested that complex interactions between parent drugs and metabolites might influence the dependence obtained.

The authors identified three different syndromes of withdrawal from the different agonists tested. A relatively high incidence of clonic convulsions and relatively low BPAS scores characterized withdrawal from nordiazepam and alprazolam. Withdrawal from diazepam was characterized by relatively high BPAS scores and a high incidence of tonic-clonic convulsions. Withdrawal from halazepam was characterized by a relatively low incidence of clonic convulsions and high BPAS scores. Martin et al. concluded that these differences in withdrawal syndromes may be due to differences in the mechanisms and sites of action of the benzodiazepines or their metabolites.

The intensity of precipitated withdrawal is directly related to the plasma levels of flumazenil in dogs (Wala et al., 1988a). Thus, interpretation of the differences in dependence-inducing effects of benzodiazepine agonists is complicated by the observation that plasma levels of flumazenil, when it is injected following chronic administration of an agonist, may vary depending on the specific agonist. Wala et al. (1988b), in an abstract, reported higher plasma levels of flumazenil (after i.v. and p.o. administration) in nordiazepam-dependent dogs than in naive dogs. In contrast, the plasma levels of flumazenil in diazepam-dependent dogs did not differ from those in naive dogs. In a subsequent abstract, Wala et al. (1989) reported differences in plasma concentrations of flumazenil in dogs chronically treated with several benzodiazepines, which appeared to depend on the specific agonist administered. The results reported were complex and

their significance difficult to ascertain in the absence of a complete report; however, if the changes in flumazenil kinetics have functional consequences, these results may have important implications for comparisons of precipitated withdrawal in subjects treated with different benzodiazepine agonists.

The series of studies conducted by Martin and colleagues comparing benzodiazepines with respect to their dependence-producing effects are important in part because they go further than any previous studies toward sound comparisons among benzodiazepines. However, these comparisons are ultimately flawed for several reasons. First, it is important that pharmacologically equivalent doses are utilized when making this type of comparison. Some basic effect that is common to all of the drugs should be used as a means of determining this equivalence. Martin and colleagues, in several of the studies, increased doses until subjects lost weight. Unfortunately, this effect could not be obtained with all of the drugs, complicating some comparisons. Furthermore, this method may establish toxicological equivalence rather than an equivalence that is pharmacologically relevant. Investigators in previous studies of chlordiazepoxide dependence have used the chronically equivalent, maximally tolerable dosing regimen, in which a comparable degree of intoxication is maintained by adjusting dosage throughout treatment on the basis of a complex scale of CNS depressant effects (Boisse and Okamoto, 1978). This technique, although labor intensive, could be used to ensure the pharmacological equivalence of doses of the drugs tested and to control for unequal rates of tolerance that may develop to these effects.

Martin and colleagues, in some of their studies, compared agonists whose durations of action are similar but not really equivalent. These differences can also complicate comparisons among drugs. Relatively rapid clearance of a drug, prior to the next occasion on which it is administered, results in a drug-free period in which withdrawal can occur. These drug-free periods may allow a readaptation period which may, in turn, limit the dependence that develops (see section III.B.2.e.ii). Continuous exposure to the drug, through continuous infusion or depot delivery devices, may provide a less complicated means of comparing the dependence that develops to different agonists.

With the chronic administration of each of the drugs, Martin and colleagues measured the accumulation of parent drugs or metabolites and noted the difficulties of determining which of these agents was responsible for the dependence that developed. One problem in interpreting these results is that often the pharmacological activity of the various metabolites has not been characterized. It is inappropriate to attribute the dependence that develops after administration of a parent compound to its metabolite on the basis simply of relatively high plasma or brain levels of the metabolite; such an attribution neglects the relative pharmacological activities of the parent and metabolite.

Cross-dependence studies could be profitably used to aid in the characterization of different dependence states or withdrawal syndromes that may develop with different benzodiazepine agonists. As described in section III.B.1, in these studies the withdrawal syndrome is allowed to unfold after administration of one agonist. Test drugs are then administered, and their efficacy in reversing the withdrawal syndrome is assessed. Alternatively, the drugs to be characterized may be substituted for the drug on which the subjects are dependent, and their relative abilities to prevent the development of a withdrawal syndrome can be assessed. Drugs that produce similar dependence states will suppress each other's withdrawal signs; for example, methadone will suppress morphine withdrawal.

Studies of this kind should reduce some of the complications involved in comparing agonists. For example, this type of study could be used to gauge the contribution of metabolites to dependence, by assessing whether the metabolites can reverse withdrawal from the parent drug and whether the effect occurs at relevant doses. The dependence-producing effects of a parent drug could be assessed by determining whether it suppresses withdrawal from another drug at times when the metabolites of the parent drug were not present or at relatively low concentrations.

Finally, it is important when assessing cross-dependence to evaluate effects on individual withdrawal signs to determine the extent to which the test drug completely suppresses withdrawal from the reference drug. This information is critical when attempting to differentiate types of dependence and, ultimately, to identify their different mechanisms. For example, it would be of interest to determine whether the convulsions associated with nordiazepam withdrawal were suppressed by halazepam, a drug that does not produce a high incidence of withdrawal convulsions. These results would indicate whether the difference observed in spontaneous withdrawal from these drugs could be attributed to different mechanisms of dependence or to other factors, e.g., pharmacokinetics.

ii. Short-acting and long-acting agonists. In several studies discussed in our previous review, the short-acting midazolam was compared with other benzodiazepines with respect to their potentials to produce dependence. Cumin et al. (1982) had reported no apparent withdrawal following injection of flumazenil in squirrel monkeys that had been treated with 30 mg/kg, p.o., of midazolam; they suggested that more frequent administration of the agonist might be necessary for this short-acting compound to produce dependence. In addition, Kubota et al. (1986) examined dependence in cynomolgus monkeys given 0.3 mg/kg of midazolam or 0.03 mg/kg of triazolam i.v. every 8 h for 4 wk. Signs of withdrawal

were observed in none of the four subjects treated with midazolam and in only one of the four subjects treated with triazolam. One subject of three exhibited some signs of withdrawal after another 4 wk of exposure at higher doses (1.2 mg/kg of midazolam; 0.12 mg/kg of triazolam). Flumazenil precipitated withdrawal in two of three subjects treated with triazolam but in none of the subjects treated with midazolam.

Midazolam was examined more closely in subsequent studies. Falk and Tang (1987) used schedule-induced polydipsia to produce dependence on midazolam in rats during 3-h experimental sessions conducted once daily. Oral intakes of approximately 17 mg/kg/d were achieved in two groups of subjects. During the course of 26 wk, the subjects drinking midazolam showed a progressive increase in frequency of audiogenic seizures (see above).

Boisse et al. (1990) examined dependence on midazolam in rats, using four different dosing regimens. Subjects were treated with 120 mg/kg four times per day for 3 d. This dosing regimen produced a degree and duration of sedative effects equivalent to that produced by a single 450-mg/kg dose of chlordiazepoxide, which had been shown reliably to produce acute dependence (Boisse et al., 1986b). After this treatment, the maximum intensity of withdrawal was observed 3.8 d after the last dose of midazolam and subsided by the fifth day. In addition, subjects lost approximately 6% of their body weights; that weight loss was sustained after other signs of withdrawal had subsided.

A second regimen consisted of the same 120-mg/kg dose given only twice per day for 21 d. After this treatment, the maximum intensity of withdrawal was observed 2.2 d after the last dose and required 9 d to subside fully. Weight loss subsided with the other withdrawal signs.

The third regimen consisted of dose adjustment as tolerance developed to maintain a consistent degree of intoxication during a 5-wk period; the initial dose of 120 mg/kg twice per day was eventually increased to 180 mg/kg. After this treatment, the maximal intensity of withdrawal was observed 1.8 d after the last dose. Signs subsided fully after 14 d.

As described in section III.B.2.d, a single dose of 120 mg/kg was examined for its capacity to produce acute dependence. This single dose produced no obvious signs of withdrawal.

This study clearly demonstrated that dependence can develop to midazolam and that the signs of withdrawal are similar to those obtained with other benzodiazepines. Furthermore, it indicates that, like the dependence produced by other benzodiazepines, midazolam dependence is influenced by the dose and duration of treatment (see also Sannerud et al., 1989, described in section III.B.2.b).

Several investigators have suggested that withdrawal may be more intense after treatment with short-acting as compared with longer acting benzodiazepines (Tyrer et al., 1981; Busto et al., 1986; Rickels et al., 1986a). Boisse et al. (1990) examined treatments with midazolam that produced degrees of intoxication comparable to those produced previously by the longer acting chlordiazepoxide (Ryan and Boisse, 1983; Guarino et al., 1988). Despite the more rapid elimination of midazolam, the intensity of withdrawal from this drug was comparable to that following treatment with a regimen of chlordiazepoxide that produced an equivalent degree of intoxication (Boisse et al., 1986b). Differences between the two drugs in onset of withdrawal signs could not be determined from the data presented (chlordiazepoxide withdrawal was examined beginning 4 d after the last dose, when withdrawal intensity had already reached maximum). The duration of the withdrawal syndrome, however, was clearly greater for chlordiazepoxide than for midazolam.

Sloan et al. (1990) examined dependence on alprazolam (half-life 0.7 h) in dogs given 48 mg/kg/d orally in four equal doses. The dose was gradually increased over a period of 18 to 26 d, and subjects were stabilized on this dose for at least 1 wk. Withdrawal was precipitated by oral flumazenil (6 to 36 mg/kg) or a continuous i.v. infusion until clonic or tonic-clonic convulsions were induced. Modifed NPAS scores after oral flumazenil were consistently higher than those observed in benzodiazepine-naive subjects; however, changes in these scores did not depend on flumazenil dose. Flumazenil produced clonic and tonic-clonic convulsions not observed after placebo administration or in the group treated chronically with placebo. Because the alprazolam-treated group showed significant accumulation of α-hydroxyalprazolam, the authors suggested that this metabolite may contribute to the dependence observed with chronic alprazolam treatment.

Two of the alprazolam-treated subjects showed a behavioral syndrome characterized by repeated episodes of wild running, barking, lunging as if at objects, and splaying of limbs, with rigidity and jerks (canine delirium) after flumazenil administration. These signs were not observed in dogs dependent on other benzodiazepines. Furthermore, the NPAS scores were lower for alprazolam-dependent subjects than for subjects exposed to either diazepam but not nordiazepam (Martin et al., 1990b). The authors did not consider differences between benzodiazepines with respect to duration of action.

In several recent studies of neurochemical mechanisms underlying dependence, investigators examined benzodiazepines with different durations of action. The methods of these studies were sufficiently similar to allow direct comparisons of results. As described in section III.B.2.a, Miller et al. (1988a,b) examined chronic administration of lorazepam in mice via osmotic minipumps. This method of administration produces constant brain levels of the drug during the treatment period. $GABA_A$ receptor function during treatment and withdrawal was assessed by examining in vivo and in vitro benzodiaze-

pine receptor binding, [^{35}S]TBPS binding to the chloride channel, and muscimol-stimulated chloride flux. Discontinuation of lorazepam increased the number of benzodiazepine receptors 4 d after the last dose, the time at which there were rebound increases in locomotor behavior. In addition, [^{35}S]TBPS binding also indicated increases in numbers of sites 4 d after the last dose, and there were increases in the stimulation of chloride channel function by muscimol. Increases in in vivo binding were obtained in several brain regions, including cerebellum, hypothalamus, hippocampus, and cortex. During withdrawal, there was a general upregulation of benzodiazepine and $GABA_A$ receptor function, opposite that seen during the chronic administration of the agonist.

In a comparable study, Miller et al. (1989) reported effects of chronic treatment with alprazolam. Initial effects of treatment on in vivo [^{3}H]flumazenil binding and in vitro [^{3}H]flunitrazepam and [^{35}S]TBPS binding were generally similar to those obtained with lorazepam; however, there were differences in binding in particular brain regions. Discontinuation of alprazolam produced biochemical effects that were generally opposite those obtained with chronic alprazolam treatment; both in vivo and in vitro binding was increased, as was the muscimol-stimulated uptake of chloride in cortical synaptosomes (Lopez et al., 1990). Binding of [^{35}S]TBPS was increased but not significantly. These effects were correlated with locomotor activity increases occurring 2 and 4 d after discontinuation of treatment. In general, the upregulation of $GABA_A$ function that occurred with alprazolam withdrawal was similar to that observed with lorazepam withdrawal; however, it first appeared earlier (at 2 versus 4 d), and there were some differences in brain regional specificity. Lorazepam withdrawal was associated with increases in benzodiazepine binding in the cerebellum that did not occur with alprazolam.

Chronic administration of clonazepam via osmotic minipumps at a dose of 1.5 mg/kg/d for 2 wk also produced downregulation of $GABA_A$ function, as indicated by benzodiazepine binding, both in vivo and in vitro, and by [^{35}S]TBPS binding (Galpern et al., 1991). Following discontinuation of treatment, there was an increase in locomotor activity at day 4 and a corresponding upregulation of $GABA_A$ function; an increase in in vivo benzodiazepine binding and receptor number was determined in vitro. The binding of [^{35}S]TBPS in the cortex was also increased 4 d after termination of clonazepam treatment. In contrast to lorazepam withdrawal, there was an increase in benzodiazepine binding only in the cortex with clonazepam.

One significant difference between the results obtained with the different benzodiazepines in these studies is the time at which withdrawal-induced changes were apparent. Increases in benzodiazepine receptor binding, chloride channel binding, and muscimol-stimulated chloride flux were obtained 2 d after the last dose of alprazolam, versus 4 d after the last doses of lorazepam or clonazepam. In addition, results of these studies suggest regional differences in central sites associated with withdrawal from different benzodiazepines. However, further studies are necessary to determine whether the differences observed are due to specific differences in the pharmacological activity of these drugs or to differences in their pharmacokinetics.

In summary, studies of short-acting benzodiazepines have clearly indicated that physiological dependence can develop with these drugs, providing a sufficient duration of exposure. Moreover, studies in animals have also indicated that the latency to onset of withdrawal is briefer following the last dose of short-acting than of long-acting compounds. Direct comparisons of benzodiazepines with different durations of action, however, have not adequately addressed whether there are differences in the magnitude of the dependence that develops. Boisse and colleagues indicated that the intensity of withdrawal was similar for chlordiazepoxide and midazolam. Martin and colleagues demonstrated some differences between syndromes of withdrawal from alprazolam and diazepam; however, it was not clear whether these reflected pharmacodynamic or pharmacokinetic differences. Finally, studies of neurochemical mechanisms underlying withdrawal syndromes from short- and long-acting benzodiazepines have not elucidated possible differences in magnitude of dependence or intensity of the syndrome.

iii. Partial agonists. Martin et al. (1988) compared precipitated withdrawal in squirrel monkeys treated with diazepam (40 mg/kg once daily for 10 d) and the benzodiazepine partial agonist bretazenil (Ro 16–6028; 2.5 or 40 mg/kg either once or twice daily for 10 d). On the 11th d, all drugs were administered twice. Flumazenil was administered to all subjects at several times up to 7 d following the last dose of the agonist. The investigators reported no clear signs of precipitated withdrawal following either 2.5 or 40 mg/kg of bretazenil administered either once or twice daily. In contrast, clear signs of precipitated withdrawal were obtained in all subjects treated with diazepam. The lowest dose of each of these drugs to produce signs of sedation or muscle relaxation were 40 mg/kg of bretazenil or 1 mg/kg of diazepam. Thus, a minimally sedative dose of bretazenil (40 mg/kg) was compared to a dose of diazepam 40 times greater than its minimally sedative dose. In the case of partial agonists whose intrinsic efficacy is lower than that of full agonists, it may be difficult to achieve pharmacological equivalence of doses.

In another study reported in abstract form (Martin et al., 1990a), bretazenil was compared with vehicle or alprazolam. Squirrel monkeys received injections three times daily for 11 d and were challenged with 0.25 mg/kg i.v. of the benzodiazepine partial agonist, Ro 15–3505 (sarmazenil). In subjects receiving 1 or 3 mg/kg/d of

alprazolam, convulsions were observed in two or four of four subjects, respectively. In subjects receiving 3, 10, or 30 mg/kg/d of bretazenil, convulsions were observed in zero, one, or two of four subjects, respectively. The authors commented that bretazenil has a higher potency than alprazolam in diverse pharmacological tests. The higher potency of bretazenil suggests that it would be utilized at lower doses, leading these investigators to conclude that bretazenil has a lower potential for physiological dependence than does alprazolam. Although the they examined a range of doses, there was no attempt to establish pharmacologically equivalent doses.

Moreau et al. (1990) examined precipitated withdrawal after administration of triazolam, alprazolam, diazepam, and bretazenil in convulsion-prone DBA/2J mice. In the first experiment, the drugs were administered continuously for 1 wk via osmotic minipumps. Different groups of subjects were given vehicle or the drugs at several doses: triazolam (0.15, 0.44, 1.4, 5 mg/kg/d), alprazolam (4.4, 15, 32, 45 mg/kg/d), diazepam (4.7, 15, 47 mg/kg/d), or bretazenil (4.4, 13.5, 45 mg/kg/d). A 3-mg/kg dose of sarmazenil was injected i.v. 5 h after the minipump was removed, and mice were observed for the appearance of tremors, wild running, and clonic and/or tonic convulsions. The incidence of each of the withdrawal signs was directly related to the dose of triazolam, alprazolam, or diazepam. Withdrawal signs were not precipitated in either the vehicle- or bretazenil-treated groups.

Results of in vivo receptor occupancy studies conducted with alprazolam and bretazenil delivered by the osmotic minipumps confirmed that the drugs were bioavailable in the CNS. After 7 d with implanted pumps delivering 45 mg/kg of bretazenil or alprazolam or vehicle, subjects were injected i.v. with [^{3}H]flumazenil at a dose of 150 μCi/kg. Bretazenil and alprazolam produced 90.2% and 68.4%, respectively, cerebral benzodiazepine receptor occupancy. Similar studies indicated that the 3-mg/kg dose of sarmazenil was sufficient to produce 88% receptor occupancy. The differences between bretazenil and alprazolam in producing dependence were thus apparently not due to a lack of CNS bioavailability of bretazenil. In fact, at the doses compared, bretazenil produced a greater receptor occupancy than alprazolam. Results of these studies, therefore, suggest that, assuming equivalence of other treatment parameters, such as duration of action, the differences between these drugs in producing physiological dependence are due to differences in their intrinsic efficacy.

In a subsequent study reported in the same paper, these investigators administered alprazolam (1, 3, or 10 mg/kg), bretazenil (10, 30, or 100 mg/kg), or vehicle p.o. twice daily to mice for 17 d. Withdrawal was precipitated by 3 mg/kg sarmazenil i.v. in the group treated with 3 and 10 mg/kg of alprazolam. The 3-mg/kg dose of alprazolam is 38 times higher than its anticonvulsant ED_{50} dose. Withdrawal was not observed in any of the bretazenil-treated subjects at doses up to 53 times higher than its anticonvulsant ED_{50} dose. A comparison of dependence potential of doses approximately equivalent on the basis of a pharmacological effect was attempted in this study, and, again, little potential of the partial agonist to produce dependence was found.

Von Voigtlander and Lewis (1991) have described a procedure for rapid evaluation of dependence-producing effects of benzodiazepines. Mice were given two daily doses of an agonist for 3 d. Intravenous flumazenil was administered 24 h after the last dose, and the threshold for electric shock-induced seizure was determined. Flumazenil lowered seizure threshold in dependent mice as compared with nondependent mice. For each compound whose administration was followed by flumazenil-induced reduction in seizure threshold, a 10-fold lower dose of the agonist was studied in another group of subjects to determine the minimally effective dependence-inducing dose. Significant lowering of seizure threshold was found with several benzodiazepine agonists and related compounds, including chlordiazepoxide, diazepam, flurazepam, alprazolam, triazolam, midazolam, and zopiclone, as well as the partial agonists, bretazenil and Ro 17–1812. In contrast, several other compounds, zolpidem, tracazolate, and CL 218,872, did not alter the threshold.

These findings are of particular interest in that minimal doses producing dependence were compared with the ED_{50} dose for inhibition of in vivo binding (although the report did not detail the methods used in the in vivo binding experiments). At least partly because of the tenfold dose increments at which dependence was evaluated, the study did not show a good linear relation between the binding ED_{50} and the minimal dose producing dependence. However, the ED_{50} values for several drugs can be compared. The bretazenil and alprazolam ED_{50} values for in vivo binding were similar, although the dose of bretazenil required to produce any sign of dependence was ten times greater than that of alprazolam. Similarly, the ED_{50} values of the full agonist triazolam and the partial agonist Ro 17–1812 were similar, although tenfold higher doses of Ro 17–1812 were required to produce signs of dependence. These data are consistent with the conclusion that drugs with limited efficacy have less liability for producing physiological dependence.

Löscher et al. (1990) examined the effects of chronic treatment of dogs with abecarnil, a β-carboline derivative that has agonist activity at benzodiazepine receptors. Abecarnil was administered s.c. once daily at 4 mg/kg for a period of 40 d. At day 38, flumazenil (1 mg/kg) was administered 2 h after the abecarnil injection. The threshold for pentylenetetrazol-induced seizures was assessed 3 d following termination of treatment and at weekly intervals thereafter. The results with abecarnil were compared with those obtained in a similar study of oral clorazepate (Scherkl et al., 1989). Signs of withdrawal were generally absent in abecarnil-treated sub-

jects, both after administration of flumazenil and as evidenced by a decrease in pentylenetetrazole thresholds; only one of seven subjects showed a lowered threshold for seizures following cessation of abecarnil treatment. In another study of abecarnil administration in baboons, reported in abstract form, Sannerud and Griffiths (1990) found some signs of withdrawal that were less intense than those precipitated after diazepam administration. In contrast to results with abecarnil, clorazepate produced a marked withdrawal syndrome (Scherkl et al., 1989). Although abecarnil has been reported to have partial agonist actions, some of its unique pharmacological effects are not fully explained by limited intrinsic efficacy (Turski et al., 1990; Stephens et al., 1990).

f. EFFECTS OF TYPE OF ANTAGONIST. At the time of our previous review, only two antagonists had been studied, and they had not been extensively compared. However, we noted that results of a study by McNicholas and Martin (1986) had suggested differences between flumazenil and CGS 8216 in their effects on diazepam-dependent rats; the dose-effect curve for CGS 8216 was not as steep, and appeared to reach a plateau, compared to that for flumazenil.

As noted, McNicholas et al. (1988) have confirmed this earlier finding in dogs. Other investigations have indicated similar effects. For example, Lamb and Griffiths (1987) compared dose effects of flumazenil and CGS 8216 in baboons receiving continuous i.g. diazepam at 20 mg/kg/d; the overall intensity of withdrawal precipitated by flumazenil was greater than that precipitated by CGS 8216. In addition, the intensity of the effect was dose related only with flumazenil. It is possible to account for some of the differences between the antagonists on the basis of differences in their pharmacokinetics; however, CGS 8216 was administered at doses that had proven effective in antagonizing behavioral effects of lorazepam in other studies with baboons.

Giorgi et al. (1988) rendered cats dependent on diazepam by administering 7 mg/kg i.p. twice per day for 21 d. Withdrawal was precipitated with flumazenil (10 mg/kg), as well as with the partial inverse agonist Ro 15–4513 (10 mg/kg, sapazenil). In contrast, two β-carbolines with antagonist or inverse agonist activity, ZK 93426 (10 mg/kg) and FG 7142 (10 mg/kg), did not precipitate withdrawal. These antagonists were approximately equally effective in blocking the acute ataxic and muscle relaxant effects of diazepam. The failure of FG 7142 to precipitate withdrawal was also documented by Ongini et al., 1985. In another study, Giorgi et al. (1989) replicated these effects and documented that none of the antagonists, with the exception of FG 7142, had activity in nondependent subjects. In addition, CGS 8216 also precipitated withdrawal, although not to the same extent as flumazenil or Ro 15–4513. The authors concluded that antagonists with a β-carboline structure do not precipitate withdrawal.

Löscher et al. (1989) compared the withdrawal precipitated by flumazenil and ZK 93426 in dogs dependent on diazepam (1 mg/kg given three times per day for 1 wk). Withdrawal was precipitated by slow infusion of the antagonists up to 20 mg/kg. Withdrawal was characterized by relatively mild behavioral disturbances that were apparent in some subjects after flumazenil treatment but were not clearly evident after ZK 93426. After administration of 2 mg/kg of diazepam three times daily for 2 wk, withdrawal was more pronounced. Both antagonists produced withdrawal; however, the signs of withdrawal were different. Flumazenil produced rigidity in posture and walking with increased muscle tone, tremor, twitches, and jerks. In contrast, ZK 93426 induced myoclonic jerks and tonic-clonic seizures but did not alter motility. The investigators noted that the withdrawal signs observed after ZK 93426 were similar to those observed after spontaneous withdrawal, whereas the rigid postures and immobility observed after flumazenil were unique signs.

These findings of different constellations of effects after administration of various antagonists in dependent subjects suggest that different mechanisms may be responsible for particular withdrawal effects. However, this suggestion requires support by quantitative studies examining several doses of various antagonists. Nevertheless, it is encouraging that several benzodiazepine antagonists are now available for study, and it is clear that their availability will advance research concerning benzodiazepine dependence.

g. EFFECTS OF ANTAGONIST TREATMENT ON THE DEVELOPMENT OF DEPENDENCE. The results of electrophysiological studies have suggested that benzodiazepine tolerance with chronic treatment can be attenuated by a single injection of flumazenil (Gonsalves and Gallager, 1985). Because tolerance and dependence often occur together, these investigators also examined whether flumazenil administration can reverse the dependence that develops to benzodiazepines (Gallager et al., 1986). Rhesus monkeys were given injections of diazepam twice daily at total doses of 1.5 or 6.0 mg/kg/d. Half of the subjects were treated every third day with flumazenil (5 mg/kg) 4 h after the first daily diazepam injection; the other half was treated with flumazenil vehicle. Both groups of subjects were given 5 mg/kg of flumazenil on the 12th day of treatment and were observed for withdrawal signs. The subjects treated with flumazenil showed significantly fewer withdrawal signs than did the subjects treated with vehicle. These authors suggested that periodic exposure to a benzodiazepine antagonist might be a useful therapeutic approach to counteracting the dependence that can develop with long-term exposure to benzodiazepines.

Decreases in intensity or frequency of withdrawal signs after repeated flumazenil injections was also reported in baboons (Lamb and Griffiths, 1985). In this study, two

baboons dependent on diazepam (20 mg/kg/d, i.g.) or triazolam (5 mg/kg/d, i.g.) were given injections of flumazenil (5 mg/kg) every day or every third day. At least 1 mo without antagonist administration separated these series of flumazenil injections. Initial injections of flumazenil produced a withdrawal syndrome, as characterized previously by these investigators (Lukas and Griffiths, 1982). With successive injections, however, signs decreased in duration or frequency, until some signs were absent.

Nutt and Costello (1988) examined seizures produced by the benzodiazepine partial inverse agonist, FG 7142, following lorazepam treatment. Lorazepam was administered for 3 d at 2 mg/kg/d delivered in two doses. Subjects were treated with either flumazenil (two doses of 10 mg/kg) or saline on the fourth day and were given FG 7142 on the fifth day. In normal subjects, FG 7142 did not produce convulsions, whereas seizures were observed in 60% of the lorazepam-treated subjects that received saline on the fourth day. Seizures were observed in 10% of the subjects that had received flumazenil on the fourth day. Similar results were obtained with the inverse agonist, methyl 6,7,dimethoxy-4-ethyl-β-carboline-3-carboxylate.

Löscher and Rundfeldt (1990) studied seizures in rats with bipolar electrodes implanted in the amygdala. Daily electrical stimulation of the amygdala at subthreshold intensities eventually resulted in seizures (kindling). Clobazam was administered three times daily (30 mg/kg/d) for 15 d in two groups of subjects, one of which also received flumazenil each third day. Tolerance developed to the anti-seizure activity in these subject; however, during withdrawal there were no significant changes in seizure activity in either group. Behavioral changes characterized as hyperexcitation and reduced exploratory behavior were observed in subjects treated with clobazam but not in those treated with clobazam and flumazenil.

Baldwin et al. (1990) studied social interactions of rats after withdrawal from diazepam using a procedure claimed to serve as an indication of withdrawal-induced anxiety (see section III.B.3). Diazepam was given daily at 4 mg/kg i.p. for 21 d. Flumazenil (4 mg/kg i.p.) was given on either day 7 or 14, approximately 24 h after the last diazepam injection. Rats engaged in significantly fewer social interactions 24 h after the last injection of diazepam than did rats that received vehicle injections. In rats treated with flumazenil, however, social interactions were similar to those observed in control rats, suggesting an attenuation of this "withdrawal" effect.

Each of the aforementioned reports is suggestive of some unique effect of flumazenil injection during chronic benzodiazepine administration. However, results of other studies indicate that these effects may not be obtained under other conditions. For example, Sloan et al. (1991a) found an increase in flumazenil-precipitated withdrawal in subjects receiving diazepam three times per day at a daily dose of 12 mg/kg. After 5 wk of treatment (dose was increased to 12 mg/kg during the first 2 wk), flumazenil was administered once per wk for the next 3 wk and biweekly during treatment weeks 9 through 14. Withdrawal precipitated by oral flumazenil (18 mg/kg) was assessed with the BPAS. Across the entire 14 wk of treatment, there was a linear increase in withdrawal scores rather than the decrease that might have been expected based on the findings of Gallager and colleagues described before. Similarly, Sloan et al. (1991b) found a stable response to flumazenil in dogs treated chronically with flunitrazepam.

Thus, findings are contradictory with respect to whether administration of flumazenil during chronic benzodiazepine treatment decreases the degree of dependence that develops. Resolution of the differences in these results will require systematic studies that parametrically investigate various treatment regimens, different antagonists, and possibly different withdrawal effects. At present, the few observations of decreased withdrawal following flumazenil administration must be regarded as curious phenomena lacking a strong empirical or theoretical basis.

3. Procedures hypothesized to measure withdrawal anxiety. There has been a recent increase in the variety of procedures used in studies of animals following chronic treatment with benzodiazepines. Most of these procedures have some face validity and purport to measure manifestations of anxiety analogous to the rebound anxiety that has been reported in humans undergoing benzodiazepine withdrawal. However, the behaviors examined have not been validated as functionally equivalent to the anxiety observed in humans. In addition, if these behaviors are to be construed as withdrawal phenomena, they should be shown to meet the conventional criteria for such phenomena, i.e., the behavioral changes following the cessation of drug treatment should be shown to be time limited and to be reversible by the resumption of treatment with drugs from the same pharmacological class. In addition, the phenomena should exhibit pharmacological specificity; it should be shown that drugs from other classes do not affect the behavior in the same way as benzodiazepines do.

One method of determining whether a drug specifically affects withdrawal is to examine its effects on the broad array of phenomena that comprise the withdrawal syndrome. Drugs acting specifically on withdrawal are generally those that alter most, if not all, of the signs of withdrawal (Martin and Sloan, 1977). One limitation of the studies discussed in this section is that the investigators often examined only one behavioral change rather than the spectrum of changes occurring during withdrawal. Thus, it is often difficult to assess the specificity of the effects obtained.

In one procedure that has been used in the attempt to

assess anxiety in animals, rats are placed in a maze, elevated above the floor, which consists of two perpendicular runways each intersecting the other at its midpoint, yielding four arms. Two opposing arms have open sides, allowing the subject to perceive that the maze is elevated (hence, the name "elevated plus-maze"). The other two opposing arms have closed sides. The proportion of the subject's time spent in the arms with closed sides (measured as percentage of entries or percentage of total time) is purported to be a measure of anxiety (see, however, Brett and Pratt, 1989).

File et al. (1987) found that, 24 h following 22 d of treatment with chlordiazepoxide at 5 or 20 mg/kg/d (i.p.), there was a reduction both in the time spent in the open arms and in the proportion of entries into the open arms. In a subsequent study (Baldwin and File, 1988), these investigators demonstrated that a similar effect could be obtained after treatment with a single dose of 10 mg/kg of chlordiazepoxide and that this effect could be reversed by treatment with the benzodiazepine antagonist, flumazenil. The investigators argued that the reversal of the effect by the antagonist suggests an endogenous mediator of this "rebound anxiety." Alternatively, this effect might be a late-appearing agonist action that is reversed by the antagonist or an intrinsic action of the antagonist.

Other purported indications of anxiety in animals have also been studied during benzodiazepine withdrawal. For example, Rock and Barrett (1987) have shown increased punishing effects of electric shock after withdrawal from treatment with 2.5 mg/kg of diazepam for 10 d. Other investigators (Barry et al., 1987) have examined the distribution of time spent in either of two compartments of an experimental chamber, one brightly illuminated and one dark. Withdrawal from diazepam (either 2.5 or 10 mg/kg twice per day for 7 d) increased the amount of time spent in the dark side of the chamber, an effect opposite to that seen after acute administration of the drug. This pattern generally returned to control conditions within 96 h of the last dose. The higher dose of diazepam also tended to disrupt the behavior more than the lower dose (Onaivi et al., 1989).

In several studies, Emmett-Oglesby et al. (1987, 1990) attempted to examine rebound-anxiety-like effects of withdrawal using drug discrimination procedures. In these studies, subjects are trained with food reinforcement to press one of two levers after administration of pentylenetetrazol and the other lever after saline injection. After performances reach some criterion of accuracy, training is suspended, and a regimen of benzodiazepine administration is initiated. Following the completion of this regimen, subjects are placed in the experimental chamber, and their responses on the two levers are recorded following saline injections. It has been suggested that the extent to which the subjects show the response previously reinforced only after pentylenetetrazol administration is a measure of withdrawal anxiety.

The authors of these studies suggested that the pentylenetetrazol discriminative effect represents an action related to anxiety for several reasons. Pentylenetetrazol has been reported to produce anxiety in man (Rodin and Calhoun, 1970). In addition, the pentylenetetrazol discriminative effect is antagonized by clinically effective anxiolytics, whereas benzodiazepine inverse agonists produce pentylenetetrazol-like effects. Finally, anticonvulsants that are not anxiolytic are ineffective in antagonizing these discriminative effects of pentylenetetrazol (Emmett-Oglesby et al., 1987).

Pentylenetetrazol-like effects following benzodiazepine withdrawal have been examined in several studies. In one study (Emmett-Oglesby et al., 1983), subjects selected the pentylenetetrazol lever on 56% of opportunities following a saline injection 8 h after the last dose of a 7-d regimen of diazepam (20 mg/kg/8 h). In addition, subjects receiving flumazenil 15 min after a dose of diazepam exhibited a dose-related increase in selection of the pentylenetetrazol lever. These data suggest that both spontaneous and precipitated withdrawal from diazepam produce discriminative effects like those associated with pentylenetetrazol. Results of additional studies have indicated that the pentylenetetrazol-like effect of flumazenil depends on the dose of diazepam administered previously. With increases in the dose of diazepam, there were increases in these effects of 20 mg/kg of flumazenil. Flumazenil was ineffective in producing these effects when administered 39 d after termination of diazepam treatment (Emmett-Oglesby et al., 1988).

4. Summary and discussion. Recent studies have confirmed that signs of withdrawal from benzodiazepines are more frequent or of greater magnitude (*a*) following administration of higher doses or doses with greater effects and (*b*) following longer durations of treatment. Some investigators in studies reviewed previously had suggested possible exceptions to the finding that withdrawal varies in direct relation to dose; these suggestions have not been further examined. Also, the issue of whether continuous rather than intermittent drug administration increases the intensity of withdrawal has not been addressed in recent studies. However, results of some studies have indicated that ingestion of midazolam once daily, at doses that are eliminated well before the next opportunity to ingest the drug, produces dependence.

Studies of once-daily administrations of benzodiazepine hypnotics are particularly relevant to issues concerning clinical use, because this is the typical pattern of use of hypnotics. Investigators should examine, for example, how dependence develops with once-daily administration of these compounds, whether there are differences in the development of dependence when exposure is intermittent or continuous, and whether some measure

of cumulative benzodiazepine exposure might predict the development of dependence when exposure is intermittent.

Studies of precipitated withdrawal have confirmed that it is rapid and dependent on agonist dose and duration of treatment. Results of several studies have indicated that different antagonists may have different effects in dependent subjects. However, it is premature to conclude that these differences represent some basic differences between antagonists with a β-carboline structure and antagonists with a benzodiazepine structure. Quantitative comparisons of the effects of different benzodiazepine antagonists will require more precise indications of the degree and direction of their intrinsic efficacy (agonist or inverse agonist) or of their nonbenzodiazepine pharmacological activity. In this regard, it is promising that several benzodiazepine antagonists are now available for study. However, the availability of more compounds that are pure antagonists, with differing affinities for benzodiazepine receptors, will allow more methodologically sophisticated studies.

Results of some earlier studies had suggested that benzodiazepines might vary in their potential to produce physiological dependence. For example, despite administration of doses up to 48 times the minimally effective sedative doses, no dependence was observed after chronic treatment with lormetazepam (Yanagita et al., 1985). Also, despite comparable or greater effects of chronic nitrazepam, Stockhaus (1986) found more intense withdrawal following treatment with diazepam. Ozawa et al. (1991) recently suggested unique receptor-binding effects of lormetazepam. However, for the most part, these suggestions regarding physiological dependence have not been pursued or substantiated to date.

On the other hand, some recent studies have provided additional evidence that benzodiazepines may differ in their potential to produce dependence or in the characteristics of the dependence they produce. In particular, results of studies by Martin and colleagues suggest that the withdrawal syndromes following administration of different benzodiazepine agonists may consist of overlapping but distinct constellations of signs. Studies with the β-carboline abecarnil, as well as studies with benzodiazepine partial agonists, suggest that these compounds may have less potential to produce dependence than full agonists. However, many of these results are difficult to interpret because of the limited conditions under which different compounds have been directly compared. In addition, there have been suggestions that the kinetics of the benzodiazepine antagonist, flumazenil, when administered following administration of a benzodiazepine agonist, may vary depending on the agonist involved; if these preliminary reports are substantiated, it will be very difficult to interpret the significance of studies of the relative intensity of precipitated withdrawal following administration of different agonists. This possibility suggests that comparisons between natural and precipitated withdrawal may be necessary to compare the dependence produced by different benzodiazepines.

Recent advances have been made in studies of benzodiazepine partial agonists that may have antianxiety efficacy but limited potential to produce dependence. One rigorous experimental study of one of these compounds has provided particularly convincing evidence that the physiological dependence that develops to these drugs may be very limited. In addition, as noted in section II.B, there have been suggestions that these drugs are not effective as reinforcers. Further quantitative comparisons among partial and full agonists would be very useful. These comparisons should utilize methods that equate effects during the entire benzodiazepine exposure period.

The results of several studies reflect a hazard in making comparisons among drugs with regard to dependence-producing effects on the basis of inadequate parametric information. For example, in one study, the incidence of withdrawal was compared after administration of equieffective doses of each of several benzodiazepines. At one time, the drugs showed differences that were less marked at a later time. Conclusions based on the data from only one or the other of these times would have been quite different.

The possibility that the dependence that develops to short-acting drugs may be more intense than the dependence that develops to the longer acting benzodiazepines can be addressed with the results of recent studies of midazolam. Midazolam was administered for a period comparable to the duration of the effects of a single dose of chlordiazepoxide. Natural withdrawal after this regimen of midazolam was comparable in intensity to that seen with chlordiazepoxide, despite the more rapid elimination of midazolam. Further studies in which the benzodiazepines are equated according to all dosing parameters, except their speed of elimination, will be of importance in verifying these results. On the basis of the information currently available, it appears that the intensity of withdrawal observed after treatment with short-acting benzodiazepines is not different from that after longer acting benzodiazepines.

There has been a substantial increase in the number of behavioral procedures that purport to assess rebound anxiety using animal models. In the majority of these procedures, the models used have not been validated in the context of established behavioral and pharmacological criteria. It has not been established that the animal behaviors measured are functionally equivalent to human anxiety. Neither has it been established that these behaviors meet pharmacological criteria for withdrawal phenomena. Few of these studies to date have made a substantial contribution to the understanding of benzodiazepine withdrawal.

C. Studies in Humans

The risk of development of physiological dependence on prescribed therapeutic doses of benzodiazepines is of considerable concern for physicians, patients, and researchers. Recent excellent reviews of benzodiazepine dependence and withdrawal (Roy-Byrne and Hommer, 1988; Noyes et al., 1988; Swinson et al., 1987) are helpful in defining withdrawal, discussing conditions that may increase the risk of dependence, and describing procedures for reducing and treating withdrawal signs.

In our previous review (Woods et al., 1987), we discussed the research and clinical evidence indicating that dependence can develop in patients taking therapeutic doses of benzodiazepines. Among the issues that remained unclear were the proportion of users of benzodiazepines who could be expected to show withdrawal signs when the drug was discontinued, the influence of dose and duration of benzodiazepine use on the probability that dependence would develop, and the possibility that the incidence and severity of withdrawal signs might vary in relation to the duration of action of the particular benzodiazepine administered. The last two of these issues, as well as comparisons of withdrawal signs following abrupt as compared with gradual benzodiazepine discontinuation, have received the majority of experimental attention in studies of benzodiazepine withdrawal in humans in the past few years. Most of the studies that will be described are summarized in table 2.

1. Dependence on short half-life benzodiazepines. Reports of studies in which withdrawal from short-acting benzodiazepines was evaluated, either singly or in comparison with longer acting benzodiazepines, have appeared regularly in the past few years. One of the short half-life drugs that has been frequently evaluated in this context is alprazolam, a triazolobenzodiazepine with a plasma half-life of 12 to 15 h that was introduced for the treatment of anxiety and anxiety-depression. (Data concerning benzodiazepine half-lives are presented in table 1. The values given in the discussion of studies are those indicated by the investigators.)There was some suggestion that alprazolam might also be useful in the treatment of panic attacks (Fawcett and Kravitz, 1982). It was recommended for this purpose (Sheehan et al., 1985) and became quite widely used in the management of patients with panic disorder. Within a few years, a number of cases of possible alprazolam withdrawal reactions surfaced (reviewed by Browne and Hauge, 1986). One concern about these reactions was that tapering the dose according to the manufacturer's recommendation might not be sufficient to prevent alprazolam withdrawal symptoms (Dickinson et al., 1990).

Clinical studies have indicated that this concern was warranted. Mellman and Uhde (1986) evaluated ten patients, eight of whom were being treated for panic and agoraphobia, who had been taking between 1 and 12 mg of alprazolam daily for periods ranging from 4 to 22 mo. The patients' customary alprazolam doses were maintained, provided in a substitute form that could not be distinguished from later doses, and then the doses were tapered in a blind fashion at an average rate of 0.19 mg each day. Symptoms occurring during the last 5 d of the tapering regimen—which varied in duration among individual patients—and the first 2 d after complete discontinuation of alprazolam were compared with symptoms occurring during a later 7-d period, beginning an average of 18.3 d after complete discontinuation of alprazolam. During this latter "postwithdrawal" week, the patients appeared to have returned to their baseline levels of psychopathology. The patients' anxiety ratings (on the Spielberger State-Trait Anxiety Inventory), as well as cortisol levels, were significantly increased in the withdrawal as compared with the postwithdrawal period. Nonsignificant increases in pulse rate and systolic blood pressure were observed, but no differences in diastolic blood pressure or hours of sleep were noted. The authors commented that, even though doses of alprazolam had been tapered at one third of the recommended rate in eight of the ten patients, all of these patients showed signs of withdrawal. They found no relation between intensity of withdrawal and the dose or duration of alprazolam administration prior to tapering.

Eighteen patients were treated for panic disorder and agoraphobia in an open trial of alprazolam (Fyer et al., 1987). After 13 wk, in those who responded to treatment, the drug was maintained for an additional 12 wk and then tapered; in those who did not respond, the medication was tapered after the initial 13-wk period. The tapering schedule approximated a dose decrement of 10% of the original dose every 3 wk. Symptoms were recorded by patients using a diary and reported on a weekly basis. Panic attacks and related conditions were recorded, as were new withdrawal symptoms from a list of items reported to accompany benzodiazepine withdrawal.

Of the 18 patients, 16 experienced a decrease in panic attacks. These patients were panic free before alprazolam withdrawal. Only four subjects were able to complete the alprazolam-tapering period according to the protocol. Of the 13 subjects who dropped out of the study during withdrawal, seven did so because of the recurrence of panic attacks, five because of recurrence of panic and the presence of new symptoms, and one because of the presence of new symptoms. One subject dropped out for unrelated reasons.

Because many of the patients were allowed to resume taking medication before tapering was complete, either with alprazolam or with another antipanic medication, it could not be determined with certainty whether the increase in panic attacks would continue or whether their occurrence during alprazolam tapering was indicative of rebound panic and, hence, temporary. Apparently, premedication baseline measures of panic attack frequency had not been taken for comparison. Six subjects did

become drug free by the end of the study; three of these remained free of panic attacks, and two had infrequent attacks.

By far the most comprehensive study of alprazolam withdrawal in patients suffering from panic attacks and phobic avoidance was a multicenter, parallel-group, double-blind, placebo-controlled evaluation conducted by Pecknold et al. (1988) in 126 subjects. To be included in the study, the subjects had to have experienced at least one spontaneous panic attack per week for the previous 3 wk. They were randomly assigned to placebo or alprazolam conditions. Each capsule of alprazolam contained 1 mg, and the goal was to reach six capsules (drug or placebo) per day by the end of the third week of the 8-wk treatment phase. The average dose at the end of the treatment phase was 4.8 mg/d (range 1 to 10 mg/d).

During the tapering phase of the study, capsules were reduced at the rate of one every 3 d unless symptoms required slowing the reduction to one capsule per week. All medication was withdrawn during a 4-wk period. The first and fourth weeks of medication tapering were evaluated, as were the first and second weeks after all medication was withdrawn.

Of the patients receiving placebo, 46% (29 patients) did not complete the treatment phase of the study because of a lack of treatment effectiveness. However, 77% (49) of these patients entered the tapering and discontinuation phase of the study. Three (4.8%) of the alprazolam-treated subjects discontinued the treatment phase because of adverse effects, and one refused to start the tapering phase. Sixty (95%) alprazolam-treated patients entered the tapering and discontinuation phase of the study. Of these, 44% did not complete the discontinuation program. Most of these tapered off drug completely and then could not continue in the study because their clinical condition deteriorated. Of the patients receiving placebo who started the tapering phase, 70% were able to complete it.

The dropout rate in each phase by each group made comparisons difficult. However, the total number of panic attacks was significantly increased in the alprazolam-treated group as compared with the placebo-treated group in the last week of medication tapering and the first week with no medication. By the second week with no medication, the groups no longer differed in frequency of panic attacks.

Other measures that indicated significantly more severe symptoms in the alprazolam group included scores on the Phobia Scale and scores on the physician-rated HAM-A in the last week of tapering and on the Physician's Global Assessment Scale in the first week with no medication. Signs of rebound were reported in none of the placebo-treated group and in 21 (35%) of the alprazolam-treated patients; rebound panic attacks were reported in 16 (27%) members of the alprazolam group. The frequency of panic attacks returned to predrug levels in 50% of these patients by the second week with no drug.

Twenty-one (35%) of the alprazolam-treated patients and one of the placebo-treated patients reported a cluster of four or more of 11 symptoms indicative of withdrawal. Symptoms included confusion, clouded sensorium, heightened sensory perception, and muscle cramps and twitches. These symptoms were most frequent in the second tapering week and the first week of complete drug withdrawal.

The magnitude of the withdrawal signs did not appear to vary in relation to the different doses of alprazolam that the patients had taken. The authors pointed out that none of the withdrawal symptoms was life threatening and that more than half of the patients showed no rebound or withdrawal symptoms during the alprazolam-tapering period. On the basis of their findings, however, they suggested that a 4-wk tapering program is probably too short for alprazolam withdrawal and that a more prolonged tapering schedule might reduce the discomfort of withdrawal.

2. Comparisons of short and longer half-life benzodiazepines. Withdrawals following termination of short-acting and longer acting benzodiazepines have been compared in a number of studies. Rickels et al. (1988a) evaluated the incidence of rebound anxiety and return of original symptoms in patients who were given either clorazepate, which is long-acting by virtue of its metabolism to desmethyldiazepam, or the short-acting benzodiazepine lorazepam for symptoms of GAD. Patients had not taken benzodiazepines or other medication for 1 mo prior to initiation of the study. After a 1-wk period of observation under placebo conditions, 32 patients were assigned to take clorazepate (15 to 30 mg/d), and 30 patients were assigned to take lorazepam (2 to 4 mg/d). Drugs were administered for 4 wk, and then abruptly placebo was substituted for the drug, under double-blind conditions, for two thirds of each group; the remaining one third continued to take their assigned medication. Patients were evaluated during the following 2-wk period for changes in anxiety as indicated by the HAM-A, the Covi Anxiety Scale, and the anxiety-tension factor of the POMS.

Both benzodiazepines produced an improvement in anxiety symptoms. When placebo was substituted for active drug, more than 70% of the patients in both drug conditions maintained some clinical improvement, in that their anxiety ratings did not return to predrug baseline levels. However, temporary increases in anxiety developed in those patients switched abruptly to placebo. These increases in anxiety scores, on average, did not reach the predrug baseline level. On the third day following abrupt benzodiazepine discontinuation, anxiety increased in both treatment groups; the increase was greater in those switched from lorazepam. By withdrawal day 7, the anxiety scores of the patients withdrawn from

TABLE 2
Studies of discontinuation of benzodiazepine treatment in humans

Subjects	Drug	Dose/d	Duration	Withdrawal regimen	Measure*
GAD, somatoform disorders	Clotiazepam	15 mg	2 wk 5 wk	Abrupt	Petursson and Lader symptom checklist
GAD of 6 mo duration	Diazepam Placebo Buspirone	10-mg (4 d) 10-mg increments to max = 40 mg	4 wk	Abrupt	HAM-A Clinical Global Impression of Severity of Illness New symptom checklist
GAD, panic disorder	Clorazepate Buspirone	Mean = 33 mg	24 wk	Abrupt	PCWS HSCL HAM-A New symptoms POMS Daily withdrawal symptom rating
GAD	Diazepam Buspirone	5–20 mg	6 and 12 wk	Abrupt	BAS CPRS
≥60 yr of age ≤55 yr of age	Various	Therapeutic	≥1 yr	Gradual, 25%/wk	HAM-A HAM-D HSCL Covi withdrawal cluster PCWS
Panic disorder	Alprazolam Placebo Diazepam	7.1 mg 55 mg		1 cap every 3 d until 2 cap/d, then 12 cap every 3 d	Global Assessment
GAD, panic disorder, depression	Short half-life Lorazepam Alprazolam Long half-life Diazepam Clorazepate	5–40 mg diazepam or equivalent	>1 yr	Taper: 25%/wk if possible	HAM-A HSCL Covi withdrawal cluster, 2nd withdrawal cluster PCWS
GAD, panic disorder, depression None	Short half-life Lorazepam Alprazolam Long half-life Diazepam Clorazepate	5–40 mg diazepam or equivalent	>1 yr	Abrupt, if possible	HAM-A HSCL Covi withdrawal cluster, 2nd withdrawal cluster PCWS
Anxiety	Diazepam in study	20 mg	At least 6 mo prior to study Mean of 4 yr	Gradual (procedure not stated) Abrupt	HAM-A HAD Symptom VAS A withdrawal symptom checklist A global assessment of severity of illness

* Abbreviations of names of scales: HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; HSCL, Hopkins Symptom Checklist; POMS, Profile of Mood States; MMPI, Minnesota Multiphasic Personality Inventory; PGAS, Physician's Global Assessment Scale; SSEC, Symptoms and Side Effects Checklist; CPRS, Comprehensive Psychopathological Rating Scale; HAD, Hospital Anxiety and Depression Scale; VAS, Visual Analog Scale; BAS, Brief Anxiety Scale; BWSQ, Benzodiazepine Withdrawal Symptom Questionnaire; PCWS, Physician's Checklist of Withdrawal Symptoms.

TABLE 2—*Continued*

How often	No. of subjects	Authors	Results
Beginning of treatment; 2, 3, 5, and 6th wk	18 17	Orsini et al., 1990	Both groups showed increased perceptual changes of similar magnitude and duration
Weekly	16 (4 dropped out) 16 (4 dropped out) 16 (1 dropped out)	Fontaine et al., 1987	Increased HAM-A anxiety scores in diazepam patients
Daily	150 started 61 had usable data 38 completed	Rickels et al., 1988c	For clorazepate, temporary increase in anxiety that did not reach predrug levels. No effect of buspirone withdrawal
Every 2 wk for 14 wk	51 (11 dropped out)	Murphy et al., 1989	For diazepam only, temporary increase in anxiety over 2-wk period to near predrug levels, then subsided
Weekly	19 22	Schweizer et al., 1989	Elderly patients suffered less intense withdrawal and fewer new symptoms
	10 5 15	Burrows et al., 1990	20–30% showed withdrawal Diazepam withdrawal slightly more intense than alprazolam withdrawal
Weekly	38 (16 dropouts) 25 (8 dropouts)	Schweizer et al., 1990	No difference in intensity of withdrawal for short or long half-life drugs with tapering regimen
Days 1–5 and 8 after discontinuation	21 (12 dropped out) 26 (7 dropped out)	Rickels, 1990b	Short-half-life drugs produced more withdrawal symptoms than long-half-life drugs
Every 2 wk for 16 wk	16 (2 dropped out) 15 (2 dropped out)	Cantopher et al., 1990	11 suffered mild withdrawal 14 suffered mild-severe withdrawal (a total of 80% showed some withdrawal signs)

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Subjects	Drug	Dose/d	Duration	Withdrawal regimen	Measure*
Psychiatric outpatients with apparent benzodiazepine dependence	Diazepam Lorazepam Bromazepam	2–12 mg diazepam equivalents	>6 mo; 4 wk on study medication	Gradual: 25% decrease every 2 wk; complete discontinuation in 10 wk	CPRS BAS BWSQ
Long-term benzodiazepine users	Various: 8 short-acting 11 long-acting	Therapeutic	Long-term: >3 mo	Abrupt Taper: 3.5 mg diazepam equivalents/wk	New symptoms Standardized symptom checklist ARF Clinical Inst. withdrawal assessment Anxiety levels Severity of symptoms
Psychiatric inpatients	Various	>21 mg diazepam equivalents <21 mg diazepam equivalents	1–18 yr	5 abrupt 2 taper Abrupt	Withdrawal, anxiety, depression scales and questionnaires
Panic disorder	Alprazolam Placebo	1–10 mg (mean = 4.8 mg)	8 wk	1 mg every 3 d, if possible	Phobia Scale HAM-A PGAS New symptoms Panic and Anxiety Attack Scale Panic attack frequent SSEC
GAD	Lorazepam Clorazepate	2–4 mg 15–30 mg	4 wk	Abrupt in 2/3; continued in 1/3	HAM-A Covi Anxiety Scale POMS Global assessment of improvement
Panic disorder	Alprazolam	5.25 mg	Mean = 29.4 wk	10% every 3 d if possible	2 panic and phobia scales Withdrawal scales
Panic disorder	Alprazolam	(1–12 mg) mean = 5 mg	(4–22 mo) mean = 11.7 mo	Taper: mean = 0.19 mg/d decrement	Sleep, anxiety, cortisol

TABLE 2—*Continued*

How often	No. of subjects	Authors	Results
At 2-wk intervals until 4 wk after complete discontinuation	22 (6 dropped out) 23 (10 dropped out) 23 (7 dropped out)	Murphy and Tyrer, 1991	No statistically significant difference in withdrawal based on drug half-life. More intense withdrawal in those taking benzodiazepine for 5 yr or more
Weekly	19 21	Busto et al., 1986	Tapered withdrawal less severe than abrupt withdrawal for first 6–7 wk, then reverse. Those on short-acting benzodiazepine had more rapid onset of withdrawal but intensity no greater. Dropout problem
Daily	7 women 7 women	Schmauss et al., 1987	Withdrawal onset delayed but more protracted in larger dose group. No difference in severity based on dose or half-life
1st and 4th wk of taper, 1st and 2nd wk after discontinuation Daily diaries	63 (4 dropped out during treatment; 26 dropped out during taper) 63 (26 dropped out during treatment; 10 dropped out during taper)	Pecknold et al., 1988	Alprazolam group: increase in panic, increase in phobia, decrease in PGAS, increase in HAM-A; 35% showed rebound; 35% showed new symptoms
Weekly during treatment; days 1, 2, 3, 7 and 14 of withdrawal	30 (4 dropped out during withdrawal) 32	Rickels et al., 1988a	37% showed rebound anxiety; more rapid onset and more intense than clorazepate. 45% showed rebound anxiety
Weekly Patient diary	18 (13 dropped out)	Fyer et al., 1987	14/17 subjects reported new symptoms during withdrawal
Last 5 d of taper, 1st 2 d of no-drug vs. 7-d period starting 18 d later	10	Mellman and Uhde, 1986	Increased levels of anxiety and cortisol during withdrawal

TABLE 2
Studies of discontinuation of benzodiazepine treatment in humans

Subjects	Drug	Dose/d	Duration	Withdrawal regimen	Measure*
Panic (1/wk for 3 wk)	Alprazolam (1 mg caps) Diazepam (10 mg caps) Placebo	Therapeutic 1–10 caps	Most, 8 mo	1 cap every 3 d until 2 cap/d, then ½ cap every 3 d	HAM-A Self-rated Anxiety Scale Frequency of panic attacks Global improvement ratings Global ratings of intensity of anxiety New symptoms Withdrawal symptom checklist
Anxious (panic or GAD)	Alprazolam (1 mg tabs) Diazepam (10 mg tabs) Placebo	Mean = 4.3 mg Mean = 56 mg	6 wk	Taper for 2 wk: 1 tab every 3–5 d, abrupt thereafter	HAM-A Panic frequency

lorazepam had returned to the prewithdrawal levels, and the scores of those withdrawn from clorazepate had increased somewhat. Increased anxiety was noted in 37% of those withdrawn from lorazepam and 45% of those withdrawn from clorazepate. Four patients receiving lorazepam dropped out of the study after day 3 and two patients receiving clorazepate dropped out after day 7 because of problems with anxiety. The authors emphasized that not all patients showed increased anxiety after a 4-wk course of long- or short-acting benzodiazepine administration but that, among those who did experience this effect, it had a more rapid onset and was more severe in those withdrawn from the shorter acting drug.

Rickels et al. (1990b) and Schweizer et al. (1990) published two very interesting studies of the relative effects of abrupt and gradual benzodiazepine withdrawal. Their main objective was to compare the intensity of withdrawal produced by discontinuation of short half-life benzodiazepines (lorazepam and alprazolam) with that following termination of long half-life benzodiazepines (diazepam and clorazepate dipotassium) under both abrupt and gradual withdrawal conditions.

Fifty-seven patients who indicated that they had used either short-acting or long-acting benzodiazepines daily for at least 1 yr were given their regular medications in identical capsules for 3 wk (Rickels et al., 1990b). Baseline assessments during this period included measures of affective disorders, personality, anxiety (HAM-A), depression (HAM-D), and benzodiazepine withdrawal (Physician Withdrawal Checklist; the Covi withdrawal cluster and another withdrawal cluster, both from the Hopkins Symptom Checklist). Under double-blind conditions, the medication of 47 patients was switched to placebo, and ten patients continued to receive their medication. Measures of anxiety, depression, and withdrawal were made daily during the initial 5 d of withdrawal, and blood samples were obtained for benzodiazepine level determination. Final assessments were made after a total of 5 wk.

Abrupt discontinuation of short half-life benzodiazepines produced a markedly more intense withdrawal syndrome than did abrupt discontinuation of long half-life benzodiazepines during the 5-d period following drug discontinuation. Withdrawal from the short half-life benzodiazepines peaked at about day 2; this finding makes it clear that daily rather than weekly measures of withdrawal from these drugs are necessary to describe accurately the progress and changes in intensity of these signs. It is not clear that the attenuated observation period (days 1 through 5 and day 8) allowed a full characterization of withdrawal from long-acting benzodiazepines, because results of other studies have indicated that the withdrawal from these drugs peaks in the second week. Thus, it is possible that the main difference between withdrawal from short-acting and longer acting benzodiazepines is that withdrawal from the short-acting compounds occurs more quickly.

Plasma levels of benzodiazepines decreased more rapidly for those taking short half-life than those taking long half-life compounds. Plasma levels of the latter drugs remained high even on the eighth day following withdrawal.

A larger percentage of subjects taking short half-life benzodiazepines (57%) than those taking long half-life

TABLE 2—*Continued*

How often	No. of subjects	Authors	Results
Weekly until 2 wk after discontinuation	25 (16 dropped out) 19 (11 dropped out) 6 (2 dropped out)	Noyes et al., 1991	68% = severe to extreme anxiety 23% = severe or extreme anxiety 16.7% = severe anxiety Increase in anxiety began sooner and reached peak earlier in subjects taking alprazolam than in those taking diazepam
Weekly during treatment; 2 wk during taper; 1 wk after abrupt discontinuation	24 (11 dropped out) 22 (7 dropped out) 25 (13 dropped out)	Roy-Byrne et al., 1989	Increased anxiety with abrupt withdrawal for active drug group. Alprazolam withdrawal more intense than diazepam withdrawal

benzodiazepines (27%) thought it necessary to resume benzodiazepine administration within 1 wk of discontinuation of the medication. Of 19 subjects who had not relapsed to use of long half-life benzodiazepines at the 1-wk evaluation, seven had relapsed at the 5-wk evaluation. Of the ten subjects who had not relapsed to use of short half-life benzodiazepines at the 1-wk evaluation, two relapsed within the 5-wk postdiscontinuation period. Thus, at the end of the study, 46% of those previously taking long half-life drugs and 38% of those previously taking short half-life drugs were abstinent.

In the study of gradual tapering of benzodiazepine medication, Schweizer et al. (1990) studied a similar population of 63 patients who had been taking either a long-acting (primarily diazepam or clorazepate) or a short-acting benzodiazepine (primarily lorazepam or alprazolam) daily for 1 yr or more. The baseline stabilization period and assessments were as in the study just described. The tapering schedule, conducted under double-blind, placebo-controlled conditions, consisted of a 25% reduction in dose each week, so that withdrawal was completed in 4 wk. Subjects who had difficulty with this schedule were permitted to slow the rate of tapering, take an antidepressant or hypnotic medication as symptoms indicated, or drop out of the study and resume their medication.

Fifty-seven percent required either a slowing of the tapering regimen or supplemental antidepressant or hypnotic medication during the course of discontinuing benzodiazepine treatment. Those who could not strictly comply with the original tapering schedule tended to be those who had been taking larger doses of benzodiazepine at baseline, those who had more severe withdrawal signs, and those with diagnoses other than panic or depression. Problems associated with withdrawal tended to occur during the last half of the tapering schedule. During the last quarter of the tapering schedule, the dropout rate was greater among those taking short-acting than among those taking long-acting benzodiazepines. Peak withdrawal signs tended to appear slightly earlier in those tapered from short-acting benzodiazepines. Although withdrawal from long-acting benzodiazepines was slightly more prolonged, the overall intensity of withdrawal did not differ between the two drug types during the 4 wk of withdrawal. With this schedule of tapering, plasma levels of benzodiazepines declined at the same rate for short and long half-life compounds.

Only three of 17 subjects who successfully completed tapering from long half-life drugs and two of 22 who succeeded in discontinuing short half-life drugs had resumed drug use 5 wk later. Thus, a total of 56% of those who began the regimen of gradual discontinuation of long-acting benzodiazepines and 53% of those who began tapering from short-acting benzodiazepines completely withdrew and remained abstinent at the 5-wk postdiscontinuation assessment, indicating little difference in ability to successfully taper from long- as compared with short-acting benzodiazepines.

The effects of alprazolam or diazepam administration and withdrawal was examined in 121 patients with panic disorder (Noyes et al., 1991). The patients received no medication for 1 wk and then received 1-mg capsules of alprazolam, 10-mg capsules of diazepam, or placebo capsules in a double-blind fashion. Dosage was adjusted to maximize benefit for each patient. After 8 wk of treat-

ment, patients could elect to continue their medication for an additional 6 mo under the double-blind conditions; drug discontinuation then began. Sixty-two patients elected to continue medication, and 50 of these reached the discontinuation phase of the study. Of these, 25 had been taking alprazolam, 19 diazepam, and six placebo.

Discontinuation was accomplished by requesting that patients reduce their medication by one capsule every 3 d until they were taking only two capsules each day. Half-dose capsules of medication then replaced the original dose, and medication was again reduced by one capsule every 3 d. Evaluation of anxiety and withdrawal symptoms was conducted weekly until the patients had been without medication for 2 wk. It is not clear whether the evaluations requested information about symptoms experienced during the preceding week or just at the current time. Weekly evaluations are probably too infrequent to detect the peak intensity of alprazolam withdrawal.

Patients differed in the number of capsules they were taking; therefore, the discontinuation phase lasted for varying periods of time, from 1 to 5 wk. Comparisons were made of symptoms reported at baseline (prior to medication), end of treatment, the last 3 wk of dose reduction, and the first 2 wk following drug discontinuation. Thirty-six percent of those who had been taking alprazolam, 42% of those taking diazepam, and 67% of those taking placebo were able to complete discontinuation and remain free of medication for 2 wk.

Rebound anxiety, i.e., anxiety rated as worse than that experienced prior to treatment, was reported by 60% of patients who had been taking alprazolam, 26% of those taking diazepam (a significant difference), and 17% of those taking placebo. New symptoms, which the investigators considered indicative of withdrawal, were noted by 60% of the alprazolam-treated patients, 63% of the diazepam-treated patients, and 33% of the placebo-treated patients. Recrudescent anxiety increased and peaked earlier among alprazolam-treated patients than diazepam-treated patients during and following medication tapering. Mean frequency of panic attacks returned to premedication levels rapidly following tapering and discontinuation of alprazolam but remained low for patients tapering from and discontinuing diazepam. Withdrawal symptoms, such as decreased appetite, impaired coordination, and increased sensitivity to light, peaked during the first week after discontinuation and returned to pretreatment levels during the second week; they were more severe in patients withdrawn from alprazolam than from diazepam.

The authors concluded that discontinuation of alprazolam resulted in greater withdrawal distress than did discontinuation of diazepam and that withdrawal distress peaked more rapidly after discontinuation of alprazolam than diazepam. They also found that a dose reduction of 0.3 mg of alprazolam every 3 d was too rapid for dependent patients.

A companion study was conducted in Australia using an identical protocol (Burrows et al., 1990). Preliminary results were reported for 88 of the 120 subjects; only 30 had taken drug for the additional 6 mo of the study. Ten of these had been assigned to alprazolam (mean dose 7.1 mg/d), 15 to diazepam (mean dose 55 mg/d), and five to placebo. During the tapering phase of drug discontinuation, marked withdrawal signs, as measured by a global assessment scale, developed in 20% to 30% of those withdrawing from either alprazolam or diazepam. Patients receiving tapering doses of diazepam had slightly more withdrawal problems than those receiving tapering doses of alprazolam. These data, therefore, conflict with those of Noyes et al. (1991), who found more severe withdrawal effects in individuals receiving tapering doses of alprazolam. The fact that the tapering was not done under double-blind conditions, i.e., subjects were instructed to reduce their medication in a specific manner, may account for some of the variability observed in these two studies. Furthermore, the small number of patients examined by Burrows et al. (1990) may not adequately represent the population of patients taking these medications.

The effects of tapered withdrawal followed by abrupt withdrawal of alprazolam, diazepam, or placebo was evaluated in 88 anxious patients, of whom 71 had panic attacks either prior to or during the initial treatment phase of the study; the remainder had GAD with no panic attacks (Roy-Byrne et al., 1989). Subjects received either alprazolam (1-mg tablets; mean of 4.3 mg/d), diazepam (10 mg tablets; mean of 56 mg/d), or placebo (mean of 7.5 tablets/d) for 6 wk. Dosage was reduced by approximately one tablet every 3 to 5 d; after 2 wk, dosage had been reduced by approximately one half. Patients were then abruptly withdrawn to placebo for 1 wk; placebo was then "tapered" for 1 wk before subjects stopped taking any tablets. The subjects did not know that their medication had been abruptly withdrawn in the final week.

Subjects were evaluated for anxiety (HAM-A) and for number of panic attacks at baseline (following a 1-wk placebo washout period for prior medication), during treatment (an average of the first 3 wk of drug administration), at the end of full-dose treatment, after 2 wk of medication tapering, and after 1 wk of abrupt withdrawal. Although there was a large dropout rate (14% to 38%) during the study, this did not appear to differ by diagnosis or drug. Thus, drug discontinuation did not appear to contribute to dropout rate.

All patients improved on measures of anxiety during the treatment phase. Anxiety scores did not change for any drug group during tapering; however, subjects who had received alprazolam or diazepam showed increased anxiety scores following abrupt withdrawal, whereas sub-

jects who had received placebo throughout the study showed continued decreases in anxiety during abrupt "withdrawal." The anxiety scores were significantly higher for those who had been taking alprazolam than for those taking diazepam. As the authors noted, a further week of withdrawal might have revealed more anxiety in the diazepam-treated patients, because this drug is eliminated more slowly than is alprazolam, and daily rather than weekly assessment might have shown a more intense withdrawal profile in the alprazolam-treated subjects.

Both diazepam and alprazolam, but not placebo, produced decreases in number of panic attacks. Frequency of panic attacks did not increase significantly following abrupt withdrawal of the various medications; however, there was a trend for fewer patients in the placebo group to show increased panic (10%) as compared to the alprazolam (46%) or diazepam (33%) groups. Because alprazolam-treated patients had a greater frequency of panic attacks at baseline, the authors suggested that the increased number of panic attacks following abrupt withdrawal might have represented a return of symptoms rather than a true withdrawal sign in these subjects.

Higgitt et al. (1988) conducted a detailed crossover study of the development of dependence on three benzodiazepines with different durations of action. Twelve normal volunteer subjects took each of the three benzodiazepines (0.5 mg of triazolam, 2.5 mg of lorazepam, or 30 mg of ketazolam) or placebo at bedtime for 15 d, with at least a 2-wk washout period between exposures to the different drugs. Subjects were evaluated daily for 1 wk following each drug treatment. Withdrawal signs were measured through self-reports of changes in drowsiness, contentedness, anxiety, and sleep. Serious questions about the validity of the data are raised by the fact that discontinuation of placebo appeared to lead to marked changes in every measure. Drowsiness and contentedness, for example, decreased on the seventh day following placebo withdrawal, anxiety measures were elevated during the entire post-placebo week, and "goodness-of-sleep" was more profoundly disturbed following placebo withdrawal than following withdrawal of any of the active medications. These findings further complicate interpretation of the data regarding discontinuation of active medication, which are confusing in their own right. Discontinuation of lorazepam resulted in some apparently anomalous effects about which the authors did not elaborate, except to suggest that the effects of lorazepam withdrawal on sleep (sharp increase in goodness-of-sleep on withdrawal day 3) might have been due to an adverse effect on sleep during drug administration. Lorazepam withdrawal also produced an increase in drowsiness on the first 2 d of withdrawal, followed by a decrease in drowsiness on withdrawal days 5 and 6, a marked decrease in contentedness that peaked on withdrawal day 5, and a reduction in anxiety on withdrawal days 2 through 5. Ketazolam withdrawal resulted in an immediate decrease in drowsiness as compared with placebo but was not markedly different from placebo withdrawal (which, it should be recalled, was associated with distinct changes) in measures of contentedness, anxiety, or goodness-of-sleep. Triazolam withdrawal produced the most marked effect on measures of drowsiness, which decreased 3 d after discontinuation of this drug. Other changes following triazolam withdrawal were slight compared to prewithdrawal baseline measures. It is unfortunate, given the interesting design of this study, the use of normal subjects, and the amount of time required to carry it out, that more consistent and interpretable results were not obtained.

Murphy and Tyrer (1991) noted no difference among the three benzodiazepines in a comparison of withdrawal signs upon gradual discontinuation of long-acting (diazepam) or short-acting (lorazepam or bromazepam) benzodiazepines. Because measures of potential withdrawal were taken only at 2-wk intervals, it is unlikely that the course of withdrawal was well described for any of the drugs administered.

3. Studies of parameters that might affect withdrawal. A variety of factors that might be considered to affect the pattern of withdrawal have been evaluated by several investigators. These include the effects of abrupt versus tapered drug discontinuation, the relation of MMPI profile to withdrawal signs, and the influence of drug dose and duration of administration on withdrawal.

a. GRADUAL VERSUS ABRUPT DISCONTINUATION. Busto et al. (1986) compared the effects of abrupt benzodiazepine discontinuation with those of tapered diazepam withdrawal in a double-blind, placebo-controlled design. Patients were self-selected, referred by a physician or pharmacist or responding to a newspaper ad soliciting "people concerned with their long-term benzodiazepine use." The subjects were taking a variety of benzodiazepines (mostly diazepam), for a variety of medical reasons, for variable lengths of time, and at different doses. For the first 2 wk, subjects continued to take their medication as they had been taking it previously. They were then randomly switched, in a double-blind manner, to a regimen of either placebo tablets or identically appearing tablets of diazepam in a dose approximating that of the benzodiazepine they had been taking. The dose of diazepam was tapered at an average rate of 3.5 mg/wk, with a goal of zero dose within 5 to 6 wk. Patients were told they could supplement their study medication with their original benzodiazepine if they thought that their condition clearly warranted it.

Subjects reported increased fear, difficulty concentrating, and tension following drug discontinuation or decreases in dose; these effects could not be distinguished from a return of predrug symptoms. Other symptoms, including persistent tinnitus, involuntary muscle twitching, paresthesias, perceptual changes, and confusion were

considered new symptoms indicative of withdrawal. During the first 3 wk of withdrawal, subjects whose medication was abruptly switched to placebo had more withdrawal symptoms than those whose medication was tapered from diazepam. By weeks 6 and 7, the situation had reversed with respect to numbers of symptoms. The abrupt-withdrawal group had returned to their prewithdrawal symptom level, and the diazepam-taper group was exhibiting significantly more withdrawal symptoms. Withdrawal symptoms were more severe in those abruptly withdrawn as compared to those tapered from their benzodiazepine.

Eight of the 19 patients who were abruptly withdrawn had been taking a short-acting benzodiazepine (lorazepam or oxazepam). The onset of their withdrawal signs began within the first day of drug discontinuation, but they were not significantly more severe than those of the remaining 11 subjects who had been taking diazepam. In this latter group, withdrawal signs began to appear on the fifth day following drug discontinuation. It is interesting, and perhaps important, that seven of the eight patients abruptly withdrawn from short-acting benzodiazepines refused to continue to take the placebo after withdrawal signs appeared but asked to receive tapering doses of their own medication. It is not clear from the report how these dropouts may have affected the overall comparison of subjects withdrawn abruptly versus slowly.

Schweizer et al. (1990) compared the effects of abrupt and gradual discontinuation of long and short half-life benzodiazepines as reported by themselves and by Rickels et al (1990b). The authors noted that, with short half-life benzodiazepines, abrupt discontinuation produced much more severe withdrawal signs than did gradual withdrawal. No difference was reported in the intensity of withdrawal of long half-life benzodiazepines in abrupt, as compared to gradual, benzodiazepine discontinuation (table 9 in the paper by Schweizer et al., 1990). Direct comparisons of graphic presentations in the report indicate that withdrawal signs following abrupt withdrawal (followed for 8 d after discontinuation) were considerably less than those following tapered withdrawal (measured after each week of dose reduction for a minimum of 4 wk). This unlikely result suggests that an 8-d period of observation of withdrawal signs following abrupt discontinuation of long-acting benzodiazepines probably does not provide sufficient information concerning the intensity of withdrawal.

Rickels et al. (1990a) also compared the data of Rickels et al. (1990b) and Schweizer et al. (1990) concerning abrupt versus gradual discontinuation of short or long half-life benzodiazepines. They noted that factors related to the drugs, such as half-life, daily dose, and duration of use, predicted intensity of withdrawal during abrupt but not gradual discontinuation. On the other hand, variables related to the patients—depressive diagnosis, high levels of Eysenck neuroticism, high levels of MMPI dependence, and female gender—predicted intensity of withdrawal in both gradual and abrupt discontinuation paradigms. These patient variables are considered further in section III.C.3.b.

Cantopher et al. (1990) compared the effects of gradual discontinuation of diazepam with that of abrupt withdrawal in combination with propranolol. Subjects who had been taking at least 15 mg of diazepam for at least 6 mo (mean of 9 yr) consented to undertake benzodiazepine discontinuation. After 3 wk of baseline measures, the medications of 15 of the subjects were switched abruptly to placebo under double-blind conditions, and 16 began a stepwise reduction of their diazepam dose. The parameters of diazepam tapering were not stated except that it occurred over a 10-wk period. Those whose medication was abruptly switched to placebo received propranolol (40 mg three times per day), but this did not appear to modify the withdrawal pattern. Withdrawal measures, taken every 2 wk after initiation of drug discontinuation protocols, included the HAM-A, the Hospital Anxiety and Depression Scale, a withdrawal symptom checklist, and a global assessment of illness severity; differences between the groups were indicated as well by the dropout rate. Five of those whose medication was tapered dropped out of the study, only two of these because of withdrawal symptoms. Eleven of those abruptly withdrawn dropped out, all of them because of withdrawal symptoms. Those who were gradually withdrawn showed less intense withdrawal signs than those abruptly withdrawn. Withdrawal signs included anxiety, insomnia, depression, and restlessness.

These findings of more intense withdrawal during abrupt rather than gradual discontinuation do not agree with those of Rickels et al. (1990b) and Schweizer et al. (1990), who found no difference in intensity of withdrawal signs during abrupt and tapered discontinuation. The most likely explanation for this discrepancy is that the duration of tapering in the study by Schweizer and coworkers was 4 wk, as opposed to 10 wk in the study by Cantopher et al.; discontinuing diazepam over a 4-wk period may not differ significantly from abrupt discontinuation. As Schweizer et al. observed, the 25% reduction per week was too rapid for most of the patients, particularly in the second half of the paradigm.

b. PERSONALITY FACTORS. Rickels et al. (1988b) attempted to determine personality factors that might be related to the intensity of benzodiazepine withdrawal. A retrospective study was made of 125 chronic users of benzodiazepines who were withdrawn from their drug and evaluated daily for 1 wk. The patients suffered from major depressive disorder ($n = 34$), GAD ($n = 45$), and panic disorder ($n = 30$) or had no diagnosis ($n = 16$). Personality variables were assessed with the MMPI. A subscale of the MMPI, labeled the "dependence scale," was composed of items that reflect inadequacy, low self-

confidence, conformity, and passivity. At the time of recruitment, the patients who had psychiatric diagnoses had higher scores on the MMPI and on measures of anxiety than did a control group of untreated patients with panic disorders. Patients with low scores on the MMPI dependence scale had less intense withdrawal scores. For reasons that were not explained, a low dose of benzodiazepine predicted less intense withdrawal signs in one analysis but not in a second analysis that appeared to apply to the same population using the same procedure.

In their study of differences in the intensity of withdrawal from short and long half-life benzodiazepines, Rickels et al. (1990b) also measured the effects of personality variables. They found that withdrawal was more likely to be severe in those with a highly dependent personality (measured by MMPI scores), high initial levels of anxiety or depression, and less education. There was no influence of sex, depressive state, tobacco use, or ethanol use on intensity of withdrawal. The investigators identified six factors involved in the withdrawal scores; only the "adrenergic" cluster of nervousness, agitation, nausea, and diaphoresis was more severe in those taking short half-life benzodiazepines. Factors related to irritability, perceptual distortions, confusion, neurasthenia, and muscular symptoms were not different in the two treatment groups.

Murphy and Tyrer (1991) found that patients with passive-dependent personality disorders had much higher scores on their Benzodiazepine Withdrawal Symptom Questionnaire than those without such disorders following gradual withdrawal of either diazepam, lorazepam, or bromazepam. In fact, personality status was the best predictor of degree of withdrawal in this study.

c. DOSE. Schmauss et al. (1987) studied 14 female patients who were admitted to a hospital for controlled withdrawal of a variety of benzodiazepines, which they had been taking for periods ranging from 1 to 18 yr. The patients had no history of drug abuse and were taking no medication except the benzodiazepines. They were divided into two groups, one that was taking more than 21-mg diazepam equivalents per day and one that was taking less than this amount. Each of the seven subjects taking the smaller dose and five of the seven subjects taking the larger dose were abruptly withdrawn. The remaining two subjects taking the larger dose received tapered decrements in their dose of diazepam. Patients rated their symptoms daily on the Withdrawal Symptoms Questionnaire, the Withdrawal Symptom Scale, the self-rated Anxiety Scale, and the self-rated Depression Scale. Increments in each of these ratings were seen in patients withdrawn from benzodiazepines. The time of onset of withdrawal signs was delayed in the larger-dose as compared to the smaller-dose group, but the duration of withdrawal appeared more protracted in the smaller-dose group. In fact, those who had been taking smaller doses of benzodiazepines showed elevated scores during the 18-d course of withdrawal, suggesting that they may have experienced reappearance of symptoms rather than withdrawal. There was no apparent difference in the intensity of withdrawal between the two groups, and those withdrawing from short-acting benzodiazepines did not report a more intense withdrawal than those withdrawing from longer acting benzodiazepines. Two patients in the larger-dose group exhibited psychotic reactions, although they had no history of psychosis. The authors believed that this was the clearest evidence of withdrawal reactions.

Rickels et al. (1990b) reported that patients receiving larger daily doses of benzodiazepines demonstrated more intense withdrawal signs. Murphy and Tyrer (1991), who evaluated withdrawal from diazepam, lorazepam, and bromazepam, divided their patients into low-dose (less than 6-mg diazepam equivalents), medium-dose (between 6- and 10-mg diazepam equivalents), and high-dose (greater than 10-mg diazepam equivalents) groups. They found generally higher withdrawal scores in the high-dose group, but there was no significant difference among the three groups.

d. DURATION. Patients who had been taking their benzodiazepine for more than 5 yr showed higher scores on the benzodiazepine withdrawal questionnaire than those who had been taking the drugs for less than 5 yr (Murphy and Tyrer, 1991). However, Rickels et al. (1990b) found no relation between duration of benzodiazepine use and withdrawal intensity. Duration of use had previously been found to be related to withdrawal intensity in patients who had been taking benzodiazepines for a relatively shorter time (8 mo or less) (Rickels et al., 1983). In the later study (Rickels et al., 1991), patients had been taking the drugs for more than 1 yr (average of 8 yr); the authors suggested that, when duration of use is 1 yr or longer, no greater amount of dependence develops.

Orsini et al. (1990) evaluated withdrawal following either 2 or 5 wk of daily administration of 15 mg of clotiazepam in 36 subjects with GAD. Withdrawal symptoms were measured during therapy and 1 wk following abrupt discontinuation using the Petursson and Lader Checklist. There was no difference between the two groups with respect to the development of withdrawal signs in the wk following drug discontinuation. Statistically significant increases in symptoms related to perceptual changes occurred with both the 2- and the 5-wk administration periods, but these effects were of nearly the same magnitude in both groups. As we have stated before, it is possible that weekly evaluations are not sensitive to changes that occur during benzodiazepine withdrawal. Clotiazepam is a short-acting compound (half-life of approximately 4 h, with no active metabo-

lites), and peak withdrawal may have occurred during the first 2 to 3 d following discontinuation.

4. Comparisons of dependence on benzodiazepine and nonbenzodiazepine anxiolytics. The development of dependence on a benzodiazepine has been compared with dependence on the nonbenzodiazepine anxiolytic, buspirone, in several studies. One of the problems with these studies is that it is difficult to equate doses of benzodiazepines with those of buspirone. Without the confidence that the doses compared are of equal therapeutic efficacy, it is difficult to interpret findings about differences in withdrawal intensity.

Fontaine et al. (1987) studied abrupt withdrawal from either diazepam or buspirone in a group of 38 patients who had a diagnosis of long-standing anxiety disorder. Prior to entering the study, 67% of the subjects had taken benzodiazepines. After a 1-wk wash-out period, patients were randomly assigned to 4 wk of treatment with either diazepam or buspirone. For the first 4 d, 10 mg of each drug was given daily and every 3 to 4 d the dose was increased by 10 mg/d to a maximum of 40 mg/d on treatment days 12 to 28. Doses were increased to obtain maximal therapeutic benefit, and the final dose varied among the patients. Abrupt, placebo-controlled, double-blind withdrawal from medication occurred after 4 wk of treatment and was assessed for 3 wk.

Measures of anxiety (HAM-A and Clinical Global Impression Scale), adverse effects, and new symptoms (checklists) were taken weekly. Anxiety scores declined in all treatment groups. The reduction was significantly greater among those receiving diazepam than among those receiving buspirone or placebo; reductions in the latter groups were not significantly different. Anxiety scores increased significantly more among patients withdrawn from diazepam than among those withdrawn from buspirone; patients in whom buspirone was discontinued did not show increases in anxiety relative to patients receiving maintenance doses of placebo. Patients withdrawn from diazepam showed more nausea, agitation, sweating, and tremors than those withdrawn from buspirone or placebo.

Rickels et al. (1988c) compared the effectiveness of clorazepate and buspirone, as well as the severity of rebound anxiety that followed termination of chronic administration of these drugs. During the first 4 wk of the study, the amount of drug administered was increased to a maximum of 60 mg/d of clorazepate (actual mean daily dose at the end of 4 wk was 31 mg) or 40 mg/d of buspirone (actual mean daily dose of 27 mg), depending on the clinical response. If a satisfactory response was obtained during this initial period, this dose was maintained for an additional 20 to 21 wk and then abruptly discontinued under double-blind, placebo-controlled conditions. Measures of effectiveness and rebound were made by the patients using the Hopkins Symptom Checklist, POMS, and a checklist of withdrawal symptoms completed each day. Physicians also rated the patients using the HAM-A and the Physician Checklist of Withdrawal Symptoms.

Clorazepate produced a rapid decrement in HAM-A scores, which was maintained during the 24 wk of drug administration. Upon withdrawal, anxiety rapidly increased and peaked during the first week of withdrawal; anxiety did not reach the pretreatment level and within 4 wk of withdrawal returned to the low levels observed at the end of treatment. Only 24% of patients, excluding those who dropped out during withdrawal, showed a return to predrug levels of anxiety during the 4 wk following drug discontinuation. These may be conservative estimates of rebound anxiety, because 22 (55%) patients apparently dropped out during the withdrawal phase, and their data were not carried over past the time they dropped out. New symptoms, indicative of withdrawal, developed in 72% of the 40 subjects who were withdrawn from clorazepate. The authors commented that these "new" symptoms, although often cited as being symptoms of withdrawal, are not uncommon features of clinical anxiety and, therefore, may be rebound effects as well. Forty percent of the patients supplemented their placebo medication with their own active medication during withdrawal.

Although patients were required to be benzodiazepine free for 2 wk prior to the initiation of the study, and underwent a 1-wk period of placebo administration prior to the chronic drug administration regimen, the subjects varied with respect to history of benzodiazepine ingestion. Withdrawal scores were more severe and/or more prolonged for prior users on both measures of withdrawal but did not seem related to the duration of previous use or to the interval since previous use.

Patients receiving buspirone were more likely to drop out of the study during administration of active medication (45% discontinued during the first 4 wk of dose increment, and an additional 26% dropped out during the maintenance phase), primarily due to a lack of therapeutic response. Those who continued to receive the medication showed a similar, although delayed, decrease in anxiety scores but no evidence of rebound or new symptoms upon withdrawal.

Another comparison of the effectiveness and dependence liability of buspirone and diazepam was reported by Murphy et al. (1989). Patients suffering from GAD were required to be without any psychotropic medication for at least 3 wk prior to initiating the study. Half of the subjects received 5 to 20 mg of either drug for 6 wk, and the other half received the same dose for 12 wk. Their status was evaluated with a Brief Scale of Anxiety and the Comprehensive Psychopathological Rating Scale prior to initiation of the medication, during the several weeks of drug administration, and for at least 2 wk after medication was withdrawn. Subjects were abruptly withdrawn to placebo under double-blind conditions.

Those subjects who took buspirone for either 6 or 12 wk showed an improvement in their anxiety scores and no evidence of rebound when medication was discontinued. Subjects who took diazepam also showed a decrease in anxiety. When drug was discontinued, those who had been taking diazepam for 6 wk showed a marked increment in symptoms on both rating scales, particularly the Brief Scale of Anxiety. Symptoms increased to nearly predrug levels over a 2-wk period and then subsided nearly to levels reached prior to drug withdrawal. In patients abruptly withdrawn from 12 wk of diazepam administration, anxiety and psychopathological ratings increased 2 wk following withdrawal but to a lesser extent than in the group that received diazepam for 6 wk. Although this appears anomalous, it should be noted that ratings stopped at wk 14, when withdrawal signs following 12 wk of diazepam administration were at a peak; these signs might have increased further after ratings stopped.

Although Rickels et al. (1988c) speculated that "new" symptom appearance during withdrawal might really be the development of rebound anxiety, Murphy et al. (1989) suggested that the appearance of new symptoms, such as hypersensitivity to noise, light, touch, and smell, muscle twitching, and gastrointestinal distress, might be more indicative of withdrawal than of a temporary increase in anxiety-like symptoms.

Pertinent to this issue are two publications of findings that symptoms indicative of benzodiazepine withdrawal can occur in untreated normal or anxious subjects. Merz and Ballmer (1986) described briefly their finding that alterations in perception, which are thought to be characteristic of or specific to benzodiazepine withdrawal, occur in normal volunteers and occur about five times more frequently in untreated anxious patients. A more detailed report, showing similar results, was published by Rodrigo and Williams (1986). They evaluated the occurrence of "unusual perceptual phenomena" in a group of 72 young, healthy female students prior to and following a course examination. Subjects reported significantly more perceptual disturbances, particularly changes in sensitivity to noise, taste, touch and lights, and greater anxiety prior to the examination than following it. These data suggested that perceptual changes might well occur concomitantly with increased levels of anxiety and, therefore, might not qualify as "new" symptoms in patients discontinuing benzodiazepine treatment. Certainly, these findings emphasize the importance of double-blind, placebo-controlled studies with careful attention to baseline measures of the variables to be studied.

5. Surveys of dependence. There have been a number of surveys of benzodiazepine dependence, particularly among inpatients or new admissions to general or psychiatric hospitals. In many of these studies, the diagnostic criteria of abuse and dependence are combined. In this section, we consider the data concerning dependence from those studies in which these conditions were evaluated separately; information regarding abuse in these populations can be found in section V.F.1.

Schmidt et al. (1989) carefully and appropriately defined benzodiazepine dependence in a study of 15,296 patients admitted to two German university psychiatric hospitals. Although they combined the categories of abuse and dependence in much of their discussion, a table of the data indicates that 2% of the patients were dependent on benzodiazepines alone, and an additional 0.7% were dependent on benzodiazepines in combination with other compounds. Benzodiazepine dependence was observed most frequently in patients with anxiety neuroses. Dependent patients tended to be older than nondependent patients; 44.3% were taking low doses (less than 30-mg diazepam equivalents per day), 40.7% were taking intermediate doses (between 30- and 80-mg diazepam equivalents), and 4.3% were taking large doses (more than 80-mg diazepam equivalents). In 10.7%, the dose could not be determined. Among dependent patients, 19.3% had taken one or more benzodiazepines for less than 1 yr, 33.6% had taken them for 1 to 4 yr, 25.0% for 4 to 10 yr, and 8.6% for more than 10 yr. Withdrawal signs in these patients included tremor/shakiness (54.1%), agitation/restlessness (53.3%), sweating (42.6%), sleep disruption (32.8%), anxiety (15.6%), perceptual disturbances (9.8%), delirium (4.9%), and seizures (1.6%).

Similar, appropriate definitions of dependence and abuse were used by Wolf et al. (1989a). Of the 9408 patients admitted to the Psychiatric Department of the University of Munich from May 1980 to December 1985, 633 (6.7%) either abused or were dependent on benzodiazepines, 440 of them in combination with one or more other drugs of abuse. Of the 193 (2.1%) patients who abused or were dependent on benzodiazepines alone, 108 (1.1%) were considered to be physiologically dependent on benzodiazepines and showed withdrawal signs. The signs of tremor, sweating, insomnia, palpitations, and gastrointestinal distress began between 2 and 7 d after the drug was discontinued and continued for 1 or 2 wk or, occasionally, for as many as 4 mo. Eleven patients showed a long-lasting withdrawal psychosis, and three developed seizures. In the 193 patients using benzodiazepines alone, 44% were taking less than 30-mg diazepam equivalents per day; 48% had as much as tripled the therapeutic dose; 8% were taking even more. Duration of intake was less than 1 yr in 12%, 1 to 5 yr in 54%, and more than 5 yr in 34%.

The authors noted that patients who were dependent on other substances, such as alcohol, appeared to have an increased risk of developing benzodiazepine dependence as well. In 55 patients, however, dependence on benzodiazepines preceded dependence on other drugs. They also observed that those dependent only on ben-

zodiazepines were likely to be women who were exposed to the drugs in a therapeutic situation, whereas those who used benzodiazepines concurrently with other drugs were more often younger men with problems with alcohol.

Fleischhacker et al. (1986) evaluated the charts of 10,861 patients admitted to Innsbruck's University Department of Psychiatry. One hundred sixty (1.5%) of these patients showed benzodiazepine dependence, as defined by World Health Organization and/or DSM-III criteria for dependence or abuse. It was unfortunate that dependence and abuse were not evaluated separately, because these terms are very different in their meaning and significance. Only 30 of the 160 patients were considered to have "pure" benzodiazepine dependence, presumably indicating that they were not taking other drugs. Of these 30 patients with "pure" dependence, 16 to 18 were described as exhibiting withdrawal signs. It was not stated by what criteria the remainder of the patients were classified as dependent. Withdrawal signs were not reported (or may not have been observed) for those who were described as benzodiazepine dependent other than those with pure benzodiazepine dependence. Half of the 160 patients were men, the mean age was approximately 41 yr, and, except for an overrepresentation of housewives, the social status of these patients was not distinctive. The types of benzodiazepines used reflected the distribution of these drugs on the Austrian market. Of the 160 benzodiazepine-dependent patients, 57% had been alcoholics who switched to benzodiazepines. The remaining 43% developed primary benzodiazepine dependence, although it is not clear how this 43% relates to the 19% with pure benzodiazepine dependence.

Based on a finding that, on a certain day, 70% of the patients in the department were using benzodiazepines, the authors estimated a 1.7% risk of benzodiazepine dependency for psychiatric inpatient benzodiazepine users. Between one third and one half of the dependence had been induced by medical prescription, and the authors urged caution in prescribing these drugs to alcoholics or other high-risk individuals.

A survey of benzodiazepine use among the general population was published by Dunbar et al. (1988). They questioned 4148 people about their drug use and identified 295 people (7.1%) as users of benzodiazepines, 151 (3.6%) of these as current users of benzodiazepines. Of current users, 74 had tried on occasion to stop taking their benzodiazepine; 45 (61%) reported difficulty when they attempted to discontinue benzodiazepine use.

6. Benzodiazepine dependence in the elderly. The problems that can develop in older patients taking benzodiazepines chronically were emphasized in a study by Whitcup and Miller (1987). Using stringent guidelines for indications of drug dependence and withdrawal, they reviewed the charts of 90 patients older than the age of 65 yr admitted to a New York acute-care psychiatric facility. Of the female patients older than 65 yr admitted to the facility during 1 yr, 18% were chemically dependent on benzodiazepines at the time of admission. This dependence on benzodiazepines in older women was unlikely to be diagnosed at the time of admission. Of these 12 patients, 11 were dependent on benzodiazepines alone, and the diagnosis of dependence was not made in 75% of these. Patients without such a diagnosis, and, therefore, untreated, were much more likely to show signs of withdrawal, together with increased heart rate and body temperature. Although a number of chemically dependent older men were admitted, they were more likely to be dependent on alcohol, to have appropriate diagnoses, and to be treated.

Foy et al. (1986) also evaluated elderly patients admitted to the hospital. Of 103 admissions, 52 had positive urine screens for benzodiazepines. Benzodiazepines were abruptly discontinued at the time of admission for 33 patients, and confusional states that abated following administration of diazepam developed in seven of these. A confusional state developed in only two patients from a control group of 51 nonusers and one patient whose benzodiazepine medication was continued.

A direct comparison between the development of benzodiazepine withdrawal signs in older as compared with younger patients was made by Schweizer et al. (1989). They evaluated 19 patients, 60 yr of age or older, and 22 patients younger than 55 yr. These groups had both been taking benzodiazepines for 1 yr or more and were referred to the study because of their wish to discontinue their medication. The groups were matched for dose, duration, and type (short- versus long-acting) of benzodiazepine taken. A thorough psychiatric and drug history was obtained from each patient, and ratings were made of baseline depression and anxiety. All patients underwent gradual withdrawal, unblinded, with a 25%/wk reduction in their daily benzodiazepine dose. A slowing of this regimen was required by 33% of the older and 50% of the younger patients. Withdrawal scores were significantly higher in the younger as opposed to the older group of subjects, and younger patients reported more new symptoms than did the older subjects. The authors speculated that withdrawal might have been less severe in the older patients (*a*) because they metabolized the benzodiazepines less rapidly and thus had a more protracted and gradual withdrawal course; (*b*) because they suffered more from depression than panic, as compared with the younger patients, and this could have modified the withdrawal course; or (*c*) because the neurotransmitter-dependent functions that might be disrupted during withdrawal were already reduced at baseline in the older patients. In any case, it is interesting that the available data indicate that elderly people do not have more severe withdrawal signs and may, in fact, have less severe withdrawal signs than younger people.

7. Studies of rebound insomnia. Rebound insomnia is

defined as the exacerbation of sleep disturbance as a consequence of the administration and subsequent discontinuation of a drug. Rebound insomnia, like rebound anxiety, can be considered a withdrawal sign and, thus, as evidence of dependence on hypnotic drugs. Because measures of sleep changes are frequently carried out using EEG measures under carefully controlled conditions of sleep laboratories, measures of sleep patterns before, during, and after hypnotic administration can provide sensitive indicators of rebound effects.

Findings of rebound insomnia have been reported fairly consistently upon discontinuation of short- to intermediate-acting benzodiazepines. When longer acting benzodiazepines have been studied in insomniac subjects, a carryover of hypnotic effect is observed rather frequently, and rebound insomnia is not observed (Woods et al., 1987; Lader and Lawson, 1987; Gillin et al., 1989; Roehrs et al., 1990). These findings suggest that long-acting benzodiazepines may effectively self-taper, preventing the appearance of rebound insomnia.

An effect of duration of administration on this phenomenon was reported by Monti (1988), using one of the shortest acting benzodiazepines, midazolam (15 or 30 mg). The drug produced little rebound effect when discontinued after 3 d of administration. When the drug was given in either of these doses for 2 wk, however, rebound insomnia was clearly evident upon discontinuation. In contrast, Allen et al. (1987) found that 1 to 3 mo of nightly administration of 15 mg midazolam did not lead to rebound insomnia, as measured by postsleep questionnaires. In fact, patients slept better upon drug withdrawal than they had during baseline periods of observation. Allen and coworkers thought that they might have actually treated the underlying, perhaps conditioned, causes for insomnia in these subjects by disrupting the insomnia for a 3-mo period. Francescangeli et al. (1987) reported no rebound insomnia following 2 wk of administration of 15 mg of midazolam in geriatric insomniacs. Results of these recent studies, therefore, appear to challenge the findings of earlier research (Kales et al., 1983), which demonstrated a marked and consistent rebound effect following discontinuation of this short-acting benzodiazepine. This discrepancy, in particular, calls for further studies, in which placebo controls and parametric variations in the doses and durations are tested.

Either placebo or the short-acting benzodiazepine brotizolam was given to 63 insomniacs for 3 wk; after 1 wk of nightly dosing with one tablet (0.25 mg of brotizolam), subjects were permitted to increase their dose to two tablets for the final 2 wk (Rickels et al., 1986b). Subjects kept daily sleep logs in which they recorded various aspects of their previous nights' sleep and filled out sleep questionnaires weekly. Placebo proved effective in improving sleep, although the active drug was more effective than placebo. Upon discontinuation, only the group receiving brotizolam showed rebound insomnia during the first withdrawal night.

Brotizolam's effects on sleep and rebound were evaluated in elderly subjects by Mamelak et al. (1989); the drug is thought to have a longer duration of action in older individuals. Insomniac subjects were given either brotizolam (0.25 mg), flurazepam (15 mg), or placebo nightly for 14 consecutive nights. Placebo-controlled withdrawal evaluations were conducted for two nights following drug administration. Subjects completed questionnaires each morning relating to their previous night's sleep. Brotizolam produced increases in estimated total sleep time but upon withdrawal caused a significant decrease in this parameter. Other parameters such as latency to sleep, frequency of awakenings, and soundness of sleep were also disrupted during withdrawal. Increased anxiety was also reported during the day following brotizolam withdrawal.

Alprazolam (1 mg) produced rebound insomnia on the third withdrawal night following 1 wk of nightly administration (Kales et al., 1987).

Rebound effects following triazolam administration have been studied by several investigators, because this drug is prescribed as an hypnotic and has a short duration of action. Roehrs et al. (1986b), using EEG measures, found that triazolam (0.25 mg) did not produce rebound insomnia after 6 d of administration to normal volunteers; a larger dose of triazolam (0.5 mg) did cause drug-discontinuation withdrawal but was no more effective than the smaller dose in promoting sleep. A placebo control group was also used in this study, which made the demonstration of rebound effects much more convincing. Kales et al. (1991) reported significantly increased total wake time in insomniac patients on the first night of withdrawal of 0.5 mg of triazolam after four nights of administration. Mamelak et al. (1990) demonstrated objectively and subjectively disrupted sleep in subjects after a single administration of 0.5 mg (but not 0.25 mg) of triazolam. Sleep was subjectively better on the night triazolam was given than it had been the night before and was disrupted on the subsequent night. Scharf et al. (1990) found rebound effects from a much smaller dose of triazolam (0.125 mg) as well as from an 0.25-mg dose after 14 consecutive days of administration. The rebound effects following the 0.125-mg dose were evident as an increased number of awakenings. Following withdrawal of 0.25 mg of triazolam, subjects showed what was described as a significant increase in sleep latency and a significant decrease in total sleep time. Altamura et al. (1989b) observed rebound symptoms in subjects following 8 wk of triazolam (0.5 mg) administration.

Studies in elderly subjects indicate that discontinuation of triazolam can result in sleep disturbances in this population. Elie et al. (1990) used a placebo-controlled design to evaluate the effects of triazolam in elderly insomniac patients. Triazolam, 0.125 mg, was adminis-

tered nightly for 1 wk; a dose of 0.25 mg per night was then given for an additional 2 wk. Questionnaires were administered each morning to evaluate the quality of sleep the previous night. Discontinuation of triazolam resulted in a reported increase in latency to fall asleep and a decrease in sleep soundness and quality. Mouret et al. (1990) also studied the effects of triazolam (0.25 mg) administration and withdrawal in elderly insomniac patients. The drug was administered nightly for 18 nights, following which evaluations continued during four nights of placebo administration. EEG recordings indicated that triazolam produced a rebound effect that did not reach a statistically significant level; however, the information concerning rebound was averaged over three nights of withdrawal. Graphic information indicated a marked decrease in total sleep time on the first withdrawal night, followed by recovery to normal sleep patterns on subsequent withdrawal nights.

On the other hand, Francescangeli et al. (1987) found no rebound insomnia after discontinuation of 2 wk of treatment with triazolam (0.5 mg). Greenblatt et al. (1987) studied triazolam (0.5 mg) for a 7-d period in insomniac patients. The drug was abruptly withdrawn from half of the subjects after 1 wk, and the dose was gradually tapered over a 4-d period in the other half. The former group showed increased insomnia on the first two nights following drug discontinuation; the latter group also showed some rebound insomnia but of a lesser magnitude.

Fleming et al. (1990) administered 0.25 mg of triazolam to insomniac subjects for 21 consecutive nights and evaluated their sleep quality with morning questionnaires. Indices of anxiety and withdrawal were taken as well. Triazolam lost its effectiveness on measures of sleep during the final 2 d of administration. During withdrawal, insomnia was the primary complaint of the subjects. Sleep induction, duration, and soundness were reported slower or worse on the first night of triazolam withdrawal. Sleep quality improved during the subsequent withdrawal days. No increases in anxiety were recorded on the HAM-A during triazolam withdrawal, but this test was given on the fourth day of withdrawal and may have missed earlier increases in anxiety. Forty-two percent of the subjects reported moderate to severe adverse effects during triazolam administration, although the nature of these effects was not specified.

Adam and Oswald (1989) observed a particularly interesting effect of triazolam, given nightly to 40 subjects selected because of their reports of being poor sleepers. A dose of 0.5 mg was administered nightly for 25 nights, following 15 nights of placebo administration. Separate groups continued to receive placebo or were switched to 2 mg of lormetazepam. Rather than evaluating the effects of these treatments on insomnia or measuring rebound insomnia upon drug discontinuation, the investigators queried their subjects in the evening, using a VAS, about their level of anxiety during the day. Levels of daytime anxiety increased dramatically over time in subjects taking triazolam, decreased in subjects receiving placebo, and remained generally unchanged in those taking lormetazepam. Subjects taking triazolam also gave more written comments of distress, showed a greater weight loss, and were more likely to demonstrate signs of paranoid psychosis than those taking lormetazepam or placebo. The authors rejected the possibility that these signs might represent withdrawal from triazolam, because impaired patients recovered quickly when the drug was discontinued. Rather, they suggested that these effects were related directly to drug administration, either because of a toxic metabolite or because triazolam interacts with a different set of benzodiazepine receptors than most other benzodiazepines. It is interesting that other investigators of triazolam administration did not report these striking effects; however, Adam and Oswald used the largest recommended dose and administered it for a longer time than did other investigators. It is possible that either these effects did not occur in other studies or other investigators simply did not look for effects of this kind.

Temazepam is a longer acting benzodiazepine with an elimination half-life of approximately 10 h. Although Kales et al. (1986) found rebound insomnia on the first drug withdrawal night following a 2-wk period of nightly administration of 15 mg of temazepam, Allen et al. (1987) found no rebound insomnia following a 1- to 3-mo period of nightly administration of 30 mg. Kales et al. (1991) evaluated the effects of temazepam (30 mg), given for five nonconsecutive nights (three or four consecutive "drug nights" followed by one or two "placebo nights" and one or two additional drug nights) on sleep and rebound. The drug effectively reduced total wake time. No increase in total wake time was observed during the first withdrawal period after three or four drug nights, but a significant increase was shown on the second "withdrawal night," after a total of five drug nights. Scharf et al. (1990) administered either 15 or 30 mg of temazepam to insomniac subjects for 14 d. Polysomnographic measures indicated that both doses were effective in maintaining sleep. Rebound insomnia in the form of decreases in total sleep time was shown following withdrawal of the 30-mg but not the 15-mg dose.

Tham et al. (1989) observed the effect of abrupt or gradual withdrawal of temazepam (10 mg) in geriatric patients who had been taking the drug for 1 mo or more. Sleep measures were taken hourly by the nursing staff during the last 7 d of drug administration prior to and during withdrawal. No rebound effects were seen under either the abrupt or the gradual withdrawal condition. Because no difference was observed in the duration of sleep before and after treatment, the authors suggested that this dose may be ineffective as an hypnotic.

The two longer acting hypnotic benzodiazepines, flur-

azepam and quazepam, have been evaluated for rebound insomnia. As discussed in our previous review, flurazepam is more likely to have residual sleep-promoting effects than it is to result in rebound insomnia upon discontinuation. This has been confirmed in recent literature. Mamelak et al. (1989) found that flurazepam (15 mg) produced increased estimates of total sleep time during 14 d of administration to elderly insomniac subjects. During two nights of withdrawal, total sleep returned to baseline measures, but an estimate of number of awakenings during the night indicated that flurazepam had a residual therapeutic effect on this measure. Interestingly, in this placebo-controlled study, subjects receiving placebo for 14 d also showed increased sleep; their estimated sleep parameters continued to improve during the 2 d of withdrawal. These data underscore the importance of including placebo controls in measures of effectiveness of hypnotic drugs.

A larger dose of flurazepam (30 mg) was administered for 28 d in a placebo-controlled study of insomniac patients (Elie et al., 1990). Subjects rated their sleep as improved during the course of either flurazepam or placebo administration. When drug was withdrawn, sleep ratings continued to improve in the placebo group; those receiving flurazepam maintained the improvement seen during active treatment. No rebound insomnia was demonstrated.

Quazepam is a more recently developed benzodiazepine hypnotic with a long duration of action. No rebound insomnia has been reported after 2 (Kales et al., 1986), 3 (Bonacci et al., 1987), or 8 (Altamura et al., 1989b) wk of administration of 15 mg of quazepam.

Diazepam (10 mg) produced a mild but nonsignificant rebound effect that peaked on the sixth night following drug discontinuation (Kales et al., 1988).

In general, these data support earlier findings that long-acting benzodiazepines produce no rebound insomnia, whereas the shorter acting drugs are more likely to produce disruption of sleep when they are discontinued. There are some exceptions to these general results; some investigators have not found rebound insomnia following discontinuation of short-acting benzodiazepines. The discrepancy between these findings and those of studies in which no such rebound insomnia was found does not appear to be a result of differences in methodologies or subject selection procedures. These interesting and important discrepancies suggest the need for more careful, placebo-controlled parametric research into this effect.

8. Outcome and long-term withdrawal. Several of the studies just described, in which benzodiazepines were withdrawn from subjects, included evaluations of subjects' status at various intervals following discontinuation of treatment. In general, the almost incidental reports of the short-term outcome of these patients indicate that they were doing as well or better without benzodiazepines as they were at baseline, when they were taking therapeutic doses of these drugs. Cantopher et al. (1990), for example, commented that "Those who were successfully withdrawn in our study were no worse, and may even have been better, on every measure when off their benzodiazepines than they were at baseline" (p. 410). Schweizer et al. (1990) observed that 79% of their subjects, who had been using benzodiazepines for 1 yr or longer, had met DSM-III diagnostic criteria prior to initiating benzodiazepine withdrawal; 5 wk after benzodiazepine discontinuation by gradual tapering, there was a "modest but significant improvement in clinical scores compared with pretapering scores, despite benzodiazepine discontinuation" (p. 912). Rickels et al. (1990b) noted that ". . . for those patients who have been able to stay free of benzodiazepines for at least 5 wk, Physician Withdrawal Checklist and HAM-A scores had returned to pre-benzodiazepine-discontinuation levels or below. In fact, at 5-wk follow-up, HAM-A scores were significantly lower than they were at pretapering baseline" (p. 905).

These observations may reflect a subgroup of anxious patients in whom benzodiazepines may lose their effectiveness with chronic use and, indeed, may actually exacerbate symptoms of anxiety. It is also possible that these observations reflect a subgroup of anxious patients who, because of spontaneous change in their condition, are able to withdraw and maintain abstinence from benzodiazepines and can cope as well or better without benzodiazepines as they did during treatment with these drugs.

In a few studies, investigators have looked at outcome following benzodiazepine discontinuation in a more rigorous fashion and over a longer term. These studies have focused on outcome, as indicated by benzodiazepine abstinence, over the course of several months or years. Ashton (1987) observed 50 patients who had discontinued use of benzodiazepines in a clinic setting 10 mo to 3.5 yr earlier. At the time they initiated benzodiazepine withdrawal, these patients had shown symptoms of depressive illness, agoraphobia, and apparently psychosomatic illness, which had developed during the course of chronic benzodiazepine therapy. Seventy percent of the patients showed good or excellent outcome following benzodiazepine discontinuation, i.e., they had not relapsed to benzodiazepine use, and had few or no symptoms; an additional 22% were not taking benzodiazepines but required other psychoactive drugs for their persistent symptoms, and 8% had relapsed to use of benzodiazepines. The 70% who were not taking psychoactive medication claimed to feel better since they had stopped benzodiazepine use. The symptoms that had developed while they were taking benzodiazepines, such as depression and agoraphobia, dissipated after benzodiazepine use was discontinued. The factor that appeared to be most related to ability to maintain abstinence from benzodiazepines was younger age, although the four patients

who did most poorly were in the younger age group. The duration of benzodiazepine use, age at onset of chronic benzodiazepine use, dose taken at time of initiation of withdrawal, type of benzodiazepine used, rate of withdrawal, severity of withdrawal symptoms, marital status, and sex were not related to ability to maintain benzodiazepine abstinence.

Rickels et al. (1991) reported a follow-up study of 123 patients who had been evaluated for a benzodiazepine discontinuation program 3 to 6 yr earlier. Forty-five percent were not using benzodiazepines at follow-up, and these subjects were also less likely than those currently taking benzodiazepines to be using other psychotropic medication. Subjects who had been exposed to the tapering program were less likely to be taking benzodiazepines at follow-up than were those who did not enter the program. Seventy-three percent of those who successfully completed the tapering program, 39% of those who entered but did not complete the program, and 14% of those who did not enter the program were benzodiazepine free at follow-up. Program participation, shorter period of benzodiazepine treatment, and younger age were the variables most positively related to maintained benzodiazepine abstinence. Type of benzodiazepine used, type of withdrawal program (abrupt versus tapering), dose of benzodiazepine, or severity of withdrawal did not relate to benzodiazepine abstinence at follow-up. Interestingly, anxiety and depression were significantly less for those patients who were not using benzodiazepines at follow-up than for those who continued to take these drugs.

Golombok et al. (1987) evaluated 46 patients who had been treated for benzodiazepine dependence 1 to 5 yr earlier. The subjects were interviewed and filled out questionnaires related to their demographic status, past drug use history, psychiatric history, and withdrawal history. Fifty-four percent had not used a benzodiazepine for at least 1 mo prior to the follow-up evaluation. The subjects had been abstinent from benzodiazepine use for an average of 19 mo. Subjects who were no longer taking benzodiazepines reported continuing anxiety-related symptoms. Fifty-six percent showed moderate to severe anxiety, and 38% noted moderate to severe depression. Nevertheless, those who had successfully discontinued benzodiazepine use were significantly more likely to report their "accommodation" (not defined) to be adequate than those who continued to use benzodiazepines. Golombok et al. found, as did other researchers, that the type of benzodiazepine subjects had previously used, the duration of time they had been taking benzodiazepines, and the dose they had been taking were not related to their ability to maintain abstinence from benzodiazepines. In contrast to the other studies, however, these researchers did not find that age was related to ability to successfully discontinue benzodiazepine use but did find that women were significantly more likely to discontinue benzodiazepine use than were men.

Holton and Tyrer (1990) evaluated 41 patients who had participated in a treatment program for long-term benzodiazepine use. An attempt was made to interview these patients exactly 5 yr after they had entered the program. Although 75% had taken benzodiazepines at some time in the 5 yr subsequent to their participation in the program, only 36% were taking them at the time of follow-up. The authors did not attempt to identify the variables related to relapse to benzodiazepine use or to determine the relative status of patients who did and did not relapse to benzodiazepine use. They noted that it seemed possible for many patients to take benzodiazepines for a short period of time, even though they had previously taken the drugs chronically. The authors expressed concern that physicians continued to prescribe benzodiazepines to these particular patients but noted that this might be due to the fact that there was no practical alternative therapy.

These studies raise the interesting question of whether long-term use of benzodiazepines is appropriate for patients who take the drug for problems related to anxiety, depression, and insomnia. They suggest that the majority of patients who have taken benzodiazepines on a sufficiently chronic basis to develop dependence continue to show psychopathology (as reflected also in surveys of benzodiazepine users). They further suggest that some psychopathology may develop during the course of benzodiazepine treatment and that some patients may show improvement in these symptoms after the drugs have been discontinued. Clearly, further longitudinal studies of long-term benzodiazepine users are needed to determine whether some patients might be aided whereas others are hindered by continued administration of these drugs.

9. Summary and discussion. The majority of studies that have been concerned with issues of physiological dependence on benzodiazepines in humans have focused on dependence at therapeutic doses. Results of these studies confirm and extend the evidence that, for those drugs that have been investigated, dependence can occur at therapeutic doses. Findings from recent studies of unselected chronic users (i.e., patient populations other than those referred specifically because of reported problems with benzodiazepine discontinuation) have supported earlier findings that not all patients who use benzodiazepines on a chronic basis develop dependence. However, the investigators tended to concentrate their research on those who did experience withdrawal, leaving us with little evidence as to why some escaped this discomfort, and it remains unclear what proportion of patients can be expected to exhibit withdrawal signs when their benzodiazepine is discontinued. A number of authors have suggested that there may be relationships between dependence development and personality traits, age, prior drug use, dose magnitude, and/or duration of drug use. None of these factors has been sufficiently well

evaluated; they need to be more carefully studied in clinical populations until their effects on benzodiazepine dependence development are well understood and can be brought to bear on prescribing practices.

Authors of the various reports concur that, upon abrupt discontinuation, short half-life benzodiazepines result in a more rapidly developing withdrawal syndrome. There is also general agreement that withdrawal distress is greater when short-acting drugs are discontinued, but investigators who have compared short- and long-acting benzodiazepines have not usually examined the phenomena over a sufficiently long period to capture the full spectrum of withdrawal from long-acting benzodiazepines. Withdrawal from longer half-life drugs is certainly more protracted, and, therefore, likely to be less intense, but very thorough comparisons, for example, of areas under the curve of withdrawal reactions from short and long half-life benzodiazepines have not been described; such comparisons might reveal that total withdrawal scores over time are similar for the two types of drugs. Nevertheless, the rapid withdrawal from short half-life benzodiazepines may be more distressing to patients, as evident in a larger dropout rate in studies of discontinuation of the shorter acting drugs.

Limited observations have suggested that the effects of gradual discontinuation of long-acting benzodiazepines may not differ from those of abrupt discontinuation of these drugs, unless the tapering schedule is very slow (10 wk or more). Gradual withdrawal of short half-life benzodiazepines does appear to reduce the intensity and duration of withdrawal from these drugs. In any case, however, gradual discontinuation of either short or long half-life benzodiazepines does not completely prevent the emergence of withdrawal signs, and patients frequently describe various degrees of discomfort during the last part of a tapering regimen and when the drug is finally totally withdrawn.

Evaluation of rebound insomnia following discontinuation of benzodiazepine administration continues to be quite popular. As we concluded in our previous review, long-acting benzodiazepines do not appear to produce rebound insomnia. With respect to short-acting benzodiazepines, by far the majority of studies, although not all, have found rebound insomnia following discontinuation of these drugs.

There have been some recent suggestions that benzodiazepine withdrawal may be more protracted than had previously been recognized (Ashton, 1991; Tyrer, 1991). The signs and symptoms reported to continue for several weeks following drug discontinuation include headache, dizziness, tinnitus, depression, and paresthesias. According to Ashton (1991), these signs continued to abate for several months after withdrawal. The amount of research concerning protracted benzodiazepine withdrawal signs is as yet too limited to warrant conclusions about whether these signs are a consequence of prior administration of benzodiazepines, are reappearances of symptoms, or are nonspecific effects. Neither is any information available about the percentage of persons who might develop protracted withdrawal or what factors might contribute to the likelihood that it will occur.

Finally, results of studies of the long-term outcome of patients who have discontinued benzodiazepine medication suggest that ability to maintain benzodiazepine abstinence may be greater among those who successfully completed a program of gradual discontinuation. Women and younger patients may also be less likely to resume benzodiazepine use on a chronic basis. There is also some evidence suggesting that a significant proportion of those who become and remain benzodiazepine abstinent have fewer problems with anxiety and depression than they had during chronic benzodiazepine use.

D. Summary and Discussion

As we concluded previously, studies of benzodiazepine dependence in animals have shown that, at high doses, benzodiazepines are capable of producing physiological dependence. Although most investigators of benzodiazepine dependence in animal studies have continued to examine the effects of relatively high doses of the drugs, some have examined the development of dependence at lower doses. The results of these studies have uniformly indicated that the intensity of the withdrawal syndrome is directly related to the dose of the benzodiazepine administered.

Many of the results of studies of dependence in humans parallel the findings of studies in animals. However, there is no strong evidence from clinical studies that either the dose of the benzodiazepine or the duration of treatment plays a role in the development of dependence; the few studies in which these variables have been examined indirectly have produced inconsistent results. This may be due, in part, to the fact that clinical investigators have typically examined the effects of therapeutic doses rather than the wide range of doses often studied in animals.

As we found in our previous review, not all patients using benzodiazepines chronically experience withdrawal symptoms when drug treatment stops. More recent research has supported this finding, although it remains unclear what proportion of chronic users are in fact dependent. Despite some attempts to establish the determinants of dependence development, the available information remains insufficient to identify specific time or cumulative dose thresholds beyond which dependence can be expected to develop. Many of the important questions about the development of benzodiazepine dependence are probably pursued most effectively in animal research. For example, is the risk of dependence at a given dose of one compound comparable to the risk at the equivalent of half that dose of another compound that has twice the duration of action? To answer a

question of this kind ultimately requires information regarding the mechanism of dependence development, the degree of adaptive change in the CNS as dependence develops, and the rate of change in the CNS as it resumes normal functioning during periods when the agonist is removed. We now have the capability to derive this kind of information about benzodiazepine exposure in animal studies. Another factor best studied in animals is the effects of previous exposure to other CNS depressants, including ethanol. Results of studies in both animals and humans suggest that such prior exposure may be a factor in the development of benzodiazepine dependence. Unfortunately, recent studies have not pursued this or other possible predisposing factors.

Human studies are the only means of exploring several factors that may predispose to the development of physiological dependence on benzodiazepines or that may augment such dependence. For example, results of studies in humans have indicated that certain personality traits or age may predispose to development of dependence on benzodiazepines. The effects of such factors are, however, difficult to pursue outside of prospective studies, which are often logistically prohibitive in clinical research.

There is considerable current interest in whether short-acting benzodiazepines are more likely to produce withdrawal effects than longer acting compounds. Clinical study results support the conclusion that the withdrawal associated with short-acting benzodiazepines develops more rapidly and may be more intense than that occurring with longer acting drugs. Findings from animal studies support a more rapid onset of withdrawal but are not sufficient for a conclusion regarding the intensity of withdrawal. There is no evidence, however, that dependence is more likely to develop with the short-acting compounds. In addition, the more intense withdrawal that follows discontinuation of these drugs may be a function of their more rapid elimination rather than of the degree of dependence produced.

To address whether short-acting drugs produce a greater degree of dependence than long-acting drugs, it would be necessary to conduct animal studies that equate the efficacy and exposure of the drugs compared (i.e., a short-acting drug would have to be given at a frequency that ensures that the exposure is comparable to that obtained with a longer acting drug). In the one comparison of this kind that has been made in animals, there were no differences in observed withdrawal signs between the short-acting drug midazolam and the longer acting chlordiazepoxide.

It is conceivable that further animal studies will reveal differences in the intensity or frequency of withdrawal signs following exposure to agonists with different durations of action. Expression of withdrawal depends on the degree of dependence (the degree of CNS adaptive change that took place during treatment) and the rate of receptor uncovering that occurs as the agonist is eliminated. After treatment with drugs of differing dissociation kinetics or durations of action, receptors are uncovered at different rates. Drugs that are eliminated in a manner that results in a relatively gradual uncovering of receptors may allow a more controlled recovery from the CNS changes associated with dependence, such as that achieved with dose tapering during withdrawal. Therefore, agonists producing the same degree of adaptive change in the CNS may display different intensities of withdrawal due to differences in their elimination kinetics, which may allow different degrees of CNS readaptation during the withdrawal period (for an example with opioids, see Himmelsbach, 1939).

Under the worst circumstances, insomnia is a problem that occurs once daily, and hypnotic medications are usually prescribed and used in a single nightly dose. The advent of short-acting drugs for the treatment of insomnia has thus introduced the phenomenon of repeated intermittent, rather than continuous, exposure to the agonist. The issue of whether this type of therapeutic regimen might produce repeated episodes of acute dependence and withdrawal has not yet been addressed. It should be an important objective of future experimental research to identify and measure the behavioral and biochemical correlates and consequences of this type of treatment regimen, which is clearly distinct in its implications from the typical anxiolytic regimen of multiple daily doses.

Results of at least one clinical study have suggested that once-daily repeated administration of ultrashort-acting benzodiazepines may result in episodes of interdose anxiety or other psychiatric disturbances. Unfortunately, in no other studies of human subjects has this issue been addressed. Despite the capability for examining this dosing regimen in animals, issues associated with chronic administration of short-acting compounds have been addressed only in a few animal studies.

We previously concluded that there was no definitive evidence of differences among the benzodiazepines with respect to their relative potentials to produce physiological dependence. Studies in which benzodiazepines are adequately compared are difficult to conduct. Basic pharmacological considerations dictate that, to assess differences in dependence produced by two drugs, subjects should be affected by the drugs to a comparable degree, or the two drugs should produce the same receptor occupancy, for a comparable period of time. Such comparisons have been included in few studies.

More recent study findings have further suggested that there may be differences among benzodiazepines with regard to the type of dependence that they produce. These results have indicated that there may be differences in the constellations of signs that characterize the withdrawal syndromes associated with different benzodiazepines. Investigation of the mechanisms underlying

these differences will be difficult but important for determining the full implications of these findings.

Possibly more convincing demonstrations of differences among benzodiazepines with respect to dependence are those in which compounds with differing degrees of intrinsic efficacy have been compared. Results of these studies suggest that partial agonist-type compounds may be less likely to produce dependence; if it can be shown that these compounds are therapeutically effective, they may represent promising alternatives to classical benzodiazepine agonists.

IV. Adverse Behavioral Consequences of Benzodiazepine Use

A. Introduction

In this section of the review, we address evidence regarding behavioral changes associated with the use of benzodiazepines that may represent adverse effects for individual patients. In many of the studies reviewed, the authors assessed how these drugs alter performances on laboratory tests of "psychomotor skills." Other investigators focused more directly on behavior in situations more typical of those actually encountered by the patients for whom these medications are prescribed (e.g., driving). Finally, we consider both experimental and epidemiological studies of the effects of benzodiazepine use on the risk of accidents; the risk of automobile accidents has been the focus of the majority of these studies.

B. Effects of Benzodiazepines on Psychomotor Performance

A wide variety of performance tasks have been used to study the behavioral effects of benzodiazepines in human subjects. It has been suggested that procedures assessing the effects of benzodiazepines on reaction times, choice reaction times, tracking abilities, divided attention tasks, and vigilance tasks may provide estimates of the contribution of use of these drugs to risks of accidents. Other procedures have been used that are lacking the face validity of those mentioned above. Measures of flicker-fusion threshold, sorting playing cards, and mental arithmetic have been shown to be sensitive to the effects of many psychotropic drugs and have been used to evaluate the effects of benzodiazepines. Inevitably, however, questions remain regarding the predictive validity of these procedures (Landauer, 1986).

In our previous review (Woods et al., 1987), we concluded that all of the benzodiazepines examined had effects on psychomotor performance at doses within the therapeutic range. These effects appeared to diminish after several days of repeated administration. The effects of benzodiazepines on performance in anxious subjects did not differ from those in normal subjects. Of the test procedures most frequently examined, the threshold for distinguishing flickering light (critical flicker fusion frequency) appeared to be most sensitive to the effects of benzodiazepines. Although previous reviewers had found that performances involving speed of response were particularly sensitive to the effects of benzodiazepines, we did not find definitive evidence to support that conclusion.

For this current review, we have surveyed the more recent literature concerning these matters. As in our previous review, to provide a sense of the generality of the results, we tabulated the frequencies with which the various benzodiazepines were found to produce various behavioral effects. The tables were designed to indicate the consistency with which the drugs tested were found to produce each type of effect and whether the effect was observed following administration of therapeutic doses. In the tables, we have summarized the results of each dose comparison within each study; i.e., if more than one dose was examined or the same dose was examined twice, the findings are represented by two entries in the tables. Unless otherwise noted, the route of administration was oral.

Studies included in the tables were those in which effects of benzodiazepines on behavior were examined with similar types of procedures. Unfortunately, this approach excluded several studies in which innovative procedures were used. Some of these studies are discussed below. As in our previous review, our summary considers that a performance was adversely affected by a drug even if only one of several tested aspects of the performance was so affected.

1. Effects in normal subjects. A summary of results of studies comparing effects of acute therapeutic doses of benzodiazepines on performance in normal subjects is shown in table 3. (Note that the results of the individual studies on which these total values are based are shown in "Appendix.") For studies of the effects of repeated dosing, effects of the first dose administered (if reported) are shown. The values shown in the table indicate ratios of the number of times therapeutic doses produced performance decrements to the number of times those doses were studied.

For each of the drugs studied with some consistency, the ratios in the table generally are greater than 0 and less than 1. Ratios of approximately 0.5 indicate that a performance decrement was reported in approximately half of the studies, whereas it was not in the other half. For example, diazepam doses within the therapeutic range affected DSST performance in six of ten observations, for a ratio of 0.6. In instances in which a single dose of a drug was compared across studies, the results were generally somewhat more consistent, although there was still considerable variability. For example, in five of seven studies of the effects of 10 mg of diazepam on DSST, this dose was found to impair this performance (data not shown).

In many cases, the number of entries for individual

TABLE 3

*Effects of therapeutic doses of benzodiazepines on psychomotor performance in normal subjects**

Drug	Route	CFF	TAPP	DSST	TRAC	RT	CRT	CANC	ARITH
Adinazolam	p.o.			2/2	1/2		2/2		
Alprazolam	p.o.	1/1		1/1	0/2		1/2		
Alprazolam	i.v.			2/2					
Bromazepam	p.o.	0/1		1/2			1/2		
Clobazam	p.o.	0/5	0/1	0/2		0/1	0/4		0/1
Clorazepate	p.o.			0/1	0/1		0/1		
Diazepam	p.o.	3/7	1/5	6/10	4/9	1/6	4/9	1/3	3/4
Diazepam	i.v.	0/1		1/1	1/1		0/1	0/1	
Flunitrazepam	p.o.		1/1			1/1		1/1	
Flurazepam	p.o.			0/1	1/1				
Loprazolam	p.o.	1/1		1/1			1/1		
Lorazepam	p.o.	2/7	1/4	6/6	2/4	3/5	5/6	3/3	1/3
Lormetazepam	p.o.	3/3			1/1	1/1	3/3		
Midazolam	p.o.	3/3	1/1	2/3		2/3	1/2		
Midazolam	i.v.	2/2		2/2	1/1	1/1	1/2	1/2	3/3
Nitrazepam	p.o.	0/1				1/2	0/1		
Oxazepam	p.o.	0/1	1/1	1/1			1/1	1/1	
Prazepam	p.o.			0/1					
Quazepam	p.o.	0/1		0/1	1/1		1/1		
Temazepam	p.o.	2/3		1/2	3/3	0/1	2/3		
Triazolam	p.o.	4/6	1/1	5/7	2/3	2/3	1/1	0/3	
Totals	p.o.	0.48 (40)	0.43 (14)	0.63 (41)	0.56 (27)	0.48 (23)	0.59 (39)	0.55 (11)	0.50 (8)
Previous review		0.73 (59)	0.44 (16)	0.65 (48)	0.52 (60)	0.44 (48)	0.55 (42)	0.54 (26)	0.38 (13)
Cumulative totals		0.63 (99)	0.44 (30)	0.64 (89)	0.54 (87)	0.45 (71)	0.57 (81)	0.54 (37)	0.43 (21)
Flunitrazepam	p.o., h.s.								
Flurazepam	p.o., h.s.			0/3		0/1	3/3		
Ketazolam	p.o., h.s.			0/1				0/1	
Loprazolam	p.o., h.s.								
Lorazepam	p.o., h.s.	1/1					1/1	0/1	
Lormetazepam	p.o., h.s.	0/3			0/3		0/3	0/1	
Midazolam	p.o., h.s.		0/1	0/2	0/1	0/1	0/1	0/2	0/1
Nitrazepam	p.o., h.s.		0/1		0/1			0/1	
Quazepam	p.o., h.s.				0/1		0/1		
Temazepam	p.o., h.s.			0/1		0/1	0/1		
Triazolam	p.o., h.s.			0/3	0/1	1/1	0/2	0/1	
Totals	p.o., h.s.	0.25 (4)	0.00 (2)	0.00 (10)	0.00 (7)	0.25 (4)	0.33 (12)	0.00 (7)	0.00 (1)
Previous review		0.28 (18)	0.29 (14)	0.53 (32)	0.28 (32)	0.17 (23)	0.29 (28)	0.18 (11)	0.50 (8)
Cumulative totals		0.27 (22)	0.25 (16)	0.40 (42)	0.23 (39)	0.18 (27)	0.30 (40)	0.11 (18)	0.44 (9)

* Entries represent the ratio of the number of dose comparisons in which a decrement in performance was found to the number of dose comparisons conducted. Entries for totals show overall proportions across rows or columns. See text for further details. References to individual studies are given in "Appendix." Abbreviations: CFF, critical flicker fusion frequency (the threshold frequency at which flickering light appears steady); TAPP, tapping (the maximal rate at which the subject can tap his or her finger); DSST, digit symbol substitution test (subjects are presented with a code in which the numbers 1 to 9 are matched with simple symbols. For a fixed time, they write the appropriate symbols below a series of numbers); TRAC, tracking (subjects indirectly manipulate an object through the use of some type of manipulandum to keep it on target); RT, reaction time (the subject is required to respond to a stimulus by pressing some type of key as fast as possible); CRT, choice reaction

drugs in table 3 is too small to allow comparisons among the various performance tests. If the data for all the drugs are totaled (bottom row), however, some comparisons are possible. The proportion of observations in which performance decrements were reported varied from 0.43 for tapping rate to 0.3 for DSST. This suggests that there was not much difference among tests in their sensitivity to the effects of benzodiazepines. In addition, as illustrated by comparing the rows of totals, the results of the studies examined in the current review did not differ appreciably from those considered in our previous review.

Considering data for individual drugs across tests (third column from the right), we find some apparent differences among the drugs with respect to the frequency with which they were found to produce effects. For example, in contrast with all of the other drugs, none of the studies of clobazam reported significant effects on psychomotor performance. This may be due, in part, to the fact that only relatively low doses of this drug were

TABLE 3—*Continued*

SORT	DV-ATT	COPY	SWAY	VIG/SD	STROOP	LOG RES	Totals	Previous review	Cumulative totals
2/2				2/2			0.90 (10)		0.90
							0.50 (6)	0.30 (10)	0.8 (16)
							0.50 (2)		0.50
				1/1			0.50 (6)		0.50
			0/1				0.00 (15)		0.00
							0.00 (3)	0.30 (20)	0.26 (23)
	2/4	1/2	2/3	2/5			0.45 (67)	0.53 (146)	0.50 (213)
			1/2				0.43 (7)	0.73 (49)	0.69 (56)
0/1							0.75 (4)	1.00 (1)	0.80 (5)
					0/1	1/1	0.50 (4)	0.76 (17)	0.71 (21)
							1.00 (3)		1.00 (3)
		2/2					0.63 (40)	0.75 (56)	0.70 (96)
					0/1	0/1	0.80 (10)		0.80 (10)
							0.75 (12)		0.75 (12)
			0/1				0.79 (14)		0.79 (14)
			1/1				0.40 (5)	0.67 (21)	0.62 (26)
				2/2			0.86 (7)	0.50 (18)	0.60 (25)
							0.00 (1)		0.00 (1)
			0/1				0.40 (5)		0.40 (5)
				0/1			0.62 (13)	0.53 (17)	0.57 (30)
1/1	1/1	1/3	1/3		0/1	1/1	0.59 (34)	0.47 (15)	0.55 (49)
0.75 (4)	0.60 (5)	0.57 (7)	0.44 (9)	0.64 (11)	0.00 (3)	0.67 (3)	0.54 (245)		
0.75 (12)	0.36 (14)						0.56 (338)		
0.75 (16)	0.42 (19)	0.57 (7)	0.44 (9)	0.64 (11)	0.00 (3)	0.67 (3)	0.55 (583)		
			1/1				1.00 (1)		1.00 (1)
2/2							0.56 (9)	0.39 (38)	0.42 (47)
							0.00 (2)		0.00 (2)
			0/1				0.00 (1)		0.00 (1)
							0.67 (3)		0.67 (3)
							0.00 (10)		0.00 (10)
1/1	0/1	0/1		0/1			0.08 (13)		0.08 (13)
1/1		0/1					0.20 (5)	0.37 (59)	0.36 (64)
							0.00 (2)		0.00 (2)
	1/1						0.25 (4)	0.23 (40)	0.23 (44)
0/2				0/1			0.09 (11)	0.33 (18)	0.24 (29)
0.67 (6)	0.50 (2)	0.00 (2)	0.50 (2)	0.00 (2)			0.20 (61)		
0.50 (12)	0.00 (1)						0.33 (179)		
0.56 (18)	0.33 (3)	0.00 (2)	0.50 (2)	0.00 (2)			0.30 (240)		

time (subjects are required to respond differentially, as fast as possible, to two stimuli that are presented in random order); CANC, cancellation (subjects are required to strike through particular letters on a printed page); ARITH, arithmetic (subjects are required to perform sequential arithmetic problems without benefit of paper and pencil); SORT, sorting (subjects are required to sort objects according to some rule, e.g., a deck of playing cards are sorted by suit); DV-ATT, divided attention (subjects are required to monitor at least two simuli that cannot be focused on simultaneously and to respond to the stimuli in different ways); COPY, copying of symbols; SWAY, body sway or balance (subject asked to stand on an unstable platform); VIG/SD, vigilance/signal detection (detection of an infrequently presented visual stimulus on a cathode ray tube); STROOP, stroop test; LOG RES, test of logical reasoning capability; h.s., administered at bedtime and tested the morning after.

examined. Therapeutic doses of clobazam can range up to 80 mg/d (Rickels et al., 1981), but the table includes data for only 10-mg doses. On the other hand, results of studies in which clobazam has been compared with other benzodiazepines at doses that appear therapeutically equivalent (Patat et al., 1991; van der Meyden et al., 1989) have indicated that clobazam has fewer effects, if any, on psychomotor performance. In contrast, findings of several clinical studies indicated that clobazam was not different from other benzodiazepines in producing sedation (Brogden et al., 1980). One such study indicated that clobazam and diazepam were equally effective in producing "sedation" but that diazepam produced greater "dizziness" (Jacobson et al., 1983).

In contrast to clobazam, adinazolam reliably showed effects on performances in most of the dose comparisons. These effects occurred across doses from 15 to 40 mg; therefore, they cannot be explained on the grounds that only high doses were studied. However, because this drug is used for the treatment of panic disorders, it may be

TABLE 4

Effects of higher than therapeutic doses of benzodiazepines on psychomotor performance in normal subjects

Drug	Route	CFF	TAPP	DSST	TRAC	RT	CRT	CANC
Adinazolam	p.o.			1/1				
Alprazolam	p.o.	1/1	1/1	6/6	4/4		1/1	1/1
Bromazepam	p.o.			1/1				
Clobazam	p.o.	1/4	0/2	0/2		0/2	0/2	0/1
Clonazepam	p.o.	1/3		2/2			1/2	
Clorazepate	p.o.			0/1	0/1		0/1	
Diazepam	p.o.	7/7	4/8	11/11	7/11	2/2	5/6	1/4
Diazepam	i.v.							
Flunitrazepam	p.o.		1/1			1/1		1/1
Lorazepam	p.o.	4/5	3/3	5/5	6/6	3/4	7/7	1/1
Midazolam	p.o.						1/1	
Oxazepam	p.o.		1/2			1/1		0/1
Quazepam	p.o.			1/1	1/1		1/1	
Triazolam	p.o.	2/2		7/7	6/6		3/3	1/1
Totals	p.o.	0.73 (22)	0.59 (17)	0.92 (37)	0.83 (29)	0.70 (10)	0.79 (24)	0.50 (10)
Therapeutic doses		0.48 (40)	0.43 (14)	0.63 (41)	0.56 (27)	0.48 (23)	0.59 (39)	0.55 (11)
Diazepam	p.o., h.s.	0/1		0/1	0/1		0/1	
Flunitrazepam	p.o., h.s.	1/1		2/2		1/1	2/2	
Lorazepam	p.o., h.s.			1/1				1/1
Triazolam	p.o., h.s.	1/1		0/2	0/1		0/2	0/1
Totals	p.o., h.s.	0.67 (3)		0.50 (6)	0.00 (2)	1.00 (1)	0.40 (5)	0.50 (2)
Therapeutic doses		0.25 (4)	0.00 (2)	0.00 (10)	0.00 (7)	0.25 (4)	0.33 (12)	0.00 (7)

that the therapeutic doses are functionally higher than those of benzodiazepines used to treat anxiety.

Data concerning residual daytime effects after nighttime administration are shown in the lower portion of table 3. In general, the frequencies with which residual daytime effects were reported were lower than those for effects assessed immediately after drug administration. Again, the numbers of individual entries are too small to assess reliable differences among tests for single drugs. If the data for individual tests are considered across drugs, the ratios of findings of residual effects varied from 0 (several tests) to 0.67 (card sorting). If the data for individual drugs studied with some frequency are considered, the proportions of findings of residual effects ranged from 0 (lormetazepam) to 0.67 (lorazepam). As mentioned before, these proportions tended to be lower than those obtained when effects were assessed immediately after drug administration; the proportions were relatively low for certain drugs studied under both dosing conditions, e.g., midazolam, nitrazepam, temazepam, and triazolam.

Effects of doses exceeding the therapeutic range are shown in table 4. As in the previous table, numbers of individual entries are too small to assess reliable differences among tests for single drugs. If the data for individual tests are considered across drugs ("Totals"), the proportions of dose comparisons in which effects were reported varied from 0.5 (letter cancellation) to 1.0 (vigilance). If the data for individual drugs studied with some frequency are considered, the proportions in which effects were reported ranged from 0.06 (clobazam) to 1.0 (alprazolam). In most cases, these proportions were higher than those obtained when effects of therapeutic doses were assessed, as illustrated by comparing the two right-most columns of table 4. Notable exceptions to this generalization are oxazepam, for which the frequency of effects reported at the higher doses is lower than that reported at lower doses; flunitrazepam, for which the frequencies are similar; and clobazam, for which the frequencies of effects reported at both dose ranges approach or equal 0.

Studies of residual daytime effects after nighttime doses that exceed the therapeutic range are also shown in table 4. In general, frequencies of reports of residual daytime effects following these doses were lower than those reported for effects of high doses assessed immediately after drug administration. As with the immediate effects, residual effects of high doses were reported more frequently than residual effects of therapeutic doses.

The effects of benzodiazepines on performance over dosing periods of several days have been assessed in some studies. Table 5 is a summary of reported effects of several benzodiazepines on performance during regimens of at least 3 d of repeated dosing. The total dose administered per day and how the drug was given, i.e., how many times per day and whether administration was at bedtime, are listed.

Diazepam has been studied most frequently. Several

TABLE 4—*Continued*

ARITH	SORT	DV-ATT	COPY	SWAY	VIG/SD	LOG.RES.	Totals	Therapeutic doses
							1.00 (1)	0.90 (10)
			1/1	3/3			1.00 (18)	0.50 (6)
					1/1		1.00 (2)	0.50 (6)
1/2				0/1			0.06 (16)	0.00 (15)
				2/2			0.67 (9)	
							0.00 (3)	0.00 (3)
4/4	2/2	2/2		1/4			0.75 (61)	0.45 (67)
				1/1			1.00 (1)	0.43 (7)
	0/1						0.75 (4)	0.75 (4)
1/1		1/2		1/1	2/2		0.92 (37)	0.63 (40)
							1.00 (1)	0.75 (12)
2/2	1/2					0/1	0.56 (9)	0.86 (7)
				1/1			1.00 (4)	0.40 (5)
		1/1	1/1	5/6	1/1		0.96 (28)	0.59 (34)
0.89 (9)	0.60 (5)	0.80 (5)	1.00 (2)	0.74 (19)	1.00 (4)	0.00 (1)	0.77 (194)	
0.50 (8)	0.75 (4)	0.60 (5)	0.57 (7)	0.44 (9)	0.64 (11)	0.67 (3)	0.54 (246)	
							0.00 (4)	
					1/1		1.00 (7)	1.00 (1)
			1/1				1.00 (3)	0.67 (3)
	0/1		0/1	1/1			0.20 (10)	0.09 (11)
	0.00 (1)		0.50 (2)	1.00 (1)	1.00 (1)		0.50 (24)	
0.00 (1)	0.67 (6)	0.50 (2)	0.00 (2)	0.50 (2)	0.00 (2)		0.20 (61)	

studies have shown continued effects of diazepam on DSST during repeated administration. Effects on other procedures, such as critical flicker fusion frequency, tracking, reaction time, and choice reaction time, were reported in some studies but not others. Two studies reliably reporting effects on several tests assessed performances after 4 or 7 d of drug administration. In general, in studies in which the effects were examined after longer periods of drug administration, effects were less likely to be found. Effects of alprazolam were generally absent on all tests studied, whereas lorazepam produced effects more reliably. When morning-after effects were assessed, occasional performance decrements were reported. Too few of these studies were reported to determine whether dose or duration of treatment influenced the likelihood of a reported effect.

In several of the studies in which effects during repeated administration were reported, doses above the therapeutic range were tested. Relative to the effects of acute supratherapeutic doses, repeated dosing above the therapeutic range appeared to produce fewer effects, suggesting that tolerance to these effects develops during repeated dosing with benzodiazepines.

2. Effects in anxious and insomniac subjects. In several recent studies, the effects of benzodiazepines in anxious subjects were examined. In two studies (Galuszko, 1988a,b), 30 mg of diazepam were administered in three divided doses during 1 d, and the effects on performance were assessed the following morning. Both reaction time and visual-motor coordination were adversely affected. In another study, Sakol and Power (1988) examined discontinuation of benzodiazepine medication (primarily diazepam) in anxious subjects who were selected for the study on the basis of reported difficulty in stopping their medication. Before any reduction in dose, the subjects had significantly poorer performance on measures of choice reaction time and on a vigilance task, as compared with a group of normal controls. Tapping rate was similar in the two groups of subjects before dose reduction. As the dose was reduced in the anxious patients, performances became similar to those of the controls. These data suggest that chronic benzodiazepine treatment adversely affected performance in the anxious subjects. However, in an abstract, Lucki et al. (1990) reported that anxious subjects treated chronically with alprazolam were affected less by an acute dose of alprazolam than normal subjects, suggesting tolerance to the effects in patients using this drug.

Lader (1987a; see also Golombok et al., 1988) attempted to assess the toxic effects on cognitive function of chronic benzodiazepine exposure. Three groups of anxious subjects were compared. The first group was currently taking medication, the second had taken these drugs for at least 1 yr but had not taken them for at least 6 mo prior to inclusion in the study, and a third had never taken these drugs or had taken them in the past for less than 1 yr. A global measure of benzodiazepine intake was calculated for each subject by multiplying the duration of time for which the subject had taken a drug with its dose and summing use of all benzodiazepines for

TABLE 5

*Tolerance to effects of therapeutic doses on psychomotor performance**

Reference	Drug	Dose (mg/d)	Days	CFF	TAPP	DSST	TRAC
Smith and Kroboth, 1987	Alprazolam	1	4			NE	
Smith and Kroboth, 1987	Alprazolam	4	4			NE	
Smith and Kroboth, 1987	Alprazolam	4	4			NE	
Subhan et al., 1986	Alprazolam	1.5	6	NE			NE
Schaffler and Klausnitzer, 1989a	Bromazepam	6	7				
McKay et al., 1989a	Clobazam	20	8	NE			
Mattila, 1988	Diazepam	20	8	NS	D	D	NE
Mattila and Mattila, 1989	Diazepam	20	8	NE		D	NE
Brosan et al., 1986	Diazepam	25	21				D
McLeod et al., 1988	Diazepam	15	42			D	
Ghoneim et al., 1986	Diazepam	h.s. 14–21†	21		D		
Eves and Lader, 1989	Diazepam	10	4	D	NE	D	
Mattila et al., 1987	Diazepam	15	7	D		D	D
Altamura et al., 1989a	Lorazepam	3	3				
Subhan et al., 1986	Lorazepam	6	6	NE			D
Aranko and Mattila, 1986	Lorazepam	2	7	D			
Ghoneim et al., 1986	Oxazepam	h.s. 56–84‡	21		D		
Residual effects							
Jurado et al., 1989	Alprazolam	0.5	7				
Krueger, 1986	Brotizolam	0.25	3				NE
Mattila et al., 1987	Diazepam	15	7	NE		D	D
Krueger, 1986	Flurazepam	30	3				D
Roehrs et al., 1986a	Flurazepam	30	9			NE	
Higgitt et al., 1988	Ketazolam	30	15			D	
Jurado et al., 1989	Lorazepam	2	7				
Higgitt et al., 1988	Lorazepam	2.5	15			D	
Godtilibsen et al., 1986	Midazolam	15	7		NE		NE
Agnoli et al., 1989	Nitrazepam	5	14				
Godtilibsen et al., 1986	Nitrazepam	5	7		NE		NE
Schaffler et al., 1989	Quazepam	15	21				D
Roehrs et al., 1986a	Temazepam	30	9			NE	
Higgitt et al., 1988	Triazolam	0.5	15			NE	

* Entries represent whether the dose comparison indicated a decrement (D) or no effect (NE) on performance. See text for further details. References to individual studies are given in "Appendix." Abbreviations are as described for table 2, with the following additions: STRO, Stroop test; Time est, estimation of the passage of time; PEG, peg board (fitting pegs into appropriate holes).

† For the first 15 d, 14 mg; for 7 d thereafter, 21 mg.

‡ For the first 15 d, 56 mg; for 7 d thereafter, 84 mg.

that subject. This measure of benzodiazepine intake was correlated with outcome on seven of 23 performance measures. Anxiety scores and performance were correlated with outcome on three of the 23 performance measures. There was no significant difference in performance scores, however, between the subjects currently taking benzodiazepines and those who had ceased taking similar amounts of these drugs; however, this comparison was possible only for subjects with a relatively low cumulative benzodiazepine exposure. There was also no difference between subjects who had never taken these drugs and those who had ceased drug use.

Lader concluded that low doses of benzodiazepines taken for a short time have few, if any, cumulative effects; this conclusion appears appropriate. However, his conclusion that a "high intake is most certainly harmful" seems premature, because he did not compare results from subjects exposed to high doses with results from drug-free subjects. This conclusion would require extensive comparisons of individuals exposed to benzodiazepines on a long-term basis and controls appropriately matched on several parameters, including demographic and psychiatric variables.

Johnson et al. (1987) examined effects of repeated doses of benzodiazepines on psychomotor performance in subjects suffering from insomnia. They studied the effects of 0.25 and 0.5 mg of triazolam during consecutive nights on sleep and on the the subjects' response to an alarm. During the first night, there was a significant improvement in sleep and a reduction in the arousing effects of the alarm. Over five nights of treatment, tolerance developed to the effects of triazolam on the responsiveness to the alarm, whereas the drug's sleep-inducing effects did not change significantly.

The effects of bedtime administration of flurazepam (15, 30, and 45 mg) and midazolam (15 mg) for 2 wk were examined in a series of studies (Judd et al., 1990; Moskowitz et al., 1990; Moskowitz and Chen, 1990). The lowest dose of flurazepam was without residual effects throughout the treatment period, whereas the two higher

TABLE 5—*Continued*

RT	CRT	CANC	ARITH	SORT	DV-ATT	COPY	STRO	Time est	PEG	Notes
	NE									
D										
	I									
	NE									
NE	NE									Tested with 15 mg
							D			
NE	D									
			D	D					NE	
D						NE				NE on articulation
	D									
D										
	D									
					NE					Tested with 3 mg
			D	D					NE	
NE								NE		
NE										
	D									
D										
NE	NE				NE					
		D				NE				
D								NE		
		D				D				NE for COPY-day 8
		NE		NE		D			D	
					D					
		NE		D		NE			D	
	D									
NE	NE				NE					
		NE				NE				

doses affected performances on several tests throughout the treatment period. In contrast, midazolam produced no effects throughout the treatment period.

3. Effects in elderly subjects. Results of epidemiological studies indicate that the elderly take proportionately more benzodiazepines than does the population younger than 50 yr. As observed in our previous review, older people are also more likely to take these drugs chronically, and there is evidence that the elderly are more sensitive to the effects of benzodiazepines than are younger people.

The immediate effects of benzodiazepines on the performance of elderly subjects have been examined in several recent studies. Nikaido et al. (1987) examined the effects of diazepam at doses of 5, 10, or 15 mg in subjects averaging 68.6 yr of age. The two lower doses had no effects on performances on DSST, tracking, and body sway. Both 10- and 15-mg doses affected choice reaction time, and all of the measures were affected by the highest dose. Performance decrements on different psychomotor tests were shown in elderly subjects after administration of lorazepam (Sunderland et al., 1989), triazolam (Nikaido et al., 1990; Fisch et al., 1990; Greenblatt et al., 1991), and alprazolam (Kroboth et al., 1990; Hart et al., 1991; Nikaido et al., 1990). Effects of 0.25 mg of triazolam on tracking, DSST, body sway, or sedation lasted longer in elderly than in younger subjects (Nikaido et al., 1990; Greenblatt et al., 1991). This dose affected pursuit tracking in elderly subjects but not in younger subjects (Fisch et al., 1990).

Greenblatt et al. (1991) examined triazolam plasma levels in younger (average age 30 yr) and older subjects (average age 69 yr); the older subjects had higher plasma levels, due to reduced clearance of the drug. Triazolam produced greater decrements in performance on the DSST, and observer-rated sedative effects were greater in the older subjects; both effects were related linearly to plasma triazolam concentrations. Because the relation

was similar in the older and younger subjects, the differences in effects in the two age groups reflected a pharmacokinetic rather than a pharmacodynamic difference.

No effects on DSST or a vigilance task were reported on the first and 14th days of administration of 0.25 mg of alprazolam three times per day to elderly subjects (Hart et al., 1991). In contrast, Kroboth et al. (1990) reported effects of the same alprazolam-dosing regimen on DSST, sorting, and a vigilance task during 4 d of treatment of elderly subjects.

Effects of benzodiazepines administered in the evening on early morning performance have also been examined. In subjects from 60 to 72 yr of age, 0.25 mg of brotizolam had residual effects on DSST and divided attention tasks. After 2 wk of treatment, these effects were not evident, although effects on tracking and body sway were observed. There were no effects at either time on performance on a vigilance task (Mamelak et al., 1989). Reaction times of subjects aged from 62 to 92 yr on the mornings after ten nights of treatment were affected less by lorazepam (1 mg) than nitrazepam (5 mg); there was no placebo control (Lundsgaard and Matzke, 1989). Flurazepam (30 mg) affected elderly subjects' next-morning performance on card-sorting and pegboard tests in the second week of nightly treatment; there were no effects on DSST or solving of simple arithmetic problems. Triazolam (0.125 mg) was without effects throughout the treatment period. Because effects of flurazepam were observed in the second week only, the data suggest that the effects were due to an accumulation of drug during the treatment period (Woo et al., 1991).

In an epidemiological study reported in abstract form, Bedry et al. (1990) examined 4000 elderly (65 yr or older) community residents in southwestern France. Using multivariate regression analysis with age, sex, depressive symptomatology, education level, and sensory (visual and auditory) impairment, these investigators found that benzodiazepine users generally scored lower on most behavioral tests. It was not clear from the abstract whether the score was a drug effect; a more complete presentation of this research will be necessary to evaluate the findings.

4. Effects in subjects with histories of sedative abuse. The effects of relatively high doses of benzodiazepines have been examined in subjects with histories of sedative abuse in several studies. These studies have shown effects on DSST and a variant of a tracking task (circular lights) following doses of diazepam from 10 to 80 mg (Funderburk et al., 1988, 1989; Roache and Griffiths, 1986, 1989a), doses of lorazepam from 2 to 9 mg (Preston et al., 1989a; Schneiderman et al., 1989; Funderburk et al., 1988; Roache and Griffiths, 1987a), and doses of triazolam of 2 and 3 mg (Roache and Griffiths, 1986, 1989a). Clorazepate (7.5 mg) was without an effect on DSST, tracking, or choice reaction time (Funderburk et al., 1989). In the absence of comparison groups in these studies, it is unclear whether any of these effects might reflect a sensitivity peculiar to this population.

5. Summary and discussion. Several types of effects on human psychomotor performance have been demonstrated after administration of single therapeutic doses of benzodiazepines. Studies of repeated administration show that these effects diminish over time. The effects on performance of benzodiazepines administered over longer periods have not been adequately studied. Although results of some studies suggested sustained decrements in performance or detrimental effects of long-term treatment, they cannot be regarded as conclusive and are subject to different interpretations. One study suggesting sustained impairment during treatment did not compare chronic users with an appropriate control group; however, the improvement obtained when the doses of benzodiazepines were decreased suggests at least that treatment does not incur irreversible harm.

In our previous review (see also McNair, 1973), we found that research had not demonstrated clear differences among the types of performance affected by the benzodiazepines. This finding applies also to the more recent literature. Other reviews (for example, see Wittenborn, 1978) have indicated that performances strongly contingent on speed of response may be affected more than other types of performance; the reports of studies reviewed here provided no evidence of this specific behavioral effect of benzodiazepines. The fact that these studies showed no clear differences among the types of performance affected by the benzodiazepines suggests either that these drugs do not have specific effects on the different types of behaviors tested or that the various experimental procedures used do not isolate types of behaviors that differ in susceptibility to alteration by these drugs.

In general, the results of tests of the effects of benzodiazepines on performance remain inconsistent; there is wide variation in findings regarding effects on similar tests following administration of therapeutic doses. The reason for this variability in findings is unclear. Presumably, variations in environmental conditions among the studies contributed to the differences in the effects observed.

C. Effects of Benzodiazepines on Recall

In our previous review (Woods et al., 1987), we reported that benzodiazepines have been found to produce marked deficits in the ability to recall previously learned material. This detriment was demonstrated following administration of most tested benzodiazepines, with the exception of clorazepate. In studies in which the effects of different doses were evaluated, the effect was typically found to increase with dose. One of the most consistently reported phenomena associated with benzodiazepine-induced memory deficits was that recall of stimuli presented minutes, hours, or weeks earlier (delayed recall)

was more impaired than was recall of stimuli that were presented recently (immediate recall). Another frequently reported finding was that benzodiazepine administration appeared to enhance recall of material learned prior to administration of drug if, following administration of drug, other material was presented for later recall. This retrograde facilitation most likely reflected the anterograde amnesia produced by benzodiazepines: Because subjects did not learn material presented after benzodiazepine administration, this material did not interfere with remembering information learned prior to drug administration. Both of these processes, retrograde facilitation and a time-related anterograde amnesia, appear to reflect direct effects of benzodiazepines on memory processes.

Attempts to separate the sedative effects of benzodiazepines from their effects on recall were not conclusive in earlier studies but have been evaluated to a greater extent in recent years. Experiments using the benzodiazepine antagonist flumazenil, as well as studies using chronic benzodiazepine administration, have contributed information regarding a differential effect of benzodiazepines on recall. In several recent studies, investigators have evaluated the effects of benzodiazepines on acquisition of material and whether these drugs have differential effects on recall in elderly subjects or in anxious or insomniac patients as compared with young, healthy subjects. In a number of studies, the recall-impairing effects of several benzodiazepines have been compared; however, despite the frequent finding of apparent differences among some of these drugs in their amnestic effects, the fact that these studies generally lacked appropriate potency comparisons makes it premature to draw conclusions about the drugs' relative effects.

A thorough and useful review of the literature from 1973 to 1985 concerning the effects of benzodiazepines on human recall was published by Curran (1986). It covers much of the information included in our previous review and supports many of the conclusions we drew there.

In the following descriptions, drugs were administered orally unless a different route of administration is specified.

No memory-impairing effect of benzodiazepines was found in a few recent studies. Diazepam (15 mg) did not impair immediate reverse recall of ten digits or a paired-associate task when tested 2 h (Mattila et al., 1987) or 1.5, 3, 4.5, and 6 h (Mattila et al., 1989) following drug administration. Blom et al. (1990) found that alprazolam (1 mg), quazepam (15 mg), and diazepam (10 mg) did not impair a memory-scanning test given 1.5 and 2 h following drug administration. Oxazepam (15 mg) did not impair immediate recall of words presented 2 h after drug ingestion, and nitrazepam (5 mg) did not impair immediate recall of words presented 1, 2, 5, or 10 h following drug administration. Delayed recall of previously presented words during the 10-h test period was also not impaired (Currie et al., 1990). Flurazepam (15 mg), lormetazepam (1 mg), or triazolam (0.25 mg) did not differ from placebo in effects on a fairly difficult memory-spanning task (Griffiths et al., 1986).

1. Effects of acute dosing in normal volunteers. a. IMMEDIATE VERSUS DELAYED RECALL. Measures of immediate and delayed recall, at their simplest, involve presenting subjects with a list of perhaps eight to 12 words, asking them to repeat the words immediately after they have been read or shown (immediate recall), and then requesting recall again, after a delay of minutes to hours (delayed recall). Occasionally, different word lists are shown at different times after drug administration so that the onset and offset of drug effect can be estimated. In these studies, the delayed recall request is usually made at the end of a session in which several word lists were presented for immediate recall. This design can be informative because, if words presented and recalled at a certain time after drug administration fail to be recalled at the end of the session, this indicates the time course of the amnestic effect of the drug; unfortunately, the data are rarely reported in such a way that such information might be derived.

The recall task is not always of word lists; subjects are sometimes asked to perform tasks following drug administration and then are asked to remember later what the tasks were. They may be shown pictures and later asked to recall and/or recognize the pictures that were shown. There are some standard tests of memory. One is the Sternberg memory-scanning task, in which subjects are requested to remember one, two, or three digits; they are then shown a series of 20 digits and asked to indicate which of these are the digits they were asked to remember.

The observation that benzodiazepines have a considerably greater effect on delayed as opposed to immediate recall was made in many of the studies discussed in our previous review. These findings have been substantiated in recent literature. Diazepam (0.2 mg/kg) impaired verbal recall of visual material 24 h, but not immediately, after it was shown (Black and Barbee, 1987). Midazolam (7.5 or 15 mg), taken at bedtime, impaired recall of specific tasks performed 2 h after drug administration if recall was requested upon awakening in the morning; only the larger dose produced memory decrements if recall was requested immediately after the tasks were performed (Borbely et al., 1988).

Langlois et al. (1987) evaluated the effects of midazolam (15 mg), given by both the i.v. and oral routes, on immediate and delayed recall of word lists. Lists were presented for recall prior to, and at 45 min, 90 min, and 12 h following, drug administration. Immediate recall was requested following presentation of each word list, and delayed recall of each prior word list was requested 45 min later. Immediate memory, evaluated at 45 and 90

min after drug was given, was impaired to the same extent regardless of the route of administration. Delayed recall was also equally impaired by either route and was impaired more than immediate recall. By 12 h following drug administration, scores had returned to those obtained at placebo levels.

Lorazepam (2 mg) produced an impairment in immediate recall of word lists and an even greater impairment in delayed recall requested 10 min later (Curran et al., 1987). It also produced retrograde facilitation—increased recall of word lists shown prior to drug administration, a common finding with benzodiazepines.

There was no effect on immediate recall 3 h after administration of diazepam (15 mg); delayed recall requested 30 min later was impaired (Eves and Lader, 1989). Flunitrazepam (2 mg) impaired both immediate recall of words and delayed (30 min) recall of pictures when the drug was given in the evening and testing was conducted the next morning (Bensimon et al., 1990).

Kroboth et al. (1987) administered triazolam (0.25 mg) at 10:30 p.m. and presented a picture and a color to be remembered at 12:30 a.m. Another picture and color were shown at 8:30 a.m., and recall of all items was requested at 2 p.m. The drug impaired recall of items shown at 12:30 but did not impair recall of items shown at 8:30, suggesting that the amnestic effect of this dose may not last longer than 10 h.

Triazolam (0.25 mg), given 2 h prior to showing a set of 12 pictures, impaired recall of the pictures 30 min later. Recall of different pictures shown 6 h following drug administration was not impaired 30 min after they were shown. Immediate recall of paired words, presented only once, was also impaired at the 2-h but not the 6-h evaluation period (Warot et al., 1987).

Infrequently, benzodiazepines were found to impair more immediate recall but not delayed recall. Linnoila et al. (1990a) gave subjects a battery of tests, one of which required them to indicate, during the reading of a list of words, which words were duplicates. They were asked to recall 1 min later as many of the words as possible. Two hours after administration, 30 mg of adinazolam, but not 15 mg of adinazolam or 10 mg of diazepam, impaired the subjects' ability to identify the repeated words; there was no significant impairment on 1-min delayed recall.

b. COMPARISONS OF DIFFERENT BENZODIAZEPINES. The impairment of recall produced by different benzodiazepines has been compared in several studies. Klein et al. (1986) reported that triazolam (0.5 mg) and flunitrazepam (1 mg) but not loprazolam (1 mg) produced amnesia for verbal material. These doses of triazolam and flunitrazepam also produced impairment in psychomotor tasks and unpleasant side effects, although loprazolam had none of these effects; thus, it seems likely that the test dose of loprazolam was lower than those of the other two benzodiazepines rather than that loprazolam has less effect on recall of learned material.

Curran et al. (1987) found that 2 mg of lorazepam produced a more pronounced deficit in immediate recall of word lists than did 1 mg of lorazepam or oxazepam (15 or 30 mg). Both doses of oxazepam and the 2-mg dose of lorazepam impaired delayed recall of the word lists at the end of the day. The larger dose of lorazepam also produced profound impairment of delayed recall of "news items" read to the subjects 1.5 and 3 h after drug administration (the delay was not specified but was probably relatively brief); at 1.5 h, subjects who had received 2 mg of lorazepam could recall practically nothing of the news item. The two drugs did not differ in their effects on other nonrecall tasks or the amount of drowsiness reported on subjective mood scales.

Scharf (1988) studied the effects of triazolam (0.5 mg) and temazepam (30 mg) on immediate and delayed recall of lists of ten words. Triazolam was tested in normal and insomniac subjects; temazepam was evaluated only in insomniac subjects. Neither drug impaired immediate recall either 30 min or 8.5 h after administration. Temazepam also had no effect on delayed recall of words; triazolam, on the other hand, impaired recall of words presented 13.5 or 5 h earlier. Triazolam also enhanced recall of words presented 30 min before drug administration in the insomniac subjects.

Insomniac patients were given triazolam (0.5 mg), temazepam (30 mg), or placebo on four consecutive nights and then on one or two of the next four nights (Bixler et al., 1991). Subjects were tested 30 min after awakening on immediate recall of word lists; they were asked to recall these words again that evening. In agreement with Scharf (1988), Bixler et al. (1991) found no impairment by either drug of immediate recall of word lists, but triazolam produced a significant impairment of delayed recall compared with the placebo group. Interestingly, subjects who had received triazolam showed significantly better delayed recall than either the placebo- or temazepam-treated subjects during the drug withdrawal period.

Dye et al. (1989) administered lormetazepam (1, 1.5, or 2 mg), triazolam (0.5 mg), or placebo to ten subjects in a crossover design. The drugs were given 90 min before the subjects went to bed. Immediate recall of word lists was tested 1 h following drug administration; upon arising the following morning, subjects were tested for delayed recall of lists learned at bedtime and were evaluated with the Sternberg memory-scanning task. Lormetazepam (1.5 mg) and triazolam (0.5 mg) produced a deficit in the immediate recall of word lists; all doses of lormetazepam and the 0.5-mg dose of triazolam produced a deficit in delayed recall. The Sternberg memory-scanning task was significantly impaired only by the two larger doses of lormetazepam; the deficit produced by triazolam approached but did not reach statistical signif-

icance. These data support earlier findings that benzodiazepines produce a greater deficit in delayed recall than in immediate recall tasks and also indicate that lormetazepam, and to a lesser extent triazolam, in the doses evaluated, can affect memory skills 10 h after administration.

In a comparison of the effects of diazepam (0.3 mg/kg) with those of oxazepam (1.2 mg/kg) or placebo, Mewaldt et al. (1986) evaluated immediate and delayed recall of 20-word lists throughout a 9-h test period. Both drugs impaired immediate recall during the 3 h following drug administration. The drugs had no significant effect on recall of previously presented lists at the end of the 9-h period, probably because the placebo group did extremely poorly on this task as well. This is one of the very few studies in which delayed recall appeared less impaired than immediate recall by benzodiazepines.

A 20-mg dose of clobazam was compared with a 2-mg dose of clonazepam in a battery of tests that included a Sternberg scanning test of memory (van der Meyden et al., 1989). Clobazam produced no change in performance on this task or on any of the other measures, including alertness. Clonazepam produced a significant impairment in the scanning task and on several others.

A Sternberg test of memory given at 1.5, 3.5, and 5.5 h following drug administration was also used by McKay et al. (1989a) to evaluate clobazam in comparison with lorazepam (1 mg). Lorazepam produced a profound deficit compared with placebo at the 1.5- and 3.5-h testing periods. The effects of clobazam could not be distinguished from those produced by placebo administration. When a second 10-mg dose of clobazam (10 mg) was given 3.5 h after the first, the drug was reported to significantly improve memory (McKay et al., 1989b). However, the data presented in the report were not explained, difficult to interpret, and extremely variable; this finding should be followed up more rigorously.

Results of these studies suggest that some benzodiazepines, e.g., lorazepam, flunitrazepam, and triazolam, may impair recall more than other benzodiazepines, e.g., clobazam, clonazepam, oxazepam, temazepam, and loprazolam. Although this is a very interesting observation, of potential use to clinicians who may wish to enhance or minimize the amnestic effects of benzodiazepine medication, it is still premature to consider such a generalization as definitive. In many of the studies described here, various benzodiazepines were tested in doses that were assumed to be equally potent because they were recommended therapeutic doses or constant fractions of the recommended therapeutic doses; these are not satisfactory bases on which to establish dose equivalence. Ideally, studies should include determinations of the effects of a range of doses of the benzodiazepines on some task that does not involve recall ability, as well as on a measure of recall ability; if the dose-response curves have different positions in the two measures (e.g., are 1 log unit apart on the nonrecall task but are 4 log units apart on the recall task), the proposition that they differ in their effects on recall becomes considerably more credible.

c. RETROGRADE FACILITATION. Although investigators have regarded retrograde facilitation of recall as a "paradoxical" effect of benzodiazepines, it continues to be a reliable effect of these drugs. In both of the studies described above in which recall of material learned prior to benzodiazepine administration was measured (Curran et al., 1987; Ott et al., 1988), this recall was found to be enhanced in subjects receiving drug. The degree of retrograde facilitation was proportional to the degree of anterograde amnesia; thus, retrograde facilitation would appear to be an effect of the drugs' suppression of retrograde interference by new material.

d. ACQUISITION. There is sometimes little difference between procedures purporting to study simple recall and those claiming to study acquisition. Measurement of acquisition involves giving subjects more than one exposure to the material to be recalled. This can involve simply presenting word lists several times or use of more standardized acquisition paradigms. A common acquisition task is the Buschke selective reminding task, in which word lists are presented and immediate recall is requested, much as in experiments described before. Words the subject fails to recall are presented again, with another request for recall. Forgotten words may continue to be presented for a certain number of trials or until the subject recalls a criterion number of words from the list. Another popular acquisition task is a paired associates-learning task. The stimuli—sometimes words, sometimes a name or picture of a person and an occupation—are presented in pairs. The subjects are requested to report one of the stimuli when its mate is presented, and the material is presented until a criterion level of learning is reached. A measure of repeated acquisition has been used to evaluate separately the effects of benzodiazepines on general performance and on acquisition of new information.

Benzodiazepine blood levels were determined in conjunction with tests of acquisition and immediate and delayed (24 h) recall of a word list, and with reports of sedative effects and mood, following oral administration of lorazepam (2 mg), alprazolam (1 mg), or prazepam (20 mg) (Greenblatt et al., 1988). The word list was presented six times, in different sequences, starting 3 h after drug administration. Immediate recall was requested after each presentation of the list, and the number of words recalled was scored. The pharmacokinetic profile of the three drugs was similar. The peak sedative effect of alprazolam was somewhat more rapid and greater than that of the other two drugs. At the time that acquisition and immediate recall were evaluated (3 h after drug administration), plasma concentrations of benzodiazepines were slightly below peak for each of the drugs, and

self-rated measures of sedation were high and nearly the same for those receiving active drug. Deficits in number of words learned under conditions of immediate recall were found for each of the drugs but were significant only for lorazepam. Deficits in delayed recall of the word list at 24 h were reported for both lorazepam and alprazolam.

The effects of flurazepam (15 mg), temazepam (15 mg), and triazolam (0.25 mg) (Greenblatt et al., 1989) were compared in a similar study. Triazolam's peak sedative effect had developed at 1 h and remained elevated but no longer significantly different from baseline at 3 h. Sedative effects of temazepam peaked at 2 h after administration and were significantly different from baseline at 4 but not at 6 h following administration. Although plasma levels of desalkyl flurazepam were elevated and unchanged across the 24-h measurement period, sedation scores were much lower than those reported with the other two drugs and had returned to baseline levels 4 h following drug administration. At the time recall was assessed, 3 h after drug administration, ratings of sedative effects of triazolam and temazepam had decreased markedly from their peaks. Average sedative ratings for temazepam and flurazepam were nearly identical; those for triazolam were slightly lower. None of the three treatments produced impairment in immediate recall and acquisition of the word list. When recall was again requested 24 h later, subjects who received active drugs remembered fewer words than those receiving placebo. Triazolam's effects were the largest and were themselves significantly greater than effects produced by placebo.

Ott et al. (1988) evaluated immediate (10 s) and delayed (30 min) recall of different word lists presented prior to and at four times after administration of flunitrazepam (2 mg) or lormetazepam (1 or 2 mg). A Buschke selective reminding task was used for a criterion of five trials. Each of the drug treatments produced a decrease in recall requested 30 min after word list presentation at each of the four times. The placebo group also showed a marked decrement over time, an effect that was not easily interpreted and not discussed in the report. None of the ten subjects to whom ten words were read 1.5 h after ingestion of flunitrazepam (2 mg) were able to recall a single word when asked to do so 30 min later.

Patat et al. (1987) used a similar procedure to study the effects of oral lorazepam (2 mg), diazepam (10 mg), clobazam (20 mg), and placebo. A Buschke selective reminding task was used, in which word lists were presented ten times. In addition to the immediate recall that is necessary in a selective reminding task, delayed recall of the word lists was requested 8 and 24 h after they were presented. In general, the data reflected only slight differences between each of the benzodiazepines and placebo across most of the ten presentations of the word list. Statistically significant differences were noted between lorazepam and placebo only after the first presentation and between diazepam and placebo after the seventh, eighth, and ninth repetitions and the delayed recall at 24 h. Diazepam, therefore, was reported to have a uniquely deleterious effect on long-term storage and long-term retrieval and to produce a greater amnestic effect than lorazepam. The data for clobazam were interpreted as suggesting no effect of this drug on recall.

The effects of lorazepam (1 and 3 mg) and of clobazam (10 and 30 mg) were evaluated using a Buschke selective reminding task, given 2 and 2.5 h after drug administration (Patat et al., 1991). The larger dose of lorazepam produced the most profound impairment of word recall. Both 1 mg of lorazepam and 30 mg of clobazam produced only slight deficits. The 10-mg dose of clobazam was ineffective. Clobazam also did not impair performance on a number of psychomotor tasks, whereas lorazepam had marked effects on these tasks. This led the authors to conclude that lorazepam has much more profound amnestic and sedative effects than clobazam, which has no amnestic effects when given at doses equipotent to those of lorazepam. Unfortunately, no data were presented to demonstrate that the two drugs were given in doses that were in any way equipotent; in fact, lorazepam was clearly given in considerably larger effective doses than was clobazam.

A similar acquisition procedure was used by Shader et al. (1986) to evaluate the effects of lorazepam (1.5 or 3 mg) on learning and recall. Three h after oral drug administration, subjects heard a list of 16 words and were asked to write the words immediately after all were read. The same list was read five more times, each time in a different order, and written recall was requested after each reading. Subjects were asked to recall as many of the words as possible 24 h later; finally, the acquisition phase was repeated for another six trials. A larger deficit in recall after the initial six presentations was shown following ingestion of 3 mg of lorazepam than following ingestion of 1.5 mg of lorazepam. The deficit produced by the smaller dose was greater than that shown following placebo. When recall was assessed at 24 h, both doses of lorazepam produced nearly the same degree of deficit, even greater than that shown by either dose after six learning trials. The subjects given lorazepam relearned the information at the same rate at which they had originally learned it (i.e., there was no savings). Virtually no decrease in recall was shown by the subjects 24 h after they had been given placebo. Thus, the authors concluded that oral lorazepam depressed both acquisition and recall. These data also support earlier research indicating that benzodiazepines produce a greater deficit in delayed as opposed to immediate recall.

Lormetazepam (2 mg) did not impair the initial learning of a list of words using the selective reminding task, but it did impair recall of the words 2 h after learning (Deijen et al., 1989).

In a paired-associates-learning task given 4.5 h after drug administration, lorazepam (2.5 mg) but not diazepam (15 mg) impaired acquisition (Mattila et al., 1988a). Deijen et al. (1989) paired names with occupations and gave subjects three trials to learn the association; 2 h later, a delayed recognition of the names was requested. Lormetazepam (2 mg) impaired both initial learning of the associates and delayed recognition of the learned task.

A procedure that entails repeated acquisition of behavioral chains has been used successfully to measure the effects of drugs on learning in animals. As adapted to human studies by Higgins et al. (1987), the subject is required to perform a ten-response sequence, in which each response consists of pressing keys labeled 1, 2, or 3 on a numeric key pad in response to the appearance of the numbers 0 through 9 on a video screen. If an error is made, the screen goes blank for 2 s, and then the number on which the error was made reappears, so the subject can try again to make the response appropriate for that number. When the sequence is completed correctly, a point is added to a total appearing at the top of the screen, the number returns to 0, and the response sequence is repeated.

There were two components of this schedule, one a performance component, indicated by a green background on the screen, in which the subject repeated a sequence that he or she had learned at some time in the past. A red background indicated a novel ten-response sequence for that particular session. The red and green backgrounds alternated for a total of 20 trial or 15 min.

Subjects received oral doses of 0 (placebo), 10, 20, or 40 mg of diazepam, given 85 min prior to a session. The 20-mg dose produced a selective increase in errors in the acquisition portion of the schedule; the 40-mg dose increased errors in both the acquisition and the performance components, although errors in acquisition greatly exceeded errors in performance at the larger dose. One of the ten subjects appeared to make no progress at all in acquiring the novel response sequence following the 40-mg dose.

Much larger doses were used in this study than those typically used in experimental situations. Nevertheless, the finding that diazepam impairs acquisition to a greater extent than it impairs performance is consistent with the results of other studies. Similar dose-related differential effects on acquisition as opposed to performance were reported by Bickel et al. (1990) for diazepam (10, 20, and 30 mg/70 kg), alprazolam (1, 2, and 3 mg/70 kg), and triazolam (0.25, 0.5, and 0.75 mg/70 kg). All doses of diazepam and the two largest doses of triazolam produced significant effects on acquisition. This information was not presented for alprazolam, but its effects were described as similar in magnitude to those of triazolam. The maximum effect of diazepam was less than that of the other two benzodiazepines.

e. RECALL IN ELDERLY SUBJECTS. Many of the recent studies of the effects of benzodiazepines on memory function in the elderly are difficult to interpret because drug effects in both old and young subjects were not compared (Nikaido et al., 1987; Hindmarch et al., 1988), an effective dose of drug was not used (Sunderland et al., 1989), or sufficiently sensitive evaluation procedures were not used (Hart et al., 1991). The few studies that did compare effective doses in different age groups emphasized a point made by studies considered in our earlier review: Even in the absence of benzodiazepine administration, older people are more impaired than younger people in recall tasks. The ability of older subjects to recall information is impaired by benzodiazepines, but recent data suggest that this impairment is proportionally no greater than that experienced by younger subjects.

The effects of placebo or 0.2 mg/kg diazepam were compared in three age groups matched for health, education, and lifestyle characteristics (Hinrichs and Ghoneim, 1987). Subjects were exposed to a battery of tests prior to drug administration and 60 and 145 min following drug ingestion. Among the tests was a measure of immediate free recall of a list of 20 words. Delayed recall of the words on either the predrug or postdrug lists was requested 180 min following drug administration. There was an age-related deficit in the immediate free recall task prior to drug administration, with younger subjects recalling more items than middle-aged subjects, and older subjects having the greatest impairment. Diazepam produced a further decrement in recall that peaked at the 60-min postdrug evaluation time. Drug-induced impairment was proportionally no greater for the elderly than for the younger age groups. The deficits in delayed recall were sufficiently great for all age groups (on average, less than one item was recalled in all groups) to prevent comparisons among the groups. No mention was made of greater recall of items listed prior to drug administration as compared with those listed following drug administration. The authors concluded that diazepam and age do not synergize, but each acts separately, to decrease recall capacity. Nevertheless, because older subjects are relatively limited in their performance in the absence of drug administration, the addition of drug-induced impairment to this lower baseline may make drug effects more important in the elderly.

Pomara et al. (1989) compared the effects of placebo and two doses of diazepam (2.5 and 10 mg), given at weekly intervals, in healthy young (mean age 26.3 yr) and older (mean age 67 yr) volunteers. Subjects were tested, using Buschke's selective reminding task, prior to and 1.5 and 3.0 h following drug or placebo administration. Results indicated that the performance of the elderly subjects in the recall task prior to drug administration was significantly worse than that of the younger subjects. The 2.5-mg dose of diazepam did not affect recall in either group of subjects, and the 10-mg dose

affected recall to approximately the same extent in each group. Interestingly, diazepam (10 mg) reduced the acquisition and recall ability of the younger subjects nearly to the level demonstrated by the older subjects prior to drug administration.

The effect of chronic diazepam administration was evaluated in both groups of subjects by administration of 2.5- or 10-mg diazepam capsules each night for 3 wk. At the end of this period, a further single dose of either 2.5 or 10 mg of diazepam was given, and the effects were evaluated 1.5 and 3 h later. This dose of diazepam continued to produce a substantial impairment of performance in the selective reminding task in both young and older subjects. The impairment was not as large for either group as had been shown during the acute phase of the experiment; this finding suggested the development of incomplete tolerance to the effects of diazepam.

The relation among sedative effects, mood changes, memory deficits, and plasma levels of triazolam was evaluated in young (21 to 41 yr) and older (62 to 83 yr) subjects by Greenblatt et al., 1991. Acquisition and recall were evaluated 90 min following administration of either 0.125 or 0.25 mg triazolam. A 16-word list was read to subjects six times; immediate recall of the words was requested after each reading. Subjects were asked to recall the words on the list 24 h later (delayed recall). The peak plasma concentration of each of the two doses of triazolam was greater in the older subjects, as was the area under the plasma concentration curve. Under placebo conditions, the younger subjects remembered more words from the list following both immediate and delayed recall tests than did the older subjects. There was a dose-related decrement in both immediate and delayed recall for the younger subjects, with delayed recall being more impaired. The same was true for the older subjects, but the proportional deficit following drug administration was not greater in the older subjects.

2. Amnestic versus sedative effects of benzodiazepines. Some attention has been paid recently to the question of whether the amnestic effects of benzodiazepines are related to or are independent of the sedative effects of these drugs. The issue was originally raised by studies discussed in our previous review. Roth et al. (1980) administered various benzodiazepines at bedtime and then woke the subjects 3 h later for recall tasks; recall was more impaired in the morning if the subjects returned to sleep quickly after performing the tasks. Roehrs et al. (1983) used a similar paradigm but required the subjects to remain awake for 15 min after performing the tasks. Forcing the subjects to remain awake seemed to attenuate the effects of the tested benzodiazepine (0.5 mg of triazolam) on recall of the tasks in the morning. This suggested that the sedative effects of the drugs were responsible, at least in part, for their amnestic effects.

As noted in the review by Curran (1991), there are several ways to evaluate this issue. One is to determine whether reversal of the drugs' sedative effects by flumazenil is accompanied by reversal of their amnestic effects. A second method is to determine whether tolerance develops to the same extent if amnestic and sedative effects of benzodiazepines are measured. The most direct way to evaluate the possibility that these effects are different is to compare the amnestic effects of equally sedative doses of different drugs—either benzodiazepines and nonbenzodiazepine sedatives or different benzodiazepines.

a. EFFECTS OF FLUMAZENIL ON THE RECALL-IMPAIRING EFFECTS OF BENZODIAZEPINES. The issue of whether flumazenil will antagonize the effects of benzodiazepine on memory tests has been examined most frequently in the context of whether the effects of benzodiazepines on recall ability are mediated through a different mechanism than are the effects on other tasks and skills. O'Boyle et al. (1983) reported one of the earliest studies of the interaction between a benzodiazepine and flumazenil. Effects of diazepam (20 mg) alone, diazepam (20 mg) given at the same time as flumazenil (200 mg), or placebo, all given orally, were measured on several psychomotor tasks, on a VAS of mood, and on a triple-associate acquisition task 1 h after drug administration. Training and testing on the acquisition procedure alternated until at least four items were recalled correctly three times. Immediate recall was indicated by the responses on the first trial. Learning was demonstrated by the number of words correct during four trials. Delayed recall was measured 30 min later, when subjects were asked to recall as many of the words as they could and were then prompted as in the original training procedure.

Diazepam (20 mg) slowed learning of the associated words relative to placebo, although immediate recall was not significantly impaired by this dose in this task. The group given flumazenil with diazepam did not differ significantly from the placebo group in acquisition of the word associations; flumazenil also antagonized the effects of diazepam on psychomotor performance and on mood. Thus, no difference in mechanisms for the amnestic, psychomotor, and sedative effects of diazepam was indicated in this study.

Hommer et al. (1986) administered flumazenil (0.035 mg/kg i.v.) or placebo prior to cumulative i.v. doses of diazepam (to 0.2 mg/kg). Diazepam alone produced changes in levels of sedation, anxiety, and attention, as well as impairment of recall of an unspecified verbal learning task. The prior administration of flumazenil reduced the effects of diazepam on sedation, anxiety, and attention but had no effect on diazepam's impairment of recall. These findings suggested that the recall-impairing effects of diazepam might be mediated by mechanisms other than those associated with the other observed effects of the benzodiazepine.

Birch and Curran (1990) studied the interaction between midazolam and flumazenil in patients undergoing

an inpatient surgical procedure. Patients were given midazolam (4 to 10 mg, depending on weight) i.m. prior to surgery and either placebo or flumazenil (0.5 or 1.0 mg, depending on effect) i.v. following surgery. Patients were evaluated for memory impairment using a test of immediate and delayed (end of test session) recall of word lists. Psychomotor tasks of tapping and choice reaction time were used for comparison and as indicators of sedation. Testing was carried out 15, 60, 120, 240, and 360 min following flumazenil administration. The graphic display of the results indicated that midazolam had a marked effect on both the psychomotor tasks and on immediate and delayed recall. Flumazenil at the dose tested appeared to produce a slight antagonism of all of the effects of midazolam; this antagonism was most marked 15 min following administration of the antagonist. The authors emphasized that flumazenil produced a significant attenuation of midazolam's impairment of the psychomotor task but did not produce a significant block of midazolam's effects on recall; they believed that these data supported the possibility that these two effects are mediated by different subtypes of benzodiazepine receptors. However, although the graphed data do not include measures of the variability of the obtained scores, they show a very similar pattern and degree of interaction between flumazenil and midazolam on measures of both recall and psychomotor effects. The differences do not appear sufficiently large to suggest different mechanisms or receptor subtypes.

The same issue developed in a study by Curran and Birch (1991) on the effects of midazolam in volunteer subjects. The subjects were given i.v. midazolam during two separate test sessions at a dose (4 to 11 mg) sufficient to produce slurred speech and ptosis. During one of the test sessions, midazolam administration was followed by i.v. administration of 0.5 mg flumazenil. Subjects were evaluated for recall impairment with an immediate-recall-of-word-lists task and for delayed recall of all words at the end of the test session. Different word lists were presented prior to drug administration, 15 min after midazolam administration, and at 10 and 60 min following flumazenil or placebo administration. Subjective estimates of sedation were made, and a number of psychomotor tasks were given at these times as well to provide indications of sedation.

In general, the results indicated that midazolam alone had a relatively short duration of action that was further abbreviated by the administration of flumazenil. There was a significant antagonism by flumazenil of the effects of midazolam on psychomotor tasks and measures of alertness at both the 10- and 60-min post-flumazenil test times; the antagonism was significant for the immediate recall task only at the 10-min post-flumazenil test time, a finding that the authors minimized on a statistical basis. Flumazenil did not antagonize midazolam's effect on delayed recall, but the authors did not indicate whether midazolam had any effect on delayed recall. The authors again suggested that the amnestic effects of midazolam may be mediated through a different receptor than those responsible for the sedative effects of the drug, but in the absence of a more thorough dose-effect curve analysis of the effects of flumazenil, and in light of the data presented, this interpretation is questionable.

The ability of 0.01 mg/kg of flumazenil to antagonize the sedation and memory impairment produced by i.v. midazolam (2 or 5 mg) was evaluated by McKay et al. (1990). These investigators showed normal subjects a pair of cards on which common words were written; a different pair of words was shown prior to drug administration and frequently for 13 min following drug administration. Either saline or flumazenil was given i.v. 5 min following midazolam (or saline) administration. Subjects receiving midazolam showed profound, dose-related recall impairment for words shown following drug administration. Flumazenil produced nearly complete antagonism of this impairment. Level of sedation, as measured by critical flicker fusion frequencies, was also antagonized by flumazenil in parallel with the drug's effects on recall. The authors suggested that these two functions are mediated by the same receptor system.

In a practical approach to the use of flumazenil to antagonize benzodiazepine-induced amnesia, Ghoneim et al. (1989) gave dental surgery patients i.v. infusions of diazepam to the point of producing slurred and thickened speech and maintained this level with supplemental infusions. The patients remained responsive to verbal commands. Following extraction of third molars under local anesthesia, the patients were given incremental infusions of flumazenil or placebo, under double-blind conditions, until either sedation was reversed or 10 ml (0.1 mg/ml of flumazenil) had been administered. Subjects were given tests of immediate recall of words just prior to and at 30, 60, and 120 min following antagonist or placebo administration. Apparently, measures of delayed recall were taken at these times as well, although the report is not clear regarding what material was requested or what delay was imposed. Delayed recall of all material was requested 185 min following antagonist or placebo infusion. VAS measures of subjective mood were also taken at frequent intervals.

Diazepam produced reports of sedation and produced an average 54% decrease in immediate recall of the word lists that had been presented prior to antagonist administration. Delayed recall was considerably more impaired than immediate recall at each evaluation during the 120-min test period. Flumazenil produced an incomplete reversal of the both the immediate and delayed recall deficits produced by diazepam. The reversal was maintained at the same extent across 120 min, indicating that, as long as diazepam was having an effect during this time, flumazenil was able to partially reverse this effect. Flumazenil produced a marked reversal of subjective

ratings for 1 h following drug administration. At 120 and 180 min, the antagonism was no longer evident; at these later times, however, the subjective effects of diazepam had attenuated considerably. Ghoneim et al. interpreted these results as indicating that the memory-impairing effects of benzodiazepines are not dependent on their sedative effects, because they had a different time course.

In a similar study, Ochs et al. (1990) evaluated sedation (observer ratings and subjects' VAS reports) and recall (memory card recall) in patients prior to and following induction of anesthesia with i.v. midazolam. Patients were undergoing third molar extraction, and i.v. midazolam administration was titrated until ptosis and slurred speech occurred. If the patient was markedly sedated following surgery, either flumazenil (0.2 mg every minute until return to baseline levels of alertness or 1 mg had been given) or placebo (as much as 10 ml) was given i.v. Flumazenil produced a dramatic reversal of both patient and observer reports of sedation. It also attenuated the midazolam-induced impairment of recall of the memory cards. The reversal of midazolam's effects on recall appeared less than the attenuation of the sedative effects of the benzodiazepine.

Dorow et al. (1987) were also interested in evaluating the time course of flumazenil's antagonism of benzodiazepine-induced impairment of recall. Three treatment groups and one nondrug group were compared. Group 1 received i.v. placebo, followed 15 min later by i.v. flumazenil (0.03 mg/kg); group 2 received lormetazepam (0.02 mg/kg), followed by placebo; and group 3 received the same dose of lormetazepam, followed by flumazenil. Subjects were given immediate (20 s) recall tests of seven pairs of objects and two lists of words before and after each i.v. infusion. Delayed recall and recognition of the objects and words were tested 1 h after the end of the immediate recall session. VAS of mood were also used.

Nearly perfect scores were reached by all subjects prior to lormetazepam administration. This was true as well for the nondrug and the placebo group following the initial i.v. infusion. Lormetazepam produced marked decrements in immediate recall in groups 2 and 3. A gradual return to near-baseline performance in immediate recall was seen during the next 15 min, so that performance was approaching that of control at the time flumazenil was given. Nevertheless, following flumazenil administration, an abrupt return to pre-lormetazepam levels of recall was observed in group 3. There was a dramatic and sustained decrement in delayed recall and recognition in subjects receiving lormetazepam; this decrement was immediately reversed by flumazenil in group 3. Interestingly, words and objects that had not been recalled following lormetazepam were still not recalled in the delayed recall test following flumazenil.

Preston et al. (1989a) evaluated the effects of flumazenil on recall, attention, and sedative effects of lorazepam (2 mg) in healthy volunteers. Lorazepam was administered orally, 2 h before the i.v. administration of flumazenil (0.3, 1.0, or 3.0 mg). A variety of psychomotor tasks was used; a procedure of selective reminding, described before, was used to measure acquisition of verbal material. Subjective effects were reported on a VAS. Lorazepam impaired acquisition and recall of word lists. Flumazenil (0.3 mg) had little effect on lorazepam-induced impairment, but the two larger doses produced complete attenuation of lorazepam's effects. Lorazepam produced an increase in subjective ratings of sedation; these were reversed by flumazenil in a dose-dependent manner. Thus, the investigators found no evidence that the amnestic effects of lorazepam could be dissociated from the sedative effects of the drug by administration of flumazenil.

The issue of the relation between sedation and amnesia was raised again by Gentil et al. (1989) as they studied the effects of two antagonists, flumazenil and Ro 15–3505, on behavior impaired by flunitrazepam (2 mg). The agonist was infused i.v.; 10 min later, one of the antagonists or placebo was infused until the subject was alert, as measured by a CNS depression scale and EEG recordings, or until 2 ml of solution had been administered. The average final doses achieved were 5.3 mg of flumazenil and 2.1 mg of Ro 15–3505.

Subjects were evaluated on a battery of memory tasks, including recall of a short story 20 min after it was read aloud twice. Visual recall of a geometric figure was also requested 20 min after it was shown. Different versions of these tests were given prior to flunitrazepam administration and three times following antagonist administration. Flunitrazepam followed by placebo significantly impaired the ability to recall short stories or geometric figures. Both antagonists reversed these effects nearly completely, up to 295 min following agonist administration, at which time the effects of flunitrazepam had disappeared. The antagonists also reversed the effects of flunitrazepam on measures of sedation. The antagonist effects of Ro 15–3505 appeared to be slightly briefer than those of flumazenil, and the former antagonist had some inverse-agonist effects, including increased anxiety, fear, restlessness, and irritability, that were not reported after administration of flumazenil.

There is a discrepancy in reported findings as to whether flumazenil can selectively reverse the sedative effects of benzodiazepines while having less effect on benzodiazepine-induced impairment in recall. One problem in interpreting these findings is the difficulty of determining whether measures of sedation and measures of recall are equally sensitive to drug effects. If a sensitive measure of recall is used in a study using a relatively less sensitive measure of sedation, test results may be quite different from those that might obtain with more sensitive measures of sedation. However, the studies consistently indicate that flumazenil can reverse both effects.

The issue of whether the two effects are mediated through the same receptor could be decided most definitively through quantitative assessment of the ability of flumazenil to shift dose-response functions of recall impairment and sedation. If the amount of flumazenil-induced shift in the effect of benzodiazepines on recall is equal to the amount of shift by flumazenil of the effect of benzodiazepines on sedation, then the two effects are most likely mediated through the same receptor. The answer to this question does not directly address the issue of whether the sedative effects of benzodiazepines are responsible for the amnesia they produce, however. Even if the two effects are mediated through the same receptor system, one does not necessarily cause the other.

b. EFFECTS OF CAFFEINE ON THE RECALL-IMPAIRING EFFECTS OF BENZODIAZEPINES. Although caffeine does not act on the same receptor as do the benzodiazepines, it has been found to antagonize some of the effects of benzodiazepines. It has been evaluated for its ability to modify benzodiazepine-induced amnesia in several studies. Roehrs et al. (1988) evaluated the ability of 0, 4, or 8 mg/kg of caffeine to attenuate the ability of placebo or 0.5 mg of triazolam to produce sedation and impair recall or psychomotor performance. The recall task consisted of presentation of a string of digits and items and a request for immediate and delayed (2 h) recall. Triazolam impaired both immediate and delayed recall, as well as sedation as measured by sleep latency at the initiation of a 90-min nap. It also impaired psychomotor performance. The larger dose of caffeine attenuated the effects of triazolam on psychomotor performance, but neither dose of caffeine modified impaired recall or the decreased sleep latency produced by triazolam. The authors found these data to be consistent with their earlier hypothesis that the sedative effects of benzodiazepines are related to their ability to impair recall.

Roache and Griffiths (1987b) found that caffeine antagonized diazepam-induced increases in sedation but did not consistently reverse diazepam-induced impairment in recall. These investigators gave subjects either 0, 10, or 20 mg of diazepam, 0, 200, 400, or 800 mg of caffeine, or combinations of diazepam and caffeine and evaluated the effects of each dose alone on a test battery that included immediate recall of digit lists and delayed (3 h) recall of memorized pictures. The research staff and the subjects also rated the degree of sedation the drugs produced.

The results were curious in that the largest dose of caffeine had less effect in the test situations and less ability to reverse the effects of diazepam than did the two smaller doses. The 200- and 400-mg doses of caffeine produced some attenuation of the sedative effects of diazepam, as rated by the staff and subjects. There was a less consistent antagonism by caffeine of the immediate and delayed recall impairment produced by diazepam. The authors did not discuss their results in terms of a separation of the amnestic and sedative effects of benzodiazepines but noted that caffeine and diazepam appear to act through functionally opposing mechanisms. They also made an important point about studies with disparate results, i.e., that both the drug effects and the drug interaction effects are strongly dependent on the dose used and the type of test used to show the drug effect.

c. COMPARATIVE EFFECTS OF DIFFERENT DRUGS ON SEDATION AND RECALL. One of the most direct methods for determining whether the sedative effects of drugs can be differentiated from their amnestic effects is to compare the ability of several drugs to produce sedation and to block recall. Studies of this type have been done by comparing different benzodiazepines; these studies are described in section IV.C.1.c, together with other studies in which effects of different benzodiazepines on recall were compared. Other work has involved comparisons between benzodiazepines and other drugs with sedative effects. A few of these studies are models of appropriate experimental evaluation in that they compared drugs across a range of doses. Others used single doses, usually basing the choice on the stated therapeutic dose of the compounds to be tested. This is an unsatisfactory way to compare drugs; the results of single-dose studies cannot be taken as conclusive.

Among the studies comparing benzodiazepines with drugs from a different pharmacological class is that by Curran et al. (1991). These investigators compared i.m. scopolamine (0.3 and 0.6 mg) with oral lorazepam (2 mg) and placebo. Measures of sedation included psychomotor tasks and a subjective rating inventory. A battery of memory tasks was used, including a digit span task, a prose recall task, and a paired associates interference task; in this last task, subjects learned to associate pairs of words (A-B), were then given other words to associate with one of the pairs (A-C), and were asked to recall the second association (C) in response to presentation of the stimulus word (A). Oral lorazepam had a longer duration of action than i.m. scopolamine, and the larger dose of scopolamine produced more deficits than the smaller dose. Both scopolamine and lorazepam produced sedation and impaired most of the measures taken. The digit span was impaired only by the larger dose of scopolamine. A primary difference between the two drugs was in mood ratings of contentedness; lorazepam increased ratings of contentedness, and scopolamine decreased them. Analyses of covariance indicated that sedation indices covaried more with measures on the psychomotor tasks than with measures of recall ability, supporting the point made earlier by this group that sedation and recall can be dissociated.

The recall-impairing effects of midazolam were compared with those of the opioid butorphanol in patients undergoing elective surgery under general anesthesia

(Dershwitz et al., 1991). Nine treatment groups were studied using low, intermediate, or large doses of either butorphanol (7.1 to 71.4 μg/kg), midazolam (4.3 to 42.9 μg/kg), or a combination of both drugs (3.6 + 2.1 to 35.7 + 21.4 μg/kg, respectively). Measures of sedation included psychomotor tests and observer- and subject-rated VAS of mood. Recall was assessed by showing playing cards to the subjects both before and after surgery and requesting recall of the cards on the following day. Although butorphanol had a small but significant effect on recall, midazolam's effects on recall were profound. Interestingly, the combination of butorphanol and midazolam resulted in less effect than did midazolam alone. Except for the smallest dose of midazolam, all drugs and combinations produced increases in observer and subject ratings of sedation, and there appeared to be no qualitative difference between the sedative effects of the two drugs. Therefore, it would appear that pronounced amnesia is not an invariable consequence of sedation.

One of the best comparisons of the sedative and amnestic effects of two drugs was done by Kirk et al. (1990). This group compared a range of doses of triazolam (0.25, 0.5, and 0.75 mg) with a range of doses of pentobarbital (100, 200, and 300 mg) in seven male volunteers. Measures were taken of immediate recall when the stimuli (five 8-digit numbers) were presented for varying lengths of time (3, 6, or 9 s), and of immediate and delayed (15 s) recall of a single 8-digit number. Subject and staff ratings of the sedative effects of the drugs were taken as well. Comparisons were made of the area under the curve for each index, a measure that confounds degree of effect and time course but that may facilitate statistical comparisons. Both drugs produced dose-related decreases in area under the curve for all evaluations. The effects of pentobarbital were generally longer lasting than those of triazolam. There were no differences between the drugs in measures of psychomotor performance; triazolam was from 270 to 354 times more potent than pentobarbital in these tests. The drugs were also similar in the measures of sedation (subjective and staff ratings), although the largest dose of pentobarbital produced greater subjective ratings of sleepiness than did the largest dose of triazolam. Triazolam was 312 to 345 times more potent than pentobarbital in measures of sedation.

Both drugs produced impairment in immediate recall, but triazolam produced greater impairment than pentobarbital, because the smallest dose of triazolam but not the smallest dose of pentobarbital produced deficits in the most sensitive immediate recall task (3-s stimulus presentation), and the largest dose produced more disruption than pentobarbital in the least sensitive immediate recall task (9-s stimulus presentation). The graphic presentation of the data indicate that these differences were not large. The general pattern and degree of effect of the two drugs were similar. Triazolam was approximately 440 times more potent than pentobarbital in these measures of immediate recall.

The drugs produced greater impairment of recall when a 15-s delay was interposed between presentation of stimuli and requests for their recall. However, triazolam's effects on delayed recall were significantly greater than those of pentobarbital. Again, these difference were small. Triazolam was 647 times more potent than pentobarbital on the delayed recall task.

The authors suggested that these data indicate that triazolam may interfere with time-related retention in a way that pentobarbital does not and that the effects of triazolam are not simply disruptions of perception, acquisition, or psychomotor skills. They also suggested that triazolam may produce a greater recall deficit than does pentobarbital at equally sedative doses.

Investigators in each of the studies that have compared benzodiazepines with drugs from other pharmacological classes with respect to effects on recall have found that, at doses that are equally sedative, the benzodiazepines produce greater deficits in recall. In some cases, this difference is quite large; in other cases, it is relatively small. Although there are relatively few of these studies, the results thus far suggest that drugs that produce sedation are not necessarily drugs that impair memory. Results of these studies also imply that the sedative effects of benzodiazepines are not related to their effects on recall. This issue is less satisfactorily answered by studies of different drug classes, because sedation is probably not a single entity; sedation produced by opioids or scopolamine, for example, may have different characteristics than sedation produced by benzodiazepines. Subjects may be similar with respect to some aspects of sedation, such as sleep latency, but different with respect to others, such as ease of arousal. More thorough evaluation of the attributes of sedation may be necessary before its contribution to the recall-impairing effects of benzodiazepines can be clarified.

3. Effects of chronic dosing on normal volunteers. Despite the fact that benzodiazepine treatment usually entails regimens of several days or longer, there has been relatively little study of how recall functions are altered by repeated dosing with these drugs. As noted in our previous review, a study by Ghoneim and Mewaldt (1977) demonstrated that tolerance may develop to the impairment produced by benzodiazepines on immediate recall but not to the drugs' impairment of delayed recall. Other evidence that tolerance might not develop to the memory-impairing effects of these drugs appears in studies of memory disturbances in chronic users of benzodiazepines (Lucki and Rickels, 1988).

Recently, experimental studies in humans have begun to shed more light on this issue. Ghoneim et al. (1986) administered diazepam (0.2 mg/kg/d for 15 d followed by 0.3 mg/kg/d for an additional 7 d), oxazepam (0.8 mg/

kg/d for 15 d followed by 1.2 mg/kg/d for an additional 7 d), or placebo to groups of normal volunteers. Among the various performance tests was one of immediate and delayed (60 and 115 min) recall and recognition of word lists. Lists were presented prior to and at 60 and 115 min following drug administration. A delayed recall (1 wk) evaluation was done during the subsequent session. There was substantial variability in subjects' immediate recall behavior; oxazepam produced a greater impairment than did diazepam. On the delayed recall tasks, retrograde facilitation of recall of the lists presented prior to drug administration was shown with both diazepam and oxazepam but only after the first dose of each drug. There was consistent, pronounced impairment of delayed recall of material presented following drug administration. Impairment continued across each week of drug administration but did not become worse following the increment in dose. This was taken as evidence of the development of tolerance to the benzodiazepines' effects and was found to be equal for both drugs, indicating that tolerance does not differ between an accumulating benzodiazepine (diazepam) and a nonaccumulating benzodiazepine (oxazepam). It is possible, however, to dispute the report of tolerance development to oxazepam and diazepam in these tests; delayed recall continued to be impaired, relative to control subjects, across the entire period of benzodiazepine administration. Tolerance development, if it was not due to pharmacokinetic factors, seemed clearest with retrograde facilitation, which was restricted to the first exposure to drug.

The effects of 5 d of administration of lorazepam (1 mg three times per day) or alprazolam (0.5 mg three times per day) on immediate and delayed recall of categorized lists of words was evaluated by Kumar et al. (1987). Recall was evaluated only prior to and after the fifth day of drug administration; thus, acute effects were not determined. On the last day of drug administration, prior to administration of the final dose, a word list was read to subjects and immediate recall was tested. All subjects, including those in the placebo group, showed a marked enhancement in recall, compared with their predrug performance. The two active-drug groups were impaired relative to placebo but not relative to predrug performance. Although it is difficult to assess tolerance development in the absence of a measure of the drugs' acute effects, it seems clear that some effects on delayed recall did persist after 5 d of administration of these doses of alprazolam and lorazepam.

Bickel et al. (1989) evaluated the effects of administration of diazepam (80 mg) for 3 d on acquisition of a response sequence. The behavioral paradigm was identical with that used by Higgins et al. (1987). In one component of the schedule, the response sequence (pressing on keys 1, 2, or 3 on a numeric keyboard until a predetermined ten-response sequence was successfully completed) was the same each day. On alternate components, signaled by changes in the background color of the monitor, the response sequence was new each session. Thus, the effects of diazepam on performance could be monitored as its effects on acquisition were being evaluated.

Because the four subjects were sedative abusers residing on a research ward, it was possible to get long-term measures of drug effects; each subject was evaluated for 12 h each day. Baseline levels of performance were determined for up to 2 wk during placebo administration. Tests of acquisition and performance were made at 1, 2, 3, 4, 6, 8, 12, and 23 h following drug administration. The initial dose of diazepam produced marked increases in errors in acquisition of new response sequences. There was still an effect on day 2, although it was less than that on day 1. An even smaller effect of diazepam was observed on day 3 of drug administration, and the effect diminished more quickly than on days 1 and 2.

Diazepam had little effect on the performance component of the schedule in two of the four subjects. In one of the impaired subjects, behavior returned to control levels during the 3 d of diazepam administration. In the other impaired subject, the degree of impairment remained constant over the 3 d of drug administration. Measures of rates of responding indicated that tolerance developed to diazepam-induced reduction in rate in three of the four subjects in the acquisition portion of the schedule.

There is considerable variation in the procedures that have been used to evaluate the effects of chronic drug administration on recall ability. The use of different drugs, doses, durations of administration, and tests of recall, as well as the few number of studies that have considered this issue, make it difficult to draw conclusions. In the experiments by Bickel et al., measures were made of other effects of benzodiazepines, so that tolerance shown on recall tasks could be compared with tolerance shown to other effects of the drug. This is an important consideration if a selective effect on recall is to be postulated. The evidence suggests that tolerance may develop to the effects of benzodiazepines on recall and acquisition, but the conditions under which such tolerance occurs and the degree of tolerance that can develop have not yet been defined.

4. Effects of chronic dosing on patients. A limited number of studies have been devoted to ascertaining whether patients taking benzodiazepines chronically continue to suffer from impaired recall. Peedicayil et al. (1988) administered either diazepam (5 mg three times per day) or placebo for 1 wk to patients suffering from anxiety disorders. They evaluated recall deficits with a visual reproduction test (immediate drawing of a simple geometric design that had been shown for 10 s), a paired associate word-learning test (ten pairs of words were read; 5 s later, one of each pair was read and recall of its mate requested), and a smell-matching test (in which

eight bottles of aromatic liquid were presented to subjects and they were asked to organize them according to smell into four groups each consisting of two matching bottles). The time interval between drug administration and testing was not specified. Diazepam given chronically did not impair performance on any of the memory tasks, compared with placebo, indicating to the authors that this clinically useful dose does not interfere with memory. Because the effect of acute dosing with diazepam was not determined, it cannot be said whether the drug had an effect on these tests at these doses. Therefore, the fact that impairment was not observed after chronic administration may simply reflect that an ineffective dose or insensitive tests were used rather than that tolerance developed to the drug's effects.

Golombok et al. (1988) also sought evidence for tolerance in their study of memory function in chronic users of benzodiazepines. Subjects included patients who had been taking benzodiazepines for 1 yr, others who had not taken benzodiazepines for at least 1 yr or ever, and subjects who had taken benzodiazepines for 1 yr in the past but not for the 6 mo immediately prior to inclusion in the study. Recall tests included evaluation of immediate recall and delayed (90 min) recall of word lists. The lists were presented three times, so that acquisition, rather than simple recall, was assessed. The report did not specify how long after drug administration the tests were given. No alteration was observed in recall as a function of current administration of benzodiazepines, indicating to the authors that, during chronic administration of benzodiazepines, tolerance develops to the drugs' effects on recall. Again, because there was no indication of whether memory was ever impaired by the benzodiazepines taken by these patients or that the tests were sensitive to such impairment, the fact that impairment was not observed after chronic treatment does not necessarily indicate tolerance development.

Results of these two studies suggest that people taking benzodiazepines on a chronic basis can expect to have little problem with recall. This does not correspond to clinical reports of complaints of memory problems by patients taking benzodiazepines chronically (Busto et al., 1986). A possible reason for the discrepancy appears in a study by Lucki and Rickels (1988), in which the time parameters of impaired recall were closely examined in chronic benzodiazepine users. Of 39 anxious subjects, who had not taken benzodiazepines for at least 2 wk prior to the trial, some were assigned to take placebo and the remainder received diazepam (5 mg) for 7 d in an increasing dose (15 mg/d on days 1 to 3; 20 mg/d on days 4 to 7). On each of these 7 d, subjects were evaluated for their ability to recall words immediately as well as 20 and 70 min after administration of one dose. On day 8, the patients were reevaluated, but on this occasion the final recall test was given approximately 3 h following administration of the test dose.

On the first test day, diazepam produced no change in immediate recall but significantly impaired recall 20 min after word presentation. Following 8 d of chronic administration, there was a nonsignificant impairment of delayed recall (3 h). The fact that recall was not significantly impaired after 8 d of diazepam administration could indicate the development of tolerance or, as suggested by the authors, the possibility that evaluation 3 h after ingestion of diazepam (5 mg) was different from evaluation 70 min after ingestion of this dose.

In a subsequent evaluation of 54 subjects who were currently taking benzodiazepines daily for treatment of anxiety, and who had been doing so for at least 1 yr, recall testing was done at initial evaluation, several hours following the last dose, and, later, for 20 of the subjects, 60 to 90 min following ingestion of their medication. No impairment of recall was found on the initial test. However, when testing was carried out within 90 min of taking the test medication, a significant impairment of delayed recall was found. Thus, it is apparent that recall abilities may be impaired, even in those who have used benzodiazepines daily for 1 yr or more, but only for a narrow window of time following drug ingestion. The investigators noted a "critical period of susceptibility," which they determined was not related to plasma levels of drug, because these levels were high both when recall was and when it was not impaired. This finding could have significant implications for those who take their medication in divided doses each day.

5. Effects of benzodiazepines on episodic and knowledge memory. During the past two decades, theories of learning and memory have typically emphasized processes such as short-term memory, consolidation, long-term memory, and retrieval functions, as described by Atkinson and Shiffrin (1968). There is a much different approach to describing memory, however, with a corresponding novel categorization of the effects of drugs such as benzodiazepines on memory. In the alternative theories, two types of memory are described. Different investigators apply different names to the two memory types: episodic, explicit, direct, overt, or declarative memory on the one hand; knowledge, implicit, indirect, covert, or procedural memory on the other. The former, episodic memory, is the memory of specific events and their context, the recollection of which is a deliberate behavior. Knowledge memory, in contrast, does not require deliberate recollection but involves knowledge of language, rules, and motor skills and ability to learn motor skills. Acquisition of classically conditioned behavior also falls into the latter category. The need to distinguish between these two types of memory became apparent when it was recognized that profoundly amnestic patients, such as those suffering from Korsakoff's disease or postencephalitic amnesia or those undergoing electroconvulsive shock therapy for depression, did not lose their knowl-

edge of language and were able to learn motor tasks and solve puzzles.

Some investigators have raised the question whether benzodiazepines produce recall impairments similar to those found in patients with organic amnesias. Roy-Byrne et al. (1987) evaluated the ability of subjects receiving diazepam (10 mg) to freely recall word lists (episodic memory) and to identify which words in the lists had been read twice (attention). Subjects were also asked to name as many members of a specified category as possible in a 90-s period (knowledge memory). The subjects were most impaired in their ability to signal that a given word had been presented twice. There was a trend for free recall to be impaired as well, but there was no impairment in the subjects' ability to name members of a category. Thus, episodic but not knowledge memory appeared to be impaired.

Wolkowitz et al. (1987) conducted a similar test of the ability of subjects to indicate when a word had been presented twice on a list and to generate their own lists of objects appropriate to a specified category. Approximately 90 s later, subjects were asked to recall words from the original list. Subjects receiving diazepam (cumulative i.v. doses of 8.8, 35.1, and 140.1 μg/kg) were impaired in their ability to indicate when a word had been read twice. They were also impaired in free recall but were as able as subjects receiving placebo to create lists of categorized words. As in the study by Roy-Byrne et al. (1987), the authors concluded that diazepam selectively impaired episodic memory, sparing knowledge memory.

Preston et al. (1988) found that lorazepam (0.5, 1.0, or 2.0 mg) impaired free recall on a Buschke selective reminding task but did not impair knowledge memory as measured by a category and letter fluency task. Curran et al. (1991) noted that lorazepam (2 mg) produced an impairment in paired associate learning but did not modify a word fluency task.

More detailed evaluation has shown that, although the ability of patients with organic amnesias to recall or recognize material may be severely impaired, they are not so impaired in recall tasks in which there is "priming." In priming, material related to the task has been presented recently and incidentally to the task. For example, a list of words is presented, followed soon thereafter by a list of word stems consisting of the first three letters of several possible words, including some words from the list. The subject is asked to make words from the stems; a measure of the effect of priming is the number of words made that were from the original list, compared with the number of list words made from the stems by subjects who were not shown the list. Subjects with amnesia do very well on this test, i.e., make as many words that were on the original list as subjects who do not have amnesia, although they may be completely unable to recall or recognize words from the priming list.

Because there are many similarities between the impairment of recall produced by benzodiazepines and that found in organic amnestic syndromes, several investigators have evaluated the effects of benzodiazepines on priming tasks. Brown et al. (1989) evaluated the effects of lorazepam (2.5 to 3 mg, depending on body weight) or placebo on normal subjects exposed to a word completion task with priming. Subjects were given predrug experience completing three-letter word stems (unprimed). Seventy-five minutes after drug ingestion, they were exposed to a 20-word list, of which 16 words were priming words, i.e., they could be used to complete stems in the subsequent task. Five minutes later, subjects were asked to make words from 25 unique three-letter stems. All of the stems had several completion solutions, 16 of which could be completed by words from the priming list.

Subjects receiving lorazepam completed significantly fewer word stems with words from the priming list, indicating to the investigators that "in lorazepam amnesia, priming is not a preserved memory function."

Curran and Birch (1991) also found that midazolam, given i.v. to the point of slurred speech (4 to 11 mg), reduced the number of words completed using information from a priming list. This impairment was not reversed by a dose of flumazenil that antagonized other effects of midazolam on memory and behavior.

Fang et al. (1987) evaluated the effects of priming on word completion by subjects following diazepam (approximately 0.3 mg/kg) or placebo administration. Fifty-five minutes following drug ingestion, subjects were exposed to a word list and subsequently to a list of word stems to complete. They were then asked to recall words from the list. Twenty-five minutes later, they were exposed to a second word list and then asked to generate words appropriate to particular categories (e.g., a category such as "flowers" was named and subjects were asked to list eight items that belong in that category). At issue was how many of the generated words were from the list shown earlier. Eighty-five minutes following drug administration, subjects repeated a word completion task following the presentation of a new word list, as they had done 55 min after drug administration.

As expected, the subjects receiving diazepam were significantly less able to recall words from the lists that were presented. However, there was no significant difference between the diazepam and placebo groups in the number of word stems completed with words from the priming list. In the category completion task, diazepam-treated subjects were significantly impaired in using words from the priming list; they were also impaired in several psychomotor tasks that were tested. The data indicate a dissociation between memory systems involving free recall and those requiring the completion of previously primed words. Diazepam impairs the former

but not the latter, which is presumably linked to processes that do not require verbal recollection.

In a study by Danion et al. (1989), a word stem completion task was used to assess semantic memory, and a recall test of the priming list was used to assess episodic memory. Ability to list members of a category was also evaluated in subjects who received diazepam (0.2 mg/kg). Free recall was significantly impaired by diazepam, whereas word completion responses using priming list words did not differ between the diazepam- and the placebo-treated groups. Neither was the ability to name members of a specified category different between the two groups, indicating that the effects of diazepam were limited to impairment of episodic memory and similar to the memory impairment occurring with organic amnesias.

Danion's group (Danion et al., 1990) found similar results in subjects receiving diazepam (0.3 mg/kg). Diazepam greatly impaired free recall of words from the priming list. Subjects receiving diazepam were as likely as subjects receiving placebo to use words from the priming list to complete the word stems. Interestingly, this dissociation by diazepam of knowledge and episodic memory was not found with scopolamine (6 μg/kg), which produced deficits in both types of tests.

These studies are rather consistent in their findings that benzodiazepines do not impair the ability of subjects to list words from a given category. There is conflicting evidence about whether benzodiazepines have effects on priming tasks. The majority of the evidence suggests that benzodiazepines, like organic amnesias, do not impair the ability of subjects to use priming lists to complete word stems, even if the subjects cannot recall the words on the priming lists. The mechanism that underlies this type of memory and its relation to the more commonly studied tests of memory has not been specified. The apparent similarity between organic amnesia and benzodiazepine-induced amnesia is interesting and may provide a rationale for further investigation of benzodiazepine interactions with this type of memory.

6. Transient global amnesia. We have usually elected not to examine individual case studies in our reviews of the abuse liability of benzodiazepines. However, several recent case reports of a fascinating phenomenon are considered here, because it may have important implications about the effects of some benzodiazepines on memory, and it may prove to be difficult to study experimentally.

Haecki (1986) reported the cases of five patients who, following oral ingestion of midazolam (7.5 to 15 mg), performed their daily, occasionally complex, activities, appeared normal to their friends and companions, yet were completely amnestic for the events of the remainder of the day following administration of the short-acting benzodiazepine. As an indication of the possible frequency of this phenomenon, Haecki reported that these five cases developed among a total of only 30 people to whom midazolam had been prescribed. Bixler et al. (1991) observed that five of six subjects receiving 0.5 mg of triazolam for five nonconsecutive nights reported memory problems or amnesia during the 30 d following drug administration. There were significantly more reports of memory impairment following triazolam as compared to temazepam administration.

Rager et al. (1987) reported a similar phenomenon in eight cases, some observed by the authors and others identified in the literature. Morris and Estes (1987) documented three independent cases of transient global amnesia occurring in neuroscientists traveling from the United States to Europe. Each took triazolam (0.5 mg) to help him or her sleep on the trip. Each performed a number of tasks upon arrival, including changing planes, clearing customs, filing reports of lost baggage, negotiating taxi rides, registering in hotels, exchanging money, and engaging in discussions of professional matters with colleagues. Each of these travelers was completely amnestic for the events of the day following triazolam ingestion (i.e., 8 to 11 h, considerably longer than the half-life of triazolam, which is about 2.6 h). They had seemed perfectly normal to their neurologist companions during the period for which they developed amnesia. Each of them took the drug again on the following night and had no subsequent problems.

In response to this article, several physicians wrote letters about cases similar to those of Morris and Estes, and the authors themselves reported three more cases that had been related to them by colleagues (see references 2 to 8 in Huff and Plunkett, 1989). The suggestion in some of the responses that the amnesia may have resulted from an interaction between the benzodiazepine and sleep deprivation is an interesting one that may point to a way of reproducing the syndrome and thus studying it more effectively.

In two additional cases, ER physicians took triazolam to help them sleep. One of them, the morning after nightly administration of 0.25 mg of triazolam, chaired a meeting and subsequently realized he could not recall the first 90 min of the meeting, even though a tape recording indicated he was actively and appropriately involved in the discussions. The second physician took triazolam (0.5 mg) twice, 90 min apart at night, and in the morning set about his normal daily activities. About 5 h later, he realized he was completely amnestic for the events of the morning; a review of his behavior indicated it had been regarded as normal and appropriate by his spouse and colleagues (Huff and Plunkett, 1989).

Five cases of amnesia were reported by Patterson (1987) in elderly (66 to 78 yr) patients after receiving triazolam (0.125 to 0.25 mg) in conjunction with hospitalization for surgical or diagnostic procedures. Within 30 min of receiving the benzodiazepine for sleep, each patient became confused, disoriented, and incoherent;

they either wandered about or had to be physically restrained. In the morning, all appeared normal and none recalled the events of the previous evening.

The global amnesia described for the younger, professional people is particularly interesting in that it did not appear to be associated with an inability to form new memory. Those affected behaved perfectly normally and appropriately; they simply "lost" a period of time following triazolam administration.

The confusion and disorientation, subsequently forgotten, following triazolam ingestion in the elderly patients seems more like the amnesia occurring with some head trauma or dementias. Whether these cases reflect one phenomenon that presents differently in different people or two separate phenomena, both produced by administration of short-acting benzodiazepines, remains to be determined. In any case, the effect is certainly striking, and one hopes that ways will be found to study it more completely under controlled circumstances.

7. *Summary.* Many of the studies discussed in this section represent further work along the lines of earlier research, as considered in our previous review, and their findings do not deviate substantially from our earlier conclusions. Many benzodiazepines produce profound impairment of the ability to recall information. The impairment is usually worse when recall is requested of information presented minutes or hours earlier (delayed recall) than when the information was presented seconds earlier (immediate recall). The deficits are similar whether the information is presented once or several times.

Although the evidence is not conclusive, there may be differences in the amnestic effects of different benzodiazepines, because many investigators report deficits produced by some of these drugs and not others. The possibility that such differences exist is important from a research as well as a clinical perspective. It should be pursued thoroughly using experimental designs that demonstrate relative potency differences among different benzodiazepines in recall and nonrecall measures. Ideally, the nonrecall tasks would involve measures of anxiolysis; it might then be possible to demonstrate, for example, that some benzodiazepines are able to reduce anxiety at a given dose with little detrimental effects on recall, whereas other benzodiazepines greatly modify recall ability at the doses required to reduce anxiety.

Benzodiazepines produce decrements in recall in elderly subjects, but these are no greater than decrements they produce in younger subjects. However, even in the absence of drug administration, older individuals show some impairment on recall tasks; therefore, the additional deficit produced by drug administration may represent a more severe compromise.

A number of procedures have been brought to bear on the issue of whether the amnestic effects of benzodiazepines are related to their sedative effects. In general, benzodiazepine antagonists reversed both the sedation and memory impairment produced by benzodiazepines, suggesting that both of these effects are mediated through the same receptor. On the other hand, several nonbenzodiazepine drugs that act through different mechanisms produced as much sedation as the tested benzodiazepines but did not produce as much impairment in the ability to recall information.

One clinical study suggests that, even with chronic administration, benzodiazepines appear to continue to impair remembering; recall is most impaired during a fairly brief period after the administration of each dose. Additional research, perhaps taking advantage of the time course data obtained in the patient population, may assist in clarifying whether tolerance develops to the effects of benzodiazepines on memory.

There has been considerable recent information regarding the ability of benzodiazepines to produce memory impairment in tasks that involve knowledge memory rather than episodic memory. These drugs apparently do not interfere with the ability of subjects to list words from a specified category and probably do not impair the ability to use priming lists to complete word stems. This suggests that the memory impairment produced by benzodiazepines is similar to memory impairment that occurs with organic disease, such as Korsakoff's psychosis and dementia, and may serve as a useful model of these diseases.

D. Effects of Benzodiazepines on the Risk of Accidents

The influence of benzodiazepine use on the risk of various kinds of accidents has been examined in experimental and epidemiological studies. Most of these studies have been concerned with risks associated with automobile driving. Experimental studies have included those in which automobile driving is simulated, as well as studies of actual driving; most driving simulators combine some tracking task, using a steering wheel, as well as a brake reaction time test. Drug use by people detained for driving while intoxicated and those involved in actual accidents, especially automobile accidents, has been examined in epidemiological studies. The possible contribution of benzodiazepine use to the risk of accidents other than automobile accidents has been examined in only a few studies.

1. Effects on the risk of automobile accidents. a. EXPERIMENTAL STUDIES. The studies reviewed in this section involved normal volunteer subjects, unless otherwise noted.

i. Driving simulation studies. Acute administration of diazepam (15 mg) produced an increase in errors in a tracking task that simulated maintaining a car in its lane (Linnavuo et al., 1987). Smiley and Moskowitz (1986) examined the effects of diazepam on the variability of positioning an automobile within its lane while traversing a curve in the simulated roadway and on the ability

to adjust lane position in response to simulated wind gusts. A dose of 10 mg had no effect on lane position variability but did affect control of position during wind gusts. The effect on wind gust control continued during 8 d of administration of 15 mg daily, given in two doses. Effects on tracking have also been reported for 2.5 mg of lorazepam (Linnavuo et al., 1987). In contrast, Törnros and Laurell (1990) did not find effects on tracking with either brotizolam (0.25 mg) or nitrazepam (5 mg). Increases in braking reaction times were observed following administration of 0.25 mg of brotizolam or 5 mg of nitrazepam (Laurell and Törnros, 1986b; Törnros and Laurell, 1990).

Residual effects on tracking were reported on the morning after the first treatment with 0.25 mg of triazolam but not after 5 mg of nitrazepam (Laurell and Törnros, 1986a) or brotizolam (Törnros and Laurell, 1990). These effects were absent the morning after the third night of treatment with brotizolam (Laurell and Törnros, 1986b; Törnros and Laurell, 1990) or nitrazepam (Törnros and Laurell, 1990). Residual effects on reaction times were absent on the mornings after the first, third, or fifth nights of administration of 5 mg of nitrazepam, the first or fifth nights of administration of 25 mg of oxazepam or 0.25 mg of triazolam, and after the third night of brotizolam (Laurell and Törnros, 1986a,b; Törnros and Laurell, 1990).

In summary, some aspects of simulated driving performance were affected by several of the benzodiazepines administered in single doses in the therapeutic range. Detailed driving simulation studies of tracking revealed that, although diazepam could produce decrements in the ability to compensate for wind gusts, it did not affect variability of lane position while negotiating a curve. Braking reaction times were affected by brotizolam and nitrazepam in the two studies in which performances were examined immediately after drug administration; however, these effects were absent in the mornings following nighttime administration of the drugs.

Because these results are from a relatively small number of driving simulation studies, their reliability is as yet unclear. The specificity of action of benzodiazepines on component behaviors of the simulation is also unclear. For example, the finding that diazepam did not alter routine tracking but did alter control during simulated wind gusts is interesting in that it implies a possible difference in effects on these performances. However, results from other studies of psychomotor performance suggest that the specificity of these actions may not be reliable; for example, several of the studies summarized in table 3 show specific effects on behaviors in one test of a performance battery that are not reliably obtained across studies.

ii. Studies of "actual" driving behavior. Studies of the effects of benzodiazepines on actual driving performance can be divided into those in which navigation of an automobile through a test course is examined, in which different types of tasks are required, and those in which driving takes place in actual traffic situations. Typical test courses include those that require navigation through a slalom, as well as those requiring attempts to drive a vehicle through a series of gaps of graduated widths both narrower and wider than the width of the vehicle, where the gaps are defined by pylons. Each of these tasks is scored on some basis, such as the number of times a pylon is hit. In studies conducted in actual traffic situations, the subject drives an instrumented automobile on the highway, usually for 1-h test sessions; the ability to maintain the lateral position of the automobile within the lane (measured as variability of positioning within the traffic lane) has been found to be sensitive to the effects of sedative drugs.

Volkerts et al. (1988) reported a "slight" increase in the variability of lateral positioning of the automobile within its lane on the highway after 5 mg of diazepam. There were no significant differences between the effects obtained in normal and anxious subjects. This result was reported in abstract form, and quantitative information was not provided. A single dose of 7.7 mg of diazepam decreased performance in an evasive lane change maneuver on a test course but had no effect on steering through a winding course, braking, or maintaining or reproducing a certain speed (Mortimer and Howat, 1986).

Betts et al. (1986) examined test course driving, through a slalom and through gaps of various widths, in subjects with low and high scores on the neuroticism subgroups of the Eysenck Personality Inventory, form A (Eysenck and Eysenck, 1964). Chlordiazepoxide had no effect on performance in the slalom but increased the proportion of passable gaps through which the subjects attempted to drive. With continued administration (10 mg three times per day for 7 d), this effect on gap judgment diminished. There was no significant difference in response to chlordiazepoxide between the high- and low-score neuroticism subgroups.

In a study of outpatients being treated for anxiety, de Gier et al. (1986) found that treatment with 1.5 mg of bromazepam or 1 mg of lorazepam three times daily for 2 wk had no effect on driving, as rated by trained observers. Brookhuis and Borgman (1988) reported effects of 0.5 mg of lorazepam given three times per day on variability of lane positioning in both normal and anxious subjects. Anxious patients appeared to be affected less than normal subjects, although the differences were not significant. Both oxazepam (10 mg) and clorazepate (5 mg) given three times daily had only small effects.

The studies in which driving performance has been examined in groups of subjects representative of those for whom these drugs would ordinarily be prescribed are important because it has been suggested that these drugs may improve driving in patients suffering from anxiety or insomnia (Landauer, 1986). Neither Betts et al. nor

Brookhuis and Borgman found significant differences in effects between anxious and normal patients, although Brookhuis and Borgman reported an insignificant tendency for anxious subjects to be less affected than normal subjects. In a recent interview study, Balter and Uhlenhuth (1991) examined reports of daytime sleepiness while driving by individuals suffering from insomnia; those who took hypnotic medication were less likely to report this sleepiness than those who were not treated.

Most of the more recent studies of actual driving behavior have examined the residual effects of treatment with hypnotic benzodiazepines. Neither nitrazepam (5 mg) nor oxazepam (25 mg) affected performance in an evasive lane change maneuver on a test course (Laurell and Törnros, 1986a,b). However, in another study, Betts et al. (1986) found that the same treatment increased the number of unpassable gaps attempted and also decreased performance on a slalom course. A higher dose of oxazepam (50 mg) administered for two nights increased the variability of positioning of an automobile within the traffic lane on the highway (Volkerts and Abbink, 1990). Betts et al. (1986) reported that treatment with 0.25 mg of triazolam or loprazolam for a single night had no effect on gap performance but did adversely affect performance on the slalom course. However, the same dose of triazolam did not affect performance on the evasive lane change maneuver (Laurell and Törnros, 1986a).

Volkerts and O'Hanlon (1986; see also Volkerts and O'Hanlon, 1988) examined the highway driving of women with histories of hypnotic use. Increases in variability were observed the morning after the second night of treatment with flurazepam (15 and 30 mg), flunitrazepam (2 mg), nitrazepam (5 mg), zopiclone (7.5 mg), and loprazolam (1 and 2 mg). After eight nights of flurazepam administration, the variability in lane position persisted but was less marked. Brookhuis et al. (1990) also examined driving of individuals suffering from insomnia using the same techniques. As in the previous study, flurazepam (30 mg) produced an increase in variability of lane positioning. This effect occurred the morning after the second, fourth, and seventh nights of treatment in female subjects and after the fourth and seventh nights of treatment in men. The effect was more marked and prolonged in the women. Lormetazepam, at a dose of 1 mg, was essentially inactive, as has been reported elsewhere (Volkerts and Abbink, 1990); at 2 mg, this drug had only minimal effects during the course of treatment. A summary of results of several of these studies (Brookhuis, 1989) indicated that the residual effects of several hypnotics were dose dependent, with the lowest doses sometimes lacking effects.

Other studies have demonstrated a diminished effect of these drugs with repeated treatments. For example, after 3 d of treatment with 5 mg of nitrazepam, performances on the evasive lane-change maneuver on a test course were no longer affected (Laurell and Törnros, 1986a). However, Betts et al. reported continued effects of this dose of nitrazepam, but not of 1 mg of loprazolam, on gap and slalom performances after eight nights of treatment. Residual effects of triazolam on the evasive lane change maneuver (Laurell and Törnros, 1986a) or on gap and slalom tests (Betts et al., 1986) were absent after three or eight nights of treatment, respectively.

In summary, results of several studies have indicated that benzodiazepines can have effects on particular aspects of either simulated or real driving. In driving simulations, mixed results have been obtained with respect to the ability to maintain the position of the automobile within its traffic lane (tracking). Decreases in reaction times have been reported immediately after hypnotic doses; these effects were absent the next morning. In studies of actual driving, several reports indicated that benzodiazepines can increase the variability of maintaining the automobile within its lane. This effect was dose dependent, with the lower doses of several hypnotics lacking effects when tested on the following morning. In neither study in which anxious patients and normal subjects were compared were differences found in the effects of benzodiazepines on driving, although one group of investigators reported an insignificant tendency for anxious subjects to be less affected than normal subjects. Results of a recent interview study indicated that subjects suffering from untreated insomnia reported sleepiness in the day while driving more frequently than did insomniac patients receiving hypnotic medication.

b. EPIDEMIOLOGICAL STUDIES. Epidemiological studies have attempted to assess the extent to which use of benzodiazepines may contribute to traffic accidents. In many of the studies reviewed here, the incidence of benzodiazepine use was evaluated in individuals who were arrested for driving while intoxicated but who did not have high blood alcohol concentrations or in individuals involved in accidents. However, the significance of such statistics is unclear in the absence of an appropriate context. To reasonably conclude that use of a drug contributes to the frequency of accidents, the incidence of the drug's use in accident-involved individuals must be compared with the incidence of its use in an appropriate control group of subjects not involved in accidents.

There may be differences between the individuals involved in accidents and those not involved in accidents, apart from use of medications, that may contribute to the likelihood of accidents. The most obvious of these is the reason for drug use, such as anxiety, stress, or insomnia. Moreover, survey research has shown that benzodiazepine users are also more likely than the general population to be older and to suffer from multiple somatic health problems. Individuals taking psychoactive medications may also differ from the general population with respect to their tendency to take risks. Any of these differences may influence the likelihood of accidents independently of drug use (cf. Eelkema et al., 1970;

Brenner and Selzer, 1969; Guastello, 1987; Maki and Linnoila, 1976). In addition, it has been suggested that driving performance among individuals suffering from conditions such as anxiety or insomnia might be improved by use of these medications (Linnoila, 1976; Seppala et al., 1979).

Environmental factors may also influence the likelihood of an accident. For example, those involved in traffic accidents may be driving on different roads or at different times of day than drivers not involved in accidents. Previous surveys have included case-control studies of drivers not involved in accidents who were driving at locations and times at which accidents occurred; unfortunately, these case-control studies are difficult and expensive, and few have been reported.

Studies we reviewed previously indicated incidences of benzodiazepine use ranging from 0 to 20% in drivers arrested and injured in accidents, with lower frequencies for arrested drivers than for those injured. However, the few studies in which drivers who were arrested or who were involved in accidents were compared with the general population did not consistently demonstrate an overrepresentation of benzodiazepine users in these drivers.

Most recent epidemiological studies have focused on drugs detected in body fluids of individuals arrested by authorities for driving while intoxicated. A few have included individuals injured and killed in traffic accidents in surveys of all kinds of injuries. These categories of individuals may be viewed as representing a progression of increasingly dire consequences, which may approximately correspond to a progression in degree of drug-induced impairment. Unfortunately, there have been no recent studies using case-control techniques.

i. Studies of drivers detained for driving while intoxicated. The rates of benzodiazepine detection in individuals arrested for driving while intoxicated, as shown in table 6, ranged from 2.06% to 67.1%. The lowest value is from a study of 1260 Norwegian drivers selected only on the basis of an impairment in their driving (Gjerde et al., 1986). In another Norwegian study, Solberg-Christophersen et al. (1990) examined a smaller number of impaired drivers (n = 270) and detected a higher prevalence of benzodiazepine use.

In studies in which drug use was suspected, the prevalence of drug use was generally higher, ranging from a low of 3.3% (Kirk et al., 1990) to a high of 67.1% (Bjørneboe et al., 1987). This suspicion most often arose when blood alcohol levels detected in drivers who appeared impaired were negative or lower than expected. These findings are consistent with those described in our previous review.

There was some variability in the incidences reported. For example, in 1984 in Norway, benzodiazepine use was reported in only 34.7% of subjects selected for analysis because of low blood alcohol levels (Gjerde et al., 1986). Similarly, Bjørneboe et al. (1987) reported an incidence of 37.3% in such subjects tested in Norway in 1983; however, in a 1978 survey, the same authors found an incidence of 67.1%. In contrast, Cosbey (1986) reported that benzodiazepines had been used by only 15.6% of subjects selected for testing because of low blood alcohol concentrations in Northern Ireland in 1982 to 1985.

ii. Studies of fatally and nonfatally injured drivers. The incidence of detection of benzodiazepines in nonfatally injured victims was studied by Girre et al. (1988); the results of this study are also shown in table 6. Benzodiazepines were detected in 9.6% of victims of motor vehicle accidents. The authors claimed that this prevalence was similar to that for use of these drugs in the general population, although community prevalence data were not reported.

Christensen et al. (1990) examined records of traffic offenders suspected of driving under the influence of drugs in Denmark from 1981 to 1985. Seventy-four per cent of the accident-involved individuals had ingested benzodiazepines. This number was not different from the average percentage across drug classes, suggesting that these drugs are no more likely than others to contribute to accidents.

McLean et al. (1987) reported results of a study of 200 accident victims in Australia from 1983 to 1984. Prevalence of benzodiazepine use in drivers detained for impaired driving was 2.6%; in accident survivors, it was 5.4%; and in fatalities, it was 9.5%. All of the detained drivers and accident survivors also had high blood alcohol levels, as did 50% of the fatalities.

Peel and Jeffrey (1990) examined fatally and nonfatally injured accident victims in Canada from 1985 to 1989 in a study with a relatively small sample size. Among individuals with low blood alcohol levels, 78.7% had ingested benzodiazepines; the rate was 9.7% in the fatally injured victims.

In the course of surveying drug use among Austrians, Lesch et al. (1989) also questioned respondents regarding their driving practices. Tranquilizer use did not differ between individuals involved and those not involved in accidents; 3.01% of individuals who had been involved in automobile accidents were users of tranquilizers. This was less than the 4% of the general population who reported having used tranquilizers in the 3 mo prior to survey. In addition, tranquilizer users were less likely to be drivers of cars, motorcycles, trucks, and buses than the population as a whole. Moreover, those tranquilizer users who drove cars generally drove fewer miles annually than drivers who did not use medications.

Fortenberry et al. (1986) reported that benzodiazepines were detected in 2.1% of a series of fatally injured drivers. In addition, the prevalences among passengers and pedestrians were 2.9% and 2.6%, respectively. Because drivers are more likely than passengers or pedestrians to be at fault for accidents, a greater incidence of drug

detections in fatally injured drivers than in fatally injured passengers or pedestrians might indicate a contribution of drug use to the risk of accident. Because drivers showed the lowest incidence of benzodiazepine use in this study, these data suggest that the drugs did not contribute to the risk of accidents.

2. Effects on the risk of other types of accidents. Several studies have reported rates of detection of benzodiazepines in body fluids in fatal accident victims. These rates may be suggestive of a contribution of the drugs to the risk of such accidents. To assess this contribution, as discussed before, the rates must be compared with those in an appropriate control group. In the absence of an appropriate reference group, these statistics are not readily interpretable.

Benzodiazepines were detected in urine of 3.49% of a sample of 172 occupation-related fatalities in the United States in 1984 to 1985 (Lewis and Cooper, 1989). Rivara et al. (1989) found that, in the United States in 1986, 3% of fatally injured victims of accidents, including motor vehicle accidents, and 4% of nonfatally injured victims had used benzodiazepines. Lodi et al. (1988) assessed the frequency of detection of several types of drugs in various unnatural deaths; benzodiazepines were detected in 35.1% of suicide victims, 27.4% of overdose cases, 16.7% of traffic fatalities, 12.9% of accidental deaths, and 5.6% of homicide victims.

Lindenbaum et al. (1989) examined rates of drug detection in accidental and crime-related trauma cases in the United States. Benzodiazepines were reported in 10.1% of cases, whereas several illicit drugs were reported more frequently, such as cocaine (54.4%) and cannabinoids (37.2%). Alcohol was detected in 36.1% of the accidental and crime-related trauma cases. Several licit drugs were detected less frequently; these included barbiturates (7.1%), amphetamines (4.7%), codeine (1.7%), and other opioids (8.9%).

Girre et al. (1988) compared the incidence of benzodiazepine use in 2021 victims of several types of accidents in France during 1982 to 1983 (table 6). The prevalence of benzodiazepine use in all types of accidents was 9.6%, which the authors claimed was similar to the prevalence of use in the community. Prevalence of use of benzodiazepines among those involved in work and sports accidents was lower, whereas the prevalence among those involved in household accidents was higher.

The prevalence of tranquilizer use in shipyard workers in the Netherlands during 1986 to 1987 was examined by Moll van Charante and Mulder (1990). Among those who suffered a work-related accident, 3.6% reported tranquilizer use; this was not significantly different from the 2.7% rate among case controls who were not involved in an accident.

Oster et al. (1987) examined health insurance claims among users of benzodiazepines and nonusers in the United States during 1986. The benzodiazepine users had significantly more claims associated with accidents or injuries than did a group of sex- and age-matched controls who had one nonbenzodiazepine-related claim during the sampling period. However, the benzodiazepine users also had a higher frequency of nonaccident-related claims compared with nonusers. Thus, there was a higher rate of health care utilization of all kinds among benzodiazepine users than among nonusers. On the basis of these findings, the authors concluded that it could not be determined whether benzodiazepine users were more likely to be involved in accidents.

In a related study, Oster et al. (1990) assessed the effect of benzodiazepine therapy on the risk of accidental injury by examining insurance claims during 1986 to 1987 in the United States. Diagnoses associated with claims submitted by medical care providers during the 3 mo prior to and the 6 mo following the first benzodiazepine prescription were compared with those of controls for whom other medications were prescribed. The authors concluded that accident-related care was more likely among persons for whom benzodiazepines had been prescribed, in the months during which a prescription had been recently filled, and higher in persons for whom three compared with one prescription had been filled.

In addition to the differences in claims in the months following the first benzodiazepine prescription, the authors also reported a greater-than-control frequency of accident-related claims prior to benzodiazepine therapy. These risks were not appreciably different from the risks reported after these individuals received benzodiazepine prescriptions. This suggests that some factors predisposing to accidents or accident-related health care may account for the differences in the accident frequencies in benzodiazepine users and nonusers. The authors attempted to control for such variables by adjusting their data on the basis of total claims during the 3 mo prior to benzodiazepine treatment. However, it would appear to have been more appropriate to adjust only on the basis of accident-related claims prior to treatment.

Results of epidemiological studies indicate that elderly patients account for a disproportionately large percentage of benzodiazepine prescriptions (see section V). These individuals are also at risk of episodes of falling, which can result in injury, in particular hip fracture. The epidemiology of falls and of injury associated with falls in the elderly is complex, and the results of such studies are often contradictory. In addition, factors other than medications that influence falls may interact with the effects of medications in complex ways, thus confounding seemingly simple assessments of the contribution of medication use to the risk of falls. A factor further complicating the interpretation of results of these studies is that benzodiazepines have often been grouped together with major tranquilizers (antipsychotics), antidepressants, or other sedative-hypnotic agents; only the most recent studies have become more specific with respect to

TABLE 6

Epidemiological studies of benzodiazepine use and driving for drivers detained for driving while intoxicated, accident victims, and fatally injured accident victims

Reference	Geographic area	Dates	Method of drug detection	Size of sample	% benzodiazepines	Notes
Driving under the influence						
Worm et al., 1990	Denmark	1983	Blood	877	14.82	Ss* were selected for low BAC and violent acts
Gjerde et al., 1986	Norway	1984	Blood/urine	1260	2.06	Ss with BAC <60 mg/100 ml; 34.7% of those suspected for drugged driving
McLinden, 1987	Australia	1983–85	Blood/urine	164	49.39	Ss with BAC <0.15%; 20.1% of the cases were single-drug benzodiazepine cases
Cosbey, 1986	N. Ireland	1982–85	Blood/urine	212	15.57	Ss with lower than expected BAC; 3.3% of all cases were benzodiazepine positive and ethanol negative
Bjørneboe et al., 1987	Norway	1978	Blood/urine	231	67.10	Ss with lower than expected BAC or suspicion of drugs
		1983	Blood/urine	445	47.90	Of the 165 diazepam cases only 36% were only 1 drug; diazepam cases tended to be older than cases for the other drugs
Poklis et al., 1987	USA	1983–86	Blood/urine	184	30	Ss with negative BAC; chlordiazepoxide, 6%; clorazepate, 2%; diazepam, 22%; benzodiazepine single agent in 6% of cases
Christensen et al., 1990	Denmark	1981–85	Blood/urine	461	65	Ss suspected of driving under the influence of drugs; accident and nonaccident involved; 46.6% in nonaccident involved
Solberg-Christophersen et al., 1990	Norway	1986–88	Blood	270	21.9	Ss suspected of drunken or drugged driving; rate represents % of positive cases
Gjerde et al., 1988	Norway	1983	Blood/urine	146	21.92	Ss arrested for driving under the influence of drugs or alcohol; value is the % with blood diazepam >0.01 μM; three of these Ss also had high tetrahydrocannabinol or amphetamine blood levels; four Ss were considered not under the influence despite high blood level (19% of sample driving under influence with diazepam); 50% of diazepam cases were rearrested (26 rearrests) within 3 yr (19 of these were for alcohol); 20% of alcohol cases were rearrested (21 rearrests) within 3 yr (20 for alcohol; 1 for tetrahydrocannabinol)
Kirk et al., 1990	USA	1989	Urine	123	3.3	Ss suspected of driving under the influence of drugs; concordance: full, 50%; partial, 24%; none, 27%
Burns, 1986	USA	1985	Blood	173	7.5	Arrested for driving under the influence of drugs
Clatworthy, 1986	UK	?	Blood	436	35	"Unfit to drive;" BAC below prescribed limit

McLean et al., 1987	Australia	1983–84	Blood	200	4.64 (1.03) 2.61 (0)	Total: accident victims, traffic offenders, and random testing high BAC Ss >0.5 g/liter; breath-tested drivers and passengers <0.5 g/liter)
Peel and Jeffrey, 1990	Canada	1985–89	Blood	172	48.3	Ss with BAC <100 mg/100 ml
Non-fatally injured						
Girre et al., 1988	France	1982–83	Blood	2021	9.60	All types of accidents
					9.60	Motor vehicle accident
					6.20	Work accident
					5.80	Sports accident
					14.20	Household accident
					9.40	Brawl
McLean et al., 1987	Australia	1983–84	Blood	200	4.64 (1.03)	Total: accident victims, traffic offenders, and random testing high BAC Ss <0.5 g/liter)
					5.41 (0)	Accident survivors (BAC <0.5 g/liter)
Christensen et al., 1990	Denmark	1981–85	Blood/urine	173	74	Accident involved; benzodiazepine accident victims were 42% of all driving under the influence cases (not different from overall avg.)
Lesch et al., 1989	Austria	1984	Interview	166	3.01	Tranquilizer use in accident involved and noninvolved was not different; total population use of these drugs was 4%
Peel and Jeffrey, 1990	Canada	1985–89	Blood	94	78.7	Ss with BAC <100 mg/100 ml
Deveaux et al., 1989	France	1985–86	Blood/urine	446	4.4	Accident involved drivers or pedestrians
Fatally injured						
Fortenberry et al., 1986	USA	1980–84	Blood/urine	2189	2.30	Total, 0.45% of all cases were benzodiazepine positive and ethanol negative
				1518	2.10	Drivers
				480	2.90	Passengers
				191	2.60	Pedestrians
Rivara et al., 1989	USA	1986	Urine	452 ER patients	4.00	Nonfatal
			Urine	160 medical examiner cases	3.00	Fatalities older than 10 yr
Lewis and Cooper, 1989	USA	1984–85	Urine	172	3.49	Work-related fatalities
McLean et al., 1987	Australia	1983–84	Blood	200	4.64 (1.03)	Total: accident victims, traffic offenders, and random testing high BAC Ss <0.5 g/liter)
					9.52 (4.76)	Fatalities (BAC <0.5 g/liter)
Peel and Jeffrey, 1990	Canada	1985–89	Blood	226	9.7	Ss with BAC <100 mg/100 ml
Lodi et al., 1988	Italy	1986	Blood/urine	18	5.56	Homicides
				205	35.12	Suicides
				31	12.90	Accidental
				48	16.67	Traffic fatality
				135	27.41	Overdose

* Ss, subjects; BAC, blood alcohol concentration.

types of drugs examined. The following discussion begins with studies designed to examine benzodiazepine use only as a component of use of a broader category of drugs and proceeds to studies of more specific classifications. We have generally omitted review of studies in which drugs were grouped so broadly that we could not interpret their relevance to the issues at hand, for example studies in which the effects of benzodiazepine use were examined only in the context of use of all psychoactive drugs.

Prudham and Evans (1981) conducted a relatively early (1975 to 1977) community cross-sectional study, in England, of 660 elderly (65 yr or older) individuals who had fallen and 1697 age- and sex-matched controls. Those subjects taking tranquilizers (major and minor tranquilizers) and diuretics, but not other medications such as hypnotics, showed an increased risk of falls. Other factors associated with an increased risk of falls were recent contact with a physician, problems with mobility and daily living, a recent history of cardiovascular disease, and episodes of vertigo, double vision, blackouts, and weakness.

Rashiq and Logan (1986) compared the general practice records of 102 patients with hip fractures with those of 204 age- and sex-matched controls drawn from the same practices. Surprisingly, they found that hypnotic or sedative use decreased the relative risk of hip fracture. The authors suggested that those individuals not taking drugs were either in better health or perceived themselves to be in better health and were consequently more active; they supposed that this greater activity might have increased the risk of injury due to falling.

Two studies of elderly residents of long-term care facilities more precisely categorized drug classes but examined small numbers of subjects. Wells et al. (1985) examined 41 cases and 36 controls randomly selected from the same facility during a 4-mo period of 1983. In this sample, there was an increased risk of falls associated with antihypertensive medication but not antianxiety agents or antidepressants. In a similar study of 45 cases and 30 age-, sex-, and weight-matched controls, Sobel and McCart (1983) found an increased risk of falls associated with use of diuretics and sedative-hypnotics (including flurazepam and chloral hydrate) but not with use of diazepam, antihypertensives, antidepressants, or antipsychotics.

Tinetti et al. (1988) conducted a prospective study of 336 elderly patients (75 yr or older) living at home in 1985. Those for whom sedatives (including benzodiazepines, phenothiazines, and antidepressants) and other medications (diuretics, antihypertensives, and cardiac medications) were prescribed were at an increased risk of falling. Specific drugs or drug classes were not examined. These investigators also determined that cognitive impairment and various neurological disabilities significantly increased risk of falls. Use of sedatives remained a risk when depression and cognitive impairment were controlled.

In a prospective study of 84 patients (mean age 82.7 yr) at a small hostel for aged persons in Australia, Lord et al. (1991) used a battery of sensorimotor, vestibular, and visual tests to determine physiological factors associated with falls. Decreased proprioception of the lower limbs, lowered visual contrast sensitivity, decreased reaction time, and increased sway with eyes closed distinguished those that experienced multiple episodes of falling from the other subjects. Neither psychoactive medications (sedatives, antianxiety agents, antipsychotics, and antidepressants) nor drugs with hypotensive effects (psychoactive drugs, antihypertensives, and diuretics) increased the risk of multiple episodes of falling.

These findings were not completely confirmed in another study. Taggart (1988) examined 282 elderly women (average age 83 yr) admitted to a hospital for hip fracture. Comparison with 145 control women (average age 81 yr), selected from a list of family practice patients, indicated no significant risk of fractures associated with sedatives (major and minor tranquilizers, hypnotics, and antidepressants). In this study, 54% of the group experiencing fractures, and 80% of the controls, were receiving long-acting sedatives or hypnotics.

Granek et al. (1987) examined falls among 184 elderly (65 yr or older) patients of a long-term health care facility in 1984. Medications and diagnoses were compared among the cases and controls matched solely on the basis of length of stay in the facility. Several classes of drugs, including sedative-hypnotics (barbiturates, benzodiazepines, and other hypnotics), antidepressants, nonsteroidal anti-inflammatory agents, and vasodilators increased the frequency of falls compared with controls. Osteoarthritis, depression, and to a lesser extent neurotic disorders also increased the risk of falls. The authors suggested that falling was associated more with specific drugs than with diagnoses, because a greater percentage of the drug classes (four of eight) were associated with falls compared with the diagnostic classes (two of 12). This conclusion should be considered tentative, because there was no assessment, for example, of the influence of medication among patients with a given diagnosis, possibly because the numbers of cases and controls were inadequate for this type of analysis.

Myers et al. (1991) further examined the same data set that was collected by Granek et al. This analysis determined risk factors for falling at different levels of institutional care: rehabilitation patients ($n = 38$), nursing home patients ($n = 129$), and chronically hospitalized patients ($n = 17$; those patients in an acute phase of a chronic illness). In this analysis, the authors found that the effects of sedative-hypnotics and antidepressants were significant only in the nursing home patients, whereas the contribution of nonsteroidal anti-inflammatory drugs was significant only when the three levels

of institutional care were combined for analysis, and vasodilators were significant factors only in the rehabilitation patients. Tranquilizers (not including anxiolytics) became a significant risk factor in the nursing home patients when these patients were analyzed separately. These investigators also examined the risk associated with long and short half-life sedative hypnotics (see below). Across all levels of care, short half-life sedative-hypnotic drugs produced a significant risk of falling (n = 22), whereas the risk associated with long half-life sedative-hypnotic drugs was not significant (n = 7).

The authors further examined the contribution to falls of each individual risk factor when adjusted for other factors that had been identified as potential risks; a conditional logistic regression was used to adjust for risk factors that had been identified as significant in the initial analysis, as well as their interactions, and factors identified in the literature as potential risks. This analysis was more precise in identifying the degree of risk associated with individual factors. The authors determined that the factor posing the single largest risk is a history of falling, followed by being ambulatory (walking with or without assistance), and being 90 yr old or older. Of the medications examined, only use of vasodilators emerged as a significant risk factor when the data were adjusted for other potential risk factors.

Ray et al. (1987) examined risk of accident associated with use of several types of medications among Medicaid enrollees in Michigan (United States). The 1021 cases had experienced a hip fracture during the years 1980 through 1982. The 5606 controls constituted a random sample of the Medicaid enrollees, stratified by age, sex, and race. Both cases and controls were more than 65 yr of age. A significant increase in risk of accident was observed in subjects taking long-acting hypnotics (in particular, flurazepam), tricyclic antidepressants (in particular, doxepin and imipramine), and antipsychotics (in particular, thioridazine and haloperidol). Increased risk was not observed for diazepam, chlordiazepoxide, barbiturates (excluding phenobarbital), short-acting benzodiazepines, amitriptyline, or chlorpromazine.

In a methodologically similar study, these authors (Ray et al., 1989) compared risks of hip fracture associated with use of long- and short-acting benzodiazepines among health care users older than 65 yr in Saskatchewan (Canada). The 4501 cases had experienced a hip fracture between 1977 and 1985. The 24,041 controls were a random sample of individuals older than 65 yr, using the same health care system, stratified by age, sex, and race. In this study, an increased risk of hip fracture was found in elderly patients receiving diazepam, flurazepam, and chlordiazepoxide. In contrast, the short-acting benzodiazepines triazolam, oxazepam, and lorazepam were not associated with an increased risk of hip fracture.

Sorock and Shimkin (1988) interviewed 169 elderly subjects (averaging 80 yr) during 1986 and 1987 regarding their use of benzodiazepines and accidental falls. Benzodiazepine medication alone, whether taken as needed or on a regular basis, did not increase the risk of falls. Neurological examinations were conducted to determine which of these subjects were experiencing some degree of loss of position sense in their toes. In those subjects experiencing some degree of such loss *and* regularly receiving benzodiazepines, there was a significant increase in risk of falls, although neither of these factors alone increased the risk of falls.

Grisso et al. (1991) reported an interview study of 174 cases of first hip fracture in women 45 yr and older. Each case was matched by age and hospital with a control subject. Increased risk of hip fracture was associated with lower limb dysfunction, visual impairment, previous stroke, Parkinson's disease, and use of long-acting barbiturates. Factors that appeared not to play a role in hip fracture included lower extremity numbness, use of a walking aid, alcohol consumption, and taking long-acting or short-acting benzodiazepines.

In summary, results of epidemiological studies have not consistently indicated that benzodiazepines are overrepresented in injured accident victims. Only a few of these studies have utilized control groups to assess the contribution of benzodiazepines to accident or injury. Some studies have indicated that users of benzodiazepines generally have a higher frequency of health care claims than nonusers; psychiatric morbidity may contribute to health care utilization by these individuals. The elderly may be at some increased risk of injury from falling; however, findings of the relevant studies have not consistently indicated an increased risk in association with benzodiazepine use. Two large epidemiological studies of third-party payment records have indicated that long half-life benzodiazepines increase risk of hip fracture, whereas short half-life benzodiazepines do not. However, these results have not been supported in other studies, albeit with smaller sample sizes. Several studies have indicated that diagnosis (such as neurological impairment) interacts with the effects of medication use to increase the risk of falling or injury due to falls. Few studies have adequately assessed the contribution of diagnosis to the risk of falling or injury associated with use of medications.

3. Summary and discussion. Epidemiological studies of arrested, nonfatally injured, and fatally injured drivers (excluding studies of subjects detained by police because drug use was suspected) have found rates of benzodiazepine use ranging from 2% to 9.6%. These values are, for the most part, similar to those reported in the studies reviewed previously. Because these values have been compared with controls in but a few studies, it is not possible to infer whether drug use contributes to an increased risk of accidents. As we found in our previous review, in the few studies in which the investigators

attempted comparisons with the general population or with some other reference group, it has not been consistently demonstrated that benzodiazepine users are overrepresented in the populations of drivers involved in traffic accidents. In one of the recent studies, rates of benzodiazepine detections in drivers, passengers, and pedestrians were compared; rates of use of benzodiazepines were greatest in passengers, suggesting that benzodiazepine use did not contribute to accidents. Similarly, when alcohol-positive cases were eliminated, the prevalence of benzodiazepine use in drivers detained for driving while intoxicated or those involved in fatal and nonfatal accidents was decreased dramatically; these values have been reported to be similar to the prevalence of benzodiazepine use in the general population (see section V.D). More adequate case-controlled studies are necessary to provide a clear indication as to whether, or to what extent, benzodiazepines may contribute to the risk of automobile accidents. Case-controlled epidemiological studies represent the least ambiguous epidemiological source of information from which the risk of accident associated with benzodiazepine use might be assessed. Unfortunately, such studies are difficult and expensive, because the low rates of drug use in accident victims necessitate the study of large samples; none of the studies reviewed here were case controlled.

Laboratory studies complement epidemiological studies by directly examining the effects of drugs on behavior. Results of experimental studies of both simulated driving and actual driving behavior have indicated that most of the benzodiazepines examined may adversely affect various parameters of performance in normal subjects. As we found in our previous review, findings from these studies suggest that benzodiazepines can affect behavior in a manner suggestive of decrements in ability while driving under normal circumstances. Some investigators have argued that the performance of patients typically treated with these drugs may be impaired as a consequence of the disorders for which they are treated and that treatment can improve performance in these patients. Several studies of actual driving have suggested differences consistent with this suggestion, although these differences were not statistically significant.

Risk of falls or of injury due to falling in elderly populations has been examined in recent studies. An increased risk of injury due to benzodiazepine administration has been found in some studies but not others. Results of several studies have suggested that falls are associated with use of several different types of medications, including antidiuretics and cardiac medications, as well as with use of different types of psychotropic medications including sedatives, antidepressants, and antipsychotics. Others have indicated that shorter acting benzodiazepines are not associated with an increased risk of hip fracture. Certain diagnoses (including concomitant neurological impairment) have been identified in several studies as associated with an increased risk of falling in elderly subjects. The independent contributions of diagnoses and medications have not been adequately assessed.

Thus, although experimental studies of performance and simulated driving suggest that behavioral impairment occurs with benzodiazepine administration, epidemiological evidence for increased risk of several kinds of accidents with benzodiazepine use remains inconclusive. Further studies should utilize large samples to adequately assess the effects of specific drugs; these studies should address whether benzodiazepines differ from other kinds of psychoactive medications with respect to these risks, as well as the contribution of concurrent neurological impairment to the risk of accident in elderly benzodiazepine users.

V. Epidemiology of Benzodiazepine Use and Misuse

A. Introduction

1. Importance of the context of utilization. As we argued in our previous review (Woods et al., 1987), it would be inappropriate to attempt to evaluate the evidence regarding the abuse liability of the benzodiazepines without considering this evidence in the context of the utilization of these important medications. We focused our attention in that review, as we do here, on three key aspects of this context, namely (*a*) the appropriateness of actual use of the benzodiazepines; (*b*) the patterns of their actual prescription and consumption; and (*c*) any evidence of misuse in the general population or among patients, including evidence of toxicity that might result from such misuse.

The volume of information now available concerning these aspects of the use and misuse of benzodiazepines is really most impressive. This substantially increases the impetus to consider this information as a context in which to evaluate evidence of the abuse liability of these drugs, because the patterns of actual use and misuse are now clear enough that they often provide invaluable guidance in the effort to sort out the significance and relevance, for example, of experimental findings.

A number of important caveats apply to the interpretation of data of these kinds. We have detailed some of these and discussed the general limitations of these data in our previous review (Woods et al., 1987, pp. 320–321, "General Limitations of the Data") and hope that readers will refer to that discussion.

2. Previous findings and current evidence. In our previous review, we found that, in most countries for which data were available, sales of these drugs increased steadily from the time of their introduction until the mid- to late 1970s; during this period they largely displaced the barbiturates. Sales in most countries then declined substantially until the early 1980s, when they more or less stabilized for at least a few years. Our current review of

sales data (section V.B) extends and expands this perspective, with some interesting information about the relative exposures of a number of populations in recent years, about trends in these rates of exposure, and about the dramatic shift in use from long- to short-acting benzodiazepines.

We also noted that approximately half of prescriptions for benzodiazepine anxiolytics were written by primary care physicians; half of prescriptions for these drugs were written for treatment of psychiatric disorders, and most of the remainder were for cardiovascular, gastrointestinal, and musculoskeletal problems. A preponderance of prescriptions was written for elderly patients; these prescriptions were for longer periods of use than those written for younger patients. Recent surveys of prescribing patterns, considered in section V.C, have not modified this basic picture of the circumstances under which benzodiazepine prescriptions are written, but they have filled in considerably more detail and have indicated how these circumstances vary across many regions.

The data we reviewed previously suggested that the majority of use of anxiolytics was generally appropriate, in that users interviewed in the community report high levels of emotional distress and patients who receive prescriptions tend to use these drugs conservatively.

Results of cross-national surveys conducted in 1981 indicated that an estimated average of 12% of the adult populations of a number of western European countries and the United States reported having used anxiolytics in the previous year. Use was more prevalent among the elderly than among younger age ranges and was twice as frequent among women as among men, across age categories. Of those who had used anxiolytics, approximately one in five reported taking these medications regularly for 12 mo or longer. Long-term use appeared most likely to occur in older patients with multiple chronic physical disorders. More recent interview studies, providing both a more current and a more detailed perspective on actual use of benzodiazepines, are considered in section V.D.

Evidence regarding the prevalence of long-term use among elderly patients emerged from many sources and stimulated a number of investigators to take on the important task of exploring the nature and consequences of such use. In the current review, we discuss the numerous recent publications describing this exploration. Specifically, in section V.D.4, we focus on interview studies of long-term users, and in section V.E.1, we discuss the evidence regarding the use of benzodiazepines among elderly populations in general and summarize research into the use of these drugs among the elderly in institutions.

In our previous review, we found that nonmedical and recreational use of benzodiazepines among the general population of adults and youth was trivial in extent. On the other hand, studies of populations of drug abusers appeared to find some evidence of recreational use of these substances. There was little if any evidence to suggest a preference for benzodiazepines as a primary drug of abuse among drug abusers. Studies of misuse of benzodiazepines in the general population and among drug abusers continue to proliferate, and there has been a good deal more investigation of misuse among various patient populations. Although many of the more recent studies have basically replicated in different populations the findings of earlier surveys regarding patterns of use and misuse, some recent research has added valuable new insights. The recent literature on misuse of benzodiazepines is considered in section V.F.1.

The surveys of overdose considered in our previous review indicated that benzodiazepines were reported with some frequency in these episodes, often in combination with other drugs. Overdoses with benzodiazepines alone appeared to be almost never fatal; in fatalities involving benzodiazepines in combination with other drugs, the benzodiazepines were rarely implicated causally. In section V.F.2, we review the recent literature concerning benzodiazepine overdoses. In section V.F.3, we consider evidence regarding morbidity and mortality associated with benzodiazepine misuse or dependence.

In a separate section of this update, V.G., we consider evidence regarding the effects of restrictions that have been imposed on the prescription and use of benzodiazepines.

B. Prescription Sales

Prescription sales data provide estimates of the level of consumption of benzodiazepines as a group and of individual benzodiazepines. Wholesale data are of some interest, in that they provide some indication of the exposure of some national and regional populations to benzodiazepines; these data also present an interesting practical basis for comparison of benzodiazepine consumption across countries and regions. Indeed, with the exception of a very few studies in which direct comparisons of the use of psychoactive drugs across countries have been attempted, estimates of exposure based on wholesale data represent virtually the only practical means of attempting such comparisons. It is, therefore, of considerable interest to find that, whereas estimates of this kind were limited at the time of our previous review to a few European countries, data lending themselves to cross-regional comparisons have now been published for at least a few countries outside of Europe.

Both wholesale and retail sales data portray changes in levels of use over time, within and across countries, providing an interesting history of the typical "life cycle" of these agents in areas where they are marketed. International retail sales data afford a perspective on the variation in popularity of individual benzodiazepines, relative to one another and to other drugs prescribed for anxiety and insomnia, in different parts of the world.

Such data concerning the comparative licit availability of individual benzodiazepines in different areas may also serve as a reference point in evaluations of the drugs observed in illicit traffic. These kinds of global comparisons represent the chief value of prescription sales data for the purposes of this review; sales data provide only very crude estimates of actual consumption and in themselves shed no light on the immediate circumstances of benzodiazepine use.

1. Studies of wholesale data. Data concerning drug imports or sales to retail pharmacies have sometimes been used to estimate drug exposure of populations of individual countries or regions. A standard measure of such exposure that was recommended by the World Health Organization Drug Utilization Research Group (Lunde et al., 1979), which has been used in a number of studies, is "DDD/1000/d," i.e., DDD per 1000 inhabitants per day, where "DDD" is "the average maintenance dose. . .for the assumed major, or one of the assumed major, indications for the actual drug."

Much of the published data regarding wholesale sales calculated on this basis pertains to the Scandinavian countries; as summarized in our previous review (Woods et al., 1987), sales of benzodiazepine tranquilizers in 1980 ranged from about 17 to about 35 DDD/1000/d in Finland, Sweden, Norway, Denmark, and Iceland, and sales of benzodiazepine hypnotics in these countries in 1980 averaged about 25 DDD/1000/d. Sales of benzodiazepine tranquilizers in Czechoslovakia were reported to be 13 DDD/1000/d in 1978, although sales of all hypnotics (benzodiazepines and others) were 37 DDD/1000/d at this time.

It is interesting to note this difference between the Scandinavian countries, where use of benzodiazepine anxiolytics exceeded use of hypnotics, and Czechoslovakia, where the reverse appeared to apply. On the other hand, in recent years, use of benzodiazepine hypnotics has increased in some western European countries more rapidly than has use of benzodiazepine anxiolytics and appears to have overtaken use of anxiolytics in some areas. In Sweden, for example, Rutz et al. (1990) analyzed wholesale data and found that use of benzodiazepine tranquilizers increased from 21 to 22 DDD/1000/d between 1982 and 1985, whereas use of benzodiazepine hypnotics increased from 27 to 31 DDD/1000/d. In a recent review of studies of benzodiazepine sales in various European countries, Katschnig and Amering (1990) also found that benzodiazepines are more frequently used as sedative-hypnotics in the Federal Republic of Germany, Switzerland, and Austria, whereas they are more often used as anxiolytics in France and Italy.

The United States Food and Drug Administration (Baum et al., 1986) reported sales of benzodiazepines in the United States, from 1980 to 1985, based on estimates of sales to retail pharmacies provided by IMS, a market research firm. Sales of benzodiazepine tranquilizers declined slightly between 1980 and 1983 and increased slightly between 1983 and 1985, when sales were 17.1 DDD/1000/d (table 7). However, although total sales changed only slightly during this period, sales of the longer half-life drugs, and especially of diazepam, actually declined fairly steeply, whereas sales of the shorter half-life drugs, especially alprazolam and lorazepam, increased markedly. Sales of benzodiazepine hypnotics increased during this period, from 4.0 to 5.8 DDD/1000/d; again, however, sales of the longer acting flurazepam declined by half, whereas sales of the shorter acting hypnotics temazepam and triazolam increased sharply.

A higher rate of use, but a similar pattern, was reported for Canada in a study of wholesale data by Busto et al. (1989). Although use of benzodiazepine anxiolytics and hypnotics was stable from 1978 to 1982, 33 DDD/1000/d, it began to increase in 1983, reaching 48 DDD/1000/d in 1987. This increase was due to an increase in use of rapidly eliminated benzodiazepines, which accounted for 9% of total use in 1978 and 61% in 1987.

In Ireland, use of benzodiazepine anxiolytics declined from 23.3 DDD/1000/d in 1985 to 21.5 DDD/1000/d in 1987, and use of benzodiazepine hypnotics increased during the same period from 19.0 to 19.8 DDD/1000/d (Henman et al., 1991).

In a study of IMS data reflecting sales in community pharmacies in Chile, Ruiz et al. (1989) found a fairly steady increase in utilization of benzodiazepines from 1982 to 1986, from 11.0 to 18.3 DDD/1000/d; utilization of benzodiazepine hypnotics increased linearly from 3.9 to 7.5 DDD/1000/d. The authors noted that, although the drugs could readily be obtained without prescriptions, the total population exposure was similar to that for countries where sale of benzodiazepines is more strictly controlled.

TABLE 7

Sales of benzodiazepine tranquilizers and hypnotics in the United States, in DDD/1000/d (Food and Drug Administration, 1986)

	1980	1981	1982	1983	1984	1985
Tranquilizers						
Alprazolam		0.1	0.4	1.3	2.4	3.4
Chlordiazepoxide	2.1	1.8	1.6	1.7	1.7	1.7
Clorazepate	1.8	1.6	1.6	1.5	1.5	1.4
Diazepam	11.5	10.0	9.1	8.3	7.7	7.3
Halazepam		<0.1	0.1	<0.1	<0.1	<0.1
Lorazepam	1.2	1.5	1.9	2.1	2.3	2.5
Oxazepam	0.6	0.5	0.5	0.5	0.4	0.4
Prazepam	0.2	0.3	0.4	0.3	0.4	0.3
Total	17.5	15.9	15.4	15.8	16.4	17.1
Hypnotics						
Flurazepam	4.0	3.7	3.1	2.8	2.3	2.0
Temazepam		0.4	1.3	1.7	2.0	2.1
Triazolam			<0.1	0.6	1.2	1.7
Total	4.0	4.1	4.4	5.1	5.5	5.8
Total benzodiazepines	21.5	19.9	19.9	20.9	21.9	22.9

2. Studies of retail data. a. INTERNATIONAL DATA. The sales data discussed in this section were provided by IMS International, an independent research firm that obtains sales data concerning pharmaceutical products in a number of countries representing the majority of the world pharmaceutical market. The data are collected through audits of purchases in drug stores and, for some countries, in hospitals; the pharmacies are selected to be nationally representative, and the sampling procedures are similar, insofar as this is practical, across countries.

The IMS data considered in the following discussion are those calculated as "standard dose units," for which each unit is one tablet, capsule, ampule, or vial, or 5 ml of oral liquid forms.

The data were collected in 31 countries that together account for the great majority of world sales of minor tranquilizers and sedative-hypnotics. Attention should be focused on the overall patterns indicated rather than on the absolute values associated with individual drugs, countries, or time periods: The accuracy and reliability of these absolute values is uncertain, because it is not clear to what extent sampling across countries can be accomplished in a uniform manner. In addition, the figures reflect all sales of each drug, whether it is sold as a single-ingredient product or as part of a combination product; therefore, a sale of a combination product is counted as a sale of each of its ingredients; this method of course tends to inflate values representing sales of individual drugs (although the figures for total sales of tranquilizers and sedative-hypnotics in each country do not reflect such "double counting").

Finally, it should be noted that the statistics described here differ somewhat from those presented in our previous review of similar IMS data. The differences are due to use of a different unit of measurement, to changes in the composition of the group of countries for which these data have been available, and to retrospective adjustments in the IMS database.

Annual per capita exposure of the adult populations of nine countries to benzodiazepine tranquilizers and hypnotics, estimated on the basis of IMS data reflecting sales in retail pharmacies in 1989, is presented in table 8. The countries represented are those accounting for the largest numbers of sales of these drugs worldwide and are listed in order of total benzodiazepine sales volumes. The population sizes shown are limited to persons aged 15 yr or older, because use of these drugs in younger populations is negligible.

The table indicates a wide range in benzodiazepine exposure among the nine countries with respect to both tranquilizers and hypnotics. By far the highest rate of exposure to benzodiazepine tranquilizers is that in France, which also has the highest rate of exposure to benzodiazepine hypnotics. Canada also has a relatively high rate of exposure to benzodiazepine tranquilizers and hypnotics. In the United States, which accounts for the greatest volume of sales of benzodiazepines, per capita exposure to benzodiazepine tranquilizers is approximately at the median level of the countries shown, omitting France, and exposure in the United States to benzodiazepine hypnotics is near the low end of the range for these countries.

As table 8 also indicates, the rates of exposure to benzodiazepine tranquilizers are about three to five times higher than rates of exposure to benzodiazepine hypnotics in each of these countries except the United Kingdom. In the United Kingdom, in 1989, sales of benzodiazepine hypnotics actually exceeded those of benzodiazepine tranquilizers, and per capita exposure to hypnotics was actually 39% higher than per capita exposure to tranquilizers.

This anomaly in the United Kingdom is a relatively recent development, as illustrated in table 9. Trends in pharmacy sales of benzodiazepine tranquilizers and hypnotics in each of the same nine countries represented in table 8, as well as trends in total pharmacy sales in all 31 countries for which IMS data are available, are shown in this table. As the top two rows of the table indicate, total sales of benzodiazepine tranquilizers in the 31 countries together increased by 13% between 1981 and 1989; sales of benzodiazepine hypnotics increased much more rapidly, gaining by 47% during this period.

Among the nine countries with the highest overall sales volumes, there was wide variation in trends of change. In seven countries, sales of benzodiazepine tranquilizers increased by 16% to 105%. Comparison of these figures with those in table 8 shows that in France, which in 1989 had by far the highest per capita exposure to benzodiazepine tranquilizers, this rate had apparently been even slightly higher in 1985; in fact, sales in France peaked in 1986 and declined somewhat by 1989. However, the relatively high rates of exposure to these drugs in Canada and Italy in 1989 were more recent developments: Sales in Canada had increased by 50%, and sales in Italy had increased by 53%, since 1981. In contrast,

TABLE 8

Annual per capita exposure of adult populations (age 15 yr and older) to benzodiazepine tranquilizers and hypnotics dispensed in pharmacies in 1989, based on data provided by IMS International

	Adult population (millions)*	Tranquilizers		Hypnotics	
		Millions of standard dose units	Per capita exposure per yr	Million of standard dose units	Per capita exposure per yr
USA	194.3	3,281	16.9	651	3.4
France	45.0	2,475	55.0	678	15.1
Japan	98.8	1,798	18.2	384	3.9
Italy	47.2	1,154	24.4	301	6.4
UK	46.3	411	8.9	576	12.4
Germany (FRG)	55.1	677	12.3	220	4.0
Spain	30.9	679	22.0	172	5.6
Brazil	92.0	676	7.3	127	1.4
Canada	20.7	639	30.9	161	7.8

* From Demographic Yearbook 1989, United Nations, New York, 1991.

TABLE 9

Trends in sales of benzodiazepine tranquilizers and hypnotics in all countries studied and in nine selected countries (in millions of standard dose units)

	1981	1985	1989	% Change (1981–1989)
Total				
Tranquilizers	14,777	15,910	16,660	+13
Hypnotics	3,283	4,162	4,822	+47
USA				
Tranquilizers	2,822	3,085	3,281	+16
Hypnotics	394	570	651	+65
France				
Tranquilizers	2,068	2,535	2,475	+20
Hypnotics	517	698	678	+31
Japan				
Tranquilizers	1,426	1,561	1,798	+26
Hypnotics	149	243	384	+158
Italy				
Tranquilizers	753	979	1,154	+53
Hypnotics	231	260	301	+30
UK				
Tranquilizers	968	679	411	−58
Hypnotics	634	623	576	−9
Germany (FRG)				
Tranquilizers	1,367	964	677	−50
Hypnotics	154	204	220	+43
Spain				
Tranquilizers	503	547	679	+35
Hypnotics	75	118	172	+129
Brazil				
Tranquilizers	330	330	676	+105
Hypnotics	71	74	127	+79
Canada				
Tranquilizers	425	524	639	+50
Hypnotics	99	154	161	+63

the relatively low rates of per capita exposure to benzodiazepine tranquilizers in the United Kingdom and the Federal Republic of Germany in 1989 had also developed fairly recently: Sales of these drugs in the United Kingdom had decreased by 58%, and sales in Germany had decreased by 50%, since 1981. Among the countries shown in table 9, with the exception of the United Kingdom, sales of benzodiazepine hypnotics increased by rates varying from 30% to 158%.

The United Kingdom was the only one of these nine countries in which sales of benzodiazepine hypnotics decreased during this period, although this decrease (9%) was not nearly so great as the decrease in tranquilizer sales (58%). Thus, although tranquilizer sales in the United Kingdom in 1981 substantially exceeded hypnotic sales and sales of both types of drugs declined in subsequent years, the decline in sales of tranquilizers was so much steeper that sales of hypnotics were higher than those of tranquilizers by 1987. Similar findings from an analysis of prescriptions dispensed in the northern region of Great Britain were reported by Chaplin (1988).

These declines in sales of benzodiazepines in the United Kingdom must be viewed in the light of the government's 1985 restrictions on drugs that could be prescribed on the NHS. The "limited list" of drugs available to NHS patients included only four benzodiazepine anxiolytics and three benzodiazepine hypnotics; previously, ten benzodiazepine anxiolytics and seven benzodiazepine hypnotics had been available to NHS patients (Hindmarch, 1985). According to IMS data, sales of benzodiazepine tranquilizers had actually begun to decline before the limited list went into effect, decreasing by 15% between 1981 and 1984, and sales of benzodiazepine hypnotics had increased 6% between 1981 and 1984 and begun to decline in 1985.

Tables 10 and 11 illustrate trends, from 1981 through 1989, in shares of the minor tranquilizer and sedative-hypnotic markets, respectively, for the agents that led the markets at the end of this period. The trends shown are calculated based on standard units sold in both pharmacies and hospitals in the 31 countries sampled. As indicated in table 10, 11 of the leading 13 minor tranquilizers in 1989 were benzodiazepines. Benzodiazepines altogether accounted for 83% of the total market in 1989, a slight decline from their 85.5% of the market in 1981, although these figures include some double counting of benzodiazepines used in combination products.

Diazepam clearly dominated the market in 1981, with a 30% share, but this had declined to 17% by 1989. Lorazepam accounted for a moderately increasing share of the market until 1986, when it overtook diazepam as the market leader; this agent's share slightly decreased in subsequent years, but not as rapidly as that of diazepam, and lorazepam remained the leading minor tranquilizer in 1989, with 21% of the share of unit sales in this 31-country market. Like diazepam, oxazepam and chlordiazepoxide decreased dramatically in market shares during the period, whereas shares for alprazolam and bromazepam markedly increased.

Similar data for the drugs that led the sedative-hypnotic market in these 31 countries in 1989 are presented in table 11. In interpreting these data, one should note that several of the drugs listed are plant extracts that are common ingredients in numerous combination prod-

TABLE 10

Percentage share of world market for leading minor tranquilizers, based on pharmacy and hospital sales data provided by IMS International

	1981	1982	1983	1984	1985	1986	1987	1988	1989
Lorazepam	17.2	19.3	20.5	21.0	21.4	21.7	21.5	21.0	20.7
Diazepam	30.3	27.9	26.0	23.9	22.1	21.1	19.5	18.3	17.1
Alprazolam	0.1	0.5	1.7	3.4	5.2	7.3	9.0	10.1	10.5
Bromazepam	5.8	6.8	7.5	8.1	8.7	8.8	9.1	9.3	9.7
Oxazepam	10.5	10.2	9.6	9.1	8.5	7.9	7.2	7.0	6.4
Clorazepate	7.8	7.7	7.6	7.3	6.9	6.5	6.0	5.7	5.2
Hydroxyzine	3.7	3.7	3.7	3.8	3.9	4.0	4.1	4.2	4.5
Chlordiazepoxide	7.8	6.9	6.3	5.7	5.6	4.7	4.3	3.9	4.1
Clotiazepam	1.4	1.6	1.7	2.0	2.3	2.4	2.5	2.6	2.7
Etizolam	0.0	0.0	0.0	0.3	0.9	1.3	1.7	2.2	2.5
Meprobamate	3.6	3.4	3.2	3.2	2.9	2.5	2.4	2.1	2.1
Prazepam	2.0	2.1	2.1	2.2	2.1	2.1	2.1	2.0	2.0
Clobazam	2.6	2.6	2.6	2.6	2.3	2.2	2.1	2.0	1.9

TABLE 11

Percentage share of world market for leading sedative-hypnotics, based on pharmacy and hospital sales data provided by IMS International

	1981	1982	1983	1984	1985	1986	1987	1988	1989
Phenobarbital	24.3	23.1	22.1	21.5	20.1	18.3	17.8	17.1	18.4
Triazolam	2.4	3.9	6.7	9.2	11.5	13.6	16.0	17.1	16.2
Valeriana officinalis	13.0	12.9	12.8	12.6	13.5	13.9	13.9	14.2	14.2
Crataegus oxyacantha	6.6	6.4	6.4	6.5	6.8	7.2	7.4	7.7	8.1
Passiflora incarnata	5.6	5.7	5.8	6.0	6.5	6.8	6.9	7.3	7.8
Nitrazepam	14.2	13.7	12.6	11.5	10.4	9.6	8.5	7.9	7.1
Temazepam	1.9	3.4	4.5	5.4	6.4	6.9	7.0	7.0	6.9
Flunitrazepam	4.2	5.1	5.4	5.9	6.3	6.6	6.6	6.7	6.6
Humulus lupulus	5.8	5.7	6.0	5.9	5.8	6.2	6.5	6.5	6.3
Flurazepam	10.0	9.6	8.8	7.6	6.1	5.3	4.7	4.3	3.8
Viscum album	2.4	2.4	2.6	2.5	2.6	2.8	2.9	3.1	3.1
Atropa belladonna	4.7	4.7	4.6	4.2	3.9	3.6	3.2	2.9	2.6
Diphenhydramine	2.3	2.2	2.5	2.5	2.4	2.2	2.4	2.6	2.5
Ballota foetida	0.6	0.6	0.7	0.9	1.4	1.8	1.7	2.0	2.4

ucts, sold most frequently in several western European and Latin American countries. As mentioned before, the figures given for these drugs are no doubt inflated by the method of calculation, because each sale of a combination product is counted as a sale of each of its ingredients. In this connection, it should also be recognized that, in addition to these plant extracts, agents such as phenobarbital are commonly used in combination products, and some of the nonbenzodiazepines listed are also used in combinations with benzodiazepines.

These caveats notwithstanding, the data indicate that, altogether, benzodiazepines accounted for 36% of the market in 1981 and for 50% in 1989. Despite this marked increase in the benzodiazepines' share during the period, there is still apparently much greater diversity in prescriptions of sedative-hypnotics than of minor tranquilizers (because, as mentioned, benzodiazepines accounted for 83% of the minor tranquilizer market in 1989).

Five of the 14 leading sedative-hypnotics in 1989 were benzodiazepines. The greatest increase in market share was that of the newest agent, triazolam, and shares for temazepam and flunitrazepam also increased; the older drugs, flurazepam and nitrazepam, sharply declined in market shares. Phenobarbital continued to lead the market during the entire period.

It is of interest to consider the variation in these markets across the 31 countries for which IMS data are available. Relative shares of the minor tranquilizer market and of the sedative-hypnotic market in each of the 31 countries in 1989 are presented in tables 12 and 13, respectively. These data reflect sales only in retail pharmacies, except that the data for Sweden reflect sales in both pharmacies and hospitals. Numbers in parentheses to the right of each country name are the percentages of the total tranquilizer or sedative-hypnotic market represented by all sales (not only those of the leading drugs shown) in that country. For each country, either the ten leading drugs or all drugs that had at least a 2% share of the market are shown.

As indicated in table 12, the United States (24%) and France (17%) together accounted for 41% of the 31-country total of minor tranquilizer sales; Japan (11%) and Italy (7%) accounted for the next most substantial proportions of sales. Benzodiazepines predominated among minor tranquilizers sold in all 31 countries. In western Europe, lorazepam predominated in five countries, while oxazepam led the markets in four. Diazepam accounted for the greatest market shares in nine of the 31 countries studied, and bromazepam predominated in six. The United States was the only country in which alprazolam led the minor tranquilizer market in 1989.

Similar data regarding sales of sedative-hypnotics are presented in table 13. Again, the United States (20%) and France (17%) together accounted for a substantial proportion of the 31-country total sales; the Federal Republic of Germany also accounted for a large proportion of sales of these drugs (16%). Benzodiazepines led the markets in 17 of the 31 countries. Triazolam accounted for the greatest percentage of unit sales in eight countries, as did flunitrazepam in six and temazepam in three.

However, benzodiazepines do not predominate among sedative-hypnotic markets to the extent that they do among tranquilizer markets. Phenobarbital had the greatest market shares in a number of countries. In several of the western European countries, including France, the Federal Republic of Germany, the Netherlands, Switzerland, and Austria, the most widely prescribed sedative-hypnotics appear to be combination products.

b. NATIONAL DATA. **i. United States.** Data regarding retail drug sales in the United States are collected in the NPA (IMS America Ltd.) from a representative sample of chain and independent pharmacies. As noted in our previous review (and, more recently, by Baum et al., 1988), NPA data indicated that sales of minor tranquilizer prescriptions peaked in 1975, declined until 1981, and subsequently increased slightly; sales of benzodiazepine hypnotics increased steadily from their introduction into the mid-1980s. As shown in table 14, sales of benzodiazepine minor tranquilizers increased from 1985 to 1986 and then steadily declined by a total of 13% by 1989. Sales of benzodiazepine hypnotics increased slightly from 1985 to 1986, remained stable in 1987, and subsequently declined by 15% through 1989.

The percentage share of the tranquilizer and hypnotic markets between 1985 and 1989 claimed by each of the individual agents marketed in the United States is also shown in table 14. Among the tranquilizers, the greatest changes reflected a shift in prescribing from diazepam, which declined from 37% to 25% of the market during this period, to alprazolam, which increased its share from 18% to 33%. Among the hypnotics, flurazepam sales declined from 38% to 21% of the market, whereas triazolam sales increased from 35% to 49% of the market.

TABLE 12

Sales of minor tranquilizers by market share in 1989, based on pharmacy sales data provided by IMS International

Country and drug	Market share (%)
Western Europe	
Austria (0.6)*	
Bromazepam	33
Lorazepam	26
Oxazepam	14
Diazepam	11
Prazepam	5
Meprobamate	4
Clorazepate	3
Clobazam	2
Haloperidol	2
Isopropamide hydroxide	2
Germany (FRG) (4.1)	
Oxazepam	40
Bromazepam	21
Diazepam	15
Lorazepam	8
Clorazepate	5
Prazepam	2
Clobazam	2
Chlordiazepoxide	2
Netherlands (1.3)	
Oxazepam	37
Diazepam	20
Lorazepam	17
Bromazepam	7
Chlordiazepoxide	6
Clorazepate	5
Meprobamate	2
Clobazam	2
Belgium (2.3)	
Lorazepam	36
Bromazepam	24
Oxazepam	8
Alprazolam	6
Clorazepate	6
Diazepam	6
Clotiazepam	4
Prazepam	3
Meprobamate	2
Hydroxyzine	2
Greece (1.3)	
Lorazepam	34
Bromazepam	29
Diazepam	14
Clorazepate	7
Prazepam	4
Clobazam	4
Alprazolam	3
Hydroxyzine	3
Portugal (2.5)	
Lorazepam	27
Bromazepam	21
Diazepam	17
Alprazolam	8
Clorazepate	8
Clobazam	6
Cloxazolam	5
Hydroxyzine	3
Oxazepam	2
Halazepam	2
Finland (0.5)	
Oxazepam	29
Diazepam	27
Lorazepam	18
Alprazolam	11
Chlordiazepoxide	5
Clorazepate	5
Hydroxyzine	5
Ireland (0.3)	
Diazepam	45
Bromazepam	11
Chlordiazepoxide	11
Lorazepam	10
Alprazolam	6
Clorazepate	5
Prazepam	5
Clobazam	4
Medazepam	2
Spain (4.2)	
Diazepam	24
Lorazepam	22
Clorazepate	16
Pyridoxine	12
Bromazepam	12
Thiamine	9
Alprazolam	8
Ketazolam	3
Bentazepam	2
Clobazam	2
France (17.3)	
Lorazepam	33
Bromazepam	11
Clorazepate	11
Oxazepam	7
Prazepam	6
Clobazam	6
Meprobamate	5
Phenobarbital	4
Febarbamate	4
Difebarbamate	4
Italy (6.9)	
Lorazepam	49
Bromazepam	16
Diazepam	11
Delorazepam	6
Alprazolam	5
Prazepam	4
Clotiazepam	3
Oxazepam	2
Ketazolam	2
Sweden (1.3)*	
Oxazepam	58
Diazepam	25

* Includes hospital as well as pharmacy sales.

TABLE 12—*Continued*

Country and drug	Market share (%)
Lorazepam	5
Alprazolam	4
Hydroxyzine	4
Chlordiazepoxide	2
Switzerland (0.8)	
Oxazepam	27
Bromazepam	26
Lorazepam	18
Diazepam	7
Clorazepate	4
Alprazolam	3
Phenobarbital	3
Febarbamate	3
Difebarbamate	3
Ketazolam	3
United Kingdom (2.6)	
Diazepam	50
Lorazepam	20
Chlordiazepoxide	12
Oxazepam	8
Hydroxyzine	2
Meprobamate	2
Buspirone	2
Clobazam	2
Latin America	
Argentina (3.5)	
Bromazepam	40
Lorazepam	35
Diazepam	10
Alprazolam	5
Clorazepate	4
Clobazam	2
Mexico (1.2)	
Lorazepam	26
Diazepam	22
Bromazepam	19
Clorazepate	11
Alprazolam	7
Hydroxyzine	6
Clobazam	4
Buspirone	2
Oxazepam	2
Brazil (4.2)	
Bromazepam	29
Diazepam	25
Lorazepam	22
Clobazam	7
Cloxazolam	5
Alprazolam	4
Buspirone	2
Pimethixene	2
Clorazepate	2
Venezuela (0.3)	
Bromazepam	39
Lorazepam	18
Clorazepate	17
Diazepam	17
Clobazam	4
Temazepam	2
Chlordiazepoxide	2
Chile (1.0)	
Diazepam	33
Lorazepam	22
Bromazepam	19
Alprazolam	13
Chlordiazepoxide	7
Columbia (0.4)	
Lorazepam	27
Hydroxyzine	22
Diazepam	17
Alprazolam	9
Clorazepate	8
Buspirone	8
Bromazepam	6
Clobazam	3
North America	
United States (23.9)	
Alprazolam	28
Diazepam	19
Lorazepam	15
Hydroxyzine	10
Chlordiazepoxide	9
Clorazepate	6
Meprobamate	4
Buspirone	4
Oxazepam	2
Prazepam	2
Canada (4.9)	
Lorazepam	28
Diazepam	21
Tryptophan	19
Oxazepam	10
Alprazolam	8
Bromazepam	5
Chlordiazepoxide	4
Hydroxyzine	3
Clorazepate	2
Far East	
Japan (11.2)	
Diazepam	17
Clotiazepam	14
Etizolam	13
Oxazolam	9
Alprazolam	8
Chlordiazepoxide	7
Tofisopam	6
Hydroxyzine	4
Fludiazepam	4
Medazepam	4
South Korea (0.3)	
Diazepam	49
Lorazepam	25
Hydroxyzine	13
Medifoxamine	6
Clobazam	2

TABLE 12—*Continued*

Country and drug	Market share (%)
South Pacific	
Australia (1.2)	
Diazepam	45
Oxazepam	40
Lorazepam	4
Alprazolam	4
Bromazepam	3
Chlordiazepoxide	2
Indonesia (0.3)	
Diazepam	49
Chlordiazepoxide	18
Bromazepam	10
Lorazepam	8
Meprobamate	8
Clobazam	7
Clorazepate	4
Medazepam	2
New Zealand (0.1)	
Diazepam	34
Lorazepam	29
Oxazepam	23
Bromazepam	6
Chlordiazepoxide	5
Meprobamate	2
Africa and the Middle East	
Egypt (0.4)	
Diazepam	37
Lorazepam	19
Bromazepam	12
Clorazepate	10
Hydroxyzine	10
Delorazepam	6
Clobazam	3
Temazepam	2
Morocco (0.2)	
Bromazepam	19
Lorazepam	18
Diazepam	12
Clorazepate	10
Clobazam	8
Hydroxyzine	7
Alprazolam	7
Prazepam	6
Nordazepam	3
Meprobamate	3
Saudi Arabia (0.0)	
Bromazepam	43
Diazepam	22
Sulpiride	19
Clobazam	10
Clorazepate	3
Chlordiazepoxide	3
South Africa (0.5)	
Bromazepam	24
Lorazepam	18
Oxazepam	18
Diazepam	10
Alprazolam	8
Clobazam	6
Hydroxyzine	5
Prazepam	3
Chlordiazepoxide	2
Buspirone	2

Thus, the newer, short half-life drugs gained considerably in market share, and sales of the older, longer half-life drugs declined.

A survey of prescriptions filled in a national sample of retail pharmacies provided information about the prevalence of long-term use of several benzodiazepines marketed in the United States (Oleen and Gardner, 1990). Of the patients who filled prescriptions in January 1988, a total of 5.9% continued to receive prescriptions that would have permitted regular use for 12 mo. This included 3.1% of those who initially filled new prescriptions and 9.4% of those who initially filled refill prescriptions; this latter group, therefore, represented a subgroup of patients who had continued to receive these drugs for more than 12 mo. Among the individual benzodiazepines studied, the highest rates of long-term use were those for oxazepam (7.7%) and temazepam (7.7%), and 12-mo persistence of prescriptions for clorazepate, diazepam, and alprazolam were 3.5%, 3.4%, and 3.3%, respectively.

ii. Great Britain. The Department of Health and Social Security estimated that sales of benzodiazepine prescriptions increased from about 16.5 million in 1972 to about 25.5 million in 1979 and declined to about 21 million in 1986 (Cantopher et al., 1988). Like the IMS sales data described previously in this section, these government data also indicated that benzodiazepine prescriptions had declined steadily from 1981 through 1984, i.e., previous to the government's 1985 restrictions on NHS prescriptions of these drugs.

Similar numbers of benzodiazepine prescriptions were reported to have been dispensed by the Family Practitioner Service (Taylor, 1987). Prescriptions for benzodiazepine anxiolytics increased from about 10 million in 1970 to 18 million in 1978 and declined to 12 million by 1985. Prescriptions for benzodiazepine hypnotics, however, increased steadily from less than 5 million in 1970 to 13 million in 1980 and reached about 14 million in 1985. As in other countries, there was a significant shift from the longer to the shorter acting drugs.

iii. Federal Republic of Germany. Data collected annually by the National Health Insurance Agencies indicated that 19.3 million prescriptions for benzodiazepines had been dispensed in 1984. This represented a substantial decline in prescriptions for benzodiazepine

TABLE 13

Sales of sedative-hypnotics by market share in 1989, based on pharmacy sales data provided by IMS International

Country and drug	Market share (%)
Western Europe	
Austria (1.2)	
Valeriana officinalis	43
Passiflora incarnata	26
Melissa officinalis	22
Cinnamomum zeylanicum	16
Citrus aurantium	16
Flunitrazepam	14
Humulus lupulus	13
Viscum album	13
Passiflora alata	13
Meprobamate	7
Germany (FRG) (15.6)	
V. officinalis	54
H. lupulus	38
Crataegus oxyacantha	19
V. album	18
P. incarnata	15
Hypericum perforatum	14
M. officinalis	13
Guaifenesin	10
Avena sativa	7
Mentha piperata	6
Netherlands (2.2)	
V. officinalis	25
Temazepam	17
Nitrazepam	15
Phenobarbital	12
A. sativa	9
Flurazepam	6
Lormetazepam	6
H. lupulus	5
P. incarnata	5
Flunitrazepam	5
Belgium (1.8)	
Flunitrazepam	20
Lormetazepam	17
Triazolam	16
C. oxyacantha	9
Phenobarbital	9
Nitrazepam	8
P. incarnata	7
Ballota foetida	6
Ergotamine	4
Atropa belladonna	4
Greece (0.4)	
Flunitrazepam	43
Triazolam	26
Phenobarbital	16
Temazepam	7
Nitrazepam	4
C. oxyacantha	3
P. incarnata	3
V. officinalis	3
Portugal (1.0)	
Triazolam	25
Phenobarbital	11
Composition unknown	10
Flunitrazepam	9
V. officinalis	9
Estazolam	9
Flurazepam	7
Temazepam	5
P. incarnata	3
Brotizolam	3
Finland (0.8)	
Triazolam	30
Temazepam	19
Nitrazepam	14
V. officinalis	8
Phenobarbital	8
Amobarbital	8
Codeine	8
Adonis vernalis	8
Convallaria majalis	8
Zopiclone	7
Ireland (0.4)	
Temazepam	21
Nitrazepam	16
Flurazepam	16
Phenobarbital	15
Triazolam	15
Flunitrazepam	6
Lormetazepam	4
Clomethiazole	3
Zopiclone	2
Spain (2.8)	
Triazolam	30
Phenobarbital	16
Lormetazepam	12
Flunitrazepam	10
V. officinalis	9
Flurazepam	6
Loprazolam	3
Nitrazepam	3
C. oxyacantha	3
P. incarnata	3
France (17.4)	
C. oxyacantha	24
P. incarnata	19
V. officinalis	18
Aceprometazine	14
B. foetida	14
Triazolam	14
Phenobarbital	13
Paullinia cupana	12
Cola nitida	12
Flunitrazepam	9
Italy (5.6)	
Triazolam	27
Phenobarbital	21
V. officinalis	18
Flurazepam	8
Flunitrazepam	7
Lormetazepam	7
P. incarnata	6
C. oxyacantha	4
A. belladonna	4
Bromine	4

* Includes hospital as well as pharmacy sales.

TABLE 13—*Continued*

Country and drug	Market share (%)
Sweden (1.9)*	
Flunitrazepam	31
Nitrazepam	25
V. officinalis	17
Propiomazine	15
Promethazine	3
Phenobarbital	3
Chloral hydrate acetylglycinamide	2
Clomethiazole	2
Triazolam	2
Switzerland (1.8)	
P. incarnata	34
H. lupulus	26
C. oxyacantha	24
V. officinalis	23
Geum aleppicum	14
Ilex aquifolium	14
Olea europea	14
Flunitrazepam	11
M. officinalis	11
Triazolam	11
United Kingdom (7.5)	
Temazepam	40
Nitrazepam	27
Triazolam	12
Phenobarbital	8
Clomethiazole	3
Chloral hydrate	2
Amobarbital	2
Dichloralphenazone	2
Latin America	
Argentina (1.1)	
Flunitrazepam	34
Phenobarbital	26
Triazolam	24
Midazolam	3
Nitrazepam	3
Flurazepam	2
Lormetazepam	2
Pentobarbital	2
Homatropine methylhydroxide	2
Benactyzine	2
Mexico (0.9)	
Flunitrazepam	27
Triazolam	17
P. incarnata	17
V. officinalis	17
C. oxyacantha	16
Marrubium vulgare	14
Phenobarbital	8
Calcium	7
Nitrazepam	7
Composition unknown	5
Brazil (4.7)	
Phenobarbital	48
P. incarnata	14
Composition unknown	12
C. oxyacantha	10
Salix alba	8
Flunitrazepam	8
Triazolam	7
Flurazepam	6
Calcium	6
Ergocalciferol	6
Venezuela (0.6)	
Phenobarbital	45
P. incarnata	20
C. oxyacantha	18
V. officinalis	15
S. alba	13
Flunitrazepam	11
Calcium	11
Nitrazepam	5
H. lupulus	4
Ergotamine	4
Chile (0.3)	
Flunitrazepam	31
Calcium	26
Triazolam	18
Phenobarbital	9
Midazolam	5
Ergotamine	5
A. belladonna	5
Thiamine	4
Brotizolam	3
Lormetazepam	3
Colombia (0.2)	
Triazolam	31
Flunitrazepam	26
Phenobarbital	20
Composition unknown	17
Midazolam	7
North America	
United States (19.7)	
Phenobarbital	39
Triazolam	20
Temazepam	9
Flurazepam	7
Diphenhydramine	7
Doxylamine	3
Methapyrilene	3
Composition unknown	3
Secbutabarbital	3
Salicylamide	2
Canada (2.6)	
Triazolam	42
Flurazepam	15
Phenobarbital	15
Diphenhydramine	10
Nitrazepam	5
Temazepam	4
Chloral hydrate	3
Secobarbital	2
Ergotamine	2
A. belladonna	2
Far East	
Japan (5.5)	
Triazolam	35
Phenobarbital	16
Nitrazepam	15
Ergotamine	12

TABLE 13—*Continued*

Country and drug	Market share (%)
A. belladonna	12
Estazolam	11
Flunitrazepam	7
Brotizolam	4
Flurazepam	3
P. incarnata	2
South Korea (0.3)	
Phenobarbital	59
Doxylamine	25
V. officinalis	15
C. oxyacantha	14
South Pacific	
Australia (1.8)	
Temazepam	46
Nitrazepam	28
Flunitrazepam	8
Chloral hydrate	5
Paracetamol	4
Phenobarbital	4
Promethazine	4
Indonesia (0.3)	
Phenobarbital	85
Nitrazepam	7
Estazolam	5
Flurazepam	2
New Zealand (0.4)	
Triazolam	56
Nitrazepam	11
Temazepam	10
Phenobarbital	8
Zopiclone	3
Composition unknown	3
Chloral hydrate	2
Clomethiazole	2
Lormetazepam	2
Africa and the Middle East	
Egypt (0.4)	
Bromine	83
Citric acid	70
Chloroform	69
Benzoic acid	69
A. belladonna	69
Elettaria cardamomum	69
Composition unknown	11
Chloral hydrate	3
Temazepam	2
Morocco (0.3)	
Phenobarbital	43
Calcium	41
Acetylsalicylic acid	16
Triazolam	5
Ergotamine	4
A. belladonna	4
Doxylamine	3
Bromine	3
Flunitrazepam	3
Nitrazepam	2
Saudi Arabia (0.0)	
Phenobarbital	74
Ergotamine	48
A. belladonna	48
Calcium	19
Nitrazepam	5
South Africa (0.5)	
Phenobarbital	24
Triazolam	22
Flunitrazepam	12
Temazepam	8
Diphenhydramine	5
Nitrazepam	5
V. officinalis	4
Centranthus ruber	4
Corydalis	4
A. sativa	4

anxiolytics since 1981, whereas prescriptions for benzodiazepine hypnotics had slightly increased during this period (Müller-Oerlinghausen and Schmidt, 1987).

iv. Australia. Prescriptions for temazepam, nitrazepam, diazepam, and oxazepam dispensed under the Pharmaceutical Benefits Scheme declined from 6.0 million in 1978 to 4.6 million in 1980, increased to 6.5 million in 1982, and subsequently declined to 5.8 million in 1984. IMS data provided similar estimates of the numbers of dispensed prescriptions that were written by general practitioners for these benzodiazepines between 1980 and 1984 (Mant et al., 1987a).

3. Summary and discussion. a. STUDIES OF WHOLESALE DATA. The use of the DDD/1000/d standard of measurement, which can be used to compare relative exposures of various populations to drugs, was pioneered in Norway and other Scandinavian countries in the late 1970s. This measure was applied, based on wholesale sales data, to compare rates of exposure of a few western European nations to benzodiazepines in the late 1970s and early 1980s.

More recently, similar studies using this standard have extended our awareness of relative rates of exposure to other regions. For example, the exposure of the United States population to benzodiazepine tranquilizers in 1985 was 17 DDD/1000/d, and exposure to benzodiazepine hypnotics was 6 DDD/1000/d. This rate for tranquilizers is comparable to those that had been reported for the Scandinavian countries in 1980, which ranged from 17 to 35 DDD/1000/d; however, the United States rate for exposure to benzodiazepine hypnotics is substantially

TABLE 14
Percentage shares of total prescriptions for benzodiazepine minor tranquilizers and hypnotics dispensed in United States retail pharmacies (based on data from the National Prescription Audit; IMS America, Ltd.)

	1985	1986	1987	1988	1989
Minor tranquilizers	(62.8)*	(64.3)	(63.5)	(61.6)	(56.1)
Alprazolam	18	24	28	32	33
Chlordiazepoxide	12	11	10	9	9
Clorazepate	11	11	10	9	9
Diazepam	37	33	29	26	25
Halazepam	<1	<1	<1	<1	<1
Lorazepam	15	16	17	18	19
Oxazepam	4	3	3	3	3
Prazepam	3	2	3	2	2
Hypnotics	(19.9)	(20.9)	(21.0)	(20.6)	(17.9)
Flurazepam	38	31	25	21	21
Temazepam	27	26	26	26	30
Triazolam	35	43	49	53	49

* Numbers in parentheses represent total sales of benzodiazepine minor tranquilizers and hypnotics for each of the years shown, in millions.

below that for the Scandinavian countries, which in 1980 averaged about 25 DDD/1000/d.

Rates of exposure of the population of Canada in 1978 to 1982 totaled about 33 DDD/1000/d and in 1987 increased to 48 DDD/1000/d. Lower rates were reported for Chile, where exposure to benzodiazepines in 1982 was calculated as 11 DDD/1000/d and in 1986 as 18 DDD/1000/d.

These studies have also provided indications of recent shifts within the benzodiazepine market. In some countries, including the United States and Canada, there has been a pronounced decline in sales of the older benzodiazepines in favor of the newer agents, which tend to have shorter half-lives. Another shift in several countries is that sales of benzodiazepine hypnotics have increased substantially more than sales of benzodiazepine tranquilizers.

b. STUDIES OF RETAIL DATA. Data concerning retail sales of benzodiazepines support and elaborate the findings of analyses of wholesale data. The countries with the highest volumes of pharmacy sales of benzodiazepines in 1989, in descending order, were the United States, France, Japan, Italy, the United Kingdom, the Federal Republic of Germany, Spain, Brazil, and Canada. Pharmacy sales of benzodiazepines indicate a wide variation in rates of per capita exposure among the countries studied. The highest per capita exposure was that of France, as has been the case for a number of years; the rate of exposure of the United States population was in about the middle of the range of the countries with the highest volumes of benzodiazepine sales. These findings parallel the results of cross-national household surveys.

Sales of benzodiazepine tranquilizers in 1989 were three to five times higher than sales of hypnotics in most countries studied. However, between 1981 and 1989 sales of hypnotics increased much more rapidly than those of tranquilizers; total sales of benzodiazepine hypnotics in 31 countries increased during this period by 47%, as opposed to an increase of 13% for tranquilizers.

Among the nine countries with the highest volumes of benzodiazepine sales, there was a wide variation in the rates of change in sales between 1981 and 1989. Sales of benzodiazepine tranquilizers increased in seven countries, by rates ranging from 16% to 105%; however, tranquilizer sales dramatically decreased in the United Kingdom and the Federal Republic of Germany. Sales of benzodiazepine hypnotics increased, by 30% to 158%, in each of these countries except the United Kingdom, where hypnotic sales decreased slightly.

If worldwide sales of all drugs classified as minor tranquilizers are considered, benzodiazepines accounted for 83% of the total market in 1989. Benzodiazepines were the most frequently sold tranquilizers in each of 31 countries studied. Benzodiazepines did not dominate the world sedative-hypnotic market but had increased their overall share from about 36% in 1981 to 50% in 1989; they were the market leaders in 17 of the 31 countries studied. The United States and France together accounted for 41% of all sales of minor tranquilizers in the countries studied, and these nations together with the Federal Republic of Germany accounted for 53% of the total sedative-hypnotic market. Analysis of trends in retail sales of individual benzodiazepines reveals the same pattern shown by studies of wholesale data, namely, that sales of the older agents substantially declined during the 1980s, whereas sales of the newer, short half-life drugs dramatically increased.

C. Surveys of Prescribing Patterns

The studies considered in this section provide data that reflect individual prescriptions and thus some insight into the circumstances under which benzodiazepines are prescribed. The section is divided into two subsections, in which the studies are grouped according to the types of data considered. The first subsection deals with surveys in which physicians have provided information about the prescriptions they have issued; the second deals with surveys of various types of records of prescriptions, including pharmacy records, medical records, etc.

These data are an important source of information about the prevalence of benzodiazepine prescriptions in various populations and the distribution of these prescriptions with respect to population subgroups. However, most studies of prescription records reflect only individual patient visits when drug prescriptions are written or particular, usually brief, periods during which patients are found to receive or have prescriptions; although these studies link prescriptions with some information about patients, they provide little or no information about the antecedents or consequences of prescriptions, including the patients' histories or how the

prescriptions are actually used. Some studies, on the other hand, link prescriptions with individual patients' medical records; their findings bear more clearly on the question of the extent to which the prescriptions are appropriate. Another limitation of studies that focus on prescription records is that, although many publications refer to these data as if they measured "use," in fact, almost none of them do measure actual consumption of the drugs prescribed; it is important to recall this distinction when interpreting the findings.

1. Surveys of physicians. In our previous review (Woods et al., 1987), we found, based on evidence from physician surveys, that most prescriptions for benzodiazepine anxiolytics and hypnotics are written by primary care physicians for patients who have previously consulted the same physicians and represent continued therapy for problems previously treated by these physicians. About half of the patients receiving prescriptions for these drugs have primary diagnoses of mental disorders. The prevalence of prescriptions increases with age up to about age 65 yr; among those older than 45 yr, women receive nearly twice as many as men. We also found from these studies that at least the great majority of prescriptions for benzodiazepines is consistent with what is known about the clinical utility of these medications.

a. NATIONAL SURVEYS IN THE UNITED STATES. **i. National Disease and Therapeutic Index.** The NDTI is an ongoing survey of a nationally representative sample of United States physicians in private practice, conducted by IMS America, Ltd. We examined the NDTI data presenting aggregate numbers for the benzodiazepine tranquilizers as a group for the 12 mo ending June 1991; we also compared these with equivalent data for the 12 mo ending in March 1982 and in March 1986, which we had considered in our previous review, to note any indications of changes in prescribing patterns. Of all patient visits at which a benzodiazepine tranquilizer was prescribed in 1990 to 1991, 85% were visits by patients who had been seen previously by the prescriber; 69% of all prescriptions were for patients who had previously received a prescription for the same medication from the same prescriber. The distribution of these prescriptions by patients' ages is shown in table 15. These rates and age distributions have been virtually unchanged for at least the last 10 yr.

TABLE 15

Distribution of prescriptions of benzodiazepine tranquilizers and hypnotics by patients' ages (based on 1990–1991 data from the NDTI; IMS America, Ltd.)

Age (yr)	% of prescriptions	
	Tranquilizers	Hypnotics
0–19	1	1
20–39	27	20
40–59	36	31
60–64	9	9
≥65	27	38

The total number of prescriptions for benzodiazepine tranquilizers, as estimated by the NDTI, increased by 27% between 1982 and 1986 and declined by 10% between 1986 and 1991. The percentage of these prescriptions written by primary care physicians (general practitioners, family practitioners, and internists) steadily declined from 53% to 46% during this period; the percentage written by psychiatrists increased from 19% in 1982 to 23% in 1986 and remained at that level through 1991. The percentage of prescriptions issued to patients in physicians' offices steadily increased from 59% in 1982 to 69% in 1991, whereas the percentage issued in hospitals steadily declined during this period from 28% to 16%; the proportion issued through telephone contacts between the patient and physician (or the physician's office staff) fluctuated between 10% and 15%.

In 1982, 45% of benzodiazepine tranquilizer prescriptions were written for patients whose principal diagnoses were of mental disorders; by 1991, this proportion had increased to 59%. Most of this increase related to prescriptions for patients whose principal diagnoses were of anxiety states. Physicians were also asked to record the desired actions of the drugs prescribed; at all of the times studied, approximately 70% of the prescriptions were written with the intent to reduce anxiety or tension.

There is substantial variation in diagnoses associated with prescriptions for the various individual benzodiazepine tranquilizers. For example, the proportions of prescriptions for patients with principal diagnoses of mental disorders ranged from 43%, for Valium (diazepam), to 75%, for Xanax (alprazolam). These two agents represented extremes of the ranges also for specific diagnoses of anxiety disorders (24% for Valium and 39% for Xanax) and of nonpsychotic depressive disorders (6% for Valium and 16% for Xanax). Relatively large proportions of prescriptions for certain tranquilizers were written for patients with other diagnoses. Twenty-four percent of prescriptions for Librium (chlordiazepoxide) were for patients whose principal diagnoses reflected acute alcohol withdrawal syndromes. Seventeen percent of prescriptions for Centrax (prazepam) were for patients with sprains and strains.

Examination of the NDTI data concerning benzodiazepine hypnotics indicates a 30% decline in total prescriptions between 1986 and 1991, at least with respect to the brand name versions of these drugs; prescriptions of Dalmane (flurazepam) declined the most, at 57%, prescriptions for Halcion (triazolam) declined by 21%, and those for Restoril (temazepam) declined by 24%. In 1990 to 1991, 62% of benzodiazepine hypnotic prescriptions represented continued therapy for the same indications in the same patients, and the prescribers had previously seen these patients on 82% of the occasions on which they issued such prescriptions. Thirty-eight percent of the prescriptions were written by primary care physicians, 22% by surgeons (general, orthopedic, and

other), 16% by psychiatrists, and 8% by obstetricians/gynecologists. Fifty-three percent of the prescriptions were written for patients visiting physicians' offices, 34% in hospitals, and 11% as a result of telephone contacts.

The distribution of these prescriptions by patients' ages is shown in table 15. As shown, in comparison with the distribution for tranquilizer prescriptions, a greater proportion of hypnotic prescriptions was issued to elderly patients (38% versus 27%). However, the data also indicate that the rates of hypnotic prescriptions declined with increasing age within the elderly population, i.e., 19% were issued to those between 65 and 74 yr, 14% to those between 75 and 84 yr, and 5% to those 85 yr and older. This age distribution has been virtually unchanged during at least the last 5 yr.

Most (68%) prescriptions for benzodiazepine hypnotics were written concurrently with prescriptions for other drugs, most commonly analgesics (26%) and benzodiazepine tranquilizers (11%).

The most common principal diagnoses of patients who received prescriptions for benzodiazepine hypnotics in 1990 to 1991 were mental disorders, of which most were anxiety disorders or manic-depressive psychosis. These drugs were also commonly used to promote sleep in postsurgical patients. Although sleep disturbance was the primary diagnosis in only 20% of cases for which prescriptions were issued for benzodiazepine hypnotics, 97% of these prescriptions were intended to promote sleep or provide sedation; thus, the majority of patients who received these drugs had sleep disturbance secondary to other diagnoses.

ii. National Ambulatory Medical Care Survey. The National Ambulatory Medical Care Survey is a survey of a national sample of United States physicians in private office practice; the survey is conducted by the National Center for Health Statistics. As we noted in our previous review, an analysis of the data for 1980 and 1981 (Koch and Campbell, 1983) revealed that psychotropic drugs were prescribed at 6% of all office visits and that benzodiazepines accounted for 46.5% of all psychotropics prescribed. Reports of the 1985 data regarding all office visits have not provided specific information about rates of use of benzodiazepines. However, in one report of the 1985 data, Koch and Knapp (1987) indicated that anxiolytics, sedatives, and hypnotics accounted for 3.3% of all drugs mentioned at office visits and that this rate was 17% less than in 1981. It can be assumed that benzodiazepines accounted for the vast majority of these drug categories.

In our previous review, we also noted that analyses of the 1980 to 1981 National Ambulatory Medical Care Survey data had indicated that primary care physicians were responsible for 66% of prescriptions for psychotropic drugs (Koch and Campbell, 1983) and that, at the majority (58%) of visits when psychotropics were prescribed, no mental diagnosis was recorded (Jencks, 1985). In a later study of the 1980 to 1981 data, Beardsley et al. (1988) found that, in particular, the category of psychotropics most frequently prescribed at visits to primary care physicians was anxiolytics; primary care physicians were responsible for 72.2% of anxiolytic prescriptions and for 68.9% of prescriptions for sedatives and hypnotics. These investigators also found that diagnoses of mental disorder were recorded at only 39.9% of visits to primary care physicians when an anxiolytic prescription was issued and at only 19.7% of such visits resulting in prescriptions for sedatives or hypnotics.

Commenting on the reasons for "the relatively low documentation of mental disorders" by primary care practitioners who prescribe psychotropics, Beardsley et al. noted "It is. . .unclear if [this] is due to poor record keeping, provider reluctance to list a mental disorder, or inadequate provider skills in diagnosing mental disorders." This places the emphasis differently from the interpretation by Jencks (1985), who noted that most instances in which a psychotropic is prescribed in the absence of a mental diagnosis are those involving older patients with chronic disorders; he found this consistent with hypotheses that "either (*a*) treatments are provided for conditions incidental to other chronic somatic disorders and, therefore, are not separately diagnosed or (*b*) mental treatments are provided for chronic mental conditions that are not recorded at every visit."

b. REGIONAL SURVEYS. **i. Italy: Verona, Puglia, and Calabria.** Ninety-two of the 286 general practitioners working in the area of Verona, in northern Italy, prescribed benzodiazepines for 9.5% of all adult patients seen on a survey day in 1987. Women were significantly more likely than men to receive prescriptions for psychotropics, and the rate of such prescriptions increased with age up to the 45- to 64-yr age range, after which it declined. However, the factor most strongly predictive of psychotropic drug prescription was psychiatric morbidity, independent of sex, age, physical health, and social problems (Bellantuono et al., 1989). Psychiatric morbidity also proved the strongest determinant of benzodiazepine prescriptions issued to patients of three Verona general practitioners during a 2-wk period in 1986 (Fiorio et al., 1989).

Psychiatric residents interviewed psychiatrists and examined medical records of in- and outpatients of a number of psychiatric facilities in the southern Italian regions of Puglia and Calabria (Muscettola et al., 1987). The psychotropic drugs most frequently prescribed were neuroleptics and benzodiazepines. In the case of each of these categories, the prescriptions did not appear to be limited to specific diagnoses. Benzodiazepines constituted 43% of prescriptions for anxiety disorders, 36% of prescriptions for minor depressive disorders, and 28% of prescriptions for major depressive disorders; they also accounted for at least 20% of prescriptions for "dementia," mental retardation, and alcoholism and for at least

10% of prescriptions for personality disorders, schizoaffective disorders, schizophrenia, and manic disorders. Among patients receiving benzodiazepines, 16% received more than one benzodiazepine concurrently.

ii. Federal Republic of Germany: West Berlin. Forty-two psychiatrists, representing 58% of all those in private practice in West Berlin, issued one or more benzodiazepine prescriptions to 53% of all patients for whom they prescribed psychotropic medication on a survey day (Geiselmann et al., 1989). For 70% of patients who received a benzodiazepine prescription, the prescription provided medication for 3 mo or more. Patients receiving benzodiazepine prescriptions, and especially those receiving long-term prescriptions for these drugs, were significantly older than those not receiving benzodiazepine prescriptions. Benzodiazepines were prescribed for 68% of patients with "minor psychiatric disorders" (including anxiety, depression, and others), for 62% of patients with "endogenous affective disorders," and for 18% of those with "schizophrenic psychoses." The study also included interviews with patients, who were asked to complete a self-rated symptom checklist. Patients receiving benzodiazepines had significantly more symptoms, and/or more severe symptoms, than patients who did not receive benzodiazepines; this association proved independent of patients' age.

iii. Denmark: Aarhus. Holm (1988) reported a survey of the use of psychotropic drugs by general practitioners in the county of Aarhus, which is on the eastern coast of the Danish mainland and where 11% of the Danish population reside. Benzodiazepines accounted for 67% of all psychotropic prescriptions issued in a week in 1985. The median age of patients receiving prescriptions for benzodiazepine tranquilizers was 54 yr and that for hypnotics was 66 yr. Among the 2574 patients receiving benzodiazepine prescriptions, 89.5% had received benzodiazepines previously, and 47.2% had received such prescriptions regularly or periodically for 12 mo or more. Fifty-five percent of first-time prescriptions and 83% of repeat prescriptions were issued without direct physician-patient contact, i.e., by telephone or through medical receptionists. Among patients receiving benzodiazepine anxiolytics or hypnotics, 81% or 79%, respectively, had, in the physicians' judgment, either "overt psychiatric illness" or "mild symptoms such as insomnia and anxiety." About one third of the patients receiving such prescriptions had a somatic illness which, in their physicians' judgment, required these prescriptions.

The proportion of patients receiving benzodiazepines who were judged to be mentally distressed diminished with the duration of use. However, "mental distress" was defined as "a sudden change in the patient's psychosocial situation, including self-knowledge, resulting in psychological or psychosomatic symptoms." This definition would seem to limit mental distress to acute conditions, whereas the physicians may have continued benzodiazepine prescriptions to manage more chronic problems. It is also possible that what these findings reflect is that, in the course of a physician's experience with an individual patient over time, the physician is most likely to note psychological problems at the time that they are first presented, when he or she may initiate treatment for these problems; he or she is less likely to make note of these problems, although they may persist at later consultations when other problems become more prominent in the patient's presentation. This explanation is supported by a number of studies in which prescriptions for psychoactive drugs were compared with patients' medical records, as summarized in our previous review.

Holm (1990) also reported a 1-yr follow-up of those patients who had received "first-time" benzodiazepine prescriptions in the initial study (i.e., had received no previous psychotropic prescriptions or had received no benzodiazepine prescriptions for at least the previous year). Of these 161 patients, 88 (55%) received no further prescriptions for benzodiazepines or other psychotropics during the next 12 mo, 44 (27%) continued to receive prescriptions for the same drug, and 28 (17%) received prescriptions for other psychotropic drugs, including other benzodiazepines in 16 cases; including these 16 patients whose prescriptions were switched to other benzodiazepines, a total of 60 patients (37%) received continued benzodiazepine treatment during the follow-up year. There was a significantly greater probability of continued prescriptions among those who were older and among those who received hypnotics rather than tranquilizers. Follow-up reports of the 533 patients identified in the initial study as long-term benzodiazepine users indicated that at least 429 (80%) received one or more additional prescriptions for benzodiazepines during the following year.

iv. Norway: Ostfold. Twenty-three of the 29 general practitioners in the county of Ostfold, in southeastern Norway, reported that 6% of all patient contacts during two separate weeks in 1985 resulted in a prescription for a benzodiazepine; the majority of contacts resulting in benzodiazepine prescriptions were by telephone, frequently with receptionists. Of the 343 patients receiving such prescriptions during the survey period, 280 psychiatric diagnoses and 77 musculoskeletal diagnoses were recorded. Most of these patients had been receiving benzodiazepine prescriptions regularly for long periods. The frequency of prescriptions of benzodiazepine tranquilizers increased with age up to the age range of 60 to 69 yr and declined for older groups; in contrast, the highest frequency of prescriptions of hypnotics was in the oldest group, i.e., 70 yr or older (Aga et al., 1987).

v. Australia: Bedford Park, South Australia. Physicians who treated psychiatric inpatients discharged between July 1986 and June 1987 reported that 23% had been taking benzodiazepines at the time of admission, but only 8% received benzodiazepine prescriptions when

discharged. In addition, the mean daily dose decreased from 16-mg diazepam equivalents at the time of admission to 7 mg at discharge (Brayley et al., 1989).

2. Surveys of prescriptions. In the context of this review, surveys of prescriptions are of interest to the extent that they provide information about the circumstances in which benzodiazepines are prescribed for both medical and psychiatric patients in a variety of health care settings. In this respect, they provide more detail about actual use of these drugs than do sales data. On the other hand, the knowledge that a prescription was written, under whatever circumstances, does not necessarily signify that the prescription was filled, much less whether or how the drug was actually taken. The studies considered in this section concerned a range of types of information, including records signifying only that certain prescriptions were written, records that prescriptions were actually dispensed, and records of dispensed prescriptions linked with medical records of the patient populations or of the individual patients who received the prescriptions.

The focus of interest here is the findings of these studies that bear on the appropriateness of benzodiazepine use rather than those that chiefly address the extent of use. The latter issue is better addressed by population surveys, as described in our previous review and in section V.D.

In our previous review, we found that prescription surveys helped to illuminate the diagnoses and other factors that prompt prescription of benzodiazepines. In addition, these studies raised some interesting questions about actual use of benzodiazepines. For example, they pointed out that a large proportion of patients receiving prescriptions for these drugs continue to receive such prescriptions for long periods of time, often for years: Who are these patients? What factors account for long-term use? In what instances may such use be appropriate or inappropriate? Prescription studies have also revealed that rates of prescriptions for benzodiazepines increase with age, and that a large proportion of long-term users, particularly users of benzodiazepine hypnotics, are elderly patients, many of whom have chronic physical illnesses: Why are older patients more likely to receive these prescriptions, and what is the significance of this use? Some investigators have examined medical records of patients receiving benzodiazepine prescriptions and have found that in many cases there is no associated psychiatric diagnosis: Why, then, were these prescriptions written?

Studies of prescription records, particularly in hospitals, have raised other concerns. Some have considered the possibility that a substantial proportion of long-term benzodiazepine use in the community may begin with use during hospital stays: Is this continued use necessary or appropriate?

Many of these questions and concerns have been further addressed and elaborated in a number of studies of prescriptions that have been reported since our previous review.

a. TREATMENT OF NONPSYCHIATRIC OUTPATIENTS. An interesting study of the treatment of anxiety disorders detected in general practice was reported by Tyrer et al. (1988). The authors considered two large general practices, one urban and one rural, in Nottinghamshire (United Kingdom). All patients identified by general practitioners as displaying "conspicuous psychiatric morbidity" were interviewed by a psychiatrist, who provided a diagnosis. The 131 patients with diagnoses of anxiety disorders or other neurotic disorders were followed up for 3 yr. Twenty-four percent of the patients were referred to and consulted psychiatrists, and 3% were admitted to psychiatric hospitals. However, the majority had no further formal health care during the 3 yr except that provided by their original general practitioners; 13% received no care from general practitioners or any other source.

The most frequent treatment of the patients with anxiety or other neurotic disorders was with psychoactive drugs. Tricyclic antidepressants were prescribed for 59% of the patients, and "second-generation" antidepressants were prescribed for 32% (presumably with some overlap). Benzodiazepine anxiolytics were prescribed for 35%, and benzodiazepine hypnotics were prescribed for 18%. The investigators commented: "Although general practitioners are often criticized for prescribing uncritically there is no evidence to suggest from this survey that the GPs [general practitioners] concerned were careless in their prescriptions. All the GPs were sensitive to the question of unnecessary benzodiazepine prescription and of keeping all drug treatment to a minimum. Despite this drug treatment was used more widely than other types of therapy. The relative use of different drugs was in accord with current thinking."

The drugs prescribed for the longest periods were benzodiazepine anxiolytics (mean duration 38 wk in the urban practice and 24 wk in the rural practice).

Analysis of outpatient prescriptions dispensed for the total population of Saskatchewan (Canada) showed that 9.6% of the population in 1977, versus 6.3% in 1985, filled prescriptions for minor tranquilizers; 2.5% in 1978 and 3.2% in 1985 filled prescriptions for sedative-hypnotics. During the first 3 mo of 1979, 0.9% of those filling psychotropic prescriptions were categorized as "extreme users," in that they received quantities of drug that would have provided more than the recommended maximum daily dose. Individuals filling prescriptions for sedative-hypnotics accounted for 41.5% of extreme users, and those filling prescriptions for minor tranquilizers accounted for 22%. Between 1979 and 1983, the number of extreme users of sedative-hypnotics declined by 17%, and the number of extreme users of minor tranquilizers declined by 47% (Blackburn et al., 1990).

Rosser (1987) analyzed data concerning benzodiazepine prescriptions in a large family medicine center in Ottawa (Canada) between 1977 and 1985. Consistent with the results of studies of sales data for Canada (as described in section V.B), he found that the percentage of prescriptions for long-acting benzodiazepines had declined from 88% to 19% during this period, whereas the percentage of prescriptions for short-acting agents had increased to 81%. In 1984 to 1985, in every age group, women received more prescriptions than men, and the rate of prescriptions increased with age for both sexes. Women older than 65 yr of age received 44% of all benzodiazepine prescriptions. Of 410 patients who received benzodiazepine prescriptions in 1982, 21 (5%) received more than 700 dose units.

Veje et al. (1989a,b), in two reports, described a 1986 study of prescriptions for minor tranquilizers and hypnotics (virtually all benzodiazepines) in Holbaek, "a provincial Danish town with approximately 30,000 inhabitants. . . ." During the study month, 152 patients received prescriptions for more than 100 DDD; this included 12% of all patients older than 40 yr of age who received prescriptions for such drugs. Although nitrazepam was the most frequently prescribed hypnotic overall, triazolam was the most frequently prescribed in DDD greater than 100.

A series of studies concerned information related to psychotropic drug prescriptions dispensed in Tierp, a municipality in mideastern Sweden with a relatively stable population of about 21,000. Since 1972, all prescriptions dispensed at Tierp pharmacies have been registered, together with information linking the prescriptions to individual patients, their visits to physicians, and their diagnoses. Between 1972 and 1983, purchases of prescriptions for all psychoactive drugs declined by 27%. However, the number of benzodiazepine prescriptions per 100 population increased during this period from 23.1% to 32.0% (Isacson and Smedby, 1988). Of those who purchased such prescriptions in 1980, 65% of men and 70% of women also made such purchases in the following year. Both new and continued use increased with age. Although the prevalence of use was almost twice as high among women as among men, the probability of continuing use was independent of sex.

With regard to levels of use, those who purchased these drugs in both 1980 and 1981 bought an average of 3.9 prescriptions per year; it is not clear whether these prescriptions would have provided enough medication for continuing use on a regular basis (Isacson et al., 1988). Two thirds of those who received benzodiazepine prescriptions in 1976 also received at least one such prescription in 1977, 45% continued to receive such prescriptions after 4 yr, and one third continued to receive benzodiazepine prescriptions at the end of the follow-up period, i.e., 8 yr after their 1976 prescriptions. Older patients were significantly more likely than others to continue to receive benzodiazepine prescriptions for long periods.

Prescriptions for psychotropics in general, and specifically for anxiolytics and sedative-hypnotics, were most commonly associated with diagnoses of circulatory disorders. For patients filling prescriptions for anxiolytics and sedative-hypnotics, by far the most common specific diagnosis was essential hypertension (29%). In total, only 23% of patients receiving psychotropic prescriptions had been given psychiatric diagnoses. Whereas the rate of psychotropic prescriptions increased with age, the proportion of psychiatric diagnoses among patients filling these prescriptions *decreased* with age (Westerling, 1988).

Three group general practices in the Forth Valley (Scotland), serving approximately 17,000 suburban and rural patients, identified all patients with benzodiazepine prescriptions who had received three or more consecutive prescriptions for these drugs. A random subsample of these patients, including 48 men (23%) and 157 women (77%), had a mean age of 64 yr. They had been receiving repeat benzodiazepine prescriptions for a mean period of 8 yr, with a range of 1 mo to 23 yr. Forty-eight percent received only benzodiazepine hypnotics, 39% received only benzodiazepine anxiolytics, and 14% received both. Eighty-two percent of these patients, as opposed to 63% of age- and sex-matched controls, had a history of major physical illness. Forty percent of users, versus 25% of controls, had a history of three or more major physical disorders. Users of benzodiazepine hypnotics were significantly older than users of anxiolytics, had experienced a significantly greater number of major and minor physical illnesses, and had received a significantly greater number of nonpsychotropic medications (Simpson et al., 1990b).

Of patients of a university-based health center in Belfast (Northern Ireland) who were found to have active "psychosocial problems" (e.g., anxiety, depression, insomnia, bereavement reactions) in 1984, 63% had filled prescriptions for "sedatives" (apparently including anxiolytics), hypnotics, or antidepressants. These patients were significantly more likely to live alone, to have a history of physical illness, and to have chronic physical illnesses than patients with similar problems who did not fill such prescriptions (Irwin and Cupples, 1986).

Triazolam and flurazepam were the only two benzodiazepine hypnotics on the formulary of a Veterans Administration medical center in the midwestern United States in 1986. Of 655 prescriptions for these drugs, 64% were renewals. Most were for patients whose medical records revealed one or more chronic physical illnesses. The number of doses specified in the prescriptions increased with patients' ages. Also, renewal prescriptions were significantly more likely than new prescriptions to call for 180 or more doses (Shorr et al., 1990). Those prescriptions written by nonpsychiatrists were mostly

for relatively high doses; 40% of flurazepam prescriptions called for doses of 30 mg or more, and 69% of triazolam prescriptions called for doses of 0.25 mg or more. However, prescribers apparently reduced the dosage of prescriptions of these drugs for elderly patients; the proportion of patients aged 70 yr or older who filled prescriptions for high doses of either triazolam or flurazepam was significantly lower than that of younger patients (Shorr and Bauwens, 1990).

Rates of prescriptions of benzodiazepine hypnotics dispensed by all pharmacists in the county of Arhus, Denmark, during a week of 1989 increased with patients' age (Holm, 1988).

Buchsbaum et al. (1986), in a study of records of outpatients of clinics in Richmond, VA (United States), found that information about benzodiazepine prescriptions in the patients' records was much less complete than information about prescriptions for various nonpsychotropic drugs. The extent of documentation of benzodiazepine prescriptions, and in particular of the problems for which these prescriptions were written, decreased with the patients' age.

Among outpatients of a university-affiliated hospital in Victoria (Australia), the probability of filling at least ten prescriptions for different drugs during a 3-mo period increased with patients' age, and with number of hospital admissions and clinic visits, but did not differ by patients' sex. Benzodiazepines were the drugs most commonly prescribed for patients receiving multiple prescriptions; benzodiazepines were prescribed for 64% of the polypharmacy group, as compared with 37% of a control group of patients who had filled fewer prescriptions. Polypharmacy was as strongly related to specific diseases as to age itself. Among patients older than 50 yr of age, prescribing patterns were determined by the presence of degenerative vascular disease (McMillan et al., 1986).

b. TREATMENT OF NONPSYCHIATRIC INPATIENTS. Numerous studies in recent years have been concerned with the use of benzodiazepines and other psychoactive drugs in the treatment of patients on medical, surgical, and other nonpsychiatric wards of hospitals. These studies have usually consisted of retrospective surveys of hospital pharmacy records, which have increasingly been incorporated into electronic data systems, or of patients' medical charts. Many surveys have continued to focus on the prevalence of psychotropic prescriptions in these settings; some of these have repeated earlier surveys in the same settings, providing an indication of changes over time. In general, these surveys have provided little or no data that would help to illuminate the appropriateness of the prescription of benzodiazepines in hospitals, although some of the investigators have offered intriguing speculations about the factors influencing these prescriptions. Of greater interest to the purposes of this review are the surveys that have used hospital data to track the progress of benzodiazepine use in the community, by examining not only the prevalence of prescriptions during hospitalization but also rates of use at the time of admission and at or after discharge. Both of these types of studies are considered in the following subsection.

One general point should be made before considering the data concerning hospital use of benzodiazepines. As we found in our previous review, patients tend to take less of these drugs than the doses prescribed. This may apply particularly to hospitalized patients, for whom prescriptions for hypnotics or anxiolytics are frequently for use "as needed." For example, Edwards and coworkers (1991) found that only 17% of inpatients receiving prescriptions for hypnotics actually took all of the doses prescribed, and 12% took some but less than half of the prescribed doses, and another 25% took none. The proportions of patients who actually took the drugs were higher when the prescriptions called for specific regimens.

Several recent studies of the use of benzodiazepines and other psychotropics in the treatment of nonpsychiatric inpatients are described in table 16. These studies are fairly representative of those that have tended to focus chiefly on the extent of such drug use, usually in relation to patients' age and sex as well as broad clinical characteristics. The studies involved data from various types of hospitals in widely distant geographic locations and provided estimates of the extent of drug use in diverse terms, i.e., in percentage of patients, in percentage of prescriptions, and in "DDD/100 beds/d" (a standard that has been suggested for hospital surveys of drug exposure, derived from the "DDD/1000/d" unit of measurement for community surveys).

In view of the diversity represented by these studies, perhaps the most interesting point made by their collective findings is that benzodiazepines are, in fact, prescribed in hospitals in many parts of the world and that the overall frequency of such use among nonpsychiatric inpatients is comparable, i.e., if we consider the four studies that provided rates of benzodiazepine prescriptions per 100 patients, the table indicates that, in the 1980s, between 23% and 42% of nonpsychiatric inpatients of hospitals in Italy, Spain, Brazil, South Africa, and Sri Lanka received benzodiazepine prescriptions.

Several other surveys that estimated the prevalence of use of benzodiazepines for nonpsychiatric inpatients are summarized in table 17. These studies also included the prevalence of benzodiazepine use among these patients at the time of admission, as well as the frequency with which benzodiazepines were prescribed at the time of discharge from the hospital.

With respect to prescriptions during the patients' hospital stays, the figures given can be compared with those in table 16. The rates of benzodiazepine use found in the French hospital in 1985 (34%) and in the Scottish hos-

TABLE 16

Studies of prescriptions for nonpsychiatric inpatients

Study	Population	Area	Drugs	Rates of use	Comments
				(% of prescriptions) 1977 1984 1987	
Stiefel et al., 1990	Consecutive adult patients admitted to a medical oncology unit of a cancer center in December 1987 (n = 200). Results were compared with similar, multicenter surveys conducted in 1977 (n = 1597) and 1984 (n = 602)	USA: New York, NY	Benzodiazepines Anxiolytics Hypnotics	 21 17 26 33 25 19	A majority of patients (in 1987) received prescriptions for more than one psychotropic.
				(% of patients) 1982–1985	
Magni et al., 1986	Patients, aged 60 yr or older, of a geriatric hospital in 1982–1985 (n = 331); selection criteria not stated	Italy: Padua	Benzodiazepine anxiolytics Benzodiazepine hypnotics	24 3	Patients who received psychotropics (of which 65% were benzodiazepines) had significantly higher self-reported (SCL-90) psychological distress than other patients.
				(DDD/100 beds/d) 1985	
Garcia-Diaz et al., 1987	Adult inpatients of five general hospitals during 1985 (no. of beds = 5218)	Spain: Barcelona	Benzodiazepines	(range): 25.4–40.1	In three hospitals, psychiatric patients were included, representing 3–5% of the populations studied.
				(% of patients) 1979 1982	
Bertelli et al., 1986	Random sample of records of adult patients of selected wards of two teaching hospitals during 1979–1982 (n = 1208)	Brazil: Porto Alegre, Rio Grande de Sul	Benzodiazepines	"Hospital A" 62.7 41.9 "Hospital B" 22.6 24.3	"Hospital A" serves only patients with social insurance. "Hospital B" serves mainly patients without insurance.
				(% of patients) 1986–87	
Summers et al., 1990	Pharmacy records of inpatients of a small community hospital between October 1986 and April 1987 (n = 800)	South Africa: West Rand	Benzodiazepines	22.9	Women were more likely than men to receive multiple benzodiazepine prescriptions.
				(% of prescriptions) 1984	
Angunawela and Tomson, 1988	Consecutive adult patients of two teaching hospitals, a government hospital, and a private nursing home beginning in September 1984 (n = 600)	Sri Lanka: Kandy	Sedative-hypnotics and anxiolytics	2 teaching hospitals (average): 7.1 Government hospital: 5.7 Nursing home: 11.7	Diazepam was the most frequently prescribed drug of any drug class.
				(% of patients) 1984	
			Diazepam	2 teaching hospitals (average): 30.6 Government hospital: 30.7 Nursing home: 33.0	

TABLE 17

Studies of prescriptions for nonpsychiatric inpatients before and during admission and on discharge

Study	Population	Area	Drugs	Rates of use (% of patients)			Comments
					1985		
Rona-Dessalles et al., 1989	Inpatients of nonpsychiatric services of a general hospital during January–July 1985 (n = 455)	France: Perigueux	Benzodiazepines	On admission: During stay: On discharge:	21 34 17		Study found significantly more patients with psychiatric histories among benzodiazepine users than nonusers
					1973–75	1982–83	
Smith et al., 1986	Consecutive inpatients on general medical wards of a university-affiliated hospital between 1973 and 1975 (n = 1280) and during 1982 and 1983 (n = 1200)	UK: Glasgow, Scotland	Psychotropics (Benzodiazepines accounted for 64% of 881 psychotropic prescriptions in hospital in 1973–75 and 82% of 498 in 1982–83.)	On admission: During stay: On discharge:	17.0 50.0 7.7	18.0 33.0 9.3	
Nolan et al., 1989	All patients admitted to a general hospital during 1 wk (n = 325) (date of survey not reported)	UK: London	Benzodiazepines	On admission: During stay: On discharge:	4 19 0		Study population happened to include no psychiatric patients.
					1989		
Edwards et al., 1991	All patients on selected wards of a general hospital during 4–6 wk in 1989 (n = 1277)	UK: Newcastle Upon Tyne	Benzodiazepines Benzodiazepine hypnotics	On admission: During stay: On discharge:	6.2 12.6 1.3		Only 7 patients were taking anxiolytics at admission, and only 4 received anxiolytic prescriptions in hospital. At 4–8 wk postdischarge follow-up, 6.1% were using hypnotics.
					1989		
Busto et al., 1990	All patients 65 yr or older admitted to selected wards of a general hospital during a month in 1989 (n = 246)	Canada: Toronto	Benzodiazepines	On admission: During stay: On discharge:	15 42 5		At 5-mo postdischarge follow-up, all those who had used benzodiazepines for ≥80% of their hospital stay were still using them.

pital in 1982 to 1983 (33%) are similar to those most usually found in hospitals in Spain, Brazil, South Africa, and Sri Lanka during the 1980s. The rates of use found in English hospitals in the late 1980s (19% and 13%) were somewhat lower. This is consistent with other data indicating a marked decline in use of benzodiazepines, and particularly benzodiazepine anxiolytics, in the United Kingdom, related to the government's 1985 restrictions on use of these drugs under the NHS. The relatively high prevalence (42%) of benzodiazepine prescriptions among the inpatients in the Toronto hospital, as reported by Busto et al. (1990), is explained by the older age group studied.

The studies summarized in table 17 also addressed the issue of the extent to which benzodiazepine use in hospitals may contribute to the overall prevalence of use, and particularly long-term use, in the community. As the table indicates, although there is a wide range of frequencies of benzodiazepine prescriptions issued at the time of discharge from hospitals (0 to 17%), these frequencies in every instance are lower than the frequencies of use among the patients at the time of admission. As described previously, Brayley et al. (1989) similarly found that 23% of psychiatric patients in a hospital in South Australia had been receiving benzodiazepines on admission, whereas only 8% were discharged with such prescriptions.

This suggests at least that hospitalization in itself does not increase the prevalence of use in the community, although it does not preclude the possibility that some patients receive benzodiazepines for the first time in the hospital and continue use after discharge. For example, Edwards et al. (1991) found that 6.4% of inpatients were using hypnotics when admitted to hospital; although only 1.6% received hypnotic prescriptions at the time of discharge, on follow-up 4 to 8 wk later 6.1% were using these drugs again. They concluded, "Our study has failed to show that hospital prescribing of hypnotics has any generally significant influence on community prescribing or vice versa." On the other hand, they did find that 5% of the population they studied, who had no recent history of hypnotic use before hospitalization, did receive hypnotics in hospital and were found to be taking these drugs when followed up several weeks after discharge.

A similar finding was reported by Beers et al. (1989), who studied a random sample of 197 elderly patients admitted to nongeriatric wards of a Veterans Administration hospital in Sepulveda, CA (United States) between October 1987 and March 1988. When all subjects are considered, the number of benzodiazepines prescribed per 100 subjects at the time of admission (8.6) was not significantly different from the number prescribed at the time of discharge (10.2). However, when only those subjects who had been receiving five or fewer drugs of any kind on admission are considered, the number of benzodiazepines prescribed per 100 subjects increased significantly, from 3.7 on admission to 10.4 on discharge. Other medications for which prescriptions increased significantly in this group of patients between admission and discharge included narcotic analgesics, laxatives, antibiotics, and cardiac drugs.

c. TREATMENT OF PSYCHIATRIC INPATIENTS.

i. France: Paris. On a survey day in 1987, anxiolytics (of which 71% were benzodiazepines) were prescribed for 29% of the patients of a psychiatric hospital in a district of Paris. These included 100% of patients suffering from neurotic disorders or nonpsychotic depression, 67% of those with alcohol-related problems, 43% of those with personality disorders, 27% of those with "mental deficiency," 21% of those with schizophrenia, 21% of those with manic-depressive psychoses, and 18% of those with acute or chronic psychoses. The chief uses of hypnotics were for patients with neurotic disorders or nonpsychotic depression (71% of these patients), manic-depressive psychosis (36%), and alcohol-related problems (44%). About half of all patients received more than one psychotropic drug (Fombonne et al., 1989).

ii. Great Britain: London, Newcastle. Benzodiazepines were prescribed for 20% and 52% of the patients in two London psychiatric hospitals and for 44% of patients in a psychiatric hospital in an unspecified "provincial" area of Great Britain. Most benzodiazepine prescriptions were for hypnotics. Benzodiazepine anxiolytics (virtually all diazepam) were prescribed for 5.5% and 6% of patients in the London hospitals and for 16% of those in the third hospital (Muijen and Silverstone, 1987).

Patients on long-stay wards of a large psychiatric hospital in Newcastle were considered in two groups, based on case note diagnoses; those with "chronic functional disorders" had mostly schizophrenia and affective disorders, and those with "organic mental disorders" had mostly middle- and late-stage dementia of mixed types (Clark and Holden, 1987). Prescription surveys conducted in 1983 and 1985 indicated that hypnotic drugs were prescribed for 21% and 25%, respectively, of the "chronic" patients and for 33% and 31%, respectively, of the "organic" patients. Of the chronic patients receiving hypnotics, about 80% also received neuroleptics and/or "sedative antidepressants," as did about 40% of the organic patients who received hypnotics. Anxiolytics were prescribed for 13% and 8% of the chronic patients in 1983 and 1985, respectively, and for 2% and 1%, respectively, of the organic patients.

iii. Ireland: Dublin. Murphy et al. (1990) found that 32% of patients in a Dublin psychiatric hospital received prescriptions for regular use of benzodiazepines; including prescriptions for use "as needed," 52% of patients had prescriptions for these drugs. The mean duration of prescriptions for the most commonly prescribed benzodiazepines was 35 mo for diazepam, 7 mo for chlordiaze-

poxide, 13 mo for alprazolam, 24 mo for temazepam, 25 mo for flurazepam, and 10 mo for nitrazepam.

iv. Federal Republic of Germany: West Berlin. Diazepam and flurazepam were among the drugs most commonly prescribed for patients admitted to a university psychiatric hospital in 1981 or 1982. Diazepam was prescribed for 13% of all patients, for a mean duration of 10 d and at a mean daily dose of 9.5 mg; the highest mean daily dose during the course of patient stays was 13.5 mg on the fifth day, after which the mean dose declined through discharge. Flurazepam was prescribed for 6% of all patients, for a mean duration of 12 d and at a mean dose of 27.5 mg/d; the mean daily dose was fairly stable during the course of patient stays (Schmidt et al., 1987). The prevalence of prescriptions of tranquilizers/hypnotics declined from 42% of the population in 1981 to 29% in 1984; this was due chiefly to a decline in the numbers of prescriptions for diazepam and flurazepam (Schmidt et al., 1988).

v. Norway. Among long-stay patients of ten psychiatric hospitals in Norway, 22% received prescriptions for hypnotics and 14% received prescriptions for minor tranquilizers; these categories included benzodiazepines and other agents (Oyehaug et al., 1989).

3. Summary and discussion. a. SURVEYS OF PHYSICIANS. Surveys of both physicians and prescription records indicate that, although the frequency of prescriptions for benzodiazepine anxiolytics has declined in some countries in recent years, benzodiazepines continue to rank as the most commonly prescribed psychotropic drugs and are among the most frequently prescribed drugs of any class.

A survey of a national sample of physicians in private practice in the United States (the NDTI) in 1991 indicates that more than 80% of office visits at which a benzodiazepine is prescribed are visits by patients whom the prescriber has seen previously; two of every three such prescriptions represent continued therapy for these patients. These proportions are virtually identical with those we had found in our previous review, in which we examined NDTI data for 1982 to 1986. During the last decade, the percentage of benzodiazepine anxiolytic prescriptions written by primary care physicians decreased (from 53% to 46%), whereas the percentage issued to patients in physicians' offices, rather than in hospitals, increased (from 59% to 69%). Also, the proportion of these prescriptions written for patients whose principal diagnoses were of mental disorders increased from 45% to 59%. Almost half of prescriptions for benzodiazepine hypnotics are for patients whose primary diagnoses are of mental disorders or sleep disturbance, and an additional quarter are for surgical aftercare.

In another national survey of office-based physicians in the United States (National Ambulatory Medical Care Survey), primary-care physicians were found to be responsible for about 70% of prescriptions for benzodiazepine anxiolytics and sedative-hypnotics in 1985. Mental disorders were the diagnoses at only about 40% of visits by patients who received prescriptions for benzodiazepine anxiolytics and at about 20% for benzodiazepine hypnotics. These findings are in approximate, although not exact, agreement with the data from the NDTI survey; the differences are probably due largely to differences in sampling procedures.

A number of regional surveys of physicians in other countries, chiefly in western Europe, have shown that patterns of benzodiazepine prescribing in these regions are basically similar to that in the United States and have revealed more detail of and variations on this basic pattern. Consistently, women, or at least women older than about 45 yr, are nearly twice as likely as men to receive benzodiazepine prescriptions. Also consistently, the rate of prescriptions increases with age, at least to about the age of 65 yr, after which the rate of prescriptions for anxiolytics declines somewhat; in some regions, however, the rate of prescriptions for hypnotics continues to increase with age.

Surveys of psychiatrists in the United States and other areas have shown that, although benzodiazepines are most likely to be prescribed for patients with neurotic disorders, their use is not distinctly limited to this diagnostic category. Benzodiazepines are prescribed with some frequency for patients with mood disorders and other psychiatric diagnoses. In a substantial proportion of cases, benzodiazepines are prescribed in combination with other psychotropic medications; often these benzodiazepines are hypnotics, so that the intent may be to treat sleep disturbances associated with various psychiatric disorders.

b. SURVEYS OF PRESCRIPTIONS. Recent studies of records of prescriptions for nonpsychiatric outpatients in several countries have shown, as had been demonstrated in some earlier analyses, that a relatively small proportion of the patient population receives the majority of benzodiazepine prescriptions. These patients are those who continue to receive prescriptions for long periods of time, often for relatively large numbers of doses; the repeat prescriptions are often obtained without direct contact between the patient and physician. These findings suggest that a minority of recipients of benzodiazepine prescriptions apparently use the drugs regularly on a chronic basis. Studies linking prescriptions to medical records indicate that these users tend to be older patients who have one or more chronic somatic disorders; this portrait of long-term users is consistent with findings of interview surveys, as described in our previous review.

Investigators who have examined physicians' case notes and other medical records for nonpsychiatric patients receiving benzodiazepine prescriptions, both in and out of hospitals, have found that these prescriptions are frequently poorly documented or undocumented; this underdocumentation is in contrast to prescriptions for

nonpsychotropic drugs. The reasons for benzodiazepine prescriptions, and other characteristics of these prescriptions, are particularly likely to be undocumented in records of older patients.

Surveys of prescriptions for nonpsychiatric inpatients show some variation in rates of use of benzodiazepines in hospitals, but there is a remarkable consistency in findings across geographic areas that, in the 1980s, about one patient in three received a benzodiazepine prescription in the course of hospitalization. Many of these prescriptions were, however, for use as needed, and there is little information concerning actual consumption of these drugs in these studies or in interview surveys of use (section V.D); there is some evidence, however, that consumption falls substantially short of the utilization suggested by prescription rates, even for prescriptions that call for specific regular dosage regimens.

As noted above and in our previous review, some authors have raised the question whether use of benzodiazepines in hospitals may contribute significantly to continued use in the community. A number of recent and earlier hospital studies in which rates of benzodiazepine prescriptions were considered before admission and at the time of discharge, as well as during hospitalization, have shown that, although rates of use before admission vary in accord with the community represented, rates of prescription at the time of discharge are uniformly lower than rates at the time of admission. Investigators who have followed up hospitalized patients after discharge have found that rates of benzodiazepine use tend to resume the preadmission level, i.e., approximately the prevalence rate for such use in the community. At the same time, a small percentage of inpatients may receive a benzodiazepine prescription for the first time in the hospital and continue regular use after discharge. In any case, however, the evidence suggests that hospital use of benzodiazepines has no appreciable influence on the prevalence of use in the community.

c. DISCUSSION. Certain issues have emerged recurrently in studies of benzodiazepine prescribing and deserve comment here. These include the questions raised by findings that the majority of benzodiazepine prescriptions are written for patients who are not suffering from mental disorders and that physicians are less likely to record the reasons for benzodiazepine prescriptions than for nonpsychotropic prescriptions. Another set of issues is raised by findings that a small percentage of patients who receive benzodiazepine prescriptions accounts for a large proportion of such prescriptions and that these patients are those who continue for long periods to receive repeat prescriptions, often for large numbers of doses and often without direct contact with the physician.

All of these phenomena and the issues they raise appear related to, and indeed are in large measure unified by, the evidence that use of benzodiazepines increases with age. Physicians are particularly unlikely to document mental disorders for older patients, including those for whom they prescribe benzodiazepines. Yet, it is these older benzodiazepine users who account for a disproportionately large fraction of prescriptions of these drugs and who continue to receive prescriptions for long periods of time.

Older patients are, of course, more likely to suffer from physical disorders, and interview surveys have shown that long-term users of benzodiazepines are most likely to be older patients with multiple chronic physical ailments. This may go a long way toward explaining the large proportion of benzodiazepine prescriptions written for patients for whom mental disorders are not diagnosed or documented. A number of investigators, speculating about this observation, have appropriately focused on the interaction between the patient and the typical prescriber, who is unlikely to have much training in psychiatric diagnosis. When the physician prescribes a benzodiazepine in the absence of conspicuous psychiatric morbidity, he or she is responding to his or her recognition of *some* need that may be psychological distress associated with chronic physical illness or somatic expressions of psychological problems, i.e., either actual somatization of such problems or the patient's description of psychic distress using somatic terms, such as "dizziness." (In fact, findings from most studies including self-report measures of psychological distress indicate significantly higher scores among patients who receive prescriptions for benzodiazepines than among similar patients who do not receive such prescriptions; these findings are discussed in section V.D.5). Moreover, even when a physician does diagnose a mental disorder or record a psychiatric symptom as a reason for initiating a benzodiazepine prescription, he or she is less likely to document such problems when ordering repeat prescriptions for patients whose primary complaints over time pertain to chronic physical disorders, and the vast majority of benzodiazepine prescriptions are repeat prescriptions.

D. Interview Surveys of Consumption

The epidemiological data most relevant to assessment of the abuse liability of the benzodiazepines come from surveys in which members of the community, or of some defined population, are questioned about their actual use of medications. Interview surveys represent an important complement to prescription studies in depicting drug use, because actual consumption may deviate significantly from the patterns suggested by prescription records. Prescriptions are not always filled, many patients who do fill them do not comply with the prescribed regimens, and some people use drugs not prescribed for them; these discrepancies between prescriptions and drug use may be especially likely for psychoactive drugs and specifically for anxiolytics (Woods et al., 1987).

Thus, interview surveys help to adjust the view of drug

use depicted by studies of prescriptions. On the other hand, there are some important limitations of interview data. Several studies have pointed to significant discrepancies between self-reports and laboratory findings of benzodiazepine use. In studies of overdose victims, for example, Ungerleider et al. (1980a) found that benzodiazepine use was often reported by subjects whose urine tested negative for the drugs, whereas Crane et al. (1988) found that only 18% of alcoholics with benzodiazepines in their urine had reported use of these drugs. Drug use histories provided by patients other than drug abusers are also questionable. In a study of 225 medical outpatients, Ochs et al. (1987) found that benzodiazepines could not be detected in the blood of 25 of 77 patients who reported that they were taking these drugs, whereas benzodiazepines were detected in the blood of ten other patients who had not reported using them. Similarly, Lilja et al. (1986) found that drug use histories of patients admitted for observation on medical and surgical wards of a general hospital reflected benzodiazepine use in only one third of the patients whose urine samples tested positive for the drugs.

Despite questions about the reliability and validity of self-report data, interview surveys represent the best source of information that is indispensable to assessing the overall abuse liability of drugs—information about individual patterns of use and about the appropriateness of actual use of these medications in populations.

The following section begins with a consideration of studies concerning the prevalence of use of benzodiazepines in samples of various populations, beginning with national samples (V.D.1) followed by samples of regional or other populations (V.D.2). Data from these and other interview surveys that describe patterns of use are reviewed in subsection V.D.3. In subsection V.D.4, we consider recent surveys inquiring specifically about the characteristics of long-term users. Finally, in section V.D.5, we review a number of studies bearing on the appropriateness of benzodiazepine use, in that they included ratings of psychiatric status of users compared with nonusers.

1. National surveys. a. UNITED STATES. **i. 1990 survey by Balter and coworkers.** As discussed in our previous review, the National Institute of Mental Health sponsored surveys of the legitimate use of psychoactive drugs in samples of the United States population in 1970 to 1971 (Parry et al., 1973) and in 1979 (Mellinger et al., 1984; Mellinger and Balter, 1983). Although details of the study have not yet been published, another national-sample survey was conducted by the same research team in 1990 (Balter, 1991a,b); presumably, the methods were similar to those of the earlier studies so that it is not inappropriate to consider trends in the prevalence and patterns of use during the period covered by these surveys.

The annual prevalence of use of prescribed anxiolytics and hypnotics among adults in the United States in each of the three national surveys, as reported by Balter (1991a), is shown in table 18. The frequency of use of anxiolytics was approximately the same in 1979 as in 1970 to 1971, although, as we have noted previously, sales data indicate that use of these drugs peaked in about 1973; thus, use was increasing in the earliest survey and had decreased by the time of the 1979 survey. As the 1990 data indicate, the frequency of use apparently continued to decline during the 1980s so that in 1990 only 8.3% of the adult population reported having used a minor tranquilizer during the past year. On the basis of IMS data (1990), in terms of standard dose units, benzodiazepines accounted for slightly more than 80% of these drugs sold in United States retail pharmacies in these years.

Use of prescribed hypnotics has displayed a different pattern of change, declining markedly from the 1970–1971 survey to the 1979 survey but remaining fairly stable from that year to 1990. According to IMS data, and leaving out phenobarbital (which is an ingredient of many combination products and is counted by IMS each time any of these products is dispensed), benzodiazepines accounted for 59% of hypnotics sold in retail pharmacies in the country in 1990.

Findings regarding the duration of regular use of anxiolytics and hypnotics are considered in section V.D.3, together with other interview data bearing on patterns of use. The 1990 data reported by Balter (1991a,b) also included responses to a number of questions bearing on appropriateness of use relative to respondents' psychological health and on popular attitudes toward use of psychoactive medications. Details of the findings have not yet been published in sufficient detail for appropriate consideration in this review.

ii. "Monitoring the Future" (National Institute on Drug Abuse). Annual surveys of high-school seniors showed that, in 1977, 18% reported that, at some time in their lives, they had used minor tranquilizers prescribed for them by a physician; by 1982, this figure had decreased to 12%, where it remained until at least 1985 (Johnston et al., 1987).

iii. National Survey of Personal Health Practices and Consequences. In 1980, 36% of employed men and 26% of employed women in the United States worked variable shifts. Sleeping pills or tranquilizers were used by 3.2% of men who worked variable shifts, versus 5.2% of other employed men. However, among women working variable shifts, 16% used sleeping pills or tranquilizers,

TABLE 18
Annual prevalence of use of anxiolytics and hypnotics (% of United States adult population)*

	1970–71	1979	1990
Anxiolytics	10.9	11.1	8.3
Hypnotics	3.5	2.4	2.6

* From Balter, 1991a.

as opposed to only 7.9% of other employed women (Gordon et al., 1986).

b. GREAT BRITAIN. **i. Gallup survey.** The Gallup Organization conducted personal interviews of a sample of the adult population (ages 16 yr and older) about the use of benzodiazepines in Great Britain in 1985 (Dunbar et al., 1989). Of the 4148 respondents, 7.7% reported that they had used a benzodiazepine anxiolytic or hypnotic during the previous 12 mo; this included 5.4% of men and 9.7% of women. Use during the past week was reported by 3.6% of the sample. Use of anxiolytics during the previous 12 mo was reported by 3.9%, and use of hypnotics was reported by 4.2% of the sample. Use of both anxiolytics and hypnotics was found to increase with age up to the age range of 45 to 54 yr, where the prevalence of anxiolytic use peaked; however, the highest prevalence of hypnotic use was found in those aged 65 yr and older.

An approximate comparison can be made between these findings and those of Balter et al. (1984), who conducted a survey of the use of psychoactive drugs in Great Britain and in ten other countries in 1981. The comparison can only be approximate, because there were discrepancies between the surveys with respect to the categories of drugs about which people were asked and the age range of respondents. Nevertheless, in the 1981 survey, 11.2% of the population reported having used an anxiolytic during the previous 12 mo; the comparable rate from the 1985 survey was 4.2%. If the sexes are considered separately, 6.7% of men and 15.3% of women reported use of anxiolytics in the previous 12 mo in the 1981 survey; the corresponding figures from the 1985 survey were markedly lower for men, i.e., 3.4%, and dramatically lower for women, i.e., 5.0%. Despite the methodological discrepancies between the surveys, it is likely that some of these differences reflect an actual reduction in annual prevalence of use of benzodiazepine anxiolytics. Certainly such a reduction would have been expected following the government's restriction of benzodiazepine prescribing under the NHS earlier in the year of the Gallup survey, which was indeed reflected in prescription sales data for this period (see discussion in section V.B.2).

The findings of this survey concerning patterns of use of benzodiazepines are considered in subsection V.D.3.

ii. The Health and Lifestyle Survey. Household interviews were conducted in 1985 to 1986 with 9003 individuals representative of adults (18 yr and older) living in private households in the United Kingdom, omitting Northern Ireland (Ashton and Golding, 1989). A total of 3.3% reported current use of tranquilizers or hypnotics (chiefly benzodiazepines). This percentage compares closely with the 3.6% who reported "current" use, i.e., within the previous week, in the Gallup survey described before. Likewise, in the Health and Lifestyle Survey, 4.2% of women and 2.1% of men reported current use of these drugs; an exact 2:1 female to male ratio among users of anxiolytics and hypnotics was also found in the Gallup survey.

Like the Gallup survey and the 1981 survey conducted by Balter et al. (1984), the Health and Lifestyle Survey found that use of these drugs increased with age, although it did not differentiate age groups greater than 40 yr. Results of the Health and Lifestyle Survey also indicated, consistent with the other surveys, that rates of use increased with self-reported malaise and illness. In addition, use was more prevalent in households headed by manual workers than in those headed by nonmanual workers and in households headed by the unemployed.

c. CANADA. Rawson and D'Arcy (1991) reported an examination of data concerning sedative-hypnotic drug use among adults (ages 15 yr or older) from four separate surveys of health and health care utilization conducted in Canada between 1968–1969 and 1989. In 1968–1969 and 1978–1979, respectively, 4.9% and 6.1% of the population reported that they had used a tranquilizer or hypnotic within the previous 48 h. In 1985, 11.9% of the population reported use of tranquilizers or hypnotics in the past 12 mo, and, in 1989, 5.7% reported use of such drugs in the past 30 d.

In each survey, women were approximately twice as likely as men to report use, and rates of use increased with age. Prevalence of sedative-hypnotic use was higher among those who were single, widowed, or divorced than among those who were currently married, and it was twice as high among the lower income as opposed to the higher income families. In addition, in each of the four surveys, use was most prevalent among retired persons, least prevalent among those currently employed, and in the middle of this range for the unemployed.

Of the three surveys that included questions about health and health care, each showed that the prevalence of sedative-hypnotic use was dramatically higher among those who had consulted physicians and/or been hospitalized than among those who had not, and rates of sedative-hypnotic use increased in direct relation to the number of additional drugs that respondents reported using.

In the 1968–1969 survey, the prevalence of sedative-hypnotic use increased with increasing levels of reported anxiety. In the 1978 study, "rates of sedative-hypnotic use were highest for those in whom negative feelings predominated and lowest for those in whom positive feelings predominated"; also, of those who had experienced symptoms of anxiety or depression only rarely or occasionally, less than 3% had used a sedative-hypnotic within the previous 48 h, and, of those who had experienced such symptoms frequently, 11.2% of men and 15.2% of women reported such use.

d. AUSTRALIA. In the Australian Health Surveys, Lockwood and Berbatis (1990) found that 4.8% of the noninstitutionalized national population in 1977–1978 and

3.1% of the population in 1983–1984 reported having used a tranquilizer, sedative, or other drug for "nervous conditions" during the prior 2 d; this was an overall decline of 35% during this period. In both surveys, the prevalence of use increased with age, and, in every age group greater than 14 yr, use was more prevalent among women than among men. Data provided by IMS (1990) indicate that virtually all minor tranquilizers dispensed in Australia, at least in 1983 and 1984, were benzodiazepines.

In contrast, use of "medicines for sleep" during the prior 2 d was reported by 2.7% of the population at the time of both surveys; of this group of drugs, IMS data indicate benzodiazepines accounted for two thirds in 1984. In all age categories greater than 14 yr, the prevalence of use increased with age and was greater among women than among men. The frequency of use was particularly high among those aged 65 yr or older; in this age group, as found in the 1983–1984 survey, the prevalence of use of hypnotics (12.3%) was greater than that of the tranquilizer category (8.8%).

e. SWEDEN. The Survey of Living Conditions was carried out with random samples of the population in 1975, 1977, 1980, and 1981. The individual respondents in each survey were matched with the national psychiatric inpatient case register. "Regular" use of psychoactive drugs, including prescribed sedatives, neuroleptics, and antidepressants, but excluding hypnotics, was reported by 2.2% of the combined samples from these four waves of interview (Allgulander, 1989). The rate for men was 1.6%, and that for women was 2.9%. Among these regular psychoactive users, 59% of men and 67% of women were older than 50 yr of age (as opposed to 35% of all men and 37% of all women). Virtually all reported chronic illness or disability. Of those who reported severe anxiety, only 31% also reported regular use of psychoactive drugs.

f. AUSTRIA. In a random sample of the adult population of Austria, interviewed in 1983 and 1984, use of tranquilizers in the 3 mo prior to interview was reported by 2.5% of the population; 72% of these, or 1.8% of the total population, reported having used these drugs in the prior 7 d (Lesch et al., 1989). In addition, 1% reported having used hypnotics in the prior 3 mo, of whom 60% had used them in the preceding 7 d.

g. MEXICO. A 1988 survey of use and abuse of psychoactive substances was conducted with a sample of 12,557 persons between 12 and 65 yr of age living in urban areas, representing about 65% of the national population (Medina-Mora et al., 1989). The overall lifetime prevalence of use of tranquilizers (both medical and nonmedical use) was 0.7%. Among those aged 12 to 34 yr, 0.69% of boys and men and 0.38% of girls and women had used tranquilizers in the prior year, and 0.26% and 0.17%, respectively, had used tranquilizers in the prior month. Among those aged 35 to 65 yr, 0.22% of men and 0.24% of women had used tranquilizers in the prior year, and 0.15% and 0.06%, respectively, had used such drugs in the prior month.

h. COLOMBIA AND COSTA RICA. In a survey in Colombia, Murrelle et al. (1990) found that 6% of the population used tranquilizers; in a study of 2083 subjects in Costa Rica, the authors found that 8.5% used tranquilizers. These studies apparently did not attempt to distinguish medical and nonmedical use; the report did not specify the dates of these surveys.

2. Regional and other surveys. a. GENERAL POPULATION SURVEYS. As summarized in table 19, several recent publications have described interview surveys providing information concerning use of benzodiazepines in the community. In general, remarkably similar rates of use of these drugs were found across the countries studied. The prevalence of current use, or use in the prior month, was between 5% and 8% in each study for which such a rate was reported (Koenig et al., 1987; Fichter et al., 1989; Vazquez-Barquero et al., 1989; Rush et al., 1987; Pakesch et al., 1989) except that by Rozzini et al. (1988). The figures for past-year prevalence in the study by Swartz et al. (1991) were predictably slightly higher. The studies by Rozzini et al. (1988) and Smart and Adlaf (1988) reflect the higher rates of use that would be expected among elderly populations.

Three studies provided data concerning rates of regular use, i.e., daily or almost daily. Koenig et al. (1987) found that, among residents of Munich between 30 and 69 yr of age who were interviewed in 1980 to 1981 and again in 1982, 2.9% reported regular use of benzodiazepine tranquilizers in the first interview and 0.7% reported regular use in both interviews. Rush et al. (1987) found that daily use of minor tranquilizers, of which 80% were benzodiazepines, was reported by 2.3% of the adult residents of Durham, Ontario (Canada) in 1982; as will be discussed further, daily use was reported by 9.6% of clients of various health and social services agencies at the same time. Smart and Adlaf (1988) studied samples of elderly residents of Ontario who were interviewed in 1976, 1977, 1982, and 1984; combining results for the latter two surveys, they found that 2.5% reported almost daily use of minor tranquilizers, of which all or nearly all were benzodiazepines, and 2.5% also reported almost daily use of hypnotics, of which the majority were benzodiazepines.

b. SURVEYS OF OUTPATIENT POPULATIONS. The frequency of use of benzodiazepines, as of drugs in general, is of course greater among patient populations than in the community at large. Rush et al. (1987) provided an interesting index of this difference in a single community by interviewing a random sample of residents of Durham, Ontario (Canada), as well as consecutive outpatients of local health and social services agencies about their use of minor tranquilizers and hypnotics. As shown in table

19, rates of use among outpatients were three to four times higher than among the community sample.

Several recent surveys of the use of benzodiazepines in various outpatient populations are summarized in table 20. Most of these studies surveyed elderly outpatients; 13% to 22% reported current use of benzodiazepine anxiolytics or hypnotics in surveys between 1978 and 1986 (Stewart et al., 1989; Spagnoli et al., 1989; Sullivan et al., 1988). Of such patients interviewed in 1985, 16% regularly or occasionally used hypnotics, chiefly benzodiazepines (Morgan et al., 1988). Ried et al. (1990) found that 30.5% of elderly outpatients used psychotropic drugs during a 2-yr period, and anxiolytics and hypnotics (chiefly benzodiazepines) accounted for about two thirds of these prescriptions; use of psychotropics in the year prior to the survey was the most important predictor of use in the subsequent year.

In outpatient populations not limited to the elderly, similar rates of benzodiazepine use were found in Toronto (Canada), where 12% of family practice outpatients of an urban hospital had used benzodiazepines in the prior 2 wk, and 24% reported use within the past year (Schiralli and McIntosh, 1987). A slightly higher rate of use was reported by outpatients of a cardiology service in Bonn in 1979 to 1980 (Ochs et al., 1987). Thirty-four percent reported use of benzodiazepines in the prior 2 mo, although laboratory tests confirmed the presence of benzodiazepines in the plasma of only 28%; plasma levels were low in many cases, indicating that the patients were not using these drugs on a regular basis. However, these findings are consistent with those of other studies showing a high rate of use of benzodiazepines specifically among patients with cardiovascular disorders (Najeeb, 1987; Westerling, 1988).

Three of the studies of elderly outpatients shown in table 20 also provided information about duration of benzodiazepine use. Sullivan et al. (1988) analyzed data from the Liverpool Longitudinal Study of Continuing Health, in which a random sample of patients 65 yr and older attending general practitioners were interviewed in their homes in 1982 to 1983, and 65% of the same respondents were available for interview again in 1985 to 1986. Of those who reported benzodiazepine use within the prior month in the earlier survey, 61.5% (or 7.9% of the elderly outpatients sampled) reported such use again in the later survey. At the same time, 49.5% of those who reported use in the later survey had not been users in the earlier survey, "thus indicating that the continuing high usage [14%] was not due solely to a large cohort of long-term users." Consistent with prescription sales data, the frequency of use of benzodiazepine anxiolytics substantially declined between 1982–1983 and 1985–1986, whereas the frequency of use of benzodiazepine hypnotics increased; therefore, the overall prevalence of benzodiazepine use remained fairly stable during the period in this population.

A longitudinal design was also used in the study reported by Stewart et al. (1989), in which outpatients who were 65 yr or older were interviewed in 1978 to 1980, and 62.5% of these patients were interviewed again in 1984 to 1986. Of those patients reporting use of benzodiazepines in the earlier survey (17.8%), 37% (or 6.6% of the population studied) reported use of the *same* drug in the later interview.

Respondents in the cross-sectional survey by Morgan et al. (1988) were asked about the duration of their use of prescribed hypnotics (benzodiazepines in 86% of cases). Of the 16% who reported that they used these drugs at least "sometimes," 27% reported use for less than 1 yr, 30% for 1 to 5 yr, 19% for 5 to 10 yr, and 25% for more than 10 yr. Thus, 11.7% of the entire sample of elderly outpatients reported use for longer than 1 yr. These findings bear out the prevalence of long-term use of these drugs among elderly patients.

c. SURVEYS OF BENZODIAZEPINE USERS. Data were collected from community pharmacists in Canada regarding prescriptions for triazolam, flurazepam, or oxazepam (when prescribed for sleep); the patients were interviewed by questionnaire and telephone (Baker and Oleen, 1988). For patients who were 65 yr or older, the highest strengths in which the hypnotics were available (30 mg of flurazepam, 30 mg of oxazepam, 0.5 of mg triazolam) were specified in 66% of prescriptions for flurazepam, 35% for oxazepam, and 39% for triazolam; however, the frequency with which these highest strength forms were prescribed decreased with increasing age. Fifty-eight percent reported that they used them daily, 20% used one to six doses weekly, and the remaining 22% used them occasionally or as needed. The frequency of daily use increased slightly with increasing age. Also, daily use was significantly more common among patients using triazolam (62%) or oxazepam (61%) than among those using flurazepam (42%). Three of every four patients reported that they were concomitantly using one or more other medications, most commonly for treatment of hypertension or other cardiovascular disorders.

A study of unusually good design and exemplary methods was conducted by Gené-Badia et al. (1988). This was a case-control study of use of benzodiazepines among outpatients of a family and community medicine teaching center in Barcelona. Information concerning patients' histories was obtained from their physicians' records, and the patients were interviewed in their homes by physicians who were unaware whether an individual respondent was a case (a patient who had used a benzodiazepine during the prior month) or control (a patient who had not used a benzodiazepine during the prior year). Users had significantly more chronic physical disorders (particularly cardiovascular and musculoskeletal) than controls. They were also significantly more likely to have psychiatric disorders. On a standard self-rated psychiatric scale (SCL-90R), users had significantly higher

TABLE 19

Interview surveys of benzodiazepine use in the general population

Study	Population	Area	Date of survey	Period of use	Drug	Prevalence of drug use	Comments
						(% of respondents)	
Swartz et al., 1991	Random sample of households in 1 urban and 4 rural counties comprising 1 NIMH Epidemiologic Catchment Area (n = 3798 respondents age 18 yr or more)	USA: North central North Carolina	1982–1983	Prior year	Benzodiazepine anxiolytics (chiefly diazepam and chlordiazepoxide)	Men: 6.9 Women: 10.6	Benzodiazepine anxiolytic use significantly associated with affective or panic disorder or agoraphobia with panic; use also associated with psychic distress, negative life events and health care visit during prior 6 mo.
						(% of population)	
Rozzini et al., 1988	Residents age 70–75 yr living at home (n = 1201); selection method not stated	Italy: Brescia	Not given	Current use	Benzodiazepine hypnotics	21.3	37.8% of male and 53.6% of female residents reported insomnia; only 42.6% of those with insomnia took hypnotics; 10.2% took hypnotics without having insomnia.
					All hypnotics (mostly benzodiazepines)	25.9	
						(% of population) 1980–81 / 1982	
Koenig et al., 1987	Random sample of residents aged 30–69 yr (n = 2216 in 1980–81; follow-up of 1827 in 1982).	West Germany: Munich	1980–81; 1982	Prior wk	Benzodiazepine tranquilizers (chiefly bromazepam, oxazepam, diazepam and lorazepam)	6.6 / 6.4	Most respondents taking benzodiazepines used <10-mg diazepam equivalent. Benzodiazepines were most frequently used drugs. No linkage to medical records.
						(% of 1,827 respondents interviewed in both time periods who reported "regular" use).	
						2.9 / 0.7	
						(% of population)	
					Hypnotics (one third were benzodiazepines)	0.6 / 0.2	
						(% of population)	
Fichter et al., 1989	Representative sample of residents aged 15 yr or older n = 1666)	West Germany: 3 towns in Traunstein County in Upper Bavaria	1980–86	Prior mo	Benzodiazepines	5.9	High use of psychotropic drugs associated with higher psychiatric or somatic morbidity.
						(% of population)	
Vazquez-Barquero et al., 1989	Random sample of adults aged 17 yr or older of a rural population (n = 1223)	Spain: Cantabria	Not stated	Prior 2 wk	Tranquilizers (mainly benzodiazepines)	5.7	Psychotropic drug use was associated with physical illness and with psychiatric morbidity.
					Hypnotics (mainly benzodiazepines)	1.9	

						(% of population)	
						Community	Out-Patients
Rush et al., 1987	Stratified random sample of residents aged 18 yr or older (n = 989) and consecutive outpatients from 15 health and social services agencies (n = 34)	Canada: Durham, Ontario	1982	Prior 2 wk	Minor tranquilizers (80% benzodiazepines)	5.2	17.4
						(% of population who reported daily use)	
						2.3	9.6
					Hypnotics	2.3	9.7
						(% of population)	
						1976–77	1982–84
Smart and Adlaf, 1988	Pooled sample of residents aged 60 yr or older (n = 617 in 1976–77 and n = 400 in 1982–84)	Canada: Ontario	1976–77; 1982–84	Prior yr	Tranquilizers (at least 75% benzodiazepines)	Never use	
						86.9	86.4
						≤1 mo	
						6.2	7.1
						1–5/wk	
						3.1	2.5
						Near daily	
						3.9	4.1
					Hypnotics (chiefly benzodiazepines)	Never use	
						81.6	86.0
						<1/mo	
						10.8	8.7
						1–5/wk	
						2.7	2.7
						Near daily	
						4.8	2.5
						(% of population)	
Pakesch et al., 1989	Quota sample of residents aged 15 yr or older (n = 1470)	Austria: Vienna	Not given	Current use	Tranquilizers (bromazepam, chlordiazepoxide, diazepam, lorazepam, oxazepam, and prazepam)	5.0	
					Hypnotics (flunitrazepam, nitrazepam, methaqualone)	0.9	

TABLE 20

Interview surveys of benzodiazepine use in outpatient populations

Study	Population	Area	Date of Survey	Period of Use	Drugs	Prevalence of Drug Use		Comments
						(% of population) 1978–80	1984–86	
Stewart et al., 1989	Ambulatory outpatients, aged 65 yr or older, who were participants in a health screening and referral program (n = 3234 in 1978–80 and n = 2681 in 1984–86; 2022 were included in both time periods)	USA: Dunedin, FL	1/78–12/80; 1/84–12/86	Current use	Benzodiazepine anxiolytics	11.8	8.8	
					Diazepam	7.9	3.9	
					Chlordiazepoxide	2.2	1.2	
					Chlordiazepoxide-clidinium	1.0	0.9	
					Oxazepam	0.4	0.4	
					Lorazepam	0.3	1.6	
					Alprazolam	0.0	0.8	
						(% of population)		
					Benzodiazepine hypnotics	6.0	5.5	
					Flurazepam	6.0	3.5	
					Temazepam	0.0	1.3	
					Triazolam	0.0	0.7	
						(% of population)		
Ried et al., 1990	Elderly, aged 65 yr or older, outpatients who were a subset of a random sample of enrollees of an HMO (n = 278)	USA: Puget Sound, WA	Aug. 1984	Prior yr and subsequent yr (latter determined by analysis of prescription records)	Psychotropics (of which anxiolytics represented 41% and sedative-hypnotics 23%).	30.6		Use of psychotropics in yr prior to survey was most important predictor of use in subsequent yr.
						(% of population)		
Spagnoli et al., 1989	Consecutive outpatients, aged 60 yr or older, of 46 general practitioners (n = 802)	Italy: Torino	1986	Current use	Benzodiazepines	22.4		
						(% of population) 1982–83	1985–86	
Sullivan et al., 1988	Random sample of outpatients aged 65 yr or older (n = 1070 in 1982–83, of whom n = 695 in 1985–86 follow-up)	UK: Liverpool	1982–83; 1985–86	Current use	Benzodiazepines	12.8	14.0	61.5% of those taking benzodiazepines in 1982–83 still took them in 1982–86. No link to medical records.

					Benzodiazepine tranquilizers (chiefly diazepam, lorazepam and chlordiazepoxide)	5.5	3.3	
					Benzodiazepine hypnotics (chiefly nitrazepam, triazolam and temazepam)	8.8	11.9	
					Both benzodiazepine tranquilizers and hypnotics	1.5	1.3	
						(% of population)		
Morgan et al., 1988	Random sample of outpatients aged 65 yr or older (n = 1020). Sample overrepresented those aged 75 yr or older	UK: Nottinghamshire	5/85–9/85	Current use	Hypnotics (86% benzodiazepines)	Never use Sometimes use Often use Use all the time	84 3 1 12	Of patients using hypnotics at least sometimes, 27% took ≤1 yr; 30%, 1–5 yrs; 19%, 5–10 yrs; and 25% >10 yrs. No link to medical records.
						(% of respondents)		
Ochs et al., 1987	Consecutive outpatients of a university cardiology service (n = 225)	West Germany: Bonn	12/79–4/80	Prior 2 mo	Benzodiazepines (chiefly bromazepam, diazepam or oxazepam)	Reported: 34.2 Actual: 27.6		Actual drug use detected by plasma analysis. Many patients taking benzodiazepines had low plasma levels, indicating recent but not regular use.
						(% of population)		
						Prior yr	Prior 2 wk	
Schiralli and McIntosh, 1987	Typical outpatients of family practice unit of urban hospital (n = 510)	Canada: Toronto	Not given	Prior yr, prior 2 wk	Benzodiazepines (55.4% diazepam)	24.3	12.2	Patients asked reason for taking drugs; 40% gave reason other than that for which drugs prescribed.

scores than nonusers on the depression factor, the interpersonal sensitivity factor, and the total number of symptoms. The mean duration of benzodiazepine treatment among users was 50 mo. Fifty-two percent used the drugs as needed rather than regularly. Users were significantly more likely than nonusers to abstain from use of alcohol.

3. Interview data concerning patterns of use. In our previous review, we found that interview surveys had established that most users of anxiolytics and hypnotics used these drugs only occasionally or for relatively short periods of regular daily use and that most users tended to consume less than the prescribed dosage of these medications and to decrease use over time. On the other hand, it was evident that a substantial minority of users of these drugs reported regular use for long periods of time; these long-term regular users had been found likely to be older patients with multiple chronic physical disorders.

In this subsection, we consider evidence from recent surveys bearing on patterns of use of benzodiazepines. Information from these studies concerning the prevalence of long-term use is discussed here; a number of recent surveys that have focused specifically on the circumstances and characteristics of long-term use are reviewed in the next subsection (V.D.4).

a. DATA FROM NATIONAL SURVEYS. **i. United States.** The majority of users of anxiolytics and of hypnotics in both 1979 and 1990 had used these drugs regularly only for short periods, i.e., 1 mo or less (table 21). However, the proportion of short-term users of both anxiolytics and hypnotics has declined, whereas the proportions that used these drugs regularly for 4 mo or more substantially increased. This shift is particularly pronounced among users of anxiolytics: In 1979, 15% of such users, or 1.6% of the entire adult population, had used these drugs regularly for 1 yr or more; in 1990, this proportion had grown to 25% of users, or 2% of the adult population of the country (Balter, 1991a,b).

These data appear to reflect a substantial increase in actual numbers of long-term users of benzodiazepines, but they may to some extent reflect a relatively stable number of long-term users who have come to represent a larger proportion of the shrinking population of all users. This question of interpretation might be clarified when more details on the characteristics of the 1990 long-term users are published.

TABLE 21
*Longest period of regular daily use**
(% of past-year users in the United States)

	Anxiolytics		Hypnotics	
	1979	1990	1979	1990
≤1 mo	67	52	78	70
2–3 mo	13	11	6	7
4–11 mo	6	11	6	9
≥12 mo	15	25	11	14

* From Balter, 1991a.

Users of anxiolytics in both surveys were more likely to use lower doses, rather than higher doses, than prescribed; the difference, however, was greater in 1979 than in 1990 (table 22).

Users of hypnotics were less likely than users of anxiolytics to decrease their prescribed dosage; on the other hand, this might be expected based on the fact that hypnotics are usually prescribed in a single nighttime dose, providing less opportunity for decreasing dosage than in the instance of anxiolytics, which are more often prescribed in two or three daily doses. The percentage of anxiolytic users who increased their dosage did not change between 1979 and 1990, whereas there was a slight increase in the percentage of hypnotic users who did so. However, in the interest of perspective, it is useful to note that the relative sizes of these subgroups are closely similar to the proportion of antidepressant users who increased their dosage; because antidepressants generally have little liability for abuse, these increases in dosage are likely to be associated with other factors, such as temporary increases in the severity of symptoms, etc.

ii. Great Britain. In the 1985 Gallup survey (Dunbar et al., 1989), of respondents who reported having used a benzodiazepine during the previous year, 54.6% reported that they had used it on a daily, or almost daily, basis for some period of time ("regular users"). Of these, 20.5% had used the drug for 4 wk or less, and an additional 10.6% had used the drug regularly for no more than 3 mo. However, 52.2% of the regular users (or 2.0% of the entire population) had used benzodiazepines for 12 mo or longer.

Eleven percent of all benzodiazepine users reported that they had at some time increased their dosage without their physicians' advice, but of these users, 75% had continued to take these increased doses for less than 1 mo.

Fifteen percent of current users reported that they had attempted to stop and had experienced difficulty in doing so. This experience was not associated with sex or with type of benzodiazepine but was more frequent with longer durations of use and was more frequent among respondents 45 yr of age and older.

Physical illness during the previous 2 yr was reported more frequently by both current and past users of benzodiazepines than by nonusers. This difference was especially marked for respondents aged 45 yr and older, among whom male current users were also much more

TABLE 22
*Unsupervised changes in dose**
(% of past-year users in the United States)

	Anxiolytics		Hypnotics		Antidepressants	
	1979	1990	1979	1990	1979	1990
Decrease	22	12	3	9	10	13
Increase	6	6	6	8	6	5

* From Balter, 1991b.

likely to have had physical illnesses than were male past users.

In another analysis of these data, Dunbar et al. (1988) examined concurrent use of alcohol, cigarettes, and caffeine among people who used benzodiazepines. Current benzodiazepine users were significantly less likely to use alcohol than past users, who were, in turn, less likely to use alcohol than nonusers; however, these differences were explained largely by the age differences in the groups, i.e., current users were more likely to be older and thus less likely to drink.

Regarding the prevalence of long-term regular use, i.e., daily or almost daily use for 12 mo or longer, Dunbar et al. (1989) attempted a comparison of their data with those of the 1981 survey by Balter et al. (1984). Dunbar and associates compared the 52.2% of users in their study who reported regular use for 12 mo or longer with the 27.4% of regular users in the 1981 survey who had used for 12 mo or longer. On this basis, they suggested that, although overall prevalence of use had declined, long-term regular use of benzodiazepines had substantially increased. However, in view of the discrepancies between the surveys, this comparison and conclusion are inappropriate. For example, the 1981 data explicitly excluded use of hypnotics, which were included in the 1985 data; because British practitioners have prescribed benzodiazepine hypnotics more than benzodiazepine anxiolytics in recent years, long-term use of hypnotics might have strongly influenced the 1985 findings of the prevalence of long-term use.

b. DATA FROM REGIONAL AND OTHER SURVEYS OF OUTPATIENTS. **i. Great Britain: Hereford and Worcester.** Of 127 consecutive patients attending a rheumatology clinic of a district general hospital, 37 (29%) were taking benzodiazepines, of whom 34 were women (Hardo and Kennedy, 1991). Twenty-two (59%) of the users reported regular use. The benzodiazepines had been prescribed for insomnia associated with night pain for 29 (78%) of the users. The average duration of benzodiazepine use was 4.1 yr. The benzodiazepine users were significantly older than nonusers. Users were also significantly more likely than nonusers to complain of night pain and severe pain and to use narcotic analgesics.

ii. Ireland. Nolan and O'Malley (1988) reported an interview survey, conducted in 1986, of 450 consecutive patients filling benzodiazepine prescriptions at 16 pharmacies "selected so that their catchment areas proportionately represented the urban/rural distribution and socio-economic structure of the Irish population." Sixty-seven percent of the patients were women, and 34% were 65 yr or older. Significantly more of the antianxiety prescriptions were for patients younger than 65 yr than for those older than 65 yr; insomnia was the most common indication for the prescription in those older than 65 yr. The investigators found that the doses prescribed were "conservative," with no prescribed dose exceeding the recommended therapeutic range. There was a nonsignificant trend for older patients to receive lower doses.

Ninety-one percent of the respondents had received benzodiazepine prescriptions previously. The median duration of use was 2.5 yr and was significantly longer in patients older than 65 yr (median 3 yr) than in those younger than 65 yr (median 2 yr). Duration of use did not differ by patients' sex or by indication for anxiety or insomnia. Regular daily use of benzodiazepines was reported by 83% of the patients. Twenty-two percent took lower doses than prescribed, and 7.5% reported having used higher doses than prescribed; however, the investigators noted that in all cases the doses reportedly consumed were within the recommended therapeutic range.

When asked to rate the efficacy of their benzodiazepines as "very useful," "sometimes useful," "useless," or "don't know," 68% rated the drugs as "very useful" and 29% as "sometimes useful." These ratings did not vary in relation to the specific agents prescribed.

iii. Australia: New South Wales. Of 839 adult patients who consulted general practitioners in a rural town during five survey days, 11.3% reported having used a benzodiazepine during the previous 4 wk (Lyndon and Russell, 1988). The frequency of use increased with age; 37% of respondents 70 yr or older reported use within the past month. Seventeen percent of the users had used benzodiazepines for less than 6 mo, 24% for 6 to 18 mo, 29% for 19 mo to 5 yr, and 29% for longer than 5 yr. Whereas 24% of the users reported that they used a benzodiazepine only about once a week or less often, 68% reported use daily or almost daily. Daily or almost daily use was reported by a significantly greater proportion (78%) of those who used oxazepam or lorazepam than of those who used diazepam (44%).

iv. Switzerland. Wacker et al. (1989) reported a longitudinal study of the use of tranquilizers, hypnotics, and analgesics among Swiss men. The original study population consisted of 4082 randomly selected 20-yr-old military recruits; subsamples were interviewed again in 1979 and 1985. There was a significant decrease in the proportion of those who reported repeated use of tranquilizers between 1972–1973 (8.7%) and 1985 (4.9%), as well as in the proportion of those reporting use of analgesics (28.6% to 21.0%), but no significant change in the proportion who reported use of hypnotics (5.4% to 5.2%).

Between 1972–1973 and 1985, almost twice as many men discontinued use of tranquilizers or analgesics as the number who started use of these drugs during that period. The number who stopped using hypnotics during the period, however, was only slightly more than the number who started using hypnotics. Only five men (0.6% of the sample) reported tranquilizer use in both 1972–1973 and 1985, and only seven (0.9%) used hypnotics in both 1972–1973 and 1985; in contrast, 87 respondents (10.5%) reported repeated use of analgesics at both times.

v. Pakistan. In 1986, diazepam was the only psychoactive drug prescribed in the outpatient department of the National Institute of Cardiovascular Diseases (Karachi). During a 6-wk period, 76% of the 26,756 outpatients received prescriptions for diazepam. Diazepam was most frequently prescribed in 5-mg doses as a hypnotic (57% of sample); 25% received prescriptions to take 10 mg daily to relieve anxiety. Forty-two percent of a random sample of those who received diazepam prescriptions reported that they took the drug in ways other than prescribed—more than prescribed (2%), less than prescribed (3%), or "irregularly" (37%). However, 22 patients (7%) were not taking the drug at all.

The duration of use was longer than 12 mo in 62%; specifically, 41% of the sample had been taking the drug for 1 to 5 yr, 17% for 5 to 10 yr, and 4% for longer than 10 yr. Fifty-one percent thought they could stop taking diazepam "quite easily," 18% "with some difficulty," and 19% "with great difficulty"; the remaining 12% could not give a specific response (Najeeb, 1987).

c. DATA FROM SURVEYS OF INPATIENTS. Investigators of the use of benzodiazepines and other psychoactive drugs in hospitals have usually attempted to gauge prevalence and to characterize patterns of actual use among inpatients by examining prescription records, as in the studies reviewed in section V.C. Although a few recent studies have included interviews with hospital patients about their drug use, these have often focused on the patients' use of benzodiazepines prior to admission or after discharge.

A study by Edwards and coworkers (1991) may be unique in examining actual use during hospitalization. Prescriptions for hypnotics (of which 80% were for benzodiazepines) were written for 270 of 1277 patients admitted to medical, surgical, and gynecological wards during several weeks of 1989. However, only 17% of these patients actually took all of the doses prescribed, 12% took some but less than half of the prescribed doses, and another 25% took none. The proportions of patients who actually took the drugs prescribed varied in relation to the frequency with which the prescriptions called for specific regimens: Prescriptions for gynecological patients called for use "when required," and 56% actually used the drugs; whereas regular regimens were specified in 25% of the prescriptions for medical patients and in 33% of those for surgical patients, and 78% and 86% of these patients, respectively, actually used the drugs prescribed.

At the time of admission, 6.4% of the patients had been taking hypnotics. Although only 1.6% received prescriptions for these drugs upon discharge, 6.1% were found to be taking hypnotics again when followed up 4 to 8 wk later. The investigators concluded that this study "failed to show that hospital prescribing of hypnotics has any generally significant influence on community prescribing or vice versa."

With regard to the resumption of benzodiazepine use after hospitalization, Priebe et al. (1988) published a particularly interesting study of patients admitted to the psychiatry department of a university-affiliated hospital in Berlin. Benzodiazepines were discontinued during hospitalization in 134 patients. Eighty-seven were followed up at 8 to 16 mo following discharge; of these, 25 (29%) had resumed use of benzodiazepines. Those who did and did not resume use were not significantly different with respect to primary psychiatric diagnoses, nor with respect to the relative proportions that fulfilled DSM-III criteria for benzodiazepine abuse or dependence. However, significantly more of those who resumed benzodiazepine use, compared with those who did not, reported having used these drugs for more than 3 mo prior to hospitalization.

It is of interest to compare the findings of this study with those of a study by Rickels et al. (1986a), in which 131 chronically anxious outpatients treated with diazepam for 6 to 24 wk were followed up 1 yr after ending treatment. Sixty-six percent reported experiencing a relapse of symptoms within the year, 41% relapsed and sought medical or psychiatric help, and 32% resumed use of psychoactive medication, chiefly benzodiazepines. This proportion compares closely with the 29% of psychiatric patients who resumed benzodiazepine use after withdrawal in the hospital, as reported by Priebe et al. (1988) A random sample of 264 patients was drawn for interview from the five largest departments of a university-affiliated hospital in Innsbruck (Austria) in 1985 (Fleischhacker et al., 1989). On the survey day, 22% of the sample were taking benzodiazepines, of whom 64% were taking hypnotics and 36% were taking anxiolytics. Twenty-one percent of those taking benzodiazepines at the time of the survey had been using benzodiazepines for more than than 3 mo, i.e., since before admission to the hospital. Seven percent reported that they had attempted to discontinue use but experienced difficulty in doing so; the investigators could not judge in retrospect whether these problems represented clear-cut withdrawal symptoms or reemergence of symptoms. Three patients who thought they could not stop taking benzodiazepines had been using them for 10 to 20 yr without increasing their doses.

4. Interview data concerning long-term use. As described in the previous sections, there is a striking agreement among a great many diverse sources of information that virtually every identifiable population of benzodiazepine users includes a subgroup of patients who continue to take these drugs for long periods of time. In our previous review, we noted that community surveys had indicated that these long-term users are likely to be older patients and more frequently women than men, with multiple chronic physical illnesses. Preliminary evidence from prospective studies had also suggested that long-term use is most likely to develop in patients with recur-

rent psychiatric problems of long duration, for which they have previously received psychoactive medication. We concluded that this subgroup of chronic users of benzodiazepines deserves special attention with respect to concerns about the abuse liability of these drugs.

Several reviews and discussions of the experimental, clinical, and epidemiological information relevant to the need for chronic benzodiazepine treatment and the risks and benefits of such treatment have been published in recent years. Among those especially worthy of note are reports by Rickels (1987), Tyrer (1987), Williams (1987), Nagy (1987), Gorman and Papp (1990), Chen and Lader (1990), and Gabe (1991).

Since our previous review, a number of publications have described interview research focusing specifically on long-term use of benzodiazepines. These studies have generally confirmed and elaborated the earlier findings about the characteristics of chronic users and have made at least an important beginning in the exploration of the determinants and potential consequences of long-term use of these drugs. In the following subsection, we consider these recent studies in three groups: (*a*) prospective longitudinal surveys of patients receiving benzodiazepines; (*b*) retrospective and cross-sectional surveys in which patterns of use, characteristics, and attitudes of long-term users have been examined; and (*c*) studies following up long-term users after discontinuation of benzodiazepines. Studies of long-term benzodiazepine users that took measures of psychological health, together with other studies including such measures, are reviewed in subsection V.D.5.

a. PROSPECTIVE LONGITUDINAL STUDIES. Some of the most important questions about long-term use of benzodiazepines may be pursued most productively by studies in which patients are followed from the time that they receive benzodiazepine prescriptions: Which of these patients will continue to use the drugs regularly for long periods, and how do they differ from those who stop after brief periods of use? What are the determinants of long-term use, and can they be predicted? Do long-term users experience some benefits from treatment that other users do not obtain? What are the risks of long-term use relative to the alternatives faced by similar patients who do not use these drugs or who use them only for brief periods? Prospective studies of this kind are notoriously difficult to carry out for a variety of practical reasons; therefore, it is not surprising that only two recent studies of this kind have been reported.

Sixty-two general practitioners in the area of Sydney (Australia) recruited "new users," i.e., 104 patients for whom they were prescribing a benzodiazepine or an antidepressant medication and who had not received such a prescription for at least the previous 3 mo (Mant et al., 1987b). In the ensuing 6 mo of follow-up, the median duration of use was 1.5 mo for benzodiazepines and 2.7 mo for antidepressants. At the end of 6 mo, six (10%) of the benzodiazepine users and ten (23%) of the antidepressant users had continued to use these drugs daily or had continued to use them regularly for at least 2 wk in each month. Patients older than 55 yr of age were significantly more likely to continue use than younger patients; no other patient characteristics (sex, marital status, employment status, consumption of alcohol or tobacco, perceived health, or psychological state as measured on the GHQ) were predictors of continued use. The authors commented that, because benzodiazepines are associated with "a higher dependency potential" than antidepressants, the fact that more of the antidepressant users continued drug use suggested that other factors must determine the development of long-term use.

A similar study was reported by Fiorio et al. (1990), for whom four general practitioners in Verona (northern Italy) recruited 75 "new users" of benzodiazepines or antidepressants; "new users" were defined as in the study described by Mant et al. (1987b). Fifty percent of those receiving benzodiazepines had stopped treatment in 7 wk, as opposed to 22 wk for those receiving antidepressants. At the end of 26 wk, 13 patients (23%) receiving benzodiazepines alone and seven patients (39%) receiving antidepressants alone or with benzodiazepines had continued to use these drugs. As compared with those who stopped using the drugs before 26 wk, the long-term users were significantly more likely to be 45 yr or older and to be unmarried. Long-term users had also been rated as significantly more severely ill than nonusers by the physicians at the initial visit, although subsequent ratings on standard instruments including the GHQ did not differentiate long-term users from the other patients. Patients with both psychological distress and physical disorders were significantly more likely to become long-term users.

b. RETROSPECTIVE AND CROSS-SECTIONAL SURVEYS. Retrospective and cross-sectional surveys can provide a wealth of detail regarding the association of drug use with its antecedents, correlates, and consequences, although they are inherently limited in their power to determine the extent or even the direction of causality in these associations. Nevertheless, these studies have furnished most of the information we have, or are likely to have in the near future, concerning drug use in general and long-term use of benzodiazepines in particular. They are important sources of information about the ways in which chronic benzodiazepine users actually use these drugs and about characteristics of such users, including their physical and psychological health as well as sociodemographic and other characteristics. These data provide important clues to the factors that may determine the development of long-term use and help to elucidate the correlates and potential consequences of long-term use.

i. Patterns of use among long-term users. Among 72 male outpatients of a Veterans Administration hos-

pital who had received triazolam prescriptions during the previous 6 mo, the average age was 60 yr. In telephone interviews of 48 of the patients, nine claimed that they had never used or had stopped using the drug. The remaining 39 had had active prescriptions for triazolam for an average of 7 mo. Twenty-four (62%) reported that they used the drug every night, and the remaining 15 patients used the drug an average of 2.6 nights each week. Thirty-seven reported using the dose prescribed, and two reported using half the prescribed dose (De Tullio et al., 1989).

Another study of outpatients of a Veterans Administration hospital, in Boston, MA (United States), was reported by Haskell et al. (1986). Of 196 patients filling prescriptions for diazepam in 1982, 90% reported that they had been using diazepam for 6 mo or longer, including 14% who had used the drug for 6 mo to 2 yr, 20% for 2 to 5 yr, 25% for 5 to 10 yr, and 31% for more than 10 yr.

Seventy-one percent reported that they used the drug daily. The mean dose for all patients studied was 21 mg/d. Twenty-four percent reported that they had increased their dose over time, 26% reported that they had decreased their dose, and 50% reported no change; those who reported increasing their dose were taking a mean dose of 33 mg daily. Seventy percent of the patients were taking other medications concurrently, most frequently antidepressants (14%), other benzodiazepines, usually for sleep (13%), antipsychotics (12%), and antihypertensives (9%).

Of 135 people who filled benzodiazepine prescriptions in a large Innsbruck (Austria) pharmacy during a 2-mo period, 82% had been taking the drugs for more than 1 yr (Barnas et al., 1988). Seventy-one percent reported use more than four times per week. Of these regular users, the men had a mean duration of use of 3.5 yr and the women of 6.4 yr. Five (9.8%) of the men and nine (7.5%) of the women reported that they took a higher dose than had been prescribed at least once a week; 12 of these 14 patients said that they exceeded the prescribed dose because of sleep problems. Ninety percent of the regular users thought they could not get along without these drugs, although "one third had tried in vain to stop medication." With respect to such attempts to discontinue medication among regular users, the investigators stated that "10% of the male and 5% of the female patients. . .observed somatic withdrawal symptoms. . . ." Four men (7.8%) and seven women (5.8%) reported that they regularly abused illicit drugs, mostly opiates; all of these patients also regularly abused other sedatives, and six abused alcohol as well. Three other men were dependent on alcohol.

Two studies of attempts to discontinue chronic benzodiazepine treatment in outpatients of general practices provided some information about the patterns of use of these long-term users. Of 72 patients of an English practice who had been taking benzodiazepine tranquilizers regularly for more than 6 mo, 14 (19%) were taking the dose initially prescribed, 27 (38%) were taking more than initially prescribed, and 17 (24%) were taking less than initially prescribed; the initial prescription was not known for the remainder (Morrison, 1990). However, the report does not indicate whether these adjustments from the initial dose had been made with or without medical supervision, nor does it specify the average or range of doses taken. Of 39 patients of an Israeli practice who had been using hypnotics for more than 5 yr, 82% reported nightly use (Matalon, 1990). Also, in a study of 64 long-term users in London, Rodrigo et al. (1988), described in more detail later, found that 83% reported daily use, and an additional 8% took the drugs "several times each week"; the dosages used were within the recommended therapeutic range.

ii. Physical health characteristics of long-term users. A number of sources of information about long-term users of benzodiazepines have pointed to multiple chronic physical disorders as an important distinguishing characteristic of this subgroup of users. A recent survey in which the medical records of a large number of long-term users were compared with those of age- and sex-matched controls (Simpson et al., 1990b), described in section V.C, has provided further confirmation that chronic benzodiazepine users are distinctly sicker than other patients. Some recent interview surveys have also examined physical illness among long-term users.

Of 129 patients admitted to an internal medicine unit in January 1984, 49 (38%) had used a benzodiazepine during the previous year, of whom 24 (19%) had used these drugs daily for more than 4 mo and 17 (13%) had used them for more than 1 yr. Comparison of all benzodiazepine users, i.e., long-term and others, with nonusers indicated a significantly greater likelihood of cardiovascular and/or rheumatological disorders among users; however, the difference between the subgroup of long-term users (of whom 79% had such disorders) and nonusers (62.5%) was not statistically significant. This lack of statistical significance may have been due to the high frequency of these disorders in the entire inpatient population studied, as well as to the relatively small numbers in each group. Long-term users had had significantly more surgical procedures than either intermittent users or nonusers (Halfon et al., 1988).

Two general practitioners in London in 1985 identified 82 patients (2.2% of all patients registered) who had been receiving repeat prescriptions for benzodiazepines for at least 1 yr (Rodrigo et al., 1988). Of the 64 who participated in the study, only five were younger than 40 yr of age, and 41% were 70 yr or older. The median duration of benzodiazepine treatment was 5 yr. Eighty-three percent reported daily use, and an additional 8% took the drugs "several times each week." Nine of the men (56%) and 18 of the women (37%) reported that they had one

or more physical illnesses. However, review of the physicians' records indicated that 11 (69%) of the men and 30 (62%) of the women had one or more physical disorders.

iii. Attitudes of long-term users. In a study by Salinsky and Doré (1987), of long-term users who responded to a questionnaire regarding their attitudes toward use of tranquilizers and the risk of dependence, 79% believed the drugs had been "a lot of help," and 49% thought they would feel unwell if they tried to stop using them. Slightly more than 40% wished they had never started using tranquilizers, wished they had been warned that they were habit-forming, and intended to stop using them soon.

Subjects in the survey by Barnas et al. (1991), described above, also responded to questions regarding their attitudes toward benzodiazepine use and the risk of dependence. Of these 171 patients, of whom 87% had used benzodiazepines for longer than 1 yr, 72% said that they thought that they could not manage without these drugs; this was true of 89% of those who used them more than three times per week. Eighteen patients (10.5%) always carried their pills with them, and seven (4%) said they felt uncomfortable when they missed a dose. Sixty (35%) claimed to have tried to stop taking benzodiazepines at least once; 5.9% of the men and 3.3% of the women claimed that they had experienced somatic withdrawal symptoms during these attempts to discontinue medication, although the report does not specify what these symptoms were.

Seventy-five percent of the subjects were aware of the risk of dependence on benzodiazepines. An analysis to distinguish long-term from other users found that long-term users more frequently discussed their benzodiazepine use with their physicians and were better informed about the risk of benzodiazepine dependence.

Simpson et al. (1990a) invited a random subsample of 145 long-term users to participate in a further survey regarding their attitudes toward use of these drugs. Only 44 patients (30%) agreed; the investigators speculated that those who declined might have feared that they would be asked to discontinue their medication. Of those who participated, 36 (82%) thought their medication was vital or very important to their coping, 26 (59%) were fairly or very unwilling to try to stop, and 34 (79%) would have felt very much concerned if their prescription were stopped. Only five (11%) claimed to be very concerned about continuing their medication. Thirty-one (72%) thought that it would be difficult to stop using the drugs. However, when asked their opinions about their current prescribed dosage, 36 (82%) thought it was "about right"; the remaining eight patients were equally divided between thinking the dose was "a little high" and "extremely low."

Hamilton (1989) reported interviews with 53 patients of an urban English practice who requested repeat prescriptions for benzodiazepines. The average duration of treatment for these patients was 6 yr. Forty-four percent reported believing that they would not be able to cope without their medication; whereas 56% thought they would be able to discontinue by themselves without great difficulty. When asked how they would react to discontinuation of the prescription, 17 (32%) said they would be "upset," 18 (34%) said they would be "very upset," and five (9.5%) said they would be "angry and resentful." Thirty-one patients (58.5%) said they were aware of the risk of dependence on these drugs.

Twenty-five (39%) of 64 long-term users considered the drugs helpful and 11 (17%) believed they could not manage without them. On the other hand, 13 (20%) disliked the drugs, although only eight (12.5%) wanted to reduce their dosage or stop taking them (King et al., 1990c). Forty-eight (75%) of the subjects claimed that they would pay for the prescriptions themselves if they were not available for free under the NHS. When they were asked what they would do if their prescriptions were unavailable, 26 (41%) could think of various alternatives (e.g., relaxing activities or alcohol), 25 (39%) could think of no alternatives, four (6%) said they would be extremely worried or might become mentally ill, and nine (14%) claimed they would not be particularly concerned about going without the drugs. Fifty-eight percent claimed to have tried to stop using benzodiazepines at least once in the past, most frequently because of a fear of dependence, because they felt better or because their physician had instructed them to stop.

iv. Discontinuation of long-term use. In recent years, considerable pressure has come to bear on physicians, particularly in the United Kingdom, to limit benzodiazepine use to brief periods and to attempt to discontinue chronic use of these drugs (for example, see Joughin et al., 1991). The question of what effects such discontinuation may have is of great interest, not only in the context of public policies that encourage or virtually dictate discontinuation of chronic use but also because many clinical authorities have cogently argued that use of benzodiazepines should periodically be discontinued in the interest of reassessing the need for continued treatment.

A practical test of patients' attitudes toward stopping chronic use of hypnotics was reported by Matalon et al. (1990), who invited 45 chronic users in an urban Israeli practice to an interview to discuss their use of these drugs and the possibility of discontinuing medication with the help of a psychological support group. The 39 patients (87%) who agreed to the interview had been using hypnotics, virtually all benzodiazepines, for more than 5 yr. Thirty-two (82%) took the drugs nightly. Despite having agreed to the interview, none of the 39 chronic users agreed to attempt to discontinue use of these drugs.

A more forceful approach was taken in a British gen-

eral practice, as reported by Morrison (1990). The 72 patients who had been taking benzodiazepines for more than 6 mo were asked to see their physicians before filling their next repeat prescription. In these interviews, the patients were advised that their physicians "no longer believed that the drug that they were using was useful in the long-term and that we would prefer them to stop taking it." The patients were asked whether they would agree to try to discontinue use with the physicians' help. Twenty-seven patients (37.5%) agreed to try to discontinue, 38 (52.8%) did not want to try, and seven (9.7%) were not sure.

Holton and Tyrer (1990) described the outcome of discontinuation of benzodiazepine use in 41 patients who were referred by their general practitioners to a controlled withdrawal program conducted by psychiatrists in London. The patients had taken a mean daily dose of 11.3 mg of diazepam for a mean duration of 37.5 mo. GAD was the diagnosis for most of the patients. In the withdrawal program, which took place in 1980 to 1982, 36 patients had completely discontinued medication and five had failed to achieve complete discontinuation.

Follow-up interviews of the patients were conducted 5 yr after discontinuation was attempted, and drug histories were verified by examination of medical records. Six patients (15%) had not resumed use of benzodiazepines or other psychoactive drugs at any time during the 5 yr; four (10%) had taken other psychoactive drugs, including dothiepin, propranolol, trifluoperazine, and dichloralphenazone but not benzodiazepines; four (10%) of those who had initially failed to discontinue benzodiazepines during the withdrawal program did discontinue during the follow-up period; 13 (32%) had resumed use of benzodiazepines, for periods of 2 wk to 1 yr, but were not still taking them at the 5-yr follow-up; and 14 (34%) had resumed use of benzodiazepines and were taking them at the follow-up.

It is interesting to consider these findings in relation to findings of two similar studies that we have discussed previously. Rickels et al. (1986a) also studied the effects of discontinuation of diazepam in chronically anxious outpatients. Of 131 patients followed up 1 yr after ending treatment, 66% reported experiencing a relapse of symptoms within the year, 41% relapsed and sought medical or psychiatric help, and 32% resumed use of psychoactive medication, chiefly benzodiazepines. Similarly, of 87 psychiatric patients followed up 8 to 16 mo after their benzodiazepine medication had been discontinued during hospitalization, 29% had resumed use of benzodiazepines (Priebe et al., 1988).

An inpatient program was designed to discontinue benzodiazepine use in patients who had not been able to withdraw as outpatients (Joughin et al., 1991). Twenty-one patients had taken benzodiazepines (mean daily dose of 27-mg diazepam equivalents) for 1 to 25 yr (mean of 10 yr). All patients were successfully withdrawn by the end of the inpatient program. Outcome was judged in terms of clinical status as well as continued abstinence. Eight patients had a "good" outcome, seven had an "intermediate" outcome, and six had a "poor" outcome. Fourteen patients (67%) remained abstinent from benzodiazepines after 6 mo of follow-up. However, these included four patients judged to have a "poor" overall outcome, of whom three had required admission to psychiatric hospitals. In addition, two patients committed suicide, at 4 and 14 mo following participation in the discontinuation program.

Outcome was found to be strongly related to depression; patients with "good" outcomes had significantly lower levels of depression, as measured before discontinuation on three standard rating scales. Patients with "poor" outcomes were significantly older, on average, than patients with "good" or "intermediate" outcomes. However, neither duration of benzodiazepine use nor dosage used was related to outcome.

5. Studies including ratings of psychological health. As discussed previously (section V.C), a number of investigators have found that the majority of patients receiving benzodiazepine prescriptions do not have psychiatric diagnoses and that the reasons for benzodiazepine prescriptions are often not recorded in physicians' case notes; this apparent discrepancy is particularly evident in the case of elderly patients, who receive a disproportionately large percentage of benzodiazepine prescriptions. Some authors have interpreted this discrepancy as an indication that benzodiazepines may often be prescribed inappropriately. Others have speculated that this interpretation may oversimplify the situation and have suggested a number of reasons why physicians might fail to record psychiatric problems for patients who nevertheless require benzodiazepine treatment.

As we discussed in our previous review, some national and regional community surveys of drug use have also included ratings of psychological status. We found that these studies generally showed that most use of benzodiazepines is appropriate, in that people who report using these drugs are also likely to report high levels of psychic distress, whereas few people who are not distressed report use of benzodiazepines.

A number of recent epidemiological studies in which benzodiazepine users and nonusers were interviewed or were asked to complete standardized self-report questionnaires about their psychiatric status are described in table 23. Some of these studies have been discussed in previous sections, although the focus of those discussions was on other findings. All but one of these studies (Rozzini et al., 1988) used standardized instruments widely used to measure psychiatric morbidity in community samples and/or general medical patients; the instruments are described in the footnote to the table.

In several of the studies, benzodiazepine users and nonusers from the same communities or clinic popula-

tions were compared with respect to ratings on standard instruments. These included two studies using case-control designs, in which medical patients using benzodiazepines were found to have significantly higher scores on the SCL-90R (Gené-Badia et al., 1988) or the Crown-Crisp index (Salinsky and Doré, 1987) than matched controls from the same clinical populations. Three other groups of investigators using the SCL-90 found significantly higher scores among users than nonusers on some subscales or on the total score (Swartz et al., 1991; Magni et al., 1986; Antonijoan et al., 1990). In community surveys, Vazquez-Barquero et al. (1989) and Pakesch et al. (1989) found that respondents identified as psychiatric "cases" on the basis of GHQ ratings were significantly more likely than other respondents to report recent use of psychotropics, chiefly benzodiazepines. Likewise, Bellantuono et al. (1989) found that general practice patients with "conspicuous psychiatric morbidity," as identified by use of the Clinical Interview Schedule, were significantly more likely than other patients to receive prescriptions for psychotropics (mostly benzodiazepines); psychiatric morbidity was the strongest predictor of such prescriptions among the several sociodemographic and health variables examined, and its effect on the probability of prescriptions was independent of effects of the other variables.

Clinical Interview Schedule ratings were used in two other studies. On the basis of these ratings in a community survey, Fichter et al. (1989) found a significant positive correlation between the severity of psychiatric morbidity and use of benzodiazepines. However, Fiorio et al. (1989) found that "new users" of benzodiazepines were as likely to score as only mildly distressed (48.5%) as they were to score as moderately to highly distressed (45.5%); whereas 76.5% of "new users" of antidepressants scored as moderately to highly distressed. In a similar study, Mant et al. (1987b) found that, of 60 "new users" of benzodiazepines, 53% scored as significantly distressed on the GHQ, whereas 35% had no or only mild distress; in contrast, 80% of 44 new users of antidepressants scored as significantly distressed.

In two of the studies described in table 23, ratings of benzodiazepine users were compared with ratings of groups examined in other studies. Patients receiving diazepam in the study by Haskell et al. (1986) had scores on every subscale of the SCL-80 that were equivalent to or higher than those of groups of patients in other studies, who were judged to be candidates for treatment for anxiety or panic disorders, except the scores on the Phobic-Anxiety subscale of the patients using diazepam were between those of the anxiety and panic groups. In the study by Rodrigo et al. (1988), 34% of 64 long-term users of benzodiazepines qualified as "cases" on the basis of Clinical Interview Schedule ratings; the investigators commented that this rate was not much different from the rate of psychiatric morbidity that one might expect in any general medical sample. The benzodiazepine users' scores on the self-rated Symptom Rating Test, according to the authors, "confirm the association between long term tranquiliser use and emotional distress, as the levels were higher than those previously reported from normal samples"; however, they also noted that these scores were somewhat lower than those reported from other studies of "neurotic outpatients."

In a study of people between 70 and 75 yr of age who were living at home, Rozzini et al. (1988) found that 26% used hypnotic drugs; this included 42.5% of those who reported sleep disturbances and 10.2% of those who did not report such problems. Of those who reported use specifically of benzodiazepine hypnotics, 77% reported that they suffered from insomnia.

Thus, although physicians frequently or usually do not assign psychiatric diagnoses to patients for whom they prescribe benzodiazepines, most studies in which patients are interviewed specifically about their psychiatric status find that those who receive these prescriptions are distinguished from other patients by significant psychic distress. This conclusion supports earlier findings from surveys of national samples of the United States population (Mellinger et al., 1978, 1984), which indicated that people with high levels of psychic distress were significantly more likely to use anxiolytic medications than those with low levels of distress.

This conclusion is also consistent with studies of the detection of psychiatric illness among general medical patients, as summarized by Goldberg (1985): "Over half of all medical patients with psychiatric illnesses diagnosable according to research criteria will not have their illnesses detected by the medical staff looking after them. . . .Firstly, many such patients do not provide any cues, either verbal or nonverbal, that suggest a psychological disorder, *though they will readily describe their symptoms if they are asked directly.* Secondly, patients often mention depression or anxiety at the beginning of the interview together with their presenting somatic symptoms, yet only the latter are picked up and discussed further" [Emphasis added].

In addition, although physicians may recognize *symptoms* of psychological distress in some patients, for any of various reasons they may not translate these into diagnoses. The demarcation between psychiatric symptoms and disorders is particularly important among the elderly (Blazer, 1989), for whom the discrepancy between benzodiazepine use and psychiatric diagnosis is likewise particularly pronounced.

What these findings suggest, in part, is that physicians may often prescribe benzodiazepines to treat psychiatric symptoms. This was the conclusion, for example, of a study of benzodiazepine prescribing by Geiselmann et al. (1989): ". . .physicians' [benzodiazepine] prescription behavior appears to be predicated on patients' subjective

TABLE 23

*Studies of psychiatric status of benzodiazepine users versus nonusers**

Study	Area	Population	Instruments (see footnotes)	Results
Swartz et al., 1991	USA: North central North Carolina	Random sample of households in 1 urban and 4 rural counties making up an NIMH Epidemiological Catchment Area (n = 3798 respondents aged 18 yr or older)	DIS; SCL-90 (adapted)	Respondents with DIS diagnosis of affective disorder or panic disorder, with or without agoraphobia, were significantly more likely to have used benzodiazepines in the prior year than other respondents. Self-reported psychic distress (SCL-90) was also significantly positively correlated with use.
Haskell et al., 1986	USA: Boston, MA	Outpatients of Veterans Administration hospital who filled prescriptions for diazepam (n = 196)	SCL-80	Patients receiving diazepam had scores on SCL-80 equal to or greater than those of subjects (of other studies) who were judged candidates for treatment of anxiety or panic disorders.
Ried et al., 1990	USA: Puget Sound, WA	Outpatients, aged 65 yr or older, who were enrolled in a health maintenance organization (n = 278)	Measures of depressive symptomatology and positive outlook, from Rand Health Insurance Survey	Patients who had received psychotropics (of which 64% were anxiolytics or hypnotics, chiefly benzodiazepines) in the year before the survey had more depressive symptomatology and a more negative outlook than nonusers. However, the influence of this variable on use in the following year was not significant after controlling for the influence of prior use and physical health status.
Bellantuono et al., 1989	Italy: Verona	All patients who consulted 92 general practitioners on a given day (n = 2559)	CIS	Conspicuous psychiatric morbidity was the variable most strongly associated with prescription of psychotropics (of which 71% were benzodiazepines).
Fiorio et al., 1989	Italy: Verona	All patients of 4 general practitioners who received psychotropic prescriptions during specified period and who had not received such prescriptions during the prior 3 mo (n = 75)	CIS	Of patients receiving benzodiazepines, 45.5% were judged to have moderate to high scores on 5-point scale of severity.
Magni et al., 1986	Italy: Padua	Patients aged 61 yr or older on general medical wards of a geriatric hospital during 1982–1985 (n = 331)	SCL-90	Patients who received psychotropics (of which 65% were benzodiazepines) scored significantly higher than other patients on all subscales of SCL-90.
Rozzini et al., 1988	Italy: Brescia	Noninstitutionalized elderly (70–75 yr) residents (n = 1201)	Subjective self-report	Of benzodiazepine hypnotic users, 77% reported that they suffered from insomnia.
Fichter et al., 1989	Germany: 3 towns in Upper Bavaria	Representative sample of residents aged 15 yr or older (n = 1666)	CIS (administered in respondents' homes by research psychiatrists)	Use of benzodiazepines was significantly associated with severity of psychiatric illness.

Salinsky and Doré, 1987	UK: London	All patients of a general practice who had been receiving benzodiazepine anxiolytics for >12 mo (n = 72)	Crown-Crisp index	Benzodiazepine users had significantly higher scores on all subscales of instrument than matched nonuser controls.
Rodrigo et al., 1988	UK: London	All patients of a general practice who had been receiving benzodiazepine prescriptions continuously for ≥12 mo (n = 64)	CIS; Symptom Rating Test	34% of users qualified as cases on basis of CIS ratings; investigators noted this rate is similar to that found in community samples. SRT scores of users were between those found in clinical and community samples but closer to latter.
Gené-Badia et al., 1988	Spain: Barcelona	All patients attending a family medicine center during May 1986 who had used a benzodiazepine in the prior mo (n = 107)	SCL-90R (administered in patients' homes by a physician)	Benzodiazepine users had significantly higher scores on all subscales than matched nonuser controls.
Antonijoan et al., 1990	Spain: Barcelona	Inpatients, aged 65 yr or older, of 2 geriatric hospitals (n = 112) and outpatients, 65 yr or older, of social welfare centers (n = 126)	SCL-90	Users of psychotropics (of which 84% were benzodiazepines) did not have significantly different total scores from nonusers but scored significantly higher on anxiety, depression, and obsessiveness/compulsiveness subscales.
Vazquez-Barquero et al., 1989	Spain: Cantabria	Random sample of adults (aged 17 yr or older) of a rural community (n = 1223)	GHQ-60; Present State Examination (administered in respondents' homes by psychiatrists)	Use of psychotropics (of which 85% were benzodiazepines) within prior 2 wk increased in direct relation to GHQ and PSE scores. Those identified as "cases" were significantly more likely than others to use psychotropics.
Mant et al., 1988	Australia: Sydney	Patients of 62 general practitioners, who received a prescription for a benzodiazepine (n = 60) or antidepressant during a particular 4-wk period and who had not received such a prescription in the prior 3 mo	GHQ-12 (administered in patients' homes)	53% of benzodiazepine users rated as significantly distressed (4+) on GHQ, but 35% scored as having no or mild distress.
Pakesch et al., 1989	Austria: Vienna	Quota sample of residents aged 15 yr or older (n = 1470)	GHQ-30 (administered in respondents' homes by physicians)	Respondents who qualified as "cases" were significantly more likely than others to have used a psychotropic (chiefly benzodiazepines) on the day of survey.

* Abbreviations, descriptions, and references for rating instruments: DIS: Diagnostic Interview Schedule. A structured interview used by lay interviewers in epidemiological studies; generates diagnoses for certain DSM-III disorders (Robins et al., 1981). SCL: Hopkins Symptom Checklist. A self-report symptom inventory; in addition to the SCL-90, modified versions are often used, usually designated by a suffix indicating the number of items in the inventory, e.g., SCL-80 (Derogatis et al., 1974). Rand Health Insurance Survey: an instrument that included measures of depressive symptomatology and positive/negative outlook (Ware et al., 1979). 5-point scale of severity: A scale designed for use by general practitioners to identify conspicuous psychiatric morbidity (Goldberg and Blackwell, 1970). CIS: Clinical Interview Schedule. A semistructured interview designed to measure psychological illness in community and clinical samples (Goldberg et al., 1970). GHQ: General Health Questionnaire. An instrument used to measure psychiatric morbidity among general medical patients; available in versions ranging from 12 to 60 items (Goldberg and Blackwell, 1970). Crown-Crisp Index: A self-report scale for rating psychiatric symptoms (Crown and Crisp, 1979). Present State Examination: An instrument used to measure and classify psychiatric disorders among general medical patients (Wing et al., 1974). Symptom Rating Test: A self-report instrument for rating psychiatric symptoms experienced during the previous week (Kellner and Sheffield, 1973).

symptoms and complaints rather than on a diagnosis-based model."

If patients in psychological distress consulted psychiatrists about these problems, which they do only rarely, these symptoms might or might not be translated into psychiatric diagnoses. In any case, the burden of the studies reviewed here is that patients who receive prescriptions for benzodiazepines are distinguished by significant psychological distress.

6. Summary and discussion. a. NATIONAL SURVEYS. At the time we conducted our previous review, virtually the only data concerning consumption of benzodiazepines among national populations were those provided by the surveys in the United States and a number of western European countries conducted by Balter and his associates for the National Institute of Mental Health (United States). In the last few years, several publications have reflected attempts by other investigators, some with funding by national governments, to study the consumption of psychoactive medications in general, and tranquilizers and hypnotics in particular, in various national populations. These data are of considerable interest, although in general they are limited to cross-sectional portraits of drug use at single points in time; as new surveys of these populations are conducted, it will be very interesting to see trends of change in rates and patterns of use.

Meanwhile, in 1990, Balter and coworkers conducted a new cross-national survey, including the countries surveyed previously as well as others. At this writing, the only data available from these surveys are some preliminary findings regarding use of anxiolytics and hypnotics in the United States. These data confirm evidence from sales and prescription studies that the overall prevalence of annual use of anxiolytics (of which benzodiazepines accounted for more than 80%) declined during the 1980s, from 11.3% of the adult population in 1979 to 8.3% in 1990; whereas use of hypnotics has apparently remained stable at about 2.5% of adults.

A survey of the adult population of Great Britain in 1985 found that 7.7% reported use of a benzodiazepine anxiolytic or hypnotic during the previous 12 mo. Hypnotics were used more frequently (4.2%) than anxiolytics (3.9%). The frequency of use of anxiolytics increased with age up to the age range of 45 to 54 yr; whereas the frequency of hypnotic use continued to increase to a peak among those aged 65 yr or older.

Surveys of the Australian population in 1977–1978 and 1983–1984 indicated trends similar to those in the United States. The prevalence of current use of anxiolytics or daytime sedatives decreased from 4.8% in the earlier survey to 3.1% in the later survey, whereas the rate of current use of hypnotics remained stable at 2.7%.

b. REGIONAL AND OTHER SURVEYS. Several surveys conducted in the 1980s found that 5% to 8% of community samples across geographic regions reported use of benzodiazepines within the past month. Surveys of elderly populations and of outpatient populations found higher rates. Several studies of elderly outpatients found prevalence rates of current use of benzodiazepines ranging from 13% to 22%.

As found in previous studies, recent surveys continue to show that the prevalence of benzodiazepine use among women is about twice as high as that among men and that the frequency of use increases with age.

Many recent studies have also shown that elderly patients are most likely to use benzodiazepines on a daily basis and for long periods and that these patterns of use among the elderly apply especially to use of benzodiazepine hypnotics, which many older patients continue to take nightly for many years.

c. INTERVIEW DATA CONCERNING PATTERNS OF USE. The preliminary data available from the survey of the United States population conducted in 1990 by Balter and his associates indicate that, although the overall prevalence of annual use of anxiolytics has declined, the subgroup of long-term users has increased. In 1979, 1.6% of the entire adult population reported that they had used anxiolytics for 12 mo or longer; in 1990, this figure had increased to 2.0% of the adult population. Although interpretation of this apparent trend must await publication of more details of the 1990 survey, these data suggest the possibility of a growing cohort of regular long-term users, i.e., attrition from this subgroup may be occurring more slowly than supplementation by "new" long-term users.

The 1985 survey of Great Britain found that 52% of all users of benzodiazepine anxiolytics and hypnotics had used these drugs for 12 mo or longer. These long-term users represent 2.0% of the adult population.

Regional and medical practice surveys consistently confirm the high prevalence of regular and long-term use among those who report use of benzodiazepines, especially among older patients.

d. INTERVIEW DATA CONCERNING LONG-TERM USE. A number of investigators in recent years have appropriately focused their attention on populations of long-term users. Their findings represent an important beginning in the exploration of the determinants, correlates, and consequences of chronic benzodiazepine use.

Two prospective longitudinal surveys that have followed "new users" of benzodiazepines have also followed new users of antidepressants. Both studies found that users of antidepressants were more likely than users of benzodiazepines to continue regular use over long periods. These findings are of particular interest in that they provide a point of reference for attempts to interpret the significance of chronic benzodiazepine use. For example, because antidepressants are known to have weak or no reinforcing effects, these findings indicate that long-term use of psychotherapeutic drugs is not necessarily a reflection of reinforcing effects or abuse liability.

Interviews of long-term benzodiazepine users about their patterns of drug use consistently indicate that the great majority of these users, in community samples as well as in patient populations, report daily or almost daily use. However, some caution is appropriate in interpreting these findings, because several investigators who have obtained blood samples from self-reported "regular" users have reported that many such patients in fact use the drugs only occasionally.

Studies of the health characteristics of chronic benzodiazepine users consistently find that these patients are clearly distinguished from nonusers, and even from patients who use the drugs for limited periods, in that they are in much poorer physical health. Long-term users are significantly more likely than other patients to suffer multiple chronic physical disorders.

Interviews of long-term users in which they are asked about their attitudes toward their drug use indicate that the majority are aware of the risk of dependence on benzodiazepines but believe that the drugs provide important benefits without which they would not be able to manage as well. Some claim they would like to stop using the drugs, but more are reluctant to try. Elderly users of hypnotics, in particular, appear to question the rationale for discontinuing.

Several reports have indicated that attempts to discontinue long-term use of benzodiazepines in patient populations meet with mixed success. This is probably a reflection of the diversity of long-term users. The evidence to date indicates that some patients who discontinue chronic benzodiazepine treatment appear to do well for long periods without further need for psychoactive drugs. But a majority—perhaps two thirds of such patients—experience a recurrence of symptoms within 1 yr, and about half of these patients then resume medication, usually with the same or another benzodiazepine; some proportion of these patients who relapse may need, and may benefit from, continued "maintenance" treatment with benzodiazepines. There is little or no information concerning what becomes of the patients who do not seek or at least do not get help when they relapse; for some period of time, presumably they add to the proportion of the population that goes without treatment for anxiety and related disorders. Certainly the subgroup of patients who can discontinue benzodiazepine medication without relapse makes it important to try drug-free intervals, for reassessment of the patient's condition and need for continued treatment, but the welfare of this subgroup alone does not justify the determination to discontinue benzodiazepine use in all patients.

Two other general points should be made here about studies of long-term use of benzodiazepines. The studies reviewed here have provided important information about the prevalence of chronic use, about the patterns of this use, and about the characteristics of long-term users. Very little information is available about the risks and benefits actually incurred during chronic use of these drugs. This is in large part a consequence of the historical fact that the available measures of the risks and benefits of benzodiazepine treatment were designed for the relatively brief periods of use examined in typical clinical efficacy trials. In view of our current awareness of the frequency with which these drugs are used over long periods, clearly the time has come for development of measures of the effects of chronic use of benzodiazepines. The need for such measures poses serious challenges in that long-term prospective longitudinal studies are logistically difficult, whereas cross-sectional studies, in the absence of baseline measures, would require innovative approaches to the need for appropriate controls. However, the numbers of long-term users of these drugs compel our attention to the need for careful assessment of the consequences of this use.

Second, most studies of benzodiazepine use have either focused on use of anxiolytics or have considered use of all benzodiazepines, including anxiolytics or hypnotics. Although the anxiolytics and hypnotics have clear pharmacological similarities, the hypnotics are formulated at relatively higher strengths per dose units than the anxiolytics, and the pattern of hypnotic use, i.e., a single nightly dose, is clearly distinct from patterns of anxiolytic use, which typically entail multiple daily doses. Thus, the effects of use of benzodiazepine hypnotics might well differ markedly from those of anxiolytic use. There has been little independent study of hypnotic use. Particularly because hypnotic use appears to have increased as a fraction of the use of benzodiazepines in general, and because use of hypnotics is particularly likely to become chronic, there is a clear need for assessment of the correlates and effects of this drug use as an independent set of phenomena; this applies to many kinds of experimental research, as well as to epidemiological studies.

e. STUDIES INCLUDING RATINGS OF PSYCHOLOGICAL HEALTH. A number of studies have examined the psychological health of benzodiazepine users, often in comparison with that of nonusers. Most of these studies have used standardized self-report questionnaires or psychiatric interviews that are widely used for the purpose of measuring psychiatric morbidity among community samples or general medical patients. Most of these studies, including those in which benzodiazepine users were compared with nonusers from the same communities or clinic populations, demonstrated significantly greater psychological distress among those using benzodiazepines. These findings support earlier research that found that benzodiazepine use was generally appropriate in that most users reported high levels of psychic distress. These findings suggest that physicians tend to prescribe benzodiazepines to treat symptoms of psychological distress, although for various reasons they usually do not translate these symptoms into psychiatric diagnoses.

E. Surveys of Use in Special Populations

1. Elderly patients. a. GENERAL CONSIDERATIONS. The prevalence of use of benzodiazepines is higher among the elderly than among younger age groups, and prescriptions filled by older patients account for a disproportionately large percentage of all prescriptions for these drugs. These findings were discussed in our previous review (Woods et al., 1987) and have been consistently supported and elaborated in more recent epidemiological studies, as described above. In typical community surveys, as well as in surveys of outpatient populations, between 13% and 22% of people 65 yr or older report current or recent use of benzodiazepines. It has become increasingly clear that the majority of these patients have used these drugs regularly for long periods, often for years, and that these patients constitute by far the largest single age group of all long-term users.

As discussed previously, findings of recent national surveys suggest that the prevalence of long-term use of benzodiazepines may have increased (Balter, 1991a,b; Dunbar et al., 1989). In light of the fact that long-term benzodiazepine use is most frequent among elderly patients, it is possible that such an increase has occurred, in part, as a function of the marked growth of the elderly population. The United States population aged 65 yr or older doubled between 1950 and 1985 and is expected to double again between 1995 and 2030; as a percentage of the total population, the elderly represented 9.5% in 1965 and 11.8% in 1984 and are expected to represent 13.1% in 1995 (Blazer, 1989). The elderly populations of other Western nations, including most of the countries that account for substantial sales of benzodiazepines, are also increasing rapidly as a percentage of the total populations (United States Department of Commerce, 1991).

Thus, it becomes increasingly important to study the use of benzodiazepines in the elderly population. It is a particular challenge to examine virtually any aspect of the mental health of this population. Older patients are less likely than younger patients to define their problems in psychological or emotional terms, which complicates identification of mental health problems among elderly subjects of community surveys as well as diagnosis in the clinical setting. Older patients are less likely than younger patients to seek or obtain help from providers of mental health care. When they do experience psychological distress, they are most likely to express the problem to a primary care practitioner in the context of physical complaints (Veroff et al., 1981; Blazer, 1989). On the other hand, many psychiatric disorders, especially "neurotic" disorders, anxiety disorders, and sleep disorders, are most prevalent among the elderly (Neugebauer, 1980; Blazer, 1989; Gottlieb, 1990).

This paradox is reflected in the findings, discussed previously, that physicians are especially likely to prescribe benzodiazepines for older patients, presumably because they recognize the patients' psychological distress, but they are especially unlikely to diagnose or otherwise document psychiatric problems for these patients. It is understandable that many authors have expressed concern about the rationale for this large number of benzodiazepine prescriptions; but it is inappropriate to conclude that these prescriptions are simply unjustified. Rather, the lack of documented reasons for these prescriptions represents a question that should be pursued by innovative research into the means by which elderly patients signal psychological distress and by which physicians translate these signals into therapeutic needs. Such research could not only help to estimate the extent to which benzodiazepines are appropriately or inappropriately used for elderly patients; it also has the potential to identify approaches for improving the abilities of primary care practitioners to detect and differentiate psychiatric disorders among elderly patients and thus to provide more appropriate care for these problems.

Researchers should also explore the consequences of benzodiazepine use among the elderly. Conventional clinical trials provide only limited information about these effects and virtually no information about the benefits and risks of the most typical pattern of benzodiazepine use among older patients, namely, long-term regular use.

Some indications of the risks of chronic benzodiazepine use in the elderly have been provided by studies of these patients at the time of admission to hospitals. Among 718 patients aged 50 yr or older who had been using some prescribed drugs at the time of admission to medical wards of a Winnipeg (Manitoba, Canada) hospital during a 4-mo period in 1983, 162 (23%) were found to have had some drug-related problem; of the patients who had been using benzodiazepines, 10% were found to have had problems associated with these drugs at the time of admission (Grymonpre et al., 1988). As described previously (section III.C.6), Whitcup and Miller (1987) found that, of 66 elderly (65 yr or older) female patients admitted to a New York City psychiatric hospital in 1983, 11 (17%) were physiologically dependent on benzodiazepines at the time of admission; in nine of these patients, benzodiazepine dependence was not initially recognized, and most of these experienced complicated withdrawal.

b. INSTITUTIONALIZED ELDERLY. In our previous review of studies of drug use among the elderly in hospitals or long-term care facilities, we found that about 10% to 15% receive prescriptions for anxiolytics, and about 15% to 25% receive prescriptions for hypnotics. It appeared that use of benzodiazepines, and particularly of benzodiazepine hypnotics, was more prevalent among the institutionalized elderly than among elderly persons in community samples. However, the frequency of prescriptions issued in institutions is higher than the prevalence of actual drug consumption among these patients. For example, although 40% of residents of 12 intermediate

care facilities in Massachusetts (United States) received prescriptions for sedative-hypnotic drugs during a particular month, only 28% actually used these drugs for 5 d or more of the month (Beers et al., 1988).

A number of recent studies of the use of anxiolytics and hypnotics in elderly populations in nursing homes and hospitals are summarized in table 24. Most or all were conducted in the 1980s. The prevalence of prescriptions specifically for benzodiazepines was presented, or can be deduced, for eight of the studies shown. In five of these studies, representing nursing home residents in the United States (Buck, 1988; Beers et al., 1988) and Italy (De Leo et al., 1989) and hospital patients in Italy (Magni et al., 1986) and Spain (Antonijoan et al., 1990), the prevalence rates for benzodiazepine prescriptions during institutionalization were similar, ranging from 20% to 27.5%.

Three studies indicated higher rates of benzodiazepine prescriptions for institutionalized elderly patients—42% among elderly medical patients in a Toronto (Canada) hospital (Busto et al., 1990), an average of 50% among residents of five nursing homes in Denmark (Hasle and Olsen, 1989), and 60% among residents of two aged-care facilities in South Australia (Gilbert et al., 1988).

A lower rate of prescriptions of benzodiazepines was found in the National Nursing Home Survey Pretest. Among a sample of 526 patients in 112 nursing homes in four metropolitan areas of the United States in 1984, in the 7 d preceding the survey, 5.7% of the patients had orders for anxiolytics and 6.7% had orders for hypnotics (Burns and Kamerow, 1988); benzodiazepines were specified in 72% of the anxiolytic orders and in 70% of the hypnotic orders (Beardsley et al., 1989). Similarly, 8% of 1201 residents of a random sample of 55 rest homes in Massachusetts had current prescriptions for minor tranquilizers (Avorn et al., 1989).

Two of the studies summarized in table 24 demonstrated that rates of benzodiazepine prescriptions for elderly inpatients are higher than those for other elderly populations. Among elderly patients on medical wards of a Toronto hospital in 1989, 15% had benzodiazepine prescriptions at the time of admission, whereas 42% received such prescriptions at some time during hospitalization (Busto et al., 1990). Antonijoan et al. (1990) studied 112 patients in two geriatric hospitals, as well as 126 elderly clients of eight social welfare centers, in Barcelona in 1988. Twenty-six percent of the hospitalized patients, as opposed to 14% of the nonhospitalized group, reported having used benzodiazepines during the previous week. It was also of interest that, among nonhospitalized subjects, those using psychotropics (of which 86% were benzodiazepines) scored significantly higher than nonusers on the anxiety and depression subscales of the SCL-90, and hospitalized patients using psychotropics (benzodiazepines in 82%) scored significantly higher than nonusers on the subscales of anxiety and obsessiveness/compulsiveness.

2. *Children and adolescents.* In an analysis of data from the National Ambulatory Medical Care Survey, Kelleher et al. (1989) found that, in 1985, anxiolytic drugs were prescribed in 3.6% of visits by pediatric patients (17 yr or less) to office-based physicians in the United States. Data from the NDTI (IMS America, Ltd., 1990–1991) indicate that, in 1991, patients aged 19 yr or less accounted for 1% of prescriptions of benzodiazepine anxiolytics and for 1% of prescriptions of benzodiazepine hypnotics; the majority of these prescriptions were for patients between 10 and 19 yr of age. In addition, 2% of prescriptions for clonazepam were issued for children aged 9 yr or less, and 3% were for patients aged 10 to 19 yr.

Of 184 children (ages 6 mo to 4.5 yr) with neuromotor disorders treated at a Memphis, TN, rehabilitation center in 1983 or 1986, 21% received prescriptions for muscle relaxants. Most of these prescriptions were for benzodiazepines, chiefly diazepam, which was the most frequently prescribed medication for patients of the center from 1962 through 1986 (Greer et al., 1990).

In 1985, children 14 yr of age or younger in the Federal Republic of Germany received on average about 0.8 DDD of minor tranquilizers, almost all of which were benzodiazepines; adolescents between 15 and 20 yr of age received on average about 1.4 DDD. It was estimated that about 0.5% of children and adolescents in the country received prescriptions for minor tranquilizers in 1988. Benzodiazepines had been the most frequently prescribed psychotropic drugs for children and adolescents in 1982, but use of these medications had declined by almost 20% as of 1988; in 1985, neuroleptics were the most commonly prescribed psychotropic drugs for patients in this age group (Elliger et al., 1990).

Twenty-two child psychiatrists and 83 general practitioners in Wessex (United Kingdom) had issued, on average during the previous 3 mo, one minor tranquilizer prescription for children 7 yr of age or less, two for children aged 8 to 13 yr, and seven for patients between 14 and 17 yr. The greatest number of psychotropic prescriptions for patients in this age category had been for hypnotics. Seventy-four hypnotic prescriptions had been written for patients aged 7 yr or less, and nine such prescriptions had been written for those aged 8 to 17 yr (Adams, 1991).

Minor tranquilizers were the most frequently prescribed psychotropic drugs for patients aged 19 yr or less in Saskatchewan (Canada) (Quinn, 1986). In 1981, minor tranquilizer prescriptions were recorded for 1.5% of children up to 4 yr of age, 0.9% of those between 5 and 9 yr, 0.9% of those between 10 and 14 yr, and 2.2% of those between 15 and 19 yr.

3. *Mentally retarded patients.* Bates et al. (1986) examined the records of 242 mentally retarded patients

TABLE 24
Prevalence of use among institutionalized elderly

Study	Method and population	Area	Data of survey	Period of use	Drugs	Prevalence of drug use	Comments
						(% of population ≥65 yr)	
Buck 1988	Retrospective analysis of Medicaid drug claims of all year-long nursing home inpatients aged 17 yr or more (total n = 33,351; no. of patients >65 yr = 21,354)	USA: Illinois	July 1983–June 1984	Any during study year	Chlordiazepoxide Flurazepam Temazepam	7.4 14.2 1.3	Prescription of psychotropic drugs significantly associated with primary diagnosis of functional mental illness
						(% of population)	
Burns and Kamerow 1988	Retrospective review of medical records of random sample of inpatients aged 65 yr or more from National Nursing Home Survey Pretest (n = 526)	USA: Atlanta, GA; Boston, MA; Denver, CO; Toledo, OH	1984	Prior week	Anxiolytics Sedative-hypnotics	5.7 6.7	
						(% of drug orders)	
Beardsley et al., 1989	Retrospective analysis of drug orders for random sample of inpatients age 65 yr or more from National Nursing Home Survey Pretest (n = 236 drug orders)	USA: Atlanta, GA; Boston, MA; Denver, CO; Toledo, OH	1984	Prior week	Anxiolytics (72% benzodiazepines, chiefly diazepam, oxazepam, and lorazepam) Sedative-hypnotics (70% benzodiazepines)	21 20	Half of subjects were Medicaid patients. Medical records of 21% of patients receiving psychotropic drugs did not indicate need for those drugs.
						(% of population)	
Beers et al., 1988	Prospective analysis of drug use by all inpatients from 12 representative intermediate care geriatric nursing homes (n = 850)	USA: Massachusetts	Not given	Any during study month	Benzodiazepines	20	Those taking benzodiazepines used an average of 7.3 mg of diazepam equivalents per day; 30% of those taking benzodiazepines received long-acting drugs.
						(% of population for whom drugs prescribed)	
					Sedative-hypnotics (of which 63% were benzodiazepines)	40	
						(% of population actually using drugs)	
						28	

						(% of population)	
Avorn et al., 1989	Retrospective analysis of prescriptions for all inpatients of 55 randomly selected nursing homes (n = 1201 patients; half were age 75 or more).	USA: Massachusetts	Not given	Current use	Minor tranquilizers	8	
						(% of patients)	
Magni et al., 1986	Retrospective review of records of patients aged 61 or older on general medical wards of a geriatric hospital during 1982–1985; selection procedure not specified (n = 331)	Italy: Padua (northern Italy)	1982–1985	During hospitalization	Benzodiazepine anxiolytics Benzodiazepine hypnotics	24.5 3.0	Patients receiving psychotropics (of whom 65% received benzodiazepines) had significantly higher scores of self-rated psychological distress than other patients.
						(% of population)	
DeLeo et al., 1989	Retrospective analysis of drug use by inpatients in 11 geriatric institutions (n = 1533); mean age 79 yr	Italy: Padua	1985	Current use	Benzodiazepines	21	Benzodiazepines were most frequently prescribed psychotropic drugs. No linkage to medical records.
						(% of population)	
Costa et al., 1987	Retrospective analysis of drug use by elderly inpatients of 1 nursing home (n = 91)	Spain: Malaga	Not given	Current use	Tranquilizers	28.9	Use of drugs was appropriate for patients' medical condition.
						(% of population)	
Antonijoan et al., 1990	Review of records of and interviews with inpatients aged 65 yr or older of 2 geriatric hospitals; selection procedure not specified (n = 112)	Spain: Barcelona	1988	Prior week	Benzodiazepines	26	Patients who received psychotropic drugs (of whom 81% received benzodiazepines) scored significantly higher than other patients on self-rated psychological distress (SCL-90).

TABLE 24—*Continued*

Study	Method and population	Area	Data of survey	Period of use	Drugs	Prevalence of drug use	Comments
						(% of patients)	
Busto et al., 1990	Retrospective review of records of all patients 65 yr or older admitted to selected wards of a general hospital during a month in 1989 (n = 246)	Canada: Toronto	1 mo during 1989	(See "Prevalence of drug use")	Benzodiazepines	On admission: 15 During stay: 42 On discharge: 5	At 5-mo postdischarge follow-up, all those who had used benzodiazepines for ≥80% of their hospital stay were still using them.
						(% of population)	
Gilbert et al., 1988	Retrospective review of records of residents admitted to 2 aged care institutions between November 1980 and October 1986 whose stays were 12 mo or longer (n = 397)	Australia: South Australia	November 1980–October 1986	Any use during institutionalization	Benzodiazepines	59.7	35.5% of population were judged to have used inappropriately (see text).
						(% of population)	
Hasle and Olsen, 1989	Retrospective analysis of drug use by inpatients in 5 nursing homes (n = 125)	Denmark: Colense	Not given	Past and current use	Benzodiazepine sedative-hypnotics	50	Use of sedative-hypnotics not associated with mental incapacity.

who resided in state institutions in Ohio (United States) in 1976 and for whom other psychiatric disorders in addition to retardation had been diagnosed. Forty patients (16.5%) had received anxiolytics or hypnotics (chiefly benzodiazepines) either alone or in combination with antipsychotics or antidepressants. Based on standards recommended for the treatment of the patients' psychiatric disorders other than retardation, three of the prescriptions for anxiolytics were probably appropriate, 18 were uncertain, and 19 were probably inappropriate.

A similar frequency of use of anxiolytics (18.7%) was found by Bond et al. (1989) among 75 mentally retarded patients in a psychiatric facility in Pennsylvania (United States).

Eighty-one mentally retarded patients who were discharged from two English hospitals between 1983 and 1987 were followed up after they had been resettled in the community for at least 6 mo. Five patients had been receiving benzodiazepines 2 yr before discharge from the hospital, four received benzodiazepine prescriptions at the time of discharge, and six patients were found to be receiving such prescriptions at follow-up (Thinn et al., 1990).

Among 163 mentally retarded patients in an institution in Norway in 1985, Linaker (1990) found that 3% were receiving sedatives (apparently anxiolytics) and 2% were receiving hypnotics.

F. Surveys of Misuse and Recreational Use

As indicated in our previous review (Woods et al., 1987), our definition of misuse of benzodiazepines stands quite apart from our definition of recreational use of these drugs. *Recreational use* is limited to instances of benzodiazepine-reinforced behavior, i.e., when the effects of the drug serve to maintain drug taking. *Misuse*, on the other hand, can entail use to relieve a medical or psychological problem but involves taking them in a manner other than that prescribed by a physician. Thus, taking another person's benzodiazepine to treat anxiety or taking an overdose to attempt suicide is indicative of misuse but not of recreational use.

Of course neither these definitions nor any others are universally used by investigators interested in determining the extent of recreational use or misuse of benzodiazepines. Rather, the literature is characterized by frequent use of terms such as "abuse," which is often defined vaguely or not at all. Although this term has negative connotations and might appear similar to recreational use as we define it, it is more often used to refer to misuse or a combination of misuse and recreational use or to cases in which physiological dependence has been detected.

Problems of definition of terms occur in several survey studies and in secondary analyses of survey data. Porpora (1986), for example, took the view that pharmaceutical companies actively promote benzodiazepine prescrip-

tions by physicians and that this, in turn, leads to increased abuse of these drugs. To support this argument, Porpora drew correlations between numbers of prescriptions written, as indicated by NDTI data, and abuse, as indicated by mentions in the DAWN. The correlation, not surprisingly, is fairly good. DAWN data, however, do not accurately reflect recreational use, which is probably the type of abuse that Porpora had in mind. As pointed out in our previous review (Woods et al., 1987; see also section V.F.2), the most frequently reported motive for benzodiazepine overdoses as indicated by DAWN is suicide attempts. Porpora might want to suggest that fewer benzodiazepine prescriptions would lead to fewer attempted suicides with these drugs; however, his contention that prescribing is correlated with and probably causally related to abuse is not supported by the data he uses.

A much more scientifically appropriate study of a similar issue was conducted by Busto et al. (1989). Again, however, these authors' use of the term "abuse" could easily cause confusion. In this study, trends in sales of various benzodiazepines were compared to data concerning abuse of these drugs, as indicated by reports of 284 patients in treatment for substance abuse and dependence, as defined by DSM-III (revised edition). Based on earlier reports by this group, these patients were probably either self-referred or physician referred because of problems associated with benzodiazepine administration. Most of the patients, at least in the earlier studies, were physiologically dependent on their prescribed medication; they were not recreational users. In the 1989 study, a recent increase in the total sales of rapidly eliminated benzodiazepines correlated well with increased use of these particular benzodiazepines by patients with benzodiazepine abuse or dependence. A clear interpretation of this finding would require knowing whether the increased sales of rapidly eliminated benzodiazepines were related to increased physiological dependence among patients taking these drugs as prescribed for them or to increased recreational use. Unfortunately, the authors did not provide information with respect to this distinction.

Some studies that claim to describe "dependence" are discussed in the following section because they have combined DSM-III or DSM-III (revised edition) criteria for abuse or dependence, and these two factors cannot be separated. At the same time, we cannot place much weight on the evidence from studies that do not clearly define the types or sequelae of benzodiazepine use they are attempting to measure.

1. Prevalance and patterns of misuse. a. SURVEYS OF THE GENERAL POPULATION. **i. United States.** The NIDA has conducted the National Household Survey on Drug Abuse at 2- or 3-yr intervals since 1972. The findings of this survey with regard to reported nonmedical use of tranquilizers are summarized in table 25.

TABLE 25

Percentage of United States population reporting nonmedical use of tranquilizers (National Institute on Drug Abuse, 1988c, 1989a, b, 1990a)

	12–17 yr			18–25 yr			26+ yr		
	Ever	Year	Month	Ever	Year	Month	Ever	Year	Month
1972	3	NA*	NA	7	NA	NA	5	NA	NA
1974	3	2	1	10	4.6	1.2	2	<0.5	<0.5
1976	3.3	1.8	1.1	9.1	6.2	2.6	2.7	1.2	<0.5
1977	3.8	2.9	0.7	13.4	7.8	2.4	2.6	1.1	<0.5
1979	4.1	2.7	0.6	15.8	7.1	2.1	3.1	0.9	<0.5
1982	4.9	3.3	0.9	15.1	5.9	1.6	3.6	1.1	<0.5
1985	4.8	3.4	0.6	12.2	6.4	1.6	7.2	2.8	1.0
1988	2.0	1.6	0.2	7.8	4.6	1.0	4.6	1.8	0.6
1990	2.7	1.5	0.5	5.9	2.4	0.5	5.4	1.3	<0.5

* NA, respondents were not asked in 1972 about annual or monthly use of tranquilizers.

Lifetime prevalence of such nonmedical use increased to 4.9% among youth aged 12 to 17 yr until 1982, declined by more than half to 1988, and increased slightly by 1990; increased to 15.8% among those aged 18 to 25 yr until 1979 and then declined by two thirds; and increased to 7.2% among adults aged 26 yr and older until 1985 and then declined. The decreases in these rates between 1985 and 1988 were significant for each age group. Monthly prevalence of nonmedical use of tranquilizers among youth aged 12 to 17 yr was highest in 1976, at 1.1%, and by 1990 had declined to 0.5%; monthly prevalence among those 18 to 25 yr was also highest in 1976, at 2.6%, and declined to 0.5% by 1990; among adults 26 yr and older, the highest monthly prevalence was reported in 1985, at 1.0%, and declined to less than 0.5% in 1990 (National Institute on Drug Abuse, 1988c; 1989a,b; 1991c).

In both 1975–1976 and 1981, 2% of the population of New York State between 18 and 34 yr of age had used tranquilizers without medical supervision in the prior 6 mo. Among those 35 yr and older, 1% of women and 1% of men reported such use of tranquilizers in the earlier survey; in 1981, nonmedical use of tranquilizers in the prior 6 mo was reported by 1% of women and less than 0.5% of men (Kaestner et al., 1986).

Of 50 elderly residents of Spokane, WA, identified as cases of "prescription drug abuse" (not defined) in 1988, 30% were identified as abusing diazepam, 20% flurazepam, 8% chlordiazepoxide, 2% alprazolam, and 2% lorazepam (Jinks et al., 1990). A review of the medical records of 1000 Georgian physicians who took part in an "Impaired Physicians Program" between 1975 and 1986 indicated that 16.5% had abused diazepam, although the criteria for abuse were not defined; this was the third highest rate of mentions of any single substance, after alcohol (66.4%) and meperidine (26.4%) (Talbott et al., 1987). Three percent of pharmacists and 9% of pharmacy students in a New England state had engaged in self-described recreational use of tranquilizers in the past year, and 18% of the pharmacists and 17% of the students had used tranquilizers in the past year for reported

self-medication (McAuliffe et al., 1987). Of a sample of 500 elementary and secondary education teachers in Texas, 11.3% reported that they had ever engaged in nonmedical use of tranquilizers, and 0.7% reported such use within the prior month (Watts and Short, 1990).

ii. Other countries. According to a 1988 survey, 0.8% of the population of Ecuador had engaged in daily nonmedical use of tranquilizers during the past month (Aguilar, 1989). This was the highest rate of daily drug use reported, with the exception of alcohol and tobacco.

Of a sample of the urban population of Colombia between 12 and 64 yr of age in 1987, 6% reported use of tranquilizers in the previous year; 5.4% reported use in the past month. This was the highest rate of use reported for any drugs other than alcohol and tobacco. Tranquilizer use was more frequent among women, and prevalence increased with age. The data appear to reflect medical as well as nonmedical use (Torres de Galvis and Murrelle, 1989).

Mohan et al. (1986) reported a survey of drug use conducted in 1976 among 3600 members of 1276 households in 24 rural villages of Punjab (India). Of 2064 male respondents, three (0.2%) reported that they were currently using tranquilizers without medical supervision; one other man had used tranquilizers nonmedically but was no longer doing so at the time of interview. Of 1536 female respondents, seven (0.5%) were currently using tranquilizers nonmedically.

b. SURVEYS OF YOUTH. Annual surveys have demonstrated that, except for cigarettes, alcohol, phencyclidine, and inhalant use, nonmedical use of drugs among high school seniors and young adults has been decreasing during the past several years (National Institute on Drug Abuse, 1991d). Between 1985 and 1990, the lifetime prevalence of nonmedical use of tranquilizers among high school seniors decreased from 11.9% to 7.2%, the annual prevalence decreased from 6.1% to 3.5%, and the monthly prevalence declined from 2.1% to 1.2%. The monthly prevalence among college students declined between 1985 and 1989 from 1.4% to 0.8% (Johnston et al., 1990). These rates and trends closely parallel those found among the 18- to 25-yr age group in the National Household Survey on Drug Abuse (table 25).

Numerous surveys inquiring about the use of various illicit and licit drugs among populations of youth have estimated the prevalence of nonmedical use of tranquilizers in these populations. Some of these surveys that have appeared in recent years are summarized in tables 26 through 29, which divide the studies by geographic areas. For each study, the data includes the population interviewed, the geographic region, the date the study was conducted, the prevalence of nonmedical use of tranquilizers that was found, and, for purposes of context and comparison, the prevalence of use of illicit drugs (usually cannabis, cocaine, and inhalants, which were included in most of the surveys) and of nonmedical use of other licit drugs (chiefly amphetamines, which were included in most of the surveys). Summaries of some studies in which the data reflect medical as well as nonmedical use are included in the tables; the observations that follow refer only to the studies providing data specifically concerning nonmedical use.

As shown in the tables, studies in all geographic regions indicate that, although as many as one quarter of young people report having used tranquilizers nonmedically at some time in their lives, rates of recent or current use are generally quite low. Three percent or less of most populations studied reported that they had used these drugs within the past month. The exceptions were a study (Murrelle et al., 1990; table 28) of a small number of youth living "on the street" in three Brazilian cities, of whom 8% reported that they had used diazepam in the previous month, and, as shown in table 29, studies of students in Nigeria (Adelekan, 1989) and Ethiopia (Zein, 1988), of whom 7% and 8%, respectively, reported "current" use (not defined) or use in the past month. Comparison with other drugs reportedly used in these populations indicates that the prevalence of nonmedical use of tranquilizers was lower than the prevalence of use of illicit drugs and of other licit drugs in almost all populations for whom comparative data were available.

Some of the studies from the United States and Canada (table 26) provided data from at least two times; these studies were generally consistent with the findings of the NIDA national survey of United States high school students described before (National Institute on Drug Abuse, 1991d), indicating that nonmedical use of tranquilizers among youth has declined in recent years. Studies of samples of New York State students in grades 7 through 12, using similar questionnaires, found that the 6-mo prevalence of nonmedical use of tranquilizers declined from 1978 to 1983 (Kaestner et al., 1986) as well as from 1983 to 1989–1990 (Puccio and Simeone, 1991); lifetime prevalence also declined between 1983 and 1988 (Kandel and Davies, 1991). Lifetime prevalence of nonmedical use of tranquilizers declined between 1983 and 1988 among Alaskan students (Segal, 1989) and between 1977–1978 and 1986–1987 among students on Native American reservations (Beauvais et al., 1989). Smart et al. (1985) found that, of students in grades 7 through 13 in Ontario (Canada), the annual prevalence of nonmedical use of tranquilizers increased between 1977 and 1979, declined by 1981, and remained stable until 1983; if both medical and nonmedical use are considered, the annual prevalence of use of tranquilizers among these students declined between 1977 and 1985 (Smart and Adlaf, 1986).

An interesting study not included in these tables was briefly reported by McCaul et al. (1988; also discussed in section II.C). Of 888 male students of three colleges in the eastern United States, 16% reported at least one first-degree relative who had experienced some alcohol-

TABLE 26

Prevalence of nonmedical use of tranquilizers among youth in North America

Study	Characteristics and no. of subjects	Area represented	Date of study	Prevalence of use of tranquilizers (% of population)	Prevalence of use of other drugs (% of population)
Patterson et al., 1988	Students at a southern university (1972 $n = 1032$; 1986 $n = 742$)	USA	1972, 1986	(Both medical and nonmedical) Life: 1972: 0.1; 1986: 19	Life: 1972 / 1986: Marijuana 61 / 68; Amphetamines 38 / 22; Barbiturates 19 / 11; Cocaine 10 / 40; Glue 2 / 4
Beauvais et al., 1989	Native American students in grades 7–12	USA: Native American reservations		Life	Life: Marijuana / Inhalants / Stimulants / Sedatives / Cocaine
	1975 $n = 1235$;		1975	NA	41 / 16 / 10 / 6 / 6
	1977–78 $n = 3105$;		1977–78	9	53 / 26 / 15 / 10 / 7
	1980–81 $n = 2159$;		1980–81	6	74 / 30 / 24 / 9 / 11
	1982–83 $n = 1411$;		1982–83	3	70 / 31 / 22 / 7 / 6
	1984–85 $n = 1510$;		1984–85	7	57 / 21 / 21 / 10 / 7
	1986–87 $n = 2683$		1986–87	7	61 / 24 / 25 / 11 / 8
Achalu and Duncan, 1987	Nigerian students of US universities ($n = 239$)	USA: Alabama, Texas, Illinois	1982	Life: 23.8; Yr: 5.4; Mo: 2.1	Mo: Cannabis 13.9; Amphetamines 5.3; Cocaine 0.8
Segal, 1989	Students in grades 7–12, ages 12–19 yr ($n = 4129$)	USA: Alaska (representative sample of schools from all districts)		Life	Life (1988): Marijuana 53.2; Inhalants 25.7; Stimulants 24.0; Cocaine 14.4; Hallucinogens 13.1
			1983	11.5	
			1988	9.6	
Maddux et al., 1986	Senior medical students ($n = 133$)	USA: San Antonio, TX	1984	Prevalence of use of benzodiazepines, both medical and nonmedical: Life: 37; Yr: 17; Mo: 6	Life / Yr / Mo: Marijuana 57 / 23 / 13; Opioids 40 / 19 / 6; Amphetamines 22 / 8 / 3; Cocaine 20 / 8 / 3; Sedatives 17 / 3 / 2; Hallucinogens 15 / 2 / 1

TABLE 26—*Continued*

Study	Characteristics and no. of subjects	Area represented	Date of study	Prevalence of use of tranquilizers (% of population)			Prevalence of use of other drugs (% of population)					
Clifford et al., 1989	University students (n = 683)	USA: southwest	1986–87	Life	Yr	Mo		Mo				
				13.6	4.8	2.8	Marijuana	22.4				
							Amphetamines	4.0				
							Cocaine	8.9				
Jaffe and Archer, 1987	University undergraduates (n = 186)	USA: east	Not stated	Life				Life				
				24			Marijuana	29				
							Amphetamines	40				
							Cocaine	28.5				
Kaestner et al., 1986	Stratified random samples of students in grades 7–12, ages 12–17, 1978 n = 35,300 1983 n = 27,400	USA: New York		6 Mo				6 Mo				
								Marijuana	Cocaine	Phenyl-cyclidine	Other hallucinogens	Stimulants	Sedatives (nonbenzodiazepine)
			1978	8				45	7	9	6	10	7
			1983	7				34	10	3	6	17	8
Kandel and Davies, 1991	Stratified random sample of students in grades 7–12 (1983 no. not given; 1988 n = 7611)	USA: New York		Life				Life					
								Marijuana	Cocaine/crack		Inhalants	Stimulants	Sedatives (nonbenzodiazepine)
			1983	12				46	14		22	25	12
			1988	3.6				27	6		6	11	4
Puccio and Simeone, 1991	Sample of students in grades 7–12, ages 12–18 yr (n = approximately 30,000)	USA: New York	1989–90	Life	6 Mo	Mo		6 Mo					
								Marijuana	Cocaine/crack		Inhalants	Stimulants	Sedatives
				5	3	2		17	4		9	6	4
								Mo					
								12	3		6	5	3
Goodstadt et al., 1985	Students in grades 7–13, ages 10–18 yr (n = 4306)	Canada: Toronto; west, east and north Ontario	1981	Life				Life					
				3.8			Cannabis	22.9					
							Stimulants	13.0					
							Barbiturates	4.1					
							Cocaine	3.8					
							Amphetamines	3.4					

			Yr					
				Cannabis	Barbiturates	Stimulants	Cocaine	Amphetamines
Smart et al., 1985	Students in grades 7–13	Canada: Ontatio						
	1977 n = 5842		1977	25.1	6.0	7.2	3.8	2.7
	1979 n = 4794		1979	31.7	6.8	10.6	5.1	3.6
	1981 n = 3270		1981	29.9	8.1	12.1	4.8	3.0
	1983 n = 4737		1983	23.7	6.0	15.4	4.1	3.9

			Yr (Both medical and nonmedical) 6 Mo	Yr (1985)
Smart and Adlaf, 1986	Students in grades 7, 9, 11 and 13; ages 12–19 yr (n = 4654)	Canada: Ontario		
			1968	24.8	Cannabis	20.4
					Other illicit drugs	52.3
					Stimulants	7.3
					Barbiturates	8.8

	Yr
1977	6.7
1985	4.9

related problem. These students reported drinking nearly twice as much alcohol as did those with no such family history and were significantly more likely to have used marijuana, cocaine, hallucinogens, and/or opiates at some time in their lives. In addition, 23% of those with a family history of alcohol abuse, as opposed to 0.9% of the other students, reported having used benzodiazepines; most of this use was presumably nonmedical.

c. SURVEYS OF MILITARY POPULATIONS. In samples of all active-duty personnel of all United States military services, nonmedical use of tranquilizers within the previous 30 d was reported by 3% in 1980, 2% in 1982, and 1% in 1985 (Allen and Mazzuchi, 1985; Bray et al., 1989). Three percent of a sample of Canadian Forces personnel in five countries in 1982 reported nonmedical use of tranquilizers at some time in their lives, 1% reported use in the past 12 mo, and less than 1% reported use in the past 30 d (Lanphier and McCauley, 1985). Of cases of apparent drug abuse or dependence (not defined) among French military personnel in 1982, 2.9% involved use of tranquilizers (Lefebvre and Kamel, 1984).

d. SURVEYS OF PATIENTS. Numerous studies have demonstrated the relatively high prevalence of substance use disorders among patients with anxiety and other psychiatric disorders and, conversely, the high prevalence of psychiatric disorders among alcoholics and other sedative abusers. Data from some studies in which this association was investigated have indicated that the use of alcohol and other depressants among populations with psychiatric disorders may reflect attempts at self-medication (Kranzler anid Liebowitz, 1988; Ciraulo et al., 1988b; Cox et al., 1990). There have also been reports, described below, that opiate abusers may use benzodiazepines for self-medication both of opiate withdrawal symptoms and of psychiatric disorders.

As discussed previously, epidemiological research has not, surprisingly, shown that psychiatric patients are more likely to use benzodiazepines (and other psychotherapeutic medications) than are medical patients or samples of the general population. In section III.C, we considered surveys that have attempted to estimate the prevalence of physiological dependence on benzodiazepines among psychiatric inpatients. In the following subsection, we review surveys that have investigated the use of benzodiazepines among various patient populations and that have attempted to estimate the extent of this use that may occur without medical supervision or that may exceed medical recommendations.

i. Surveys of medical and psychiatric outpatients. Rifkin et al. (1989) reviewed charts of 2719 adult outpatients of a New York City hospital. For patients who had received large amounts of benzodiazepines, they interviewed the patient's physician and completed a checklist of symptoms of abuse or dependence. Of the total of 178 patients who had received benzodiazepines,

TABLE 27

Prevalence of nonmedical use of tranquilizers among youth in western Europe

Study	Characteristics and no. of subjects	Area represented	Date of study	Prevalence of use of tranquilizers (% of population)			Prevalence of use of other drugs (% of population)			
Kandel, 1984	Young people ages 14–18 yr (n = 499)	France	1977	Life				Life		
				6			Marijuana	22		
							Barbiturates	6		
Fernandez-Crehuet-Navajas et al., 1979	University students (n = 888)	Spain: Granada	Not stated	(Both medical and nonmedical) Life			(Both medical and non medical)			
				42.9				Life		
							Amphetamines	65.0		
							Hypnotics	29.9		
							Hallucinogens	12.8		
							Antidepressants	11.8		
Queipo et al., 1988	University students (n = 2921)	Spain: Valladolid	1984	Life	Yr	Mo		Mo		
				7.4	3.6	1.9	Cannabis	7.4		
							Cocaine	0.3		
							Amphetamines	1.7		
Fonseca et al., 1985	Students ages 15–17 yr (n = 2537)	Spain: Asturias	Not stated	Life	Yr	Mo		Life	Yr	Mo
				10.3	7.4	1.9	Cannabis	20.8	15.6	5.0
							Amphetamines	7.9	5.9	1.8
							Inhalants	2.3	1.4	0.6
							Hallucinogens	2.0	1.7	0.3
							Sedatives	1.7	0.5	0.3
							Opioids	1.4	1.0	0.4
							Cocaine	1.2	0.6	0.1
Lopez-Alvarez et al., 1989	University students (n = 1010)	Spain: Asturias	1986	Life	Yr	Mo		Mo		
				19	9	3	Cannabis	7		
							Amphetamines	2		
							Cocaine	0.5		
Alvarez et al., 1989	Young people ages 14–30 yr in rural communities (n = 1886)	Spain: Castile and Leon	1987	Life	Yr	Mo		Mo		
				2.1	1.5	0.7	Cannabis	10.1		
							Amphetamines	1.0		
							Cocaine	0.8		
Bagnall, 1988	Students age 13 yr (n = 1586)	UK: Scotland, England, Wales	1986	(% using tranquilizers or hypnotics) Life				Life		
				2.4			Solvents	1.9		
							Cannabis	0.9		
							Amphetamines	0.4		
							Barbiturates	0.2		

				(Both medical and nonmedical) Life	(Both medical and nonmedical)	Life
Casselman, 1986	Students age 14–24 yr (n = 3037)	Belgium: Brussels	1973–74	6.5	Sedatives	5.4
	Young workers ages 14–20 yr (no. not stated)	Belgium: locality not stated	1979–80	7	Hypnotics	6
					Stimulants	3
Lavik et al., 1985	Junior high school students ages 15–16 yr (n = 2265)	Norway: Akershus county	1981	(Both medical and nonmedical) Life		Life
				9.5	Glue	8.4
					Cannabis	4.9
					Hypnotics	4.7
					Other psychotropics	3.2
Lavik and Onstad, 1986	Junior high school students ages 13–16 yr (n = 177)	Norway: county of Akershus	Not stated	Life		Life
				7	Cannabis	3
					Inhalants	9
Pedersen et al., 1989	High school students ages 16–19 yr (n = 1027)	Norway: Oslo	1987	Life		Life
				23	Cannabis	15
					Inhalants	14
Pedersen and Lavik, 1991	Secondary school students ages 13–18 yr (n = 1230)	Norway: Oslo	1988	(Both medical and nonmedical) Yr	(Both medical and nonmedical)	Yr
				7	Analgesics	77
					Hypnotics	5
Pedersen, 1989	Young people ages 12–19 yr (n = 1968)	Norway: Oslo	Not stated	Yr		
				12		

TABLE 28

Prevalence of nonmedical use of tranquilizers among youth in Latin America

Study	Characteristics and no. of subjects	Area represented	Date of study	Prevalence of use of tranquilizers (% of population)		Prevalence of use of other drugs (% of population)		
Carvalho, 1986	University undergraduates (n = 2475)	Brazil: Sao Paulo	1984–85	Life			Life	
				12.2		Cannabis	41	
						Amphetamines	27	
						Cocaine	12	
Carlini-Cotrim and Carlini, 1988	Students in grades 3–10, ages 9 to >18 (n = 1836)	Brazil: periphery of Sao Paulo	1986	Life	Mo		Mo	
				2.6	1.5	Cannabis	1.5	
						Inhalants	4.9	
						Cocaine	0.4	
Murrelle et al., 1990	Young people ages 7–17 yr living "on the street" (n = 120)	Brazil: Sao Paulo, Salvador, and Porto Alegre	1987	Mo			Mo	
				8 (diazepam)		Cannabis	44	
						Cocaine	11	
						Inhalants	56	
Murrelle et al., 1990	Primary and secondary school students ages 10–17 yr (n = 20,000)	Brazil: 8 cities	1987	Yr			Yr	
				3.5		Cannabis	1.6	
						Cocaine	0.4	
						Inhalants	9.5	
						Barbiturates	1.7	
Castro and Valencia, 1980	High school students ages 14–18 yr (n = 4059)	Mexico: Mexico City	1978–79	Life	Mo		Life	Mo.
				3.1	0.8	Inhalants	5.4	1.5
						Cannabis	3.8	1.1
						Amphetamines	2.7	0.6
						Sedatives	1.3	0.5
						Opium	0.9	0.3
						Cocaine	0.5	0.2
						Heroin	0.3	0.2
Castro Sarinana et al., 1982	High school students ages 14–18 yr (n = 3408)	Mexico: Mexico City	1980	Life			Life	
				2.2		Inhalants	4.4	
						Amphetamines	3.8	
						Marijuana	3.5	
						Sedatives	1.5	
						Opium	1.3	
						Cocaine	0.7	
						Heroin	0.3	

none met DSM-III (revised edition) criteria for abuse or dependence.

A prospective study of benzodiazepine misuse was conducted by Garvey and Tollefson (1986), who interviewed patients who visited a United States psychiatric outpatient clinic and who received prescriptions for benzodiazepines during an 18-mo period. Misuse was indicated if the patient increased his or her dose without consulting the physician, if the patient sought out additional sources of benzodiazepines, or if the patient or a "significant other" reported such misuse. Benzodiazepine misuse was found in five patients, two taking alprazolam, two taking diazepam, and one taking lorazepam. The misuse took the form of occasional (once or twice a week) increases in dose to alleviate intense feelings of anxiety or dysphoria. Apparently, suicide attempts were part of this misuse. The patients themselves reported the misuse in each of the five cases.

Urinalysis indicated the presence of benzodiazepines in 52 (26%) of 203 outpatients who visited a hospital in Magdeburg (Federal Republic of Germany) for a variety of medical problems. These drugs had apparently been used without prescription in 44 of these patients, or 22% of the entire study population. Only six of these 44 patients had reported use of these drugs when questioned (Kunze et al., 1989).

In 1985, Ladewig and Grossenbacher (1988) updated their 1980 survey of physicians in domicilary practice in Switzerland. A total of 359 physicians were asked to report what they thought might be benzodiazepine abuse

TABLE 29

Prevalence of nonmedical use of tranquilizers among youth in Africa, the Middle East and Asia

Study	Characteristics and no. of subjects	Area represented	Date of study	Prevalence of use of tranquilizers (% of population)	Prevalence of use of other drugs (% of population)
Flisher, 1989	Fifth-year medical students (n = 152)	South Africa: Cape Town	1987	(Prevalence of use of benzodiazepines, both medical and nonmedical) Last wk of school year: 11.8	(Both medical and nonmedical) Stimulants: Last wk of school year 3.9 Antidepressants: 2.0 Beta-blockers: 2.6
Nevadomsky, 1981	Secondary school students (n = 1500)	Nigeria: Bendel State	Not stated	(Prevalence of use of benzodiazepines, both medical and nonmedical) Life: 29	Mandrax*: Life 11 Marijuana: 10 Proplus (caffeine): 4 Other illicit drugs: 8
Adelekan, 1989	Secondary school students ages 13–20 yr (n = 911)	Nigeria: Abedkuta (State of Ogun)	1986	(Use of sedative-hypnotics including benzodiazepines) Life: 14.7 "Current": 6.9	"Current" Analgesics: 57.5 Stimulants: 34.1 Barbiturates: 1.1 Cannabis: 0.5 Cocaine: 0.3 Inhalants: 0.3
Zein, 1988	Medical and paramedical students (n = 479)	Ethiopia	1983	Life 15.2; Yr 9.6; Mo 7.7	Mo Khat†: 22.3
Soueif et al., 1982	Male technical school students ages 15–22 yr (n = 3686)	Egypt: Cairo	1979	Life: 4.6	Life Narcotics: 11.7 Stimulants: 5.9 Hypnotics: 4.8
Soueif et al., 1987	Female university students ages 17–30 yr (n = 2366)	Egypt: Cairo	Not stated	Life: 5.1	Life Cannabis: 0.8 Stimulants: 4.8
Kandel, 1984	Young people ages 14–18 yr (n = 609)	Israel	1979	Life: 4	Life Marijuana: 3 Barbiturates: 2
Tse et al., 1989	Private secondary school students ages 10–23 yr (n = 4793)	Hong Kong	Not stated	Life: 2.7	

* Methaqualone and diphenhydramine.

† Authors note that cannabis and amphetamines are not available in this area.

by their patients. The criteria for abuse were dose escalation and use of large doses without medical indication. Of the patients in whom abuse was confirmed, 74% were women, the average age was 55 yr , 55% were married, and 66% were either employed or housewives. The mean daily dose was 20 mg of diazepam or equivalent for those using benzodiazepines alone, 25 mg for those using benzodiazepines in combination with alcohol, 42 mg for those using benzodiazepines in combination with barbiturates and analgesics, and 60 mg for those using benzodiazepines in combination with opioids. The duration of use ranged from 33 mo, for those using benzodiazepines alone, to 79 mo when benzodiazepines were used in combination with other drugs. Daily use was indicated by 84% of those using benzodiazepines alone and by 73% of the multiple-drug users. Of those who combined use of benzodiazepines with narcotics, 29% reported using benzodiazepines daily, but those who used them infrequently took large doses. There had been little change in the prevalence of benzodiazepine abuse from 1980 (0.02% of the population) to 1985 (0.01%).

The prevalence of drug abuse among inner-city pregnant patients was estimated in an unusual study reported by Land and Kushner (1990). Of 290 patients admitted through the labor unit of a hospital serving inner-city Detroit, MI (United States), benzodiazepines were detected in the urine of seven patients (2.4% of those tested or 9.0% of those whose urine samples tested positive for abused drugs). Although the authors describe these as cases of misuse, it was apparently not determined whether these drugs might have been prescribed.

ii. Surveys of psychiatric inpatients. In a number of recent studies, the prevalence of drug abuse and dependence in patients admitted to psychiatric facilities was investigated. Abuse was not distinguished from dependence in many of these studies; therefore, it is difficult to interpret the findings. Those that appear more relevant to physiological dependence than to misuse were described in section III.C. Following are descriptions of studies that appear more relevant to the prevalence of abuse in these populations.

Although most of these studies have relied largely on patients' reports of their drug use histories, at least two have included urinalysis to establish what drugs were actually consumed. In 1982, nonprescribed drugs were found in the samples of 29.5% of patients newly admitted to psychiatric wards of a hospital serving New South Wales, Australia; these included benzodiazepines in 6.8% of the patients (Lewis et al., 1985). Urine samples were obtained from patients newly admitted to an Arkansas (United States) Veterans Administration hospital. As estimated based on review of the patients' medical records, benzodiazepines had apparently been used without prescriptions by 5% of psychiatric patients in 1985 and by 13% in 1987 to 1988 and, in the latter period, by 10% of medical/surgical patients and 7% of alcohol/drug abusers. Benzodiazepines were most frequently found in combination with marijuana (McMillan et al., 1989).

Müller-Oerlinghausen (1986) used DSM-III criteria to identify 1217 cases of drug abuse and dependence among 7000 admissions to the Department of Psychiatry in Gottingen (Federal Republic of Germany). Of this number, 796 showed abuse of or dependence on benzodiazepines. In addition, 78% of 895 patients admitted to West German hospitals because of drug abuse or dependence were taking benzodiazepines; 30% were taking only benzodiazepines, and "primary abuse or dependence" was found in 81% of these patients.

Priebe et al. (1989) measured the presence of benzodiazepines in the urine of all 899 patients admitted to a Berlin psychiatric hospital during a 13-mo period. Positive urine samples were found in 134 patients (15%); 88 were women, and the mean age was 44 yr. It was apparently not determined how many of these patients had prescriptions for these drugs; however, the diagnoses at the time of admission for 36 patients (4% of all patients, or 27% of those taking benzodiazepines) were diagnosed benzodiazepine abuse or dependence.

Appropriate definitions of dependence and abuse were used by Wolf et al. (1989a). Of the 9408 patients admitted to the Psychiatric Department of the University of Munich from May 1980 to December 1985, 633 (6.7%) either abused or were dependent on benzodiazepines, of whom 440 patients used these drugs in combination with one or more other drugs of abuse. Of the 213 patients who abused or were dependent on benzodiazepines alone, 73% were women, 32% suffered from depressive or anxiety neurosis, and 15% had come to the hospital because of their benzodiazepine dependence. Benzodiazepine abuse was the diagnosis for 24%, and dependence, either psychological (20%) or physiological (56%), was the diagnosis for 76%. Forty-four percent were taking less than 30-mg diazepam equivalents per day; 48% had as much as tripled the therapeutic dose; 8% were taking even more. Duration of intake was less than 1 yr in 12%, 1 to 5 yr in 54%, and more than 5 yr in 34%. Lorazepam was the most and oxazepam the least frequently misused benzodiazepine, despite the fact that oxazepam was the most frequently prescribed benzodiazepine in the Federal Republic of Germany.

Lädewig and Schroeter (1990) reported a study of all 1736 patients admitted between 1983 and 1986 to nine psychiatric hospitals in Switzerland in whom drug dependence and abuse was the diagnosis, according to International Classification of Diseases (ninth edition) criteria. Abuse of benzodiazepines alone was recorded for 106 patients (6.1% of the patients with drug dependence or abuse, or 0.4% of all patients in these hospitals). Benzodiazepines were also abused in combination with heroin in 335 cases (19.3% of all patients with drug dependence or abuse), of whom 92 also abused alcohol; of patients abusing benzodiazepines and heroin, 255 re-

ported use of flunitrazepam and 67 of diazepam. Because, as the authors state, evidence of withdrawal was not recorded systematically, the data reported must be regarded as relevant to misuse rather than to physiological dependence; in fact, the report further indicates that the doses of benzodiazepines used in some cases appeared to reflect therapeutic use rather than misuse.

e. STUDIES OF DRUG ABUSERS. **i. Use of benzodiazepines in populations of abusers of various substances.** Among female adolescents admitted for inpatient treatment of substance abuse problems between 1984 and 1986 in five states of the United States, use of alcohol, marijuana, and cocaine did not differ significantly according to history of sexual abuse, but prevalence of use of stimulants, sedatives, tranquilizers, and hallucinogens was significantly greater among those who had been victims of sexual abuse. "Regular" use of minor tranquilizers (use at least once a month) was reported by 8.4% of victims of extrafamilial sexual abuse, 10.9% of victims of intrafamilial abuse, and 14.0% of victims of both extra- and intrafamilial abuse; in contrast, 3.5% of patients who had not been victims of sexual abuse reported regular use of these drugs (Harrison et al., 1989).

Information concerning drug abuse was collected from a variety of facilities in Mexico City (Ortiz, 1989). Lifetime prevalence of use of tranquilizers increased from 9.2% in the second half of 1986 to 21.4% in the first half of 1988; the prevalence of use in the past month increased during this period from 5.4% to 14.8%. Rates of lifetime use of sedative-hypnotics decreased from 4.7% in late 1986 to 1.5% in late 1987 and then increased to 3.0% in the first half of 1988; similarly, rates of past-month use of these drugs decreased from 3.1% in the latter half of 1986 to 1.0% in the latter half of 1987 and then increased to 3.0% in the first half of 1988.

Yun and Yusof (1988) reported dramatic growth in the number of drug abusers in Malaysia since 1970. The most frequently abused drugs in 1985 were heroin (75% of abusers) and cannabis (26%). Sleeping pills were used by 3.5% of abusers and tranquilizers by 0.5%.

ii. Use of benzodiazepines in the context of polydrug abuse. Wilkinson et al. (1987) drew attention to the apparent increase in the frequency of multiple drug use among clients of drug abuse treatment programs and pointed out that, if this pattern is now "the predominant mode" of such clients, we should study and treat polydrug abuse per se rather than continuing to categorize abusers according to their "primary drug of abuse." These authors attempted to characterize distinct patterns of polydrug abuse among 256 clients of a treatment program of the Addiction Research Foundation (Toronto, Ontario, Canada), excluding those whose primary problem was opiate abuse. Sixty-two percent reported having used tranquilizers in the prior 12 mo, as opposed to 98% who had used alcohol, 95% cannabis, 86% stimulants, 77% hallucinogens, 69% narcotics, 41% sedative-hypnotics, and 9% solvents. Tranquilizers were used most frequently in a pattern of combined use of alcohol, "depressants" (tranquilizers, narcotics, sedative-hypnotics), and "recreational drugs" (cannabis, hallucinogens, stimulants) and in a pattern of use of "depressants" alone, sometimes including use of stimulants. Tranquilizers were rarely used in patterns of heavy use of "recreational drugs" or of solvents.

In a retrospective review of all of the first 128 patients of a New York City chemical dependency program, who had been admitted in 1984 to 1985, Novick et al. (1987) found that only 23% abused only a single substance; of these, most were alcoholics. The drugs most frequently identified as primary drugs of abuse were alcohol (55%), cocaine (41%), and heroin (24%). Benzodiazepines (diazepam or chlordiazepoxide) were identified as primary drugs of abuse in 11% of cases and as secondary drugs of abuse in an additional 22%.

In a Philadelphia, PA, treatment program for drug-dependent pregnant women, the greatest change between 1979 and 1987 was the increase in frequency of abuse of cocaine, from 4.5% in 1983 to 60% in 1987. During this period, abuse of diazepam and other drugs (Ritalin/Talwin, amphetamines, and alcohol) had substantially declined (Ehrlich and Finnegan, 1987).

Of 136 benzodiazepine abusers admitted to an addiction center in the southern United States, 94% also abused other substances (Malcolm et al., 1990). Most (63%) of the benzodiazepines used by these patients had been obtained by prescription. The primary benzodiazepines of abuse were diazepam (43%) and alprazolam (14%). Patients whose primary substance abuse diagnosis was benzodiazepine or alcohol abuse were equally likely to choose diazepam or alprazolam as a drug of abuse; patients whose primary substance abuse diagnosis was cocaine or opiate abuse were six times more likely to choose diazepam as to choose alprazolam.

Of 173 i.v. drug users in the area of Edinburgh (Scotland) interviewed between 1980 and 1985, 33.5% reported current use of oral diazepam and 19% reported use of temazepam. In a study of i.v. drug users recruited after 1985, Skidmore et al. (1990) showed that this group was significantly more likely to engage in current use of buprenorphine, dihydrocodeine, and temazepam. Similar findings were reported by Morrison (1989), who interviewed 135 drug abusers in Edinburgh and Ayr (Scotland) in the first half of 1988. Among the 21 i.v. drug abusers, 13 used diazepam, nine used temazepam, three used triazolam, and one used lorazepam; diazepam and temazepam were most likely to be obtained by prescription and to be injected in conjunction with other drugs such as buprenorphine. Sixty-five of those studied were polydrug abusers who administered the drugs nonintravenously. Of this group, 19 used diazepam, 12 used temazepam, and four used triazolam; these drugs were most

commonly used concurrently with cannabis, which was used by 92% of the group.

Thomsen (1988), who studied 338 young drug abusers admitted to psychiatric hospitals in the county of Aarhus (Denmark) between 1975 and 1984, also found that polydrug abuse was the most common pattern and that the drugs most frequently used were minor tranquilizers (by about 45% of the abusers) and cannabis (by about 60%). Of a national sample of 1306 young people (ages 15 to 24 yr) in the Netherlands studied in 1983, 12.2% had used cannabis; 17.0% of those who had used cannabis had also engaged in nonmedical use of tranquilizers, as opposed to 5.4% of those who had never used cannabis (Sylbing and Persoon, 1985).

Among addicts attending treatment programs in the Marche area (Italy), polydrug abuse increased by 40% between 1980 and 1983; Leone and Moretti (1986) noted that this change probably reflected the increased awareness of this problem among the physicians reporting to the system rather than an abrupt change in drug use patterns. Benzodiazepines were the most frequently abused psychoactive drugs in the region, with reported use by 85% of the addicts in 1984. These drugs were generally used in combination with opiates, other psychoactive drugs, or alcohol. Among those reported to have abused benzodiazepines, 60% abused flunitrazepam, 17% abused lorazepam, and 17% abused diazepam.

iii. Studies of opiate abusers. In Sheffield (United Kingdom), 90% of current or former opiate abusers reported having used benzodiazepines as well; the majority said they had typically used these drugs daily or almost daily. Most subjects reported having used more than one benzodiazepine; the most frequently mentioned was diazepam (83%). One third of those who reported benzodiazepine use claimed they had begun this use with medical prescriptions. Almost all claimed that the reasons they had used benzodiazepines were for self-medication (e.g., to help with sleep, to reduce anxiety, to prevent withdrawal); only two subjects reported use of benzodiazepines to augment the "high" associated with their primary drug of abuse (Perera et al., 1987).

One possible reason why physicians prescribe benzodiazepines for opiate addicts was suggested by Horn et al. (1987), who retrospectively studied records of all of the 123 patients admitted to a general hospital in Glasgow (Scotland) between 1980 and 1984 with diagnoses of drug abuse or addiction. Ninety-two percent identified heroin as their primary drug of abuse. There was no reported secondary abuse of benzodiazepines; however, 23% of the patients received benzodiazepines for prophylaxis of withdrawal symptoms.

In another report from Glasgow, Sakol et al. (1989) described an increase in abuse of temazepam among opiate users. Of 70 new clients of a drug program in 1986, 24% were abusing temazepam, of whom 12% took the drug i.v.; of 110 new clients in 1987, 38% were abusing temazepam, of whom 35% took the drug i.v. In a later study, Hammersley et al. (1990) found that, among 61 i.v. drug users in contact with other drug programs in the Glasgow area in 1989, there was more use of buprenorphine and temazepam than of heroin or other opiates; this finding agreed with that of Morrison (1989), whose study of i.v. drug users in Edinburgh and Ayr was described above. Of the 61 i.v. drug users studied by Hammersley et al., 56 (92%) reported having used temazepam in the previous year, of whom 43 had used the drug i.v. In comparison, 41 (67%) had used heroin and 45 (74%) had used other opiates. Of 150 youths, 15 to 20 yr of age, ranging from abstainers to i.v. drug users, who were not in contact with drug agencies, 73% reported having used temazepam in the previous year.

With respect to their finding that i.v. drug users were using temazepam and buprenorphine more than opiates, Hammersley and coworkers (1990) speculated that this might have resulted in part from the need of heroin users to switch to substitute drugs because of the decreasing availability of heroin; for example, Morrison (1989) noted that i.v. drug users in Edinburgh reported a decline in availability of heroin beginning in about 1984. However, Klee et al. (1990) reported a study of 272 injecting polydrug users in the northwest of England, apparently conducted in the late 1980s, when no such decline in availability of heroin had been reported; 28% were using temazepam, usually in combination with opiates, although some users had reported switching from heroin to temazepam.

Analysis of blood and urine specimens from 50 French patients undergoing detoxification in 1985, chiefly from heroin, indicated that 43 patients had also been abusing cannabis, and 25 had been abusing benzodiazepines. At the time of admission, only 14 patients had admitted use of benzodiazepines. This discrepancy between subjects' reports and toxicological detection was greater for benzodiazepines than for other secondary drugs of abuse (Parquet et al., 1987).

Similarly, of 44 male opiate users in a Berlin hospital in 1985 to 1986, 21% admitted secondary use of benzodiazepines; toxicological evidence indicated that the rate of this use was actually 30%. The discrepancy was greater for 23 female opiate users, of whom 13% admitted benzodiazepine use, whereas 35% were shown to have actually used these drugs (Schmidt et al., 1987).

Opiate users in Penang, Malaysia, were studied for use of other drugs by Navaratnam and Foong (1988, 1990). Seventy-one percent of subjects reported use of benzodiazepines during periods of opiate use. Of the licit and illicit drugs reportedly used in conjunction with opiates, with the exception of nicotine, flunitrazepam was the most frequently used, as reported by 51% of subjects; other benzodiazepines were used by much smaller proportions. Drug use histories indicated that benzodiazepines were among the last drugs adopted as adjuncts to

heroin, typically beginning 3 to 6 yr later than heroin use. Most subjects reported that they used benzodiazepines to enhance the subjective effects of opiates; a small percentage reported use of benzodiazepines for self-treatment, e.g., to diminish withdrawal symptoms, to promote sleep, or to reduce depression. Of those who reported use of benzodiazepines, 49% had used these drugs daily. As in the studies described before, Navaratnam and Foong found substantial discrepancies between self-reports and toxicological detection of benzodiazepine use. Of 48 subjects who had reported no use of flunitrazepam, drug tests were positive for 16; at the same time, urinalysis confirmed the presence of the drug in only five of 14 subjects who reported use.

iv. Studies of methadone users. Saxon et al. (1988) found considerable variation in drugs screened, urinalysis techniques, and use of multiple or confirmatory techniques among United States methadone maintenance clinics. The drugs most frequently detected in all programs were opiates, cocaine, and benzodiazepines. However, the drugs most frequently detected in the West were opiates and amphetamines, whereas those most frequently detected in the East were cocaine and benzodiazepines. Only 29% of the clinics routinely tested for cannabis.

The validity of self-reports of benzodiazepine use by methadone patients was addressed by Magura et al. (1987), who used enzyme multiplied immunoassay technique urinalyses to verify reports of 233 clients of four methadone programs in New York City in 1984. Positive tests for benzodiazepines were reported for a total of 93 patients (40%). This included positive findings in 36 (24%) of 148 patients who did not report benzodiazepine use, and in 57 (67%) of those who did report use of these drugs.

DuPont and Saylor (1989) tested urine specimens from 300 clients of each of two methadone programs in the eastern United States. Nonprescribed benzodiazepines were detected in 4% and 7% of the samples, respectively. Each specimen positive for benzodiazepines was also positive for other drugs, including tetrahydrocannabinol (28%), cocaine (27%), opiates (24%), and amphetamines (7%). The proportions of benzodiazepine use in these populations were lower than those reported in some studies of clients of other methadone programs.

Hartog and Tusel (1987) addressed the reasons why some methadone patients may use benzodiazepines. They submitted urine specimens of 114 male clients of a San Francisco, CA (United States), methadone program to three thin-layer chromatography analyses and studied 12 patients whose specimens tested positive for diazepam in each of the three tests and 19 patients whose specimens were negative for diazepam at each test. Ratings on the SCL-90 and the Addiction Severity Index indicated that diazepam users had significantly more psychiatric disturbance than the nonusers. The authors suggested that these findings pointed out the possibility that methadone clients may use benzodiazepines for self-medication of psychiatric symptoms rather than primarily to augment the euphoric effect of methadone, as others have suggested.

As noted in our previous review, some investigators have found that methadone users who abuse benzodiazepines appear specifically to prefer diazepam; it had been suggested that this possible preference might be due to some unique interaction of diazepam and methadone. However, recent reports suggest that other benzodiazepines may now be equally or more likely to be abused by methadone users. As discussed in section II.C, Iguchi et al. (1989) interviewed clients of three East Coast (United States) methadone clinics who reported having used numerous anxiolytics or hypnotics in their lifetimes; the 43 subjects rated their preferences for diazepam, alprazolam, and lorazepam as comparable to their preference for pentobarbital but significantly greater than that for oxazepam or chlordiazepoxide. Weddington and Carney (1987) reported the emergence of abuse of alprazolam in an unspecified number of methadone users in Baltimore, MD, and Chicago, IL. Five cases of alprazolam dependence were reported among clients of a Philadelphia, PA, methadone program, where alprazolam abuse appeared to be increasing (Ravi et al., 1990). Fourteen percent of 159 randomly selected methadone users in Baltimore had positive tests for benzodiazepines (Tommasello et al., 1990). Of those treated for benzodiazepine dependence, 17 of 19 named alprazolam as their preferred benzodiazepine. The authors concluded that "newer generation benzodiazepines seem to have supplanted diazepam as agents of choice among benzodiazepine abusers in methadone treatment."

At the time of our previous review, virtually all studies of illicit drug use among methadone users came from facilities in the United States. More recent studies of this kind include several describing patterns of use among methadone users in the United Kingdom and other western European nations.

Benzodiazepines were detected in 59% of all patients attending a drug dependence facility in London during 3-mo periods of both 1984 and 1985; the majority were methadone users. This rate of detection was second only to that of opioids. Seventy-six percent of those using benzodiazepines reported that they had obtained these drugs from illicit sources (Beary et al., 1987). Similarly, urinalyses were positive for benzodiazepines for 75 (54%) of 139 methadone users in London in 1987; these drugs were known to have been prescribed in only 13 cases (Lipsedge and Cook, 1987).

Based on self-report data, 53 (31%) of 170 methadone users attending a London drug dependence unit were concurrently abusing alcohol. These patients were significantly more likely than those not abusing alcohol to use benzodiazepines as well; benzodiazepine use, whether

prescribed or nonmedical, was reported by 22% of the population (Stastny and Potter, 1991).

None of 30 healthy control subjects surveyed in the area of Florence (Italy) reported use of psychotherapeutics, as opposed to 72% of 160 methadone and opiate users. Of these users, 79% used only benzodiazepines and an additional 17% used benzodiazepines as well as other psychoactives. The benzodiazepines most frequently used were flunitrazepam (58%), lorazepam (36.5%), and diazepam (31%) (Barattini et al., 1987).

Benzodiazepines were detected in 4% of 495 specimens from a broad spectrum of Swiss opiate users, apparently including current users as well as clients of both methadone and drug-free treatment programs (Lädewig and Scholer, 1990). The specific benzodiazepines detected, including oxazepam, diazepam, flurazepam, and flunitrazepam, appeared to reflect national prescribing patterns rather than representing any preference among users for one drug over others.

Methadone users in New South Wales, Australia, were divided into three groups, including 13 habitual users of heroin, ten habitual users of benzodiazepines, and a control group of nine clients whose urine had not been contaminated with other drugs for the preceding 3 mo (Bell et al., 1990). There was no significant difference among the groups with respect to dosage of methadone. Neither the heroin nor the benzodiazepine group differed significantly from controls with respect to mean trough serum level of methadone or with respect to their opinions about whether their methadone dose "held" them for 24 h. However, trough serum levels for the benzodiazepine group were significantly lower than those for the heroin group, and benzodiazepine users were significantly less likely than heroin users to believe that their methadone dose "held" for 24 h. The correlation between methadone dose and trough serum levels was very good among heroin users but quite weak among benzodiazepine users. Serum methadone levels among three of the ten benzodiazepine users were markedly lower (100 to 150 ng/ml) than expected. The investigators speculated that some benzodiazepines might induce microsomal enzymes, thereby accelerating methadone metabolism. Moreover, because the policy of the clinic was to provide methadone in doses as high as clients believed they needed, the fact that eight of the ten benzodiazepine users claimed their methadone dose did not "hold" them suggested to the investigators that these clients appeared to be seeking intoxication.

v. Studies of alcoholics. The relationship of alcohol and benzodiazepine use is complex. In a number of studies, patients using benzodiazepines have been found significantly more likely than nonusers to abstain from use of alcohol (Caplan et al., 1984, 1985; Salinsky and Doré, 1987; Gené-Badia et al., 1988; Dunbar et al., 1988). A possible corollary of these findings was reported by Cottler (1989), who found higher rates of benzodiazepine use among women with a past history of a DSM-III alcohol use disorder (21%) than among those with a recent history (11%) or no such history (13%) of such disorder; these findings suggested "that benzodiazepines may be successfully used to treat alcoholism or are used to substitute for alcohol."

Dunbar et al. (1988) pointed out that their findings of less alcohol use among benzodiazepine users could be explained by the fact that benzodiazepine users were significantly older than nonusers and, thus, less likely to use alcohol. On the other hand, some elderly patients who misuse benzodiazepines also abuse alcohol (Jinks et al., 1990), and there is some frequency of benzodiazepine use among elderly alcoholics (Lefkowiz et al., 1987). As these observations suggest, patterns of alcohol use among patients using prescribed benzodiazepines obviously do not shed much light on the relationship between benzodiazepine use and alcohol use among abusers.

Of 266 patients admitted for alcohol detoxification in a New York City hospital, 30% either reported benzodiazepine use or were found to have used benzodiazepines on the basis of enzyme multiplied immunoassay technique urinalysis; 8.4% had used barbiturates, 28% cocaine, 7% opiates, and 16% cannabis (Crane et al., 1988). Of patients whose urine specimens showed drug use, only 18% of those with specimens positive for benzodiazepines and 10% of those with specimens positive for barbiturates admitted this use in interviews; whereas 52% of those with specimens positive for cocaine, 31% positive for tetrahydrocannabinol, and 27% positive for opiates reported use of these drugs. The authors questioned why patients would be "more forthcoming about illegal drug use than about legitimate drugs illegally obtained." They suggested one possible explanation was that "some of our pharmacologically sophisticated patients were self-medicating their withdrawal with benzodiazepines and barbiturates and did not consider this worth mentioning."

Similarly, benzodiazepines were detected in the urine specimens of 29 (28%) of 103 patients admitted to an alcohol detoxification facility of the Addiction Research Foundation in Toronto (Ontario, Canada). Only 11 (38%) of these patients had admitted benzodiazepine use (Ogborne and Kapur, 1987). Also, although 25.5% of 282 chronic alcoholic patients of a Berlin hospital had taken benzodiazepines before admission, only 44% of these had reported use of these drugs. Urinalysis demonstrated high levels of benzodiazepines in those patients who had reported taking them (Schmidt et al., 1987).

Urinalysis detected the use of additional drugs in 41.3% of 906 patients admitted to a Munich psychiatric hospital for alcohol detoxification between 1978 and 1985 (Soyka et al., 1989). Benzodiazepines accounted for 78.4% of these drugs. A total of 131 patients (15%) had experienced grand mal seizures during either the index detoxification or previous detoxifications; of the 374 patients who had used drugs other than alcohol preceding

the index detoxification, 21.7% had experienced grand mal seizures, as opposed to 10.3% of the 532 patients who had not used other drugs. If only the 38 patients who experienced seizures during the index detoxification are considered, 28 were found to have used drugs other than alcohol, of whom 20 had used benzodiazepines alone or with other substances. Among the ten patients who had used no drugs other than alcohol, seizures occurred at the time of admission or within the first 24 h in seven, between the third and fifth day in two, and after more than 10 d in one; among the 20 patients who had used benzodiazepines as well as alcohol, seizures occurred in the first 24 h in nine, between 25 and 48 h in six, between 3 and 5 d in six, and between 6 and 10 d in one.

Of 427 patients registering during a 1-yr period at the Addiction Research Foundation in Toronto who met DSM-III lifetime criteria for alcohol abuse or dependence, 22% of men and 34% of women reported use of barbiturates or tranquilizers at some time in their lives (Ross, 1989).

Of 46 alcoholic outpatients in the eastern United States who reported that they had used sedatives for at least 30 d during their lifetimes, 16 (35%) reported continued use of these drugs during their current alcohol treatment (Wolf et al., 1989b). Most of the sedatives used were benzodiazepines. Seven (15%) of the sedative users were judged to have used the drugs appropriately and as medically prescribed; 61% were judged to have abused the sedatives. The remaining sedative users (24%) had engaged in appropriate use as well as misuse of the drugs at different times. Although many of the sedative users indicated that they had begun using these drugs for recreational purposes, the proportion who used them for self-medication of withdrawal from alcohol and other drugs, and of anxiety and insomnia, increased over time. The patients were also asked to rate the sedatives with which they had experience according to their preference for the drugs and to rate the intensity of the "high" associated with each of these sedatives on a 100-mm analog scale; these ratings were found to covary. Preferences for diazepam, alprazolam, and lorazepam did not differ from those for methaqualone, ethchlorvynol, or Tuinal (secobarbital and amobarbital), but ratings for diazepam were significantly greater than those for chlordiazepoxide and clorazepate. These preferences paralleled those found by this research group (Iguchi et al., 1989) among methadone users, as mentioned before.

As discussed previously (sections II.C and II.D), recent experimental research has suggested an increased preference for diazepam in moderate drinkers. Although this intriguing finding lends support to the assumption of some authors that alcoholics are at special risk of benzodiazepine abuse, the characteristics and extent of this risk are far from clear, and the relation of this risk to the benefits of benzodiazepine treatment in alcoholic patients, except for detoxification, remains controversial.

A thoughtful and interesting review of the evidence concerning these questions was published by Ciraulo et al. (1988b). The authors noted that studies of various alcoholic populations have indicated widely varying rates of use and abuse of benzodiazepines; they pointed out that the higher end of the range of these rates, i.e., about 30% to 40%, is higher than that for the general population but comparable to that for psychiatric outpatients. This is not surprising, according to the authors, "given the substantial evidence for concurrent psychiatric illness among alcoholics and the efficacy of benzodiazepines in treating alcohol withdrawal symptoms. Anxiety disorders, in particular, seem to be well-represented among alcoholics. . . .We believe that, at the present time, there is a body of literature which suggests that alcoholics. . .may be more susceptible to benzodiazepine abuse than are nonalcoholics, but there is little evidence to suggest that all or even most alcoholics abuse them" (p. 1505).

Thus, the authors suggest that, although some alcoholics may use benzodiazepines, this use is apparently not determined simply by the reinforcing effects of the drugs, or many more alcoholics would be abusing them.

Some studies have indicated the frequency with which benzodiazepines are prescribed for alcoholic patients. For example, 46% of 233 female alcoholics admitted to a detoxification program in Melbourne (Australia) between 1973 and 1985 reported having used prescribed benzodiazepines, most frequently diazepam; 32% of a larger group of male inpatients also reported such use (Blankfield, 1989).

Bailly et al. (1990) studied all 385 patients admitted to a hospital in Lille (France) during a 1-yr period of 1988 to 1989 who had a DSM-III diagnosis of substance use disorder. Of the 246 alcoholics, 73 (29.6%) reported having used a benzodiazepine during the 48 h preceding admission; of these, 55 (75%) had prescriptions for these drugs. In contrast, of the 139 patients admitted for abuse of drugs other than alcohol, 71 (51%) reported use of a benzodiazepine during the preceding 48 h, of whom only 21 (30%) had prescriptions. Of 80 alcoholic patients who reported past use of prescribed psychoactive medications, 57 (71%) had used prescribed benzodiazepines.

An unusual perspective on the effects of benzodiazepine use on alcohol abuse was offered by Kamal et al. (1987), who interviewed 125 chronic alcoholics in a Paris (France) hospital. Of 25 alcoholic patients admitted to a general medical ward for treatment of physical disorders, only two reported having used benzodiazepines; whereas 77 of 100 alcoholic patients admitted to the psychiatric service reported having used benzodiazepines. The investigators found that all of these 77 patients attributed their alcohol abuse directly or indirectly to the effects of their experiences with use of benzodiazepines. Seventeen reported that they had turned to alcohol because prescribed benzodiazepines had not relieved depression as-

sociated with anxiety; 26 claimed to have started using alcohol to treat various adverse effects of long-term benzodiazepine medication; an additional 34 reported that they had used alcohol to combat symptoms of benzodiazepine withdrawal, such as irritability and insomnia.

f. STUDIES OF CRIMINALS AND CRIMINAL ACTIVITY RELATED TO BENZODIAZEPINE USE. Bergman and Dahl-Puustinen (1989) examined 2565 prescription forgeries uncovered at retail pharmacies in Sweden between 1982 and 1986. Diazepam, oxazepam, nitrazepam, and flunitrazepam were the most frequently involved drugs and together accounted for 52% of all forgeries. However, when the incidence of forgeries was related to overall rates of utilization of the individual drugs involved, analgesics (especially codeine, pentazocine, and ketobemidone) clearly headed the list.

Hanlon et al. (1990) conducted interviews regarding criminal activity and drug use by 250 male narcotic addicts who had recently been admitted to treatment programs in Baltimore, MD (United States) and New York City in 1983 to 1984; data analysis focused on 132 subjects who gave histories of at least three periods of addiction and two intervening periods of nonaddiction. From the preaddiction period to the period of last addiction, and including intervals between periods of addiction, the mean number of days of use of diazepam per year steadily increased from 10.5 to 35.5. The investigators attributed this increase in diazepam use, as well as trends in use of certain other drugs, to "changes in the popularity of drugs over the years, that occasionally transcended the influence of addiction status. . . ." Analyses of variance in use of diazepam revealed no significant associations with race, periods of addiction and/or nonaddiction, or criminal activity during these periods.

2. Surveys of drug overdose or drug-associated deaths. Several types of studies provide information bearing on misuse and recreational use of drugs. These include surveys of hospitalizations due to ingestion of excessive doses, surveys of coroners' reports of drug-related and drug-induced deaths, and case studies of incidents of overdose. Among the surveys of hospital cases are studies of ER presentations for overdose or acute toxicity and cases that resulted in hospital admissions, either to a general ward or to an intensive care unit.

In this review, we will consider only those surveys that specifically included benzodiazepines. Studies loosely grouping drugs within categories such as "tranquilizers" are not included, unless it was clear that these groupings did not include other types of drugs, such as antipsychotics and antidepressants. To be able to compare data from various sources, in this section, we have considered rates of benzodiazepine use in terms of the number of persons in whom these drugs were identified as a proportion of the total size of the group surveyed.

Results of overdose surveys must be interpreted with caution, because many of the studies do not verify patients' verbal reports with analytical laboratory confirmation of the presence of the drug. As will be further discussed, the DAWN survey in particular has been questioned regarding the validity of the frequencies of drug use reported. Investigators have questioned the validity of drug use histories provided by patients in general and have emphasized that such histories should be confirmed by analysis of the presence of drugs in body fluids (Lilja et al., 1986). For example, in one study, analytical verification of histories in a subgroup of the cases surveyed indicated detection of drugs that had not been mentioned by the patients in almost half of the cases (Leykin et al., 1989). Schwartz et al. (1990) found that analytical results agreed with clinical impression in only 17.4% of cases; this was also approximately the rate of agreement found when only benzodiazepines were examined. Diagnosis of benzodiazepine overdose was accurate in only 65% of cases studied by Kellerman et al. (1987); this rate was not different from that reported for overdose from all drugs. Mahoney et al. (1990) reported complete concordance of analytical data and history in 52% of cases, partial concordance in 16% of cases, no drug detected in 20% of cases, and additional drugs or other drugs detected in 12% of cases; among 35 patients in whom benzodiazepine overdose was suspected, analytical data confirmed the suspicion in 17 cases (48.6%).

Many of the individual cases of both hospital admissions and coroners' reports involve ingestion of several drugs; the specific contribution of each drug to the overdose episode is often not assessed. A final caution is that studies frequently do not distinguish cases in which the drugs involved were present at therapeutic versus higher levels.

In our previous review, we compared data concerning benzodiazepine overdose with similar data for barbiturates, which were formerly used for comparable indications. At the time of that review, barbiturates had already been supplanted to a large extent by benzodiazepines for many of the same therapeutic objectives. This trend has continued to the point that there is now little use of barbiturates in most countries, with the exception of phenobarbital. Although this comparison may now, therefore, be less useful, it may still serve as a useful reference point; thus, where possible, the incidences of detection of benzodiazepines have been compared with those for barbiturates.

In our previous review, we found that the frequency of detection of benzodiazepines in overdose surveys and in coroners' reports was variable and often depended on such factors as geographic location, the period during which the survey was conducted, and specific characteristics of the population studied. In the years following the introduction of these drugs, the incidence of their detection in these surveys had increased and, in more recent years, had stabilized. Benzodiazepines were usu-

ally detected in combination with other drugs. Few cases of overdose could be attributed exclusively to benzodiazepines, and deaths ensuing from overdose with benzodiazepines alone were exceedingly rare. In general, the incidence of benzodiazepines in overdose surveys appeared to reflect the overall availability of these drugs.

We concluded that, although these studies indicated some prevalence of nonmedical use, they provided little evidence that these drugs are subject to frequent abuse. We further pointed out that the factors associated with prescription of these drugs (e.g., psychiatric morbidity) may also predispose to intentional overdose.

a. HOSPITAL CASE SURVEYS. As we found in our previous review, reports of overdose with benzodiazepines alone have suggested that the sequelae are usually innocuous and that recovery is typically complete and uneventful. However, when these drugs are taken in combination with others, complications can occur, generally due to the effects of the other agents (Greenblatt et al., 1977).

Several less extensive studies have confirmed those general conclusions (Jandric et al., 1987; Shimada and Miura, 1989). In contrast, Höjer et al. (1989) reported significant complications in 9.8% of their 144 overdose cases. Complications were observed in 12.5% of the cases of exclusive benzodiazepine overdose. Death occurred in two cases of exclusive benzodiazepine overdose (in one of which chronic obstructive pulmonary disease was a contributing factor).

The development of flumazenil, the specific benzodiazepine receptor antagonist, has considerably advanced the treatment of benzodiazepine overdose. In several studies, investigators have reported success in the use of flumazenil in the treatment of these cases (Rouzioux et al., 1988; Fantozzi et al., 1988; Geller et al., 1988; Knudsen et al., 1988). However, withdrawal reactions are occasionally observed in patients dependent on benzodiazepines (Prischl et al., 1988). In one double-blind, randomized study, 52 patients admitted to an intensive care unit because of suspected overdose with benzodiazepines alone or in combination with other drugs were given flumazenil (Höjer and Baehrendtz, 1988). Consciousness was assessed with a modified version of the Glasgow Coma Scale (Teasdale and Jennett, 1974). Significant increases in consciousness were obtained within 5 min of injection of flumazenil, whereas in the placebo group there was no change. Patients who had ingested benzodiazepines with other drugs showed less marked changes after flumazenil injection. Interestingly, patients who had ingested benzodiazepines with alcohol exhibited a response to flumazenil as great as, although somewhat later than, the response of those that had taken benzodiazepines alone. The study concluded that flumazenil was a well-tolerated, safe, and effective antidote to benzodiazepine overdose and could also be used to facilitate differential diagnosis.

In few studies has the prevalence of overdose among individuals provided with benzodiazepines for appropriate medical indications been indicated. Edwards et al. (1991) examined several medical conditions among 10,895 individuals who received prescriptions for alprazolam from family physicians during the years 1983 to 1984. Of these, 0.68% were involved in intentional overdose episodes during the period of treatment; following treatment, the rate was 0.28%. Seventy-two percent of the overdose cases involved other drugs in addition to alprazolam. None of the cases of overdose involving alprazolam alone proved lethal. Accidental overdose was reported in less than 0.3% of patients.

i. Presentations at emergency rooms. Reports of two types of survey, namely, studies of ER presentations to a single facility and studies in toxicology laboratories that identified drugs in samples of biological fluids from a number of facilities within a region, are summarized in table 30. In each of these studies, some frequency of reported or detected benzodiazepine use was found, typically ranging from 15% to 40% of cases.

Trends in such rates have been reported in two studies. Ghodse et al. (1986) reported results of a questionnaire survey of ER cases in London that was conducted in 1975 and again in 1982. The percentage of ER cases in which benzodiazepines were involved had increased from 28% to 38%. The authors noted that this change in rate did not reflect a change in the absolute number of cases involving benzodiazepines but rather a decrease in the total number of overdose cases during this period. In another study, conducted in Denmark, Möller et al. (1987) examined the records of outpatients and admissions treated for drug overdose. The annual number of ER presentations between the years 1980 and 1984 averaged 180 (range of 161 to 211). There was considerable variability in the annual rate of benzodiazepine outpatient cases from 1980 to 1985. Despite this variability, there was an increasing trend in the rates. The results of the study of admissions is reported below.

In general, the frequency of barbiturate involvement in these cases is lower than that for benzodiazepines and lower than those obtained in most of the studies considered in our previous review. Trends have also been reported for the frequency of involvement of these drugs in overdose cases. Ghodse et al. (1986) reported that the percentage of London cases in which barbiturates were involved had decreased in 1982 compared with rates obtained in 1975; this change in rate also reflected a change in the absolute number of cases involving barbiturates. Möller et al. (1987) reported a low and stable rate of barbiturate involvement in outpatients treated for drug overdose between 1980 and 1984 in Denmark. Thus, the trends associated with barbiturate incidence in overdose cases closely correspond to trends in barbiturate utilization.

ii. Hospital admissions. The rates of involvement of

TABLE 30

*Epidemiological studies of overdose cases in individuals presenting at emergency rooms, toxicology screening cases, individuals admitted to hospitals, and deaths due to overdose**

Study	Sample	Locale	Survey	No. of cases	% benzo	% barbit	Mortality % benzo	Mortality % barbit	Analytic verification	Notes
ER presentations, poisoning centers, and tox laboratories										
Kerr, 1989	ER presentations and admissions	USA	1986–88	133	32.0	1.5	0.0	0.0	Some	76% confirmation rate with analytic verification
Willox, 1985	ER	Scotland	1983	73	56.2	0.0			No	Deliberate self-poisoning; anxiolytics "most benzo"
Soslow, 1981	ER	USA	1979	82	24.4	15.8	0	0	Yes	All benzo were diazepam; confirmed by tox in 14 of 20 cases (70%; 58.9% overall)
Adams, 1991	ER	England	1978–82	3349	~4	~5	0.03		Some	Poisoning by drugs and chemicals, excluding accidents, children
Ghodse et al., 1986	ER	England	1975	413	28	27			No	Questionnaire
			1982	311	38	7	0.0	0.0		Excludes subjects <15 yr of age
Tunwashe et al., 1985	ER	Nigeria	1979–82	146	17.1	19.2	0.0	0.0	No	All poisonings
Möller et al., 1987	Outpatients	Denmark	1980–84	898	25.4	2			?	Deliberate self-poisonings
			1980	161	17	1				
			1981	193	21	3				
			1982	200	29	2				
			1983	133	20	2				
			1984	211	36	2				
Sivner and Goldberg, 1978	ER	N Manchester	1976–77	588	52.7	14.6	0	0.17	No	Prevalence of overdose related to prescript. frequency
Longmore et al., 1989	ER	USA	1989 (published)	126	2.4	0			No	Ten most frequent drugs listed
Nogue et al., 1989	ER	Spain	1989	181	56	4			No	
			1974		31	44				
Carter and Robson, 1987	ER	UK	1981	95	32.7				No	Subjects aged 10–15 yr who intentionally ingested poisons other than CO
			1985	88	17					
Horwitz et al., 1976	Tox screen	USA	1974–75	1013	5.6	19.7			Yes	Drug overdose cases only
Mononen et al., 1987	Tox screens from ER	Finland		359	13.37	2.51			Yes	
Merigian et al., 1988	Tox screens from ER	USA	1983	1710 2164	15.9	3			Yes	Numbers given are % of drugs detected (2164)
Koppel and Tenczer, 1988	Poison information center	Germany	1986–87	2942	23.7	3.7			?	
Schwartz et al., 1990	Tox screen	USA	1987	949	18.4	4.2			Yes	20.6% concordance between results and clinical impressions (with trivial drugs eliminated); 16.9% of clinicians' predictions of benzo involvement were confirmed (15.9% overall confirmation)
Kellerman et al., 1987	Tox screen	USA	1984	196	15.3	3.6			Yes	Prospective study of diagnostic accuracy in adults; benzo dropped from final diagnosis in 18 cases; benzo added to final diagnosis in 2 cases

Mahoney et al., 1990	Tox screen	USA	1984–85	164	18.9	7.9			Yes	Tox screen and history taken were completely concordant, 52%; Tox screen and history taken were partly concordant, 16%; no drug detected, 20%; other or additional drugs were detected in 12%; 48.5% of benzo suspect cases confirmed by tox
Angelo-Khattar et al., 1990	Tox screen	Kuwait	1985–88	53	5.7	18.9			Yes	Children
Admissions										
Wiseman et al. (parts 1 and 2), 1987a,b	Admissions	UK	1982–84	1163			0.0	0.0	Rare	Children <5 yr of age; sedatives/hypnotics were 9.4% of all drug cases; sedatives/tranquilizers in 1% of homes but involved in 6% of accidents
Hardwicke et al., 1986	Inpatients	Australia	1980–82	747	34.5	7.1	0.3	0.1	No	Two deaths with benzo in combination with other drugs
Ekeberg et al., 1988	Admissions	Norway	1979	354	51.1	28.5			No	1 yr before and after the withdrawal of 4 barbit and glutethimide from the market; frequency of antidepressant overdose increased
			1980	386	39.6	11.7				
Möller et al., 1987	Admissions	Denmark	1980–84	1048	30.7	6.5			?	Deliberate self-poisonings
			1980	246	33	9				
			1981	189	31	7				
			1982	217	30	5				
			1983	183	31	6				
			1984	213	28	5				
Christiansen et al., 1987	Admissions	Sweden	1972–84	1263	35.6	17.6	0.7	3.7	?	Deliberate self-poisonings (881 subjects)
Bosch et al., 1987	Admissions	South Africa	1983	389	36.8	1			No	Primarily admissions
Rostrup et al., 1989	Admissions	Norway	1984	42	57.1				?	
Wynne et al., 1987	Admissions	England	1982–86	737	50.3		<0.41		?	Self-poisonings
Koppel and Tenczer, 1988	Hospitalized	Germany	1981–87	2836	30.8	13.2			?	Analytic verification
Huang and Vicas, 1987	Admissions		1986	246					?	
Hincal et al., 1987	Admissions	Turkey	1975–84	760	3.82	23.03			?	Children aged ≤17 yr
McGrath, 1989	Admissions	Australia	1985–86	325	39.5	1.6			Rare	
Fuller et al., 1989	Admissions	UK	1984–88	1160	48.8	3.5			?	34.7% of drugs were benzo; 2.5% were barbit
Rygnestad, 1989	Admissions	Norway	1978	303	44	10	0	0	Yes	
	Some ICU		1987	425	46	1	0	0		
Nessa, 1986	Admissions	Norway	1980–81	331	12.7	3.3			No	
Wiernikowski et al., 1990	Admissions	Poland	1980–86	138	31	21				
Verstraete et al., 1990	Admissions	Belgium	1983	665	51.9				Some	Certain obsolete hypnotics placed on prescription only basis in 1988
			1984	609	40.9				Some	
			1985	538	40.9				Some	
			1986	544	41.7				Some	
			1987	545	42.0				Some	
			1988	472	47.5				Some	
			1989	437	46.9				Some	
Mackay, 1987	Admissions	New Zealand	1983	66	10.6				No	
Pearn et al., 1984	Admissions	Australia	1977–81	2024	9	4.8			No	

TABLE 30—*Continued*

Study	Sample	Locale	Survey	No. of cases	% benzo	% barbit	Mortality % benzo	Mortality % barbit	Analytic verification	Notes
Admissions to ICU										
Leykin et al., 1989	ICU	Israel	1982–84	71	50.7	21.1			Some	ICU cases represented 16.95% of the ER presentations; analytic verification in some cases; other drugs found in 46%
Höjer et al., 1989	ICU	Sweden	1972–85	3430	22.07		0.15		Yes	Number of benzo cases increased from 1972–1985 from 17–28%; deaths occurred in 5 cases, three of which had taken a benzo alone; analysis similar to that of Greenblatt
Höjer et al., 1990	ICU	Sweden	1990 (published)	105	69.5				Yes	Study of flumazenil utility
Rueda et al., 1990	ICU	Spain	1987–89	33	9.1				No	
Deaths										
Auansakul and Eiampak, 1987	Deaths	Bangkok	1971–85	416			6.0		?	
Steentoft et al., 1989	Deaths	5 Nordic countries	1984–85						Generally	Persons aged 15–34 yr submitted for tox; numbers given are incidence of detection and incidence of the drug as cause of death; cannot compare across countries
		Finland		349	15.8	14	2.9	11.7		
		Denmark		315	16.8	11.1	0.0	3.5		
		Sweden	1984	198	31.3	7.6	1.5	5.1		
		Iceland		12	41.7	16.7	0.0	0.0		
		Norway		167	30.5	1.8	1.2	1.8		
Harlow and Swint, 1989	Deaths	USA	1980–86						?	Mortality rates given
Lindesay, 1986	Suicides	England Wales	1974–83						?	Small increase in suicides with benzo in elderly
Hibbs et al., 1991	Drug-related deaths	USA	1986–88	115			25		Yes	
Froede et al., 1987	Deaths from chemicals (includes CO)	USA	1982–85	210		29.5/0.5		12.4/7.1	Yes	Barbit decreased from 14–6% during 1982–5; benzo was primary agent in 1 case; numbers given are incidence of detection and incidence of the drug as cause of death
Moens and Van de Voorde, 1989	Suicide by solid or liquid	Belgium	1971–84	2405	6	22.1				
Lodi et al., 1988	Suicides by drug	Italy	1986	205	35.12				Yes	

* Abbreviations: Tox, toxicology; benzo, benzodiazepine; barbit, barbiturate; ICU, intensive care unit.

benzodiazepines and barbiturates in studies of hospital admissions are also shown in table 30. The incidence of reported benzodiazepine use in these patients typically ranged from 30% to 50%. The mortality rate associated with benzodiazepine overdose cases was exceedingly low in those studies in which such a rate was reported.

In the study by Möller et al. (1987) in Denmark, the annual number of admissions between the years 1980 and 1984 averaged 210 (range of 189 to 246). During these years, there was no apparent increasing or decreasing trend in the rates of hospital admissions for overdose involving benzodiazepines. As noted before, the authors found an increasing trend, despite some variability, in reports of benzodiazepines in outpatients treated for overdose. The lack of change in rates of admissions suggests that the trend of increasing frequency of involvement of benzodiazepines in outpatients was more an accident of the variability than a reliable effect.

In two recent studies, unusually low numbers of cases of benzodiazepine ingestion were found. In one of these studies, Hincal et al. (1987) examined 760 accidental poisoning cases in Turkish children 17 yr of age or younger between 1975 and 1984. These findings are consistent with those of previous studies of rates of benzodiazepine involvement in poisoning among children (Pearn et al., 1984; Lawson et al., 1983). These data also suggest that accidental ingestions in children contribute minimally to the rates of benzodiazepine involvement in surveys that do not exclude children.

In another study (Nessa, 1986), conducted in Norway, only 12.7% of 331 cases between 1980 and 1981 involved benzodiazepines. In contrast, in a report of two surveys conducted in Norway in 1978 and 1987, Rygnestad (1989) found respective rates of benzodiazepine involvement of 44% and 46%. These values are more typical of those reported in other surveys.

Ekeberg et al. (1988) examined records of admissions for overdose in a Norway hospital 1 yr before (1979) and 1 yr after (1980) the withdrawal from the market of four barbiturates and glutethimide. Of 354 admissions for overdoses in 1979, the rate of benzodiazepine involvement was 51.1%. Of the 386 admissions in the subsequent year, the rate was 39.6%. The rates of barbiturate involvement declined from 28.5% in 1979 to 11.7% in 1980. The frequency of involvement of antidepressants increased in 1980. Similar results were reported by Verstraete et al. (1990). Thus, restricting availability of other sedative-hypnotics did not increase the rate of benzodiazepine involvement in admissions because of overdoses.

As with ER presentations, the frequency of barbiturate involvement in hospital admissions is generally lower than that for benzodiazepines and lower than those obtained in most of the studies considered in our previous review. Trends of this incidence have also been reported. Möller et al. (1987) reported a low and stable rate of barbiturate involvement in Danish outpatients treated for drug overdose during the period from 1980 to 1984. This rate was higher than that for outpatients, reflecting the more serious nature of barbiturate overdose cases.

iii. Admissions to intensive care units. Höjer et al. (1989) found that benzodiazepines were involved in 17% of cases of overdose patients admitted to an intensive care unit in Sweden in 1972 and in 28% of such cases in 1985; the authors attributed this increase to the increase in prescription of these drugs associated with the withdrawal of other sedative-hypnotics from the market. However, the studies by Ekeberg et al. and Verstraete et al. described before suggest that the withdrawal of other sedative-hypnotics from the market does not necessarily lead to an increase in rates of benzodiazepine involvement in overdose cases.

Leykin et al. (1989) reported that benzodiazepines were involved in 50.7% of a series of intensive care unit overdose admissions in Israel between 1982 and 1984. In a study of the utility of flumazenil in the treatment of overdose, Höjer et al. (1990) reported benzodiazepine involvement in 69.5% of cases.

b. SURVEYS OF CORONERS' REPORTS. Steentoft et al. (1989) reported the incidence of fatal intoxications during the years 1984 to 1985 among individuals between 15 and 34 yr of age in five Nordic countries: Finland (n = 349), Denmark (n = 315), Sweden (n = 198; 1984 only), Iceland (n = 12), and Norway (n = 167). Excluding Iceland due to the small sample size, benzodiazepines were detected in 15.8% to 31.3% of these fatalities; in Iceland, benzodiazepines were detected in five of the 12 cases reported. The cause of death was attributed to benzodiazepines in 0 to 2.9% of these cases. In contrast, barbiturates, which were detected in 1.8% to 14% of the cases (excluding Iceland), were named as the cause of death in 1.8% to 11.7% of these cases. The large majority of deaths of known drug addicts in these countries were attributed to opioids.

Analysis of death certificates in Texas (United States) from 1980 to 1986 indicated that between 0.22 and 0.07 deaths per 100,000 population were attributed to benzodiazepine medication alone. There was an apparent slight decrease in this rate during this period. In contrast, drug-induced deaths for opioids, cocaine, and antidepressants were generally greater than those for benzodiazepines and exhibited an increasing trend during the same period. Rates of drug-induced deaths consistently lower than those for benzodiazepines were reported only for amphetamines (Harlow and Swint, 1989).

Two additional studies from the United States conducted during the mid-1980s found similar frequencies of 25% and 29.5% of cases in which benzodiazepines were detected from samples of 115 and 210, respectively (Hibbs et al., 1991; Froede et al., 1987). In one of these studies a single case could be identified in which benzodiazepines were indicated as the cause of death (Froede et al., 1987). Neither of these studies provided informa-

tion concerning trends over time. However, in one study from the United Kingdom, Lindesay (1986) reported increases in frequency of benzodiazepine use in elderly suicides.

c. THE DRUG ABUSE WARNING NETWORK. The DAWN system, which is an operation of the NIDA, has conducted periodic surveys in the United States and issued reports regularly since 1972. The reports are generated from participating ERs and medical examiners in a number of metropolitan areas, with reporters trained to ensure concordance in definition and interpretation. The DAWN survey was initially designed for timely detection of changing trends in drug abuse. The assumption was that a broad-based examination of toxic episodes might be expected to detect emergent drugs of abuse or previously undetected or underestimated toxic effects of medications.

i. Methods. The methods of the DAWN survey have been described more fully elsewhere (National Institute on Drug Abuse, 1989c, 1991a,b). Recently, the system for reporting data collected from ERs has been modified in an attempt to render the data representative of overdose episodes occurring in 24-h, short-stay, nonfederal hospitals in the contiguous United States. Therefore, data from the most recent survey are not directly comparable with those presented in previous reports. The method and presentation of the data concerning medical examiners' cases has not changed, although the participating facilities have.

The basic datum of the DAWN system is a "mention" of a drug, i.e., an instance in which a particular drug is reportedly involved in some way in a toxic episode, either a presentation at an ER or a death. The DAWN reports cumulate these mentions for individual drugs. A typical case often involves mentions of several drugs. Information is also collected concerning what drugs are involved in each toxic episode, the reported motivation for drug taking (ER cases), the reason for the ER presentation, where or how the drug was obtained (ER cases), and various demographic characteristics.

The new DAWN survey estimation procedures for ER presentations were described in a recent report (National Institute on Drug Abuse, 1991a). Briefly, they were as follows. The hospitals participating were a random sample of all short-stay, nonfederal hospitals in the contiguous United States, stratified according to size and type of facility, with 21 metropolitan areas oversampled, and areas outside these areas stratified further. The numbers of drug-related episodes and drug mentions were weighted by the reciprocal of the probability of selection in the sample. Weights were also applied for each stratum based on the sampling proportion of the stratum. In addition, several adjustments were made for nonresponding facilities. Finally, the estimate of drug-related episodes for a particular area was weighted by the ratio of total number of ER visits according to the DAWN system to the total number of ER visits for that area according to the American Hospital Association Annual Survey.

ii. Validity of DAWN data. Previous studies have considered the reliability and validity of the data collected in DAWN. For example, Ungerleider et al. (1980a) conducted laboratory analytical verification of reports for individual patients. In their studies, 60% of the reports were only partially correct. These results are consistent with several other recent studies, described above, indicating a failure to fully verify verbal reports (history) with toxicological analysis. This issue is critically important to interpretation of the significance of DAWN data, which are often incorrectly regarded as an indication of prevalence of drug abuse.

In addition, DAWN tabulates all mentions of each drug, regardless of whether the drug significantly contributed to the ER episode. In a further study of DAWN data, Ungerleider et al. (1980b) found that, for more than half of cases in which diazepam was mentioned, concentrations of this drug in body fluids were in the therapeutic range. These data suggest that a significant number of drug mentions relate to drugs that may not have contributed to the overdose episode.

Finally, in a recent study, Pollock et al. (1991) examined frequencies of cocaine-related deaths in the United States as reported to the Centers for Disease Control (National Center for Health Statistics) and DAWN from 25 metropolitan areas during the period from 1983 to 1988. During the 6-yr period, the number of cocaine-related deaths reported to the Centers for Disease Control was 57% of those reported in the DAWN system. This difference suggests the need for additional validation of the DAWN system.

iii. Findings. In our previous review, we examined DAWN data for 1981 through 1985. In this period, the incidence of benzodiazepine mentions in ER episodes decreased from 16.5% to 10.3%. The incidence of mentions of barbiturate sedatives also declined, from 2.5% to 1.3%. In the present review, DAWN data have been examined for the years from 1986 through 1990 (National Institute on Drug Abuse, 1987, 1988a, 1989c, 1990b, 1991a,b).

The NIDA has recently reported an analysis of trends in benzodiazepine-related DAWN cases from 1976 to 1985 (National Institute on Drug Abuse, 1988b). During this period, the overall frequency of ER mentions of benzodiazepines showed a significant nonlinear decreasing trend. Of the 12 different individual drugs examined (alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, flurazepam, halazepam, lorazepam, oxazepam, prazepam, temazepam, triazolam), six (alprazolam, clonazepam, lorazepam, prazepam, temazepam, triazolam) showed an increasing trend in ER mentions during this period; five of these compounds were introduced to the market during this period. Clonazepam, which was on the market throughout the 10-yr period, showed an in-

crease in a small number of mentions, from eight in 1976 to 44 in 1985. The 1990 DAWN report (National Institute on Drug Abuse, 1991a) shows a nonsignificant decrease in ER mentions of tranquilizers (predominantly benzodiazepines) from 1989 to 1990.

In contrast to the ER mentions, there was no significant trend during the 10-yr period in benzodiazepine-related deaths reported by medical examiners. However, there was a significant decrease in diazepam-related deaths, whereas deaths related to the residual category of unidentified or unspecified benzodiazepines significantly increased. The 1990 DAWN report (National Institute on Drug Abuse, 1991b) indicates an increase (11.4%) in benzodiazepine-related deaths between 1989 and 1990, with an increase for diazepam and a decrease for the "unspecified" category.

As mentioned before, the DAWN survey questions individuals presenting at ERs about their motives regarding the overdose episode. The possible responses include "recreation," "other psychic effect," "dependence," "suicide," "other," and "unknown." Data concerning motives from the 1990 DAWN report (National Institute on Drug Abuse, 1991a) for several drug classes are presented in fig. 2. The distribution of the various motives for the toxic episodes among the drug classes mentioned is shown. Note that the motive reported for each toxic episode is assigned to all of the drugs mentioned. If the first four drug classes [tranquilizers, which are primarily benzodiazepines (open bar), antidepressants, antipsychotics, and barbiturates] are compared, it can be seen that the distributions of motives for these classes were similar.

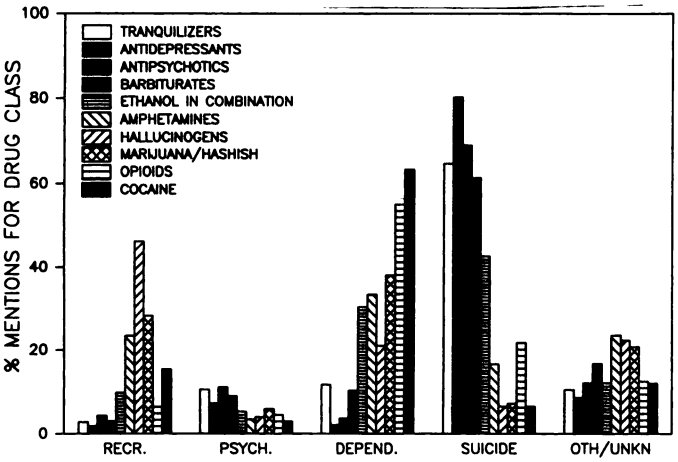

FIG. 2. Distribution of motives for emergency room episodes by drug classes in the DAWN 1990 annual emergency room data. Percentages are calculated based on weighted numbers of mentions for each drug category. For a description of the procedures for deriving these weighted estimates, see text. Motives were as follows: RECR., recreational use (use for experimentation or to enhance social situations); PSYCH., other psychic effects (use to improve or enhance mental, emotional or physical state); DEPEND., dependence (a psychic or physical state characterized by behavior that always includes a compulsion to take the drug to experience its effects or to avoid the discomfort of its absence); SUICIDE, successful or unsuccessful suicide attempt or gesture; OTH/UNKN., other or unknown (other includes self-medication, accident, or used unknowingly).

Specifically, a relatively low percentage of the episodes in which drugs from these classes were mentioned involved "recreation" or "dependence" as a motive, and a high percentage involved "suicide." Comparing this pattern with that for cocaine (solid bar, far right), a benchmark illicit drug, as well as amphetamines, hallucinogens, and marijuana/hashish, reveals a distinctly different pattern; in episodes involving these drugs, "dependence" and "recreation" were frequently cited as motivations, whereas "suicide" was reported relatively infrequently. The class of opioids displays a slightly different pattern from the other classes of illicit drugs; "recreation" and "suicide" are infrequent motives for episodes involving these drugs, whereas "dependence" is frequently cited as a motive. In this perspective, the DAWN reports show a pattern for tranquilizers that is consistent with that for the other medications prescribed for psychiatric morbidity and that is clearly distinct from the pattern observed for illicit drugs.

These data from the 1990 DAWN report are representative of motivation patterns in the DAWN surveys from the years 1986 through 1989 (National Institute on Drug Abuse, 1987, 1988a, 1989c, 1990b). A similar pattern was also observed in the analysis of the trend data in benzodiazepine-related cases from 1976 to 1985 (National Institute on Drug Abuse, 1988b). One trend evident in the data from 1976 to 1985 was a modest increase in reports of "dependence" as the motive for ER episodes involving benzodiazepines. This increase was most pronounced for diazepam, for which "dependence" was cited as the motive for three times more of the episodes involving this drug than for episodes involving the other benzodiazepines, except chlordiazepoxide. In the 1990 data, "dependence" was more frequently cited in alprazolam cases than in diazepam cases. It is unclear how to interpret these trends. It seems unlikely that patterns of benzodiazepine use from 1976 to 1985 should have changed in a manner that would lead to an actual increase in the incidence of physiological dependence or that such an increase would occur more with diazepam than with other benzodiazepines. It seems more plausible that increasing public awareness regarding dependence on these drugs, and particularly on diazepam, might have led to an increase in reports of this motivation for episodes involving diazepam. This interpretation is also consistent with the more recent report that "dependence" was increasingly cited as the motive in alprazolam overdose episodes, because this drug has become increasingly familiar to the public.

We also analyzed the 1990 DAWN data with respect to the reasons indicated for ER presentations. The possible responses included "unexpected reaction," "overdose," "chronic effects," "withdrawal," "detoxification," "accident or injury," "other," and "unknown." These

data, shown in fig. 3, are representative of these patterns in DAWN regardless of the year of the report. Comparison of the drug classes again shows that tranquilizers were more similar to the classes of drugs prescribed for psychiatric conditions than to illicit drugs. If toxic episodes involving the first four drug classes shown (tranquilizers, antidepressants, antipsychotics, and barbiturates) are compared, it can be seen that, in keeping with the frequency of suicide as the motive, overdose is the most frequent reason cited for these ER presentations. Compared to results with the first four classes, "overdose" was less frequently cited, and "unexpected reactions" and "chronic effects" were generally more frequently cited as reasons, in episodes involving amphetamines, hallucinogens, marijuana/hashish, and cocaine. "Detoxification" was also a frequently cited reason for overdose episodes involving cocaine, ethanol in combination with other drugs, marijuana/hashish, and opioids.

The reported sources for the different classes of drugs mentioned in the 1990 DAWN data are shown in fig. 4. The possible responses included "legal prescription," "street buy," "other unauthorized procurement," "other," and "unknown." As with the other figures, these data are representative of DAWN data over several previous years. As might be expected for this question, the classification of "unknown" was high for all of the drugs but highest for illicit drugs, probably reflecting a high rate of nonresponse among the overdose cases. The source of the drugs in episodes involving tranquilizers, antidepressants, antipsychotics, and barbiturates was most frequently cited as a "legal prescription" and infrequently cited as a "street buy." Second to "unknown," "street buy" was the most frequently cited source of drugs for cases involving amphetamines, hallucinogens, marijuana/hashish, opioids, and cocaine. As with the previous analyses, the sources of drugs in mentions involving tranquilizers were more similar to those involving other drugs prescribed for psychiatric indications than they were for those involving the illicit drugs, amphetamines, hallucinogens, marijuana/hashish, opioids, and cocaine.

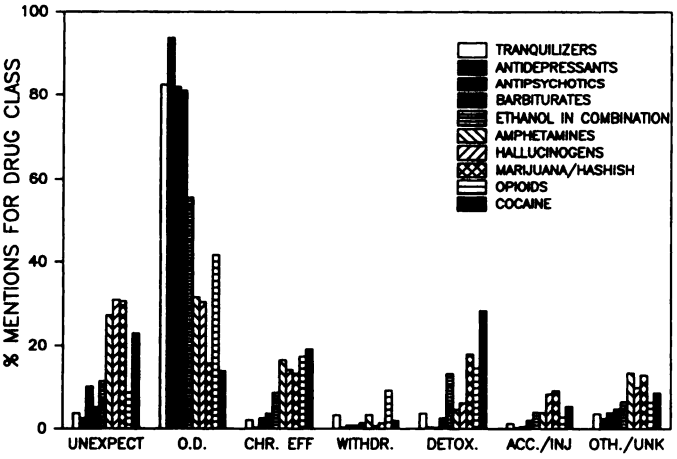

FIG. 3. Distribution of reasons for emergency room contact by drug classes in the DAWN 1990 annual emergency room data. Percentages are calculated based on weighted numbers of mentions for each drug category. For a description of the procedures for deriving these weighted estimates see the text. Reasons were as follows: UNEXPECT, unexpected reaction (effect was different from anticipated); O.D., overdose (either intentional or accidental); CHR. EFF, chronic effects (secondary conditions resulting from habitual drug use); WITHDR., withdrawal (symptoms due to physiological dependence that occur when drug administration is stopped); DETOX., seeking detoxification; ACC./INJ, accident or injury (injuries resulting from accidents caused by or related to drug abuse; OTH./UNKN, other or unknown (other includes reasons that cannot be classified into one of the above categories).

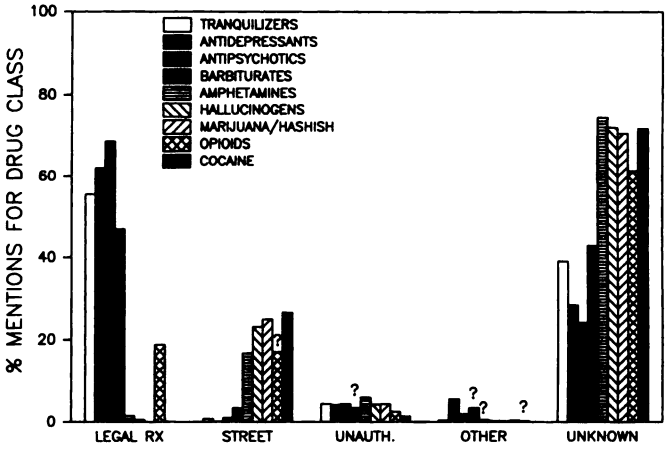

FIG. 4. Distribution of sources of drugs by drug classes in the DAWN 1990 annual emergency room data. Percentages are calculated based on weighted numbers of mentions for each drug category. For a description of the procedures for deriving these weighted estimates, see the text. Sources were as follows: LEGAL RX, subject received the drug according to a legal prescription; STREET, street buy (purchased by other than legal channels); UNAUTH., other unauthorized procurement (other than either a legal purchase or a street buy; OTHER, source of the drug that does not fit into one of the above categories; UNKNOWN, information concerning the source was not available. Question marks indicate those estimates that did not meet a standard of precision.

Medical examiners' cases also differentiated tranquilizers from illicit drugs (National Institute on Drug Abuse, 1991b). In these reports, deaths are described as "accidental/unexpected," "suicide," or "unknown." Deaths associated with tranquilizers, antidepressants, antipsychotics, and barbiturates were approximately equally reported as "accidental" or "suicide." In contrast, deaths associated with illicit drugs were most frequently reported as "accidental" (fig. 5). The distribution of age in deaths related to tranquilizers, antidepressants, antipsychotics, and barbiturates was skewed toward older individuals, compared to that for the illicit drugs. Finally, there was a low frequency of tranquilizer-related deaths in which only a single drug was implicated; in the majority of tranquilizer cases, the individuals had taken three or more drugs. Finkle et al. (1979) suggested that an indication of the safety of a drug in overdose cases is the frequency with which the drug is solely responsible for the toxicity. These DAWN data are consistent with the

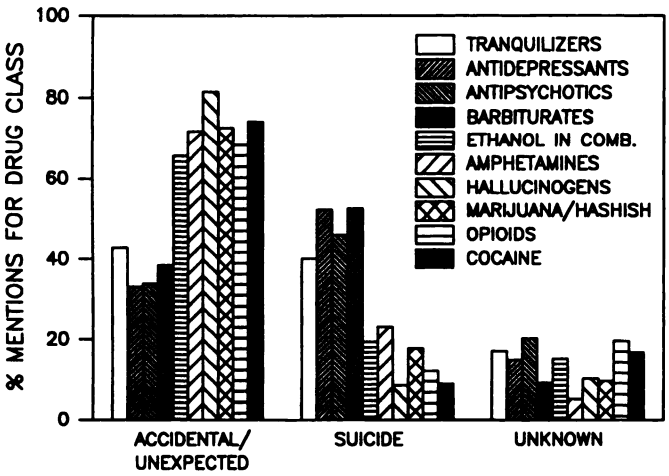

FIG. 5. Distributions by drug classes for manner of death in medical examiner cases reported to DAWN 1990 annual survey. Percentages are calculated based on total numbers of mentions for each drug category (these are not weighted values). Manners of death were as follows: ACCIDENTAL/UNEXPECTED, an unintentional drug-induced or drug-related death resulting from a drug abuse episode; SUICIDE, deliberate taking of one's own life; UNKNOWN, information concerning the death was not available.

data of Finkle et al. that indicate a low toxicity of the benzodiazepines as a class of therapeutic agents.

In summary, these data show differing spectra of characteristics of toxic episodes involving two distinct types of drugs within the DAWN reporting system. The drugs prescribed for psychiatric conditions are most frequently involved in suicide and parasuicide episodes. The antidepressants, antipsychotics, tranquilizers, and barbiturates are similar with regard to the distributions of reported motives for the toxic episodes. Consistent with these findings, "overdose" is the most frequent reason given in ER presentations involving these drugs. In addition, these drugs have most frequently been obtained legally. A contrasting picture is presented by the characteristics of DAWN episodes involving illicit drugs, including amphetamines, hallucinogens, opioids, and cocaine, which are known to be liable to significant abuse. The motives for these episodes most often include "dependence" and, with the exception of the opioids, "recreation"; "suicide" is cited relatively infrequently as a motive for these episodes. Consistent with these motivations, the reported reasons cited for ER episodes involving the illicit drugs most frequently included "unexpected effects," "chronic effects," and "detoxification" rather than "overdose." Finally, almost the only source reported for the illicit drugs is "street purchase." Similar results were obtained in an analysis of data from previous DAWN Annual Reports. Thus, there are distinct patterns in reports to the DAWN system. One is characteristic of licit drugs that are utilized by individuals with psychiatric conditions; the other is characteristic of illicit drugs of abuse.

In a recent study, Davis et al. (1991) examined data from the DAWN system together with NPA data concerning retail sales to arrive at indices of drug misuse. In accord with previous studies (Baum et al., 1986; Jones, 1977), Davis et al. analyzed the frequencies of mentions in DAWN in relation to frequencies of prescribing. Based on estimates of ER mentions per 100,000 dispensed prescriptions, the authors suggested that there has been an approximate 10% decrease in benzodiazepine misuse during three consecutive 3-yr periods from 1976 to 1985. They found that, for 1983 to 1985, DAWN data indicated 2.0 mentions of benzodiazepines per 10,000 prescriptions dispensed. In contrast, the comparable value for barbiturates was 4.1 and that for the nonbarbiturate sedative, methaqualone, was 178.2; a number of other nonbarbiturate sedatives ranged from 0.7 to 11.7. Central stimulants also showed relatively high values, which the authors attributed to the fact that a large proportion of the abused amphetamines were obtained through illicit sources. A similar analysis with comparable results was conducted with the DAWN medical examiners' cases. These authors also attempted to estimate relative fatality risks of these drugs by calculating a ratio of ER mentions and medical examiners' mentions. This gross estimate of risk indicated that, as a group, the benzodiazepines were among the safest medications, whereas the barbiturates were among those with a high degree of risk; analgesics, stimulants, and nonbarbiturate sedatives were about midway between these extremes. These data reflect the significant advantage in safety provided by benzodiazepines compared with other compounds that have been used for similar indications.

d. DRUG INTERACTIONS. Studies of overdose have indicated that, especially when used alone, benzodiazepines are associated with an extremely low risk of fatal overdose (Finkle et al., 1979). However, most overdose cases in which benzodiazepines are involved also involve consumption of one or more other drugs (National Institute on Drug Abuse, 1990b). Previous studies have suggested that the benzodiazepines contribute minimally to the toxicity observed in cases of multiple drug ingestion (Greenblatt et al., 1977).

We suggested previously that basic research studies of drug interactions would bear most directly on the question of the contribution of benzodiazepines to overdose episodes in which other types of drugs are also involved. Results of earlier studies had suggested that the LD_{50} of ethanol was not appreciably altered by diazepam, although the LD_{50} of diazepam was altered by ethanol. There were conflicting reports regarding the effects of benzodiazepines on the lethality of opioids. The findings regarding the interaction of diazepam and ethanol suggest the complexity of such interactions. These types of interactions are best characterized with isobolographic analysis (Loewe, 1953). In one such study, Etzler et al. (1969) characterized the interaction of nitrazepam and ethanol as supraadditive, although in another study Oka-

moto et al. (1985) characterized the effects of chlordiazepoxide and ethanol as infraadditive.

In a more recent study, Hu et al. (1987) examined interactions of ethanol with flurazepam in mice and found that the two drugs were infraadditive with respect to lethal effects. Doses of flurazepam up to 200 mg/kg reduced the ethanol LD_{50} by only 25%. Similarly, doses up to 3 g/kg of ethanol had no significant influence on the lethality of flurazepam. As with the lethal effects, the interactions of the two drugs in producing anesthesia were also infraadditive; however, other effects were apparently not similar.

Loss of righting reflex, sedation, and rotarod performance were affected by the two drugs in a supraadditive manner. These data suggest that the interaction was not merely kinetic, in which case the interactions for the various end points would have been similar.

e. SUMMARY AND DISCUSSION. The incidence of detection of benzodiazepines in overdose surveys and in coroners' reports varies widely. In the few studies in which trends have been examined, there is an indication that the incidence of detection of benzodiazepines increased from the 1970s to the 1980s. When examined in the context of medical utilization, this increase appears to correspond with prescribing practices. Similarly, in recent years there has been a decrease in prescribing of benzodiazepines, and this decrease is reflected in decreases in indices of misuse and toxic episodes involving benzodiazepines, such as mentions in the DAWN survey. These data suggest that the prevalence of overdose involving benzodiazepines is related more to prescribing practices, and, hence, to overall availability, than to trends in abuse of these drugs.

Fatality associated with exclusive benzodiazepine overdosage is exceedingly rare. Most studies of episodes of toxic effects, such as ER presentations, indicate that those cases involving benzodiazepines also usually involve other drugs, which are more likely to have been responsible for the toxic reactions. Few authors have systematically examined the nature of the interaction between benzodiazepines and other drugs in producing lethality. When they have, they suggested that, although benzodiazepines can increase the lethality associated with other drugs, this occurs only at high doses. In addition, such interactions are generally characterized as infraadditive, i.e., at least over the range of doses examined, the increases in lethality produced by the benzodiazepines are minimal.

3. Mortality and morbidity associated with benzodiazepine misuse or dependence. In an earlier study, Piesiur-Strehlow et al. (1986) had found no difference in mortality rates between subjects with abuse or dependence on benzodiazepines and control subjects matched for age, sex, and psychiatric or other illness. These rates were higher than those of the general population but lower than those observed in patients dependent on alcohol or illicit drugs (Piesiur-Strehlow et al., 1984). A preliminary report of follow-up studies indicates that most deaths of benzodiazepine-dependent patients were for natural reasons, with suicide as an exception (Dickmann et al., 1988).

Several authors have examined changes in brain morphology in patients with histories of long-term benzodiazepine use. These studies are included in this section about misuse of benzodiazepines because some of them involve dependent subjects. However, other authors have examined effects on brain morphology in patients receiving therapeutic doses; their findings do not necessarily represent consequences of misuse of these drugs.

The results of these studies can be complicated by the fact that long-term alcohol use can cause brain morphological changes. In addition, concurrent use of other drugs, including benzodiazepines, may increase the effects of alcohol (Mützell and Tibblin, 1989). Therefore, studies of benzodiazepines in this context should attempt to assess concurrent alcohol use, despite the difficulty of obtaining accurate histories of this use.

Poser et al. (1983) reported that several measures of cortical atrophy in patients dependent on benzodiazepines showed no difference from age-matched controls. In contrast, subjects dependent on alcohol and on alcohol as well as benzodiazepines showed significant cortical atrophy. Lader and colleagues (Lader and Petursson, 1983; Lader et al., 1984), however, reported an increase in brain ventricle areas in benzodiazepine-dependent subjects that was less than that seen in alcoholics. Definite abnormalities were reported in three of the benzodiazepine-dependent subjects, one control, and three alcoholic subjects. The authors noted that, although long-term alcohol users were excluded from the benzodiazepine group, it was possible that some used alcohol sporadically (Lader et al., 1984).

Allgulander et al. (1984) studied 55 subjects who, 4 to 6 yr previously, had been hospitalized for treatment of sedative dependence; none had abused alcohol or drugs other than sedatives. At the follow-up, 52% of the subjects were abusing drugs or alcohol. Of the 33 subjects for whom computed axial tomographic scan data were obtained, 17 showed evidence of cerebral atrophy; ten of these subjects were currently abusing drugs. Atrophy was marginal in nine of these subjects. The findings in the female subjects were compared with measures in an age-matched sample; the changes in the subjects were not different from those in controls. In a further follow-up of these subjects, Bergman and Dahl-Puustinen (1989) again found no significant difference between computed axial tomographic scans of the female subjects and their controls.

Schmauss and Krieg (1987; see also Schmauss et al., 1987) compared 17 benzodiazepine-dependent patients with age- and sex-matched controls on the basis of computed axial tomographic scans. The patients were hos-

pitalized for benzodiazepine withdrawal and reported no history of other types of chemical dependency, including alcohol abuse. Both high- and low-dose benzodiazepine users exhibited an enlargement of cerebrospinal space; values for the high-dose group were greater than those for the low-dose group. The differences between dose groups suggested to these authors that the cerebral atrophy was due to the drug treatment.

The conflicting results of these studies make an unambiguous interpretation impossible. Several results suggest significant cerebral atrophy; the most compelling are the studies by Schmauss and colleagues indicating some dose relationship. It is important that these studies attempt to rule out an effect of alcohol, which is known to produce such effects. At the same time, it is clearly difficult to have complete confidence that such controls can be effectively obtained in clinical studies. Thus, an obvious and important alternative approach to assessing this possible effect of the benzodiazepines would be research in animals, in which the exposure to benzodiazepines, as well as to alcohol, can be satisfactorily controlled.

4. Summary and conclusions. a. SURVEYS OF MISUSE AND RECREATIONAL USE. In our previous review (Woods et al., 1987), we concluded that nonmedical use of benzodiazepines in the general population was trivial in extent. In the United States, the annual prevalence of nonmedical use of tranquilizers further declined by more than half in all age groups between 1985 and 1990; in 1990, the annual prevalence was 1% to 2%, and prevalence of nonmedical use within the prior month was 0.5% or less. Numerous surveys of populations of youth in many areas of the world have found, almost without exception, that 3% or less report nonmedical use of tranquilizers within the prior month; these rates were lower than rates of illicit use of virtually all other substances in virtually every population studied. Periodic surveys in the United States and Canada have shown that nonmedical use of tranquilizers among youth has declined fairly steadily since the the late 1970s.

In the last few years, there has been a considerable increase in the number of surveys examining benzodiazepine abuse and dependence among clinical populations; unfortunately, these studies have often used inappropriate criteria for defining abuse so that the findings are difficult to interpret. Surveys of medical and psychiatric outpatients indicate a broad spectrum of findings regarding rates of nonmedical use of benzodiazepines. Much of this variance is due to differences among the studies in definitions of and criteria for abuse or misuse; in addition, in some studies, no attempt was made to distinguish nonmedical use from use of prescribed drugs. Studies applying relatively stringent definitions have indicated extremely low rates of misuse among these populations, similar to the rates of nonmedical use of tranquilizers in the community at large. Surveys of psychiatric inpatients have found higher rates of apparent benzodiazepine abuse, usually in conjunction with abuse of other drugs; however, these studies have often failed to apply appropriate definitions of abuse, to distinguish abuse from dependence, and to distinguish nonmedical from medical use of these drugs.

As we discussed in our previous review, in contrast to the general population, a substantial proportion of the drug-abusing population uses benzodiazepines, often without prescriptions for these drugs. The vast majority of this nonmedical use of benzodiazepines is in the context of polydrug abuse, which has increasingly become the predominant pattern of abuse in general. Recent studies support our earlier conclusions that benzodiazepines usually serve as secondary drugs of abuse. The particular patterns of such polydrug abuse, including the prevalence of use of benzodiazepines as well as the specific benzodiazepines most frequently used, appear to vary largely in accord with availability. In the context of polydrug abuse, benzodiazepines are often used for self-medication of withdrawal from the primary drug of abuse, as well as for treatment of anxiety disorders, which appear particularly prevalent among drug abusers; some investigators have found that many opiate and/or alcohol abusers use benzodiazepines by medical prescription. As noted in our previous review, a number of studies of the use of benzodiazepines among clients of some United States methadone programs had suggested the possibility of a unique preference for diazepam. However, on the basis of recent studies from the United States as well as other countries, it now appears more likely that the patterns of benzodiazepine use in this population, as in populations of polydrug abusers in general, vary in accord with the drugs' relative availability rather than any specific pharmacological differences among the benzodiazepines.

Several epidemiological studies have shown that patients using benzodiazepines are less likely than others to consume alcohol. On the other hand, studies of alcoholic populations consistently find frequent use of benzodiazepines, with or without prescriptions. As discussed previously, recent experimental findings suggest that even consumers of moderate quantities of alcohol show markedly greater preference for benzodiazepines than nondrinkers; these findings emphasize the importance of the epidemiological evidence of the frequency of concurrent alcohol and benzodiazepine abuse and point to the need for extensive and systematic investigation of the significance of this empirical association.

b. SURVEYS OF DRUG OVERDOSE OR DRUG-ASSOCIATED DEATHS. Several types of studies provide information bearing on misuse of psychoactive drugs. Surveys of hospitalizations due to overdose indicate that benzodiazepines are often associated with a large proportion of these episodes. Surveys of coroners' reports concerning drug-related and drug-induced deaths also indicate a

large representation of benzodiazepines among these cases. Results of these surveys must be interpreted cautiously, because patients' verbal histories were not verified with analytical laboratory confirmation of the presence of the drug in most studies. Those that did indicate a considerable inaccuracy of self-reports of drug use in these cases.

The present conclusions are consistent with our previous review, in which we also found an increasing representation of benzodiazepines in these cases over the years from their introduction to the 1970s as these drugs replaced older medications. Of the recent data, only those from the DAWN survey bear on these trends. As mentioned before, results of this survey must be treated with caution; however, it is clear from the DAWN survey that frequencies of mentions of benzodiazepines in overdose episodes have been decreasing since the mid-1970s. Few cases of overdose could be attributed exclusively to benzodiazepines, and cases of lethality due to overdose with benzodiazepines alone were exceedingly rare.

Detailed examination of DAWN reports indicates that the frequencies of drug mentions alone, which some have regarded as indications of the magnitude of the "abuse" problem presented by these drugs, may be misleading. Moreover, it is clear that the spectrum of characteristics associated with overdose episodes in which benzodiazepines are mentioned closely resembles those associated with episodes involving other drugs prescribed for treatment of psychiatric illness. This spectrum is clearly distinct from that associated with overdose episodes involving illicit drugs of abuse.

A general conclusion supported by this review, as by our previous review, is that the benzodiazepines are very safe drugs. Death is rarely seen among individuals taking even very large amounts of these drugs. When lethality is seen, it is most often attributed to the toxicity of other drugs taken in combination with the benzodiazepines. Experimental studies of toxicity in animals confirm that high doses of benzodiazepines are necessary to produce toxic effects. Additionally, the lethality of other drugs is not substantially enhanced by concomitant administration of benzodiazepines.

c. MORTALITY AND MORBIDITY ASSOCIATED WITH BENZODIAZEPINE MISUSE OR DEPENDENCE. Several recent studies have attempted to examine CNS changes (cortical atrophy) associated with chronic benzodiazepine use. The results of these studies to date are inconsistent and often confounded by exposures to other drugs, most notably ethanol. Studies examining the possibility that morphological changes in the CNS might be associated with chronic exposure to benzodiazepines would be most profitably conducted using animal subjects so that the question of history of exposure to other drugs can be controlled.

G. Studies of Effects of Benzodiazepine Restrictions

The benzodiazepine era has inevitably been marked by continuing debates about the types and levels of regulatory control appropriate to the use of these drugs. Like most issues of public policy about the use of therapeutic drugs, the history of benzodiazepine regulation has been distinguished by opinion and bias more than by dispassionate evaluation of evidence. We have argued that policies affecting the availability of therapeutic drugs should be subject to the same standards of rational evaluation as are the drugs themselves and should be allowed only if they can be shown likely to prove safe and effective (Woods, 1990; Woods et al., 1991).

Unfortunately, there has been remarkably little study of the effects of regulation of therapeutic drugs. However, a regulation recently imposed on prescription of benzodiazepines in New York State has prompted several interesting studies. Although these studies to date have been able to examine only some of the preliminary effects of this regulation, the findings provide some rare insights into the net impact of such control measures; they also add another dimension to the epidemiological perspective regarding the use and misuse of benzodiazepines.

We consider these studies separately here because their methods and outcome measures cut across the categories of research described in previous sections.

1. The New York State regulation. In January 1989, a new regulation became effective in New York State, under which prescriptions for benzodiazepines can be issued only on the State's triplicate-copy prescription forms, of which the prescriber must retain one copy for 5 yr, and the pharmacy keeps the second copy and forwards the third copy to the State Department of Health for computerized monitoring; except for prescriptions for treatment of panic or convulsive disorders, the prescriptions are also limited to a 30-d supply and cannot be refilled. This regulation was imposed, according to the State Department of Health, because of the significant "public health danger posed by benzodiazepine abuse and misuse. . . ." (Eadie, 1990).

2. Study of immediate clinical effects. The possible clinical effects of the New York State regulation include both immediate and long-term effects on patients who had been receiving benzodiazepine treatment at the time the regulation became effective, as well as a range of less direct effects on the segment of the population afflicted by the disorders for which these drugs are indicated. For example, some have pointed out that the regulation risks exacerbating the undertreatment of anxiety, which poses substantial risks (Woods, 1990; Farnsworth and Blum, 1990; Blum, 1990; Shader et al., 1991; Woods et al., 1991). It is hoped that some of these long-term and indirect effects can be evaluated. To date, however, the evidence of clinical effects, at least, is limited to immediate effects in patients who had been receiving benzodiazepines at the time the regulation went into effect.

Schwartz and Blank (1991) examined the records of all patients who presented to the ER of a New York City hospital for problems associated with benzodiazepine use

during a 3-mo period beginning 2 wk after the regulation became effective. Of the 59 cases, 24 (41%) were clearly related to the new regulation and five others (8%) were probably related. Of the 24 clearly related cases, six presented with the reemergence of an anxiety disorder that had been controlled prior to reduction or discontinuation of benzodiazepine treatment by their physicians. Three others displayed reemergence of anxiety disorders and/or symptoms of withdrawal. Four displayed clear withdrawal symptoms, including one case of acute organic psychosis. Four were dependent patients seeking continued treatment or help with withdrawal. One elderly patient was referred to the clinic by her physician because of his concern about her safety after she refused to fill a triplicate prescription to continue her benzodiazepine treatment because she was afraid of being registered with the state as a "drug user." Six other patients had histories suggesting substance abuse; five presented in withdrawal, and one was a polydrug abuser seeking a new source of medication.

3. Studies of effects on prescribing. Investigators of the effects of the New York State regulation have examined changes in sales of benzodiazepine prescriptions in New York as opposed to other states, as well as concurrent changes in sales of other psychoactive drugs that physicians might prescribe in place of benzodiazepines.

Weintraub et al. (1991) examined changes in prescribing of benzodiazepines between 1988 and 1989 in New York, based on NPA data on retail sales, data of the State's Medicaid program, and data from a regional division of Blue Cross/Blue Shield. Each of these data sources reflected a substantial reduction in benzodiazepine prescribing in New York between 1988 and 1989; the reduction was 30% according to the Blue Cross/Blue Shield data, 44% according to NPA data, and 60% according to Medicaid data. At the same time, NPA data indicated substantial increases in prescribing of several other sedative-hypnotics in New York, while prescription sales of these drugs in the rest of the country declined. Meprobamate sales increased by 125% in New York versus a 9% decline in all other states combined; methyprylon increased by 84% in New York versus a 15% decline nationally; ethchlorvynol increased by 29% in New York versus an 18% decline nationally; butabarbital increased by 31% in New York versus a 15% decline nationally; hydroxyzine increased by 15% in New York versus a 1% decline nationally; and chloral hydrate sales increased by 136% in New York, while remaining substantially unchanged nationally. Medicaid and Blue Cross/Blue Shield data also reflected substantial increases in New York State prescriptions of those nonbenzodiazepine sedatives for which these programs provide reimbursements. The data from these sources also showed that prescriptions for the nonbenzodiazepine anxiolytic buspirone, as well as for the antidepressant medication fluoxetine, increased by significantly greater extents in New York than in other states in 1989.

As the investigators noted, the patterns of substitution reflected in these data represent a negative impact of the New York regulation, because the nonbenzodiazepine sedatives may not be as effective as the benzodiazepines and in most cases pose clearly greater liability for abuse as well as toxic potential in overdose. In addition, because these alternative medications have not been prescribed in sufficient quantities to compensate entirely for the reduction in benzodiazepine prescriptions, this "may indicate undertreatment of clinically significant anxiety and insomnia, which have their own adverse effects."

Another analysis of the effect of the New York regulation was undertaken by Shader et al. (1991), who also examined NPA data of prescription sales in New York as compared with the rest of the nation. These investigators found that prescriptions for benzodiazepine tranquilizers declined in 1989 by 48% in New York as opposed to 5% nationally and that prescriptions for benzodiazepine hypnotics declined by 50% in New York as opposed to 10% nationally. At the same time, sales of meprobamate increased by 129% in New York, as opposed to a 10% decline nationally; sales of hydroxyzine increased by 18% in New York, as opposed to practically no change nationally; and sales of intermediate-acting barbiturates increased by 27% in New York, as opposed to a 15% decline nationally. Also, sales of nonbenzodiazepine hypnotics (secobarbital, pentobarbital, chloral hydrate, ethchlorvynol, glutethimide, methyprylon) increased by 87% in New York, as opposed to a 13% decline nationally. The authors commented: "Without question, numerous residents of New York State are being deprived of appropriate treatment, with the consequent cost in unnecessary human suffering and risk. . . .The concurrent increase in prescribing of older, less effective, and more hazardous 'substitute' medications is a direct consequence of benzodiazepine regulation, and in effect represents an 'unlearning' of more than three decades of clinical and scientific experience."

In another analysis of the effect of the New York regulation, Reidenberg (1991) examined data from the Geographic Prescription Services of IMS America, Ltd., study and also found increases in prescriptions of alternative medications in New York, of a similar pattern to that found in the studies described above.

4. Study of effects on overdoses. Hoffman et al. (1991) analyzed data concerning the incidence and severity of overdoses of benzodiazepines and of other sedative-hypnotics that were reported to the New York City Poison Control Center in 1988 and 1989. The nonbenzodiazepine category included chloral hydrate, ethchlorvynol, glutethimide, meprobamate, and methaqualone; barbiturates were excluded. Between 1988 and 1989, the incidence of benzodiazepine overdoses significantly declined, whereas the incidence of nonbenzodiazepine overdoses

significantly increased; the total number of overdoses with these drugs was virtually unchanged. There was no significant change in the severity of clinical outcomes of overdoses. However, the investigators pointed out that poison center data over time had demonstrated more severe toxicities in overdoses with nonbenzodiazepine sedative-hypnotics than with benzodiazepines; they suggested that substitution of these agents for benzodiazepines might therefore ultimately result in more consequential outcomes of sedative-hypnotic overdoses.

5. Summary and discussion. Preliminary evidence of the effects of a New York State regulation of benzodiazepine prescriptions indicates that many physicians reduced or discontinued such prescriptions for patients who had been receiving benzodiazepine treatment. Immediate clinical effects included the reemergence of anxiety disorders that had been controlled with these drugs, the emergence of symptoms of withdrawal, and related psychiatric and medical emergencies. No evidence has yet been reported regarding possible long-term effects in patients who had been receiving benzodiazepine treatment at the time the regulation became effective.

The total number of benzodiazepine prescriptions issued by physicians in the state declined by 40% to 50% in the year following implementation of the regulation. At the same time, prescriptions substantially increased for a number of nonbenzodiazepine drugs, which physicians apparently issued as substitutes for benzodiazepines. There is no evidence to date regarding the actual consequences of these substitutions. However, as clinical authorities have pointed out, it is unlikely that most of these substitute drugs are as effective as the benzodiazepines for treatment of the same disorders, and all pose greater toxic risks.

In the year following implementation of the state regulation, benzodiazepine overdoses in New York City significantly declined, whereas overdoses of other sedative-hypnotic drugs significantly increased. There was no overall change in the number of sedative-hypnotic overdoses.

These findings are similar to those reported from a study of overdoses in the year before and the year after barbiturates were withdrawn from the market in Norway. A significant decline in overdoses with barbiturates was accompanied by a significant increase in overdoses with antidepressants and neuroleptics; the net effect was no change in the total number of overdoses. Ekeberg et al. (1987) also found in this study that, among drug abusers as well as nonabusers, a significant increase in rates of those who obtained licit psychoactive drugs from nonmedical sources. They noted that this increase "probably also reflects the general trends in illegitimate drug use."

Based on our review of the evidence concerning the use and abuse of benzodiazepines, we have argued that it is important to ensure the availability of these drugs for their intended therapeutic purposes and that increased restrictions on their use are more likely to jeopardize than to safeguard the public health. Although it is too early to evaluate the full range of effects of the recent regulation of these drugs in New York State, the findings of studies to date represent persuasive support for this argument.

VI. General Summary and Discussion

Sedatives and hypnotics have accounted for a substantial and relatively stable fraction of all drug sales, at least in the United States, since the earliest records became available more than 100 yr ago. As we have noted previously (Woods et al., 1987), this is probably a function of the enduring prevalence of the illnesses that these drugs are used to treat. Benzodiazepines have come largely to fill this pharmacological niche in virtually all Western nations as well as in many Eastern and third-world countries. They have gained widespread clinical acceptance because of their efficacy in treatment of many common disorders and because they are markedly safer than earlier drugs used for these purposes.

This success has inevitably and increasingly attracted attention to the risks associated with the extensive use of the benzodiazepines, especially those related to their liability for abuse. In our previous review, we concluded that the benzodiazepines have limited liability for abuse: They can produce physiological dependence, but this is not usually accompanied by the reinforcing effects characteristic of "addiction." They occasion negligible misuse in the general population and little preference among drug abusers. With respect to overdose, the benzodiazepines stand in marked contrast to benchmark drugs of abuse; the frequency with which they are found in overdose cases is not disproportionate to their overall availability, and they are dramatically less toxic in overdose than typical drugs of abuse, as well as most other therapeutic drugs.

Nevertheless, in some instances, attention has focused on the risks associated with use of benzodiazepines at the expense of concern for the medical and psychiatric needs that they serve, leading to policies that limit their availability. We do not wish here to argue the appropriateness of specific regulations but to emphasize the need to regard their extensive use not as cause for alarm and hasty intervention but as an impetus to the most careful, thorough, and balanced scientific assessment. As we shall discuss, we already have at least conceptual seeds for the next generation of drugs that may permit effective treatment of anxiety and insomnia with even less risk; however, as Daniel X. Freedman (1990) has written, "until that sought-after day comes, we have in hand the benzodiazepines with a high therapeutic index, a wide window between anxiolysis and hypnosis, and, in view of the testimony of 86,000,000 annual prescriptions [in the United States alone], with an obvious value and utility

in both psychiatry and medicine. We have no ethical choice at present but to pursue the rare but bothersome problems with these drugs to make their use as rational and safe as possible and to keep society as reliably informed as possible. In any event, we cannot leave the job of defining the rational use of medicines to a vacuum that ignorance and the convenience of prejudice inexorably rush to fill."

In our previous review of the evidence regarding the abuse liability of benzodiazepines, we discussed the most important research published through 1985. The current review was motivated in part by our recognition that research in this area was growing rapidly; still, we were surprised to find that the literature had actually almost doubled between 1985 and 1990. Obviously, interest in pursuing "the rare but bothersome problems with these drugs" is alive and well.

In the current review, we have regarded the conclusions of our previous review as hypotheses to be evaluated in the light of the more recent evidence concerning these matters. To the extent that our earlier conclusions withstood this test, we consider that they are substantially strengthened. To the extent that they failed to withstand this test or proved to need substantial refinement or revision, they nevertheless serve as indicators of the evolution of our understanding of these matters and, by doing so, enhance our confidence in our current findings.

A. Epidemiological Findings

In view of the extensive worldwide experience with benzodiazepines during the past 30 yr, it is epidemiology—the study of the actual use of these medications—that should serve as our most important guide in assessing their risks, including their liability for abuse. This approach seems particularly appropriate in view of the remarkable agreement among a great many diverse sources of information about how these drugs are used. This permits an extraordinary degree of confidence in the reliability of the patterns described.

1. Frequencies of use. One of the clearest and most important points that emerges from review of this evidence is that there is considerable variation in frequencies of use of benzodiazepines across geographic areas. First, the absolute prevalence of use of these drugs in community samples varies widely across national and regional populations. Also, the frequency of use of benzodiazepines, as against other anxiolytics and hypnotics, still varies substantially across geographic areas; within the benzodiazepine class, the patterns of favoritism for particular agents are also widely varied across areas of the globe. Some of these patterns are dictated by relatively obvious factors, such as national regulations; others remain very much in need of explanation.

Enmeshed within the geographic variations in benzodiazepine use are striking similarities in the patterns of use within populations. In virtually every population studied, including both community and clinical samples, women receive about twice as many prescriptions for these drugs as men; also, use of anxiolytics increases to a peak prevalence in people aged about 50 to 65 yr and declines somewhat in older people, whereas use of hypnotics is most frequent in the oldest age range.

Certain shifts in the use of benzodiazepines have emerged across geographic areas. These shifts are seen most clearly in the United States and some western European nations, which have historically led global trends in drug use. Although use of anxiolytics has declined in many countries in recent years, use of hypnotics has remained stable or increased. At the same time, there has been a dramatic increase in use of the newer benzodiazepine anxiolytics and hypnotics, particularly those with short elimination half-lives, at the expense of an approximately proportional decline in the use of the older compounds, particularly those with long half-lives.

2. Use among the elderly. In accord with the findings mentioned before, prescriptions filled by elderly patients account for a disproportionately large fraction of benzodiazepine prescriptions. Because of the growing recognition of this fact, the last few years have brought a great increase in epidemiological information about various aspects of the use of benzodiazepines, and of psychoactive medications in general, among elderly populations. Some of these studies have shown, for example, that older patients who receive prescriptions for benzodiazepines are less likely to have psychiatric diagnoses than are younger patients who receive prescriptions for these drugs; the prescriptions for older patients are less likely to be completely documented, and the reasons for such prescriptions are less likely to be reflected in the prescribers' case notes. On the other hand, studies in which elderly people are interviewed specifically about their mental health status indicate that those who receive prescriptions for benzodiazepines suffer higher levels of psychological distress than those who do not receive such prescriptions. These apparently paradoxical findings parallel evidence from psychiatric epidemiology, which indicates that certain disorders, including anxiety and sleep disorders, are particularly prevalent among the elderly but that, for a variety of reasons, older patients are less likely than younger patients to define their problems in psychological or emotional terms so that these problems are less likely to be diagnosed.

Elderly patients who receive benzodiazepine prescriptions are also distinguished from younger users of these drugs, and from nonusers, in that they are more likely to have multiple chronic physical disorders. Accordingly, they are also more likely to have prescriptions for concurrent use of multiple medications. Evidence from various sources suggests that benzodiazepine prescriptions for elderly patients, especially prescriptions for benzodiazepine hypnotics, appropriately tend to specify lower daily dosages than prescriptions for younger patients.

Interview surveys have made it clear that older patients are significantly more likely than younger patients to use benzodiazepines on a daily basis and to continue to use these drugs for long periods of time, often for years. In typical community surveys, as well as in surveys of outpatient populations, about 15% to 20% of people 65 yr or older report current or recent use of benzodiazepines, and the majority of these people report having used these drugs regularly for 12 mo or longer. This is a matter of concern.

3. General conclusions. Results of recent research have supported the general conclusions of our previous review of the epidemiology of benzodiazepine use and abuse. As we had concluded, actual use of anxiolytics is generally appropriate, in that users surveyed in the community report high levels of emotional distress. Patients who receive prescriptions for benzodiazepine anxiolytics tend to take less of the medication than prescribed and to decrease their intake over time. Despite the wide availability and extensive medical use of benzodiazepines, there is very little misuse or recreational use of the drugs among adults or youth in the general population. To this last conclusion, we can now add that periodic surveys in the United States indicate that rates of nonmedical use in all age groups have decreased significantly in recent years.

As we noted previously, benzodiazepines are found with some frequency in overdose surveys, usually in combination with other drugs. When the frequency of overdose cases is examined in relation to the volume and patterns of prescriptions, the frequency of cases involving benzodiazepines is substantially lower than that of other prescribed drugs, e.g., analgesics, and the relative frequency of cases involving individual benzodiazepines is generally proportional to their respective medical availability. Recent survey data from the United States indicate that the frequency of overdoses involving benzodiazepines has substantially declined in recent years. These drugs are rarely implicated in fatal overdoses. Overdoses involving benzodiazepines are most likely to result from suicide attempts rather than accidental consequences of recreational use; in this respect, these overdoses are like those typical of other psychotherapeutic agents and distinct from those typical of benchmark drugs of abuse.

Information from epidemiological studies of benzodiazepine use and abuse helps to focus the following discussion of the findings of our review of other research relevant to the abuse liability of these drugs.

B. Physiological Dependence

One of the major concerns reflected in the benzodiazepine literature of the last decade is the risk of physiological dependence developing at therapeutic doses. Whereas interest in this subject has gained increasing currency in the past few years, our understanding of this risk has unfortunately not advanced appreciably, as we shall discuss.

As we noted in our previous review, physiological dependence can be shown to develop to benzodiazepines evaluated at high doses; this general finding is now primarily of historical importance. In recent animal studies, dependence has been detected at smaller doses than those traditionally examined; however, the doses used have not been related to doses recognized as therapeutic in humans. Neither animal nor human research has demonstrated differences among benzodiazepines with respect to the risk of development of such dependence. Clinical studies continue to demonstrate that gradual discontinuation, or tapering, of benzodiazepine treatment reduces the intensity of withdrawal in dependent patients, but no tapering regimen has been shown to eliminate signs and symptoms of withdrawal completely.

1. Pharmacokinetic factors. Findings of recent studies in humans leave little doubt that withdrawal from benzodiazepines with short elimination half-lives is more intense than withdrawal from the long-acting compounds. This difference takes on special significance with the recognition that actual consumption of benzodiazepines has shifted dramatically in favor of the newer short-acting drugs. Moreover, as use of these short-acting drugs has increased, clinical reports have raised the specter that dependence and withdrawal may occur on a daily basis with some of these compounds. It has been suggested, for example, that once-daily administration of triazolam as a hypnotic, even during short periods of treatment, may produce daytime anxiety and other effects that are not seen following administration of other benzodiazepines.

These reports raise a number of questions. For example, are these effects common to short half-life benzodiazepines, or are they peculiar to triazolam? This question can certainly be pursued by dose-effect studies and comparisons among different compounds. Is this apparent interdose anxiety analogous to the rebound phenomena that have been observed following administration of some benzodiazepines? Recent studies of such phenomena have presented no serious challenges to the view that they are manifestations of withdrawal, and recent sleep-laboratory research has generally supported the conclusion that rebound insomnia is a liability of short-acting but not of long-acting benzodiazepine hypnotics. However, the recent literature reveals more discrepancies than the earlier literature as to whether rebound insomnia follows administration of short half-life compounds; these discrepancies need to be examined in greater detail.

2. Clinical significance. As we noted previously, the available evidence points most clearly to the duration of administration as a risk factor for development of physiological dependence to benzodiazepines. Although it is still the case that the majority of benzodiazepine users in most countries surveyed use these drugs for relatively

short periods of time, a substantial and perhaps increasing subgroup of users of both anxiolytics and hypnotics reports having used them for 12 mo or longer. These long-term users are most frequently older patients, who are also likely to have multiple chronic physical diseases. In these characteristics, they are clearly distinct from the population of recreational users of sedatives, and they are not likely to increase their dosage or otherwise use their medications inappropriately. However, it is these patients who appear to be at greatest risk of physiological dependence.

For some monitors of drug use, this risk alone represents sufficient reason to restrict the use of benzodiazepines to cases of great need, for which they should be used only for very short periods, and to advise patients and physicians to take steps to terminate any use that has continued for more than a few weeks. This response to the risk of physiological dependence on benzodiazepines appears irrational in light of the findings of both our previous review and the present review, which indicate that this risk is, in fact, not a particularly severe one with respect to the specific consequences likely to ensue from termination of therapeutic doses; moreover, some recent evidence suggests that symptoms of withdrawal may be least severe in the population at greatest risk of dependence, the elderly. In any case, to suggest that this risk alone is sufficient to prohibit long-term use, without regard for the benefits that might accrue in some cases, amounts to moralizing about dependence itself as a consequence to be avoided at all costs. The preferred course is for the physician to balance benefits and risks of continued treatment, recognizing that some patients may do better without long-term treatment, whereas others may continue to benefit.

3. Research needs. a. RISKS AND BENEFITS OF LONG-TERM USE. We have argued that the individual practitioner is in the best position to judge the merits versus the risks of continuing to prescribe a benzodiazepine for his or her patient, and we have added here that he or she should not be counseled to regard the risk of physiological dependence alone as an absolute contraindication. On the other hand, there is a good deal not yet known about long-term use of benzodiazepines that could valuably inform this clinical judgment. Why do some patients apparently require long-term benzodiazepine treatment? There is some evidence suggesting that long-term users continue to derive benefit from this use; on the other hand, there is also some evidence to suggest that self-administration may be sustained by physiological dependence on these drugs. It may be that both of these possibilities obtain for the same or for different patients. The evidence for each of these possibilities needs a great deal more substantiation and elaboration.

Certainly, we have an immense body of knowledge about many of the effects of benzodiazepine anxiolytics and hypnotics. In contrast, the paucity of information concerning the effects of chronic treatment in humans stands out as a glaring deficiency in our knowledge, particularly in view of the numbers of patients who do use these drugs regularly for months or years. The methods for measuring the therapeutic efficacy of anxiolytics have been developed, tested, and refined for decades. It may be that our standard instruments apply best to the study of the relatively short-term changes they were designed to measure and that new techniques may be required to study efficacy during longer periods of use, but the simple fact is that we have hardly even begun to try our available methods for this purpose. With respect to the possibility that long-term use might be explained by physiological dependence, much of the evidence is anecdotal. Only a few controlled studies have approximated direct measures of whether dependence might sustain self-administration, of which probably the best was that conducted by Cappell et al. (1987). Although not definitive in itself, this study provides an important model for further research into the significance of the risk of physiological dependence associated with long-term use.

Epidemiological data indicate that, although use of anxiolytics has declined in some populations, use of benzodiazepine hypnotics has remained stable or increased. This pattern of benzodiazepine use presents a set of phenomena clearly different in many respects from that associated with use of anxiolytics. Yet, with the exception of research on rebound insomnia, there has been virtually no independent study of benzodiazepine hypnotics in the context of the risk of physiological dependence. Although clinicians are routinely advised that it has not been shown that these drug remain effective for periods longer than a few weeks, epidemiological evidence overwhelmingly demonstrates that chronic use is more the rule than the exception, especially among the elderly. As Kripke (1985) has noted, "Considering that most hypnotic prescriptions are in fact consumed by chronic users taking hypnotics for more than 4 mo continuously, the previous focus [of research] on short-term use has been misplaced."

Many authors appear to share Kripke's view that "long-term use of benzodiazepines may not in fact grant the patient any benefit. Patients might maintain their habituation to hypnotics merely to avoid the discomfort of withdrawal effects." However, both of these possibilities, regarding the benefits of long-term hypnotic use and the influence of physiological dependence on maintenance of this use, remain hypotheses to be tested. As is the case for benzodiazepine anxiolytics, there is simply insufficient evidence at present on which to base conclusions about the possible benefits of long-term use of benzodiazepine hypnotics, and it is not clear that available methods for such research, which were designed to study the effects of short periods of administration, are adequate for evaluation of the effects of chronic use. The

innovative research that seems to be required to evaluate the efficacy of long-term hypnotic use might also lead to insights into ways to improve the benefits of such use; for example, some patterns of intermittent use might prove more effective than nightly use during long periods. With respect to the risks of physiological dependence associated with chronic hypnotic use, certainly animal studies could provide some important information; for example, they could help to elucidate the differences in dependence potential between chronic administration of multiple daily doses of "anxiolytic" potency and chronic administration of single daily doses of "hypnotic" potency.

b. DETERMINANTS AND PREVENTION OF PHYSIOLOGICAL DEPENDENCE. Some of the earliest clinical studies to demonstrate physiological dependence to benzodiazepines at therapeutic doses also demonstrated that not all patients chronically exposed to the drugs became dependent; estimates of the proportion of dependent patients varied widely. More recent studies have tended to confirm the finding that not all patients become dependent following chronic administration, without providing much more information about the relative proportions who do or do not become dependent.

What are the critical differences between patients who do and do not develop physiological dependence to benzodiazepines? Research to date has provided only some suggestions of variables that might be explored, not significant empirical leads toward an understanding of these differences. Systematic exploration for the possible determinants of dependence development would, of course, entail examination of a broad array of factors, including conditions of treatment as well as patient characteristics. However, if dependence is regarded as a significant risk, studies of this kind are surely indicated in the hope of identifying potential means of intervention; for example, in addition to identifying particular types of patients at special risk of developing dependence, it might be possible to tailor treatment for individual patients in such a way as to reduce this risk.

In general, whereas there has been a great deal of attention to the frequency of long-term use of benzodiazepines and to the attendant risk of physiological dependence, there has been little consideration of avenues of research into ways by which dependence might be prevented from the onset of treatment. At least two approaches have been suggested, each of which deserves much more investigation in both animal and human studies. One is the occasional interruption of treatment, either with temporary reductions in dosage or with "drug holidays," as many clinical authorities have recommended. A second approach, which is a simple extension of animal studies conducted by Gallager and her colleagues (1986), would entail the occasional administration of a benzodiazepine antagonist, the assumption being that this would essentially "reset the clock" for the initiation of dependence. Although both of these approaches may prove effective in modulating the development of dependence, we simply do not have enough information about them. It has not been shown under controlled conditions, for example, that drug holidays actually do prevent or retard the development of dependence. Under what conditions might they be more or less effective? If we knew the schedule of drug holidays that might most effectively modulate dependence induction, how would application of this schedule affect therapeutic benefit and, ultimately, alter the benefit to risk ratio? These questions will have to be addressed with individual compounds both in animal experiments and in clinical studies.

c. NEED FOR A SYSTEMATIZING THEORY. Experimental studies of physiological dependence on benzodiazepines have attained a level of considerable technological sophistication; at the same time, research in this area at present appears rather fragmented and in need of systematization. At this juncture, both human and animal research might gain from the formulation of a theory of benzodiazepine dependence based on the work that has been done to date. This could provide an organizing set of principles and priorities for pursuing the many important questions that remain to be addressed.

C. Reinforcing Effects

Epidemiological studies of various populations of drug abusers have often found rates of nonmedical use of benzodiazepines that exceed those found in the general population; studies of opiate users and methadone users, as well as alcoholics, indicate that benzodiazepines are used with some frequency in these populations. However, studies of different drug-abusing groups provide diverse and ultimately incomplete characterizations of the reasons for benzodiazepine use and the patterns and consequences of this use. This deficiency is in large part an inevitable result of the limitations of epidemiological methods with respect to the population of drug abusers.

A significant contribution to filling this gap can be made by experimental research in both animals and humans. Indeed, as discussed in our previous review, the results of experiments in human self-administration have paralleled the epidemiological findings in that normal subjects show virtually no reinforcing effects of benzodiazepines, whereas subjects with histories of sedative abuse demonstrate some preference for high doses of these drugs. Along similar lines, although most animal studies have not shown robust reinforcing effects of benzodiazepines, some studies have demonstrated that self-administration of benzodiazepines can be obtained in animals that previously self-administered other sedative drugs. These findings present a promising approach to further research that could help to elucidate the types of drug use histories that might increase susceptibility to psychological dependence to benzodiazepines.

However, research has not advanced very rapidly in pursuit of this or other outstanding questions that can most effectively be addressed in animal studies. For example, apart from the influence of pharmacological history, another significant question that needs to be pursued in animal research is the influence of physiological dependence on the reinforcing effects of benzodiazepines. Progress in human experimental studies of the reinforcing effects of these drugs has also been disappointing. Procedures for directly examining drug-taking behaviors in humans, analogous to those used in animal research, were developed more than a decade ago. The potential of these procedures has not been broadly realized, probably because such studies are time-consuming and expensive. However, to provide a substantial empirical framework for the analysis of reinforcing effects in human populations, this technology simply must be applied more widely. Finally, we should reiterate here the concern we expressed previously, that studies of reinforcing effects in humans should use direct measures of drug-taking behavior rather than measures of subjective effects assumed to reflect equivalent phenomena; based on our current knowledge, and particularly in view of the limited resources for this research, we cannot afford to rely on such assumptions.

Some investigators, particularly of sedative abusers, have found differences among individual benzodiazepines with respect to subjective effects or to preference for one compound over another. As we noted in our previous review, these findings represent intriguing suggestions that might prove important if they prove to be reliable and generalizable to other experimental conditions and other subject populations. However, these suggestions have not been systematically pursued. More recent research has provided new suggestions regarding possible differences of these kinds. These new suggestions are also of possible importance and deserve further study. At present, however, there is insufficient evidence on which to base assumptions that the benzodiazepines vary with respect to their overall liability for abuse or dependence.

Moreover, the significance of experimental findings of this kind must be weighed against the increasing information available from epidemiological studies of benzodiazepine use among drug-abusing populations. These studies in general find that polydrug abuse has become the predominant pattern. Although benzodiazepines are frequently among the drugs abused, they tend not to be primary drugs of abuse, and findings of a number of studies suggest that at least some abusers use benzodiazepines to prevent or treat withdrawal from other substances. It is particularly relevant to the interpretation of experimental findings that the specific benzodiazepines used among polydrug-abusing populations vary considerably, reflecting relative availability and other factors; there is little support in these studies for any particular preference for individual agents across populations of abusers. In this context, it might be recalled that a number of studies of clients of methadone programs in the United States had suggested that these patients had a particular preference for diazepam; more recent studies of methadone users, in the United States and other countries, indicate use of a considerable variety of benzodiazepines, in patterns of frequency that tend to reflect availability.

A promising new approach for experimental research derives from a recent study by De Wit et al. (1989a), who found a preference for benzodiazepines among subjects with histories of moderate alcohol consumption. Further studies of these subjects, who may represent a bridge between the normal population and sedative abusers, might help to clarify the characteristics that make some people and not others susceptible to benzodiazepine abuse. Certainly moderate drinkers represent a more relevant population for research than that of sedative abusers, if only because there are so many more moderate drinkers and because they share so many more characteristics of the general population.

In addition, the frequency with which benzodiazepine use is found in alcoholic populations raises a number of questions that might be explored with other research designs. For example, the histories of these individuals should be analyzed in extensive detail in the effort to estimate the relative contributions of alcohol and benzodiazepine exposure to the state of "dual dependence" in which they are found. Other research might consider genetic contributions. The contemplation of studies in this area presents a challenge to conventional drug abuse research, in that researchers who have traditionally studied alcohol abuse have generally not studied abuse of benzodiazepines or other drugs and vice versa; however, the apparent links between alcohol and benzodiazepine abuse are certainly of sufficient importance to command interdisciplinary attention.

D. Effects on Performance

Of the types of research on the effects of benzodiazepines on performance, the greatest advances in knowledge since our previous review have been made in studies of the effects of these drugs on recall. Increased sophistication in the methods of these studies, derived in part from increased understanding of the dysfunctions of recall in general, has made it possible reliably and consistently to demonstrate that these are relatively robust effects. As we found in our previous review, the evidence indicates that acute doses of benzodiazepines can impair recall; the evidence seems particularly clear with respect to delayed recall. Recent research has focused more on the effects of these drugs in chronic administration. Probably the most definitive study of this kind was that conducted by Lucki and Rickels (1988), who found that chronic users experienced impairment of delayed recall

during relatively short periods of time following each dose.

As we found in our previous review, laboratory studies tend to show that acute administration of therapeutic doses of benzodiazepines can produce significant decrements in psychomotor performance among normal subjects, as well as anxious and insomniac subjects. Recent studies have provided more documentation that some of these decrements may be sustained with chronic dosing. However, despite the large number of such experiments, there is remarkably little consistency in findings with respect to the specific types of performance most likely to be affected or to the specific agents most likely to produce these effects.

As we had found in our previous review, laboratory studies of real or simulated driving have demonstrated that benzodiazepines can produce decrements in this performance. Although several studies in the last few years have continued to demonstrate such decrements, there has been no real progress toward answering the question of whether or to what extent benzodiazepines contribute to the risk of automobile accidents. The significance of these findings remains unclear in the absence of adequate evidence from case-controlled surveys of drivers involved in accidents. In addition, to determine whether the use of benzodiazepines contributes to the risk of accidents, it will be necessary to establish the risk of withholding benzodiazepine treatment from patients who might benefit from this medication, e.g., what is the contribution of untreated anxiety to the risk of automobile accidents?

A number of recent epidemiological studies have examined the risk of non-driving-related accidents among elderly populations. Results of some of these studies have suggested that use of benzodiazepines, and particularly of benzodiazepines with long elimination half-lives, may increase the risk of falls and/or hip fractures in elderly patients. The studies are inconsistent with respect to the statistical significance of this risk. More important, many of these studies have identified a variety of other factors prevalent among elderly patients that may increase this risk as much as or more than benzodiazepines do, including the use of other psychoactive and nonpsychoactive drugs, as well as physiological and medical conditions, especially neurological impairment. Each of these factors can contribute independently to the risk of falls, and each can interact with the others, including the use of benzodiazepines.

In summary, this research suggests that, in some circumstances, benzodiazepines can contribute to the risk of falls among elderly patients. The extent of the contribution made by benzodiazepines alone is certainly not sufficient to contraindicate use of these drugs in elderly patients in general. However, this possible influence of benzodiazepines should be considered by physicians, in the context of the other factors affecting the individual patient, in calculating the risks versus the benefits of prescribing these drugs.

E. New Leads in Development of Anxiolytics and Hypnotics

Pharmacological research into the mechanisms of the actions of benzodiazepines has been largely responsible for a number of conceptual leads toward development of compounds that could improve treatment of anxiety and/or insomnia, by reducing or eliminating the problems associated with the benzodiazepines' abuse liability. For example, the discovery of buspirone led to the concept that anxiety might be modulated by mechanisms divorced from the benzodiazepine receptor. Although buspirone has been shown to have some anxiolytic properties, it is far from clear that these are equivalent to those of benzodiazepines in clinical practice; nevertheless, the compound is of interest in that it appears to have even lesser effects related to abuse liability than the benzodiazepines.

It has been proposed that there are variations in the ways that ligands bind with benzodiazepine receptors and that these variations may be associated with different behavioral and physiological effects. One compound thought to act through a novel benzodiazepine receptor is zolpidem, which has been marketed in some countries as a hypnotic; the animal pharmacology associated with the mechanism of action of zolpidem has been described. There has been less characterization, largely because it is newer, of the β-carboline derivative, abecarnil, which appears either to act through a novel benzodiazepine receptor or to have a reduced efficacy at benzodiazepine receptors; in animals, this compound appears to share the anxiolytic, muscle relaxant, and anticonvulsant properties of the benzodiazepines. Another interesting compound is bretazenil, which operates as a partial agonist at benzodiazepine receptors. Bretazenil and abecarnil are claimed to have reduced abuse liability, with no reinforcing effects in animals, and to produce less intoxication at high doses, in comparison with full benzodiazepine agonists.

The next decade of research on pharmacological treatment of anxiety and sleep disorders will no doubt clarify the usefulness of these substances for their potential therapeutic advantages.

F. Conclusion

In the present review, as in our previous review of this subject, we have evaluated the evidence regarding the abuse liability of benzodiazepines, in part, in the context of epidemiological information concerning the actual use and misuse of this important group of medications. This information has consistently revealed that the preponderance of the extensive use of benzodiazepines is directed by physicians for the treatment of disorders in which these drugs have proven therapeutic effect and that the vast majority of people actually using these

drugs are, in fact, suffering from these disorders and are using these medications as prescribed. Epidemiological studies have also identified areas of concern, including long-term use that may lead to physiological dependence in a substantial minority of patients and some abuse among polydrug abusers, which warrant further examination.

However, misuse among the general population of adults and youth is trivial. There has been no indication of any increase in misuse of benzodiazepines in any region of the world, and an important set of findings from recent periodic surveys in the United States is that there have been significant declines in indices of misuse among the general population, at all age levels, and among the drug-abusing population. With respect to their involvement in overdoses, benzodiazepines are remarkably safe, certainly one of their greatest advantages over older classes of sedative-hypnotics.

These epidemiological findings are closely paralleled in experimental research in animals and humans, which indicates that the benzodiazepines have little or no reinforcing effects in most subjects, although some reinforcing effects can be demonstrated in subjects with histories of self-administration or abuse of other sedative drugs.

In assessing the risks posed by the benzodiazepines, one must consider the risks of the alternatives. With regard to other therapeutic modalities, including other pharmacological approaches, there is simply no alternative that has been shown as broadly effective as the benzodiazepines. On the other hand, epidemiological research has shown that the great majority of people suffering anxiety or insomnia go without treatment; this implies a clear risk of undertreatment of disorders that can certainly provoke as much or more discomfort and disability as the worst adverse effects of the benzodiazepines and in a much greater number of people.

Thus, it is clearly inappropriate to cite the benzodiazepines' abuse liability as a reason to further limit prescriptions for these drugs. The error of this narrow reasoning is exemplified by the recent restriction of benzodiazepine prescribing in New York State, which led physicians to prescribe less effective and more hazardous older drugs for some patients and to leave other patients without treatment of any kind; this ill-considered action by public health authorities has thus clearly endangered the public health (Weintraub et al., 1991; Shader et al., 1991; Glass, 1991). It is time to refocus our attention on more important problems, namely, the medical and psychiatric disorders for which these drugs represent the best available treatment.

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APPENDIX: *Individual studies summarized in tables in section IV.B**

Reference	Drug	Dose (mg)	Days	CFF	TAPP	DSST	TRAC
Aantaa et al., 1990	Triazolam	0.25		D			
Agnoli et al., 1989	Nitrazepam	5	14				
Agnoli et al., 1989	Zopiclone	7.5	14				
Altamura et al., 1989a	Lorazepam	1 (tid)	3				
Altamura et al., 1989a	Lorazepam	1					
Aranko and Mattila, 1986	Lorazepam	3		D			D
Aranko and Mattila, 1986	Lorazepam	3	7 (1 mg bid)	D			
Bensimon et al., 1990	Flunitrazepam	2		D		D	
Bensimon et al., 1990	Zolpidem	20		NE		NE	
Birch and Curran, 1990	Midazolam	4–10 (i.m.)			D		
Blom et al., 1990	Alprazolam	1		D			
Blom et al., 1990	Diazepam	10		NE			
Blom et al., 1990	Quazepam	15		NE			
Bond et al., 1991	Alprazolam	1			D	D	D
Bourin et al., 1989	Bromazepam	3		NE		NE	
Bourin et al., 1989	Clobazam	10		NE		NE	
Brosan et al., 1986	Diazepam	25 (d)	21				D
Charles et al., 1987	Nitrazepam	10		NE			
Charles et al., 1987	Temazepam	30		NE			
Chernik et al., 1990	Midazolam	5.3 (i.v.)				D	
Chernik et al., 1990	Midazolam	9.4 (i.v.)				D	
Cluydts et al., 1986	Flunitrazepam	2				D	
Cluydts et al., 1986	Triazolam	0.25				NE	
Curran et al., 1987	Lorazepam	2		NE	NE	D	
Currie et al., 1990	Oxazepam	15		NE	D	D	
Dershwitz, 1991	Midazolam	0.3 (i.v.)					
Dershwitz, 1991	Midazolam	1.0 (i.v.)					
Dershwitz, 1991	Midazolam	3.0 (i.v.)					
Duka et al., 1988	Lormetazepam	2 (i.v.)					
Dye et al., 1989	Lormetazepam	0.15		D			
Dye et al., 1989	Lormetazepam	0.15		NE			NE
Dye et al., 1989	Lormetazepam	1		D			
Dye et al., 1989	Lormetazepam	1		NE			NE
Dye et al., 1989	Lormetazepam	2		D			
Dye et al., 1989	Lormetazepam	2		NE			NE
Dye et al., 1989	Triazolam	0.5		D			NE
Dye et al., 1989	Triazolam	0.5		D			
Elie et al., 1990	Flurazepam	30 (hs)	28				
Elie et al., 1990	Zopiclone	7.5 (hs)	28				
Ellinwood et al., 1985	Alprazolam						
Ellinwood et al., 1985	Diazepam						
Ellinwood et al., 1985	Lorazepam						
Ellinwood et al., 1987	Alprazolam	2					
Ellinwood et al., 1987	Diazepam	1					

* Abbreviations are as in Table 3.

APPENDIX: *Continued*

RT	CRT	CANC	ARITH	SORT	DV-ATT	COPY	SWAY	VIG/SD	STROOP	LOG.RES	Time est	PEG
					D							
					D							
D												
D												
	D				D							
					NE							
	D											
	NE											
	D											
		D				D	D					
	NE											
	NE											
									D			
NE	NE											
NE	NE											
			D									
			D									
D	D							D				
D	NE							NE				
D						D						
	D	D						D				
								NE		D	NE	
	D											
	NE											
	D											
	NE											
	D											
	NE											
	NE											
	D											

APPENDIX: *Continued*

Reference	Drug	Dose (mg)	Days	CFF	TAPP	DSST	TRAC
Ellinwood et al., 1987	Lorazepam	4					
Ellinwood et al., 1987	Lorazepam	10					
Ellinwood et al., 1987	Lorazepam	20					
Erwin et al., 1986	Diazepam	10					NE
Eves and Lader, 1989	Diazepam	10		D	NE	D	
Eves and Lader, 1989	Diazepam	10	4	D	NE	D	
Fisch et al., 1990	Triazolam	0.25					D
Fisch et al., 1990	Triazolam	0.25					NE
Fleishaker and Phillips, 1989	Adinazolam	20				D	
Fleishaker and Phillips, 1989	Adinazolam	40				D	
Fleishaker and Phillips, 1989	Adinazolam	60				D	
Funderburk et al., 1988	Diazepam	10				D	D
Funderburk et al., 1988	Diazepam	20				D	D
Funderburk et al., 1988	Diazepam	40				D	D
Funderburk et al., 1988	Lorazepam	1.5				D	NE
Funderburk et al., 1988	Lorazepam	3				D	D
Funderburk et al., 1988	Lorazepam	6				D	D
Funderburk et al., 1989	Clorazepate	7.5				NE	NE
Funderburk et al., 1989	Diazepam	5				NE	NE
Funderburk et al., 1989	Lorazepam	1				D	NE
Galuszko, 1988a	Diazepam	10 (tid, hs)					
Galuszko, 1988b	Diazepam	10 (tid, hs)					
Galuszko, 1989	Diazepam	10 (tid, hs)					
Gentil et al., 1990	Flunitrazepam	2 (i.v.)				D	
Ghoneim et al., 1986	Diazepam	hs: 14–15 (d), 21–7	21		D		
Ghoneim et al., 1986	Diazepam	14			D		
Ghoneim et al., 1986	Oxazepam	56 (hs), 15 (d); 84 (hs), 7 (d)	21		D		
Ghoneim et al., 1986	Oxazepam	56			D		
Godtilibsen et al., 1986	Midazolam	15	7		NE		NE
Godtilibsen et al., 1986	Midazolam	15			NE		NE
Godtilibsen et al., 1986	Nitrazepam	5	7		NE		NE
Godtilibsen et al., 1986	Nitrazepam	5			NE		NE
Gorenstein et al., 1990	Triazolam	0.19		NE		NE	
Gorenstein et al., 1990	Triazolam	0.38		NE		NE	
Gorenstein et al., 1990	Triazolam	0.5		D		D	
Gótestam and Andersson, 1978	Diazepam	5					
Gótestam and Andersson, 1978	Oxazepam	15					
Greenblatt et al., 1988	Alprazolam	1				D	
Greenblatt et al., 1988	Lorazepam	2				D	
Greenblatt et al., 1988	Prazepam	20				NE	
Greenblatt et al., 1989	Flurazepam	15				NE	
Greenblatt et al., 1989	Temazepam	15				NE	
Greenblatt et al., 1989	Triazolam	0.25				D	
Griffiths et al., 1986	Flurazepam	15					D
Griffiths et al., 1986	Lormetazepam	1					D
Griffiths et al., 1986	Triazolam	0.25					D
Grunberger, 1988	Lorazepam	2		D			
Gupta et al., 1990	Triazolam	1				D	D
Hakkou et al., 1988	Loprazolam	1		D		D	
Hart et al., 1991	Alprazolam	0.25 (tid)	14			NE	
Hart et al., 1991	Buspirone	5 (tid)	14			NE	
Higgitt et al., 1986	Diazepam	5		NE	NE	D	
Higgitt et al., 1988	Ketazolam	30				NE	
Higgitt et al., 1988	Ketazolam	30	15			D	
Higgitt et al., 1988	Lorazepam	2.5				D	
Higgitt et al., 1988	Lorazepam	2.5	15			D	
Higgitt et al., 1988	Triazolam	0.5	15			NE	
Higgitt et al., 1988	Triazolam	0.5				NE	
Jansen et al., 1986	Diazepam	10		NE		D	
Jansen et al., 1988	Bromazepam	6				D	
Jansen et al., 1988	Bromazepam	12				D	
Johnson et al., 1990	Flurazepam	15				NE	

APPENDIX: *Continued*

RT	CRT	CANC	ARITH	SORT	DV-ATT	COPY	SWAY	VIG/SD	STROOP	LOG.RES	Time est	PEG
NE					D		D	NE				
NE						NE						
D						NE						
				D								
				D								
				D								
	NE											
	NE											
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	D											
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			D	D								NE
			D	D								NE
			D	D								NE
			D	D								NE
		NE		NE		D						D
		NE		D		NE						D
		NE		D		NE						D
		NE		D		NE						D
		NE				NE						
		NE				NE						
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		NE				NE						
								D				
								D				
								D				
	NE			NE								

APPENDIX: *Continued*

Reference	Drug	Dose (mg)	Days	CFF	TAPP	DSST	TRAC
Johnson et al., 1990	Flurazepam	30				NE	
Johnson et al., 1990	Triazolam	0.25				NE	
Johnson et al., 1990	Triazolam	0.5				NE	
Judd et al., 1990	Flurazepam	15 (hs)	14			NE	
Judd et al., 1990	Flurazepam	30 (hs)	14			D	
Judd et al., 1990	Midazolam	15 (hs)	14			NE	
Judd et al., 1990	Midazolam	15	14			NE	
Jurado et al., 1989	Alprazolam	0.25 (bid)	7				
Jurado et al., 1989	Lorazepam	1 (bid)	7				
Kestin et al., 1990	Midazolam	5.6 (i.v.) = avg.		D			
King et al., 1990a	Lorazepam	2.5				D	
King et al., 1990b	Temazepam	20		D		D	
King and Bell, 1990	Temazepam			D			
Kirk et al., 1990	Triazolam	0.25					
Kirk et al., 1990	Triazolam	0.5					
Kirk et al., 1990	Triazolam	0.75					
Klotz et al., 1985	Midazolam	0.005 (i.v.)					
Kroboth et al., 1987	Triazolam	0.25				NE	NE
Kroboth et al., 1988	Alprazolam	0.5 (i.v.)				D	
Kroboth et al., 1988	Alprazolam	2.0 (i.v.)				D	
Kroboth et al., 1990	Alprazolam	0.25 (tid)	4			D	
Kroboth et al., 1990	Alprazolam	0.5 (tid)	4			D	
Kroboth et al., 1990	Alprazolam	2 (bid)	4			D	
Krueger, 1986	Brotizolam	0.25	3				NE
Krueger, 1986	Flurazepam	30	3				D
Kuitunen et al., 1990	Triazolam	0.25		D		D	D
Leigh et al., 1991	Lorazepam	2.5		D	D		
Lichtor et al., 1991	Midazolam	7 (i.v.)					D
Linnoila et al., 1990b	Adinazolam	15					NE
Linnoila et al., 1990b	Adinazolam	30					D
Linnoila et al., 1990b	Diazepam	10					D
Linnoila et al., 1990a	Alprazolam	0.5					NE
Linnoila et al., 1990a	Alprazolam	2					D
Linnoila et al., 1990a	Diazepam	10					D
Lucki et al., 1990	Alprazolam	?	avg 3.2 yr				
Lundsgaard and Matzke, 1989	Lorazepam	1	10				
Lundsgaard and Matzke, 1989	Nitrazepam	5	10				
Mamelak et al., 1989	Brotizolam	0.25 (hs)	1			D	NE
Mamelak et al., 1989	Brotizolam	0.25 (hs)	14			NE	D
Mamelak et al., 1989	Flurazepam	15 (hs)	1			NE	D
Mamelak et al., 1989	Flurazepam	15 (hs)	14			NE	D
Mattila and Mattila, 1989	Diazepam	10 (bid)	8	NE		D	NE
Mattila and Mattila, 1989	Diazepam	15		D		D	D
Mattila, 1988	Diazepam	10 (bid)	8	NS	D	D	NE
Mattila, 1988	Diazepam	15		D	NE	D	D
Mattila et al., 1986	Diazepam	10.5, 21			D	D	NE
Mattila et al., 1986	Diazepam	10.5, 21			D	D	NE
Mattila et al., 1987	Diazepam	15	7	NE		D	D
Mattila et al., 1987	Diazepam	15		NE		NE	NE
Mattila et al., 1987	Diazepam	15	7	D		D	D
Mattila et al., 1987	Diazepam	15		D		D	D
Mattila et al., 1988b	Diazepam	15		D	NE	D	NE
Mattila et al., 1988a	Diazepam	15		D	D	D	D
Mattila et al., 1988a	Lorazepam	2.5		D	D	D	D
Mattila et al., 1989	Diazepam	15		D	NE	D	NE
McGlone et al., 1988	Lormetazepam	2					
McGlone et al., 1988	Oxazepam	45					
McKay et al., 1989a	Clobazam	10		NE			
McKay et al., 1989a	Lorazepam	1		NE			
McKay et al., 1989b	Buspirone	5 (bid)	8	I			
McKay et al., 1989b	Clobazam	10 (bid)	8	NE			
McKay et al., 1989b	Clobazam	10 (bid)	8	NE			

APPENDIX: *Continued*

RT	CRT	CANC	ARITH	SORT	DV-ATT	COPY	SWAY	VIG/SD	STROOP	LOG.RES	Time est	PEG
	NE			NE								
	NE			NE								
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			NE									
			NE									
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APPENDIX: *Continued*

Reference	Drug	Dose (mg)	Days	CFF	TAPP	DSST	TRAC
McLeod et al., 1988	Diazepam	5 (am) 10 (pm)	42			D	
McLeod et al., 1988	Diazepam	5				NE	
Mewaldt et al., 1986	Diazepam	20			NE		
Mewaldt et al., 1986	Oxazepam	80			NE		
Monti et al., 1989	Midazolam	15				NE	
Moser et al., 1990	Flutoprazepam	2		NE	NE		NE
Moser et al., 1990	Flutoprazepam	4		D	D		NE
Moskowitz and Burns, 1988	Diazepam	5					NE
Moskowitz and Chen, 1990	Flurazepam	45 (hs)					
Moskowitz et al., 1990	Flurazepam	15 (hs)	14				
Moskowitz et al., 1990	Flurazepam	30 (hs)	14				
Moskowitz et al., 1990	Midazolam	15 (hs)	14				
Moskowitz et al., 1990	Midazolam	15	14				
Ngen and Hassen, 1990	Temazepam	20 (hs)	7, 14	D			
Ngen and Hassen, 1990	Zopiclone	7.5 (hs)	7, 14	NE			
Nikaido and Ellinwood, 1987	Quazepam	15				NE	D
Nikaido and Ellinwood, 1987	Quazepam	30				D	D
Nikaido and Ellinwood, 1987	Triazolam	0.5				D	D
Nikaido and Ellinwood, 1987	Triazolam	1				D	D
Nikaido et al., 1987	Diazepam	5				NE	NE
Nikaido et al., 1987	Diazepam	10				NE	NE
Nikaido et al., 1987	Diazepam	15				D	D
Nikaido et al., 1990	Alprazolam	0.75				D	D
Nikaido et al., 1990	Alprazolam	0.75				D	D
Nikaido et al., 1990	Alprazolam	1.5				D	D
Nikaido et al., 1990	Alprazolam	1.5				D	D
Nikaido et al., 1990	Triazolam	0.25				D	D
Nikaido et al., 1990	Triazolam	0.25				D	D
Nikaido et al., 1990	Triazolam	0.5				D	D
Nikaido et al., 1990	Triazolam	0.5				D	D
Patat et al., 1986	Flunitrazepam	1					
Patat et al., 1986	Loprazolam	1					
Patat et al., 1986	Triazolam	0.5					
Patat et al., 1987	Clobazam	20		NE	NE	NE	
Patat et al., 1987	Diazepam	10		NE	NE	NE	
Patat et al., 1987	Lorazepam	2		NE	NE	D	
Patat et al., 1988	Diazepam	10		D	NE	NE	
Patat et al., 1991	Clobazam	10		NE	NE		
Patat et al., 1991	Clobazam	30		NE	NE		
Patat et al., 1991	Lorazepam	1		NE	NE		
Patat et al., 1991	Lorazepam	3		NE	D		
Ponciano et al., 1990	Flurazepam	30 (hs)	7, 14, 21	NE			
Ponciano et al., 1990	Zopiclone	7.5 (hs)	7, 14, 21	NE			
Preston et al., 1989b	Lorazepam	1				NE	NE
Preston et al., 1989b	Lorazepam	2				D	D
Preston et al., 1989b	Lorazepam	4				D	D
Rettig et al., 1990	Lormetazepam	1					
Rettig et al., 1990	Midazolam	15					
Rettig et al., 1990	Zopiclone	7.5					
Roache and Griffiths, 1986	Diazepam	80					D
Roache and Griffiths, 1986	Triazolam	2					D
Roache and Griffiths, 1986	Triazolam	3					D
Roache and Griffiths, 1987b	Diazepam	10				D	D
Roache and Griffiths, 1987b	Diazepam	20				D	D
Roache and Griffiths, 1987a	Lorazepam	1.5				D	NE
Roache and Griffiths, 1987a	Lorazepam	3				D	D
Roache and Griffiths, 1987a	Lorazepam	6				D	D
Roache and Griffiths, 1987a	Lorazepam	9				D	D
Roache and Griffiths, 1989a	Diazepam	80					D
Roache and Griffiths, 1989a	Triazolam	2					D
Roache et al., 1990	Lorazepam	0.53				?	
Roache et al., 1990	Lorazepam	1.05				?	
Roache et al., 1990	Lorazepam	2.1				?	
Roache et al., 1990	Lorazepam	3.2				?	

APPENDIX: *Continued*

RT	CRT	CANC	ARITH	SORT	DV-ATT	COPY	SWAY	VIG/SD	STROOP	LOG.RES	Time est	PEG
NE	D											
NE	NE											
		NE	D	D						NE		
		NE	D	NE						NE		
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D												
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NE	D		D		D			D				
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APPENDIX: *Continued*

Reference	Drug	Dose (mg)	Days	CFF	TAPP	DSST	TRAC
Roache et al., 1990	Triazolam	0.16				?	
Roache et al., 1990	Triazolam	0.32				?	
Roache et al., 1990	Triazolam	0.63				D	
Roehrs et al., 1988	Triazolam	0.5				D	D
Roehrs et al., 1986a	Flurazepam	30	9			NE	
Roehrs et al., 1986a	Flurazepam	30				NE	
Roehrs et al., 1986a	Temazepam	30	9			NE	
Roehrs et al., 1986a	Temazepam	30				NE	
Saarialho-Kere et al., 1986	Diazepam	17.5		D		D	
Saletu et al., 1990	Lorazepam	2		D			
Saletu et al., 1990	Suriclone	0.2		D			
Saletu et al., 1990	Suriclone	0.4		D			
Sanders et al., 1989	Diazepam	10.1 (i.v.)		NE			
Sanders et al., 1989	Midazolam	6.2 (i.v.)		D			
Schaffler and Klausnitzer, 1988	Diazepam	5					
Schaffler and Klausnitzer, 1989a	Bromazepam	2 (tid)					
Schaffler and Klausnitzer, 1989a	Bromazepam	6					
Schaffler and Klausnitzer, 1989a	Buspirone	5 (tid)					
Schaffler and Klausnitzer, 1989b	Midazolam	10					
Schaffler and Klausnitzer, 1989b	Midazolam	30					
Schaffler et al., 1989	Quazepam	15					NE
Schaffler et al., 1989	Quazepam	15	21				D
Schneiderman et al., 1989	Lorazepam	2					D
Schuckit et al., 1991	Diazepam	14 (i.v.)					
Schuckit et al., 1991	Diazepam	8.4 (i.v.)					
Seppala et al., 1986	Diazepam	10		D			NE
Seppala et al., 1986	Lorazepam	2.5		D			D
Smith and Kroboth, 1987	Alprazolam	0.25/h (7 am–10 pm)	4			NE	
Smith and Kroboth, 1987	Alprazolam	0.25/h (7 am–10 pm)				D	
Smith and Kroboth, 1987	Alprazolam	1 (qid)				D	
Smith and Kroboth, 1987	Alprazolam	1 (qid)	4			NE	
Smith and Kroboth, 1987	Alprazolam	2 (bid)	4			NE	
Smith and Kroboth, 1987	Alprazolam	2 (bid)				D	
Sostmann et al., 1989	Midazolam	3.75		D		NE	
Sostmann et al., 1989	Midazolam	7.5		D		D	
Sostmann et al., 1989	Midazolam	15		D		D	
Sostmann et al., 1989	Triazolam	0.25		D		D	
Steib et al., 1990	Lorazepam	2		NE	D	D	D
Stevenson et al., 1986	Diazepam	7.5 (i.v.)					D
Subhan et al., 1986	Alprazolam	0.5 (tid)	6	NE			NE
Subhan et al., 1986	Alprazolam	0.5		D			NE
Subhan et al., 1986	Lorazepam	2 (tid)	6	NE			D
Subhan et al., 1986	Lorazepam	2		D			D
Sunderland et al., 1989	Lorazepam	1					
Tazaki et al., 1989	Nitrazepam	5					
van Steveninck et al., 1990	Temazepam	5					D
van Steveninck et al., 1990	Temazepam	10					D
van Steveninck et al., 1990	Temazepam	20					D
van der Meyden et al., 1989	Clobazam	20		NE			
van der Meyden et al., 1989	Clonazepam	2		D			
Warot et al., 1987	Triazolam	0.25		D		D	
Wickstrom et al., 1989	Flunitrazepam	1			D		
Wickstrom et al., 1989	Triazolam	0.25			D		
Wildin et al., 1990	Clobazam	10		NE		NE	
Wildin et al., 1990	Clobazam	20		D		NE	
Wildin et al., 1990	Clonazepam	0.5		NE		D	
Wildin et al., 1990	Clonazepam	1		D		D	
Woo et al., 1991	Flurazepam	15 (hs)	14			NE	
Woo et al., 1991	Triazolam	0.125 (hs)	14			NE	
Young et al., 1989	Diazepam	0.01 (i.v.)				D	

APPENDIX: *Continued*

RT	CRT	CANC	ARITH	SORT	DV-ATT	COPY	SWAY	VIG/SD	STROOP	LOG.RES	Time est	PEG
					D			D				
NE	NE				NE							
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