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CURRENT ANTIDEPRESSANTS[1]

Leo E. Hollister

Departments of Medicine, Psychiatry and Pharmacology, Stanford University School of Medicine and Department of Medicine, Veterans Administration Medical Center, Palo Alto, California 94304

INTRODUCTION

Depression is very likely a heterogeneous disorder (Table 1). According to the current classification of the Diagnostic and Statistical Manual (DSM-III), several diagnoses are possible, based on the presence or absence of mania as well as the severity of the depression (1). A classification that uses somewhat older nomenclature has the advantage of offering some practical guides to treatment (2). Many other classifications are possible and the nomenclature is constantly changing.

Prior to the late 1950s, depression was treated primarily with electroconvulsive therapy and psychotherapy. The advent of effective antidepressants changed practice, so that presently drug therapy is the main modality of treatment (3). Specific types of psychotherapy may be useful alone for patients with mild depressions and may be adjunctive to drug treatment in more severe depressions. Severe depressions that constitute suicidal risk or that are refractory to drugs should be treated with electroconvulsive therapy. I shall review the current drugs used for treating depression, limiting them to those used in the United States and focusing on the newer antidepressants.

DRUGS AS TOOLS FOR UNDERSTANDING PATHOGENESIS

Drugs have been valuable tools for understanding the pathogenesis of depression. The early discovery that reserpine evoked depressive reactions led to the so-called amine hypothesis of depression. Because reserpine depleted stores of biogenic amines (e.g. norepinephrine, serotonin, and dopamine) from nerve endings, depression was associated with a depletion of biogenic amines (4).

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Table 1 Classification of depression

Source	Classification	Characteristics	Reference
DSM-III (1980)	Bipolar	Mixed manic, depressed	(1)
	Major Depressions (Unipolar)	Single or recurrent episodes	
	Others	Cyclothymic disorders, Dysthymic disorders (depressive neurosis), Atypical bipolar, Atypical depression, Schizo-affective adjustment disorder with depression	
Hollister Trichotomous Classification (1978)	Reactive	Secondary to psychosocial loss, physical illness, other psychiatric disorders—nonspecific treatment	(2)
	Endogenous	Genetic-biochemical basis; Occurs in any epoch of life—antidepressants specifically useful	
	Manic-depressive	Typically cyclic depression and mania but one or the other manifestation may predominate—most stabilized patients treated with lithium, treat depression or mania with antidepressants or antipsychotics, respectively	

Additional evidence for the amine hypothesis came from knowledge of the action of clinically effective antidepressant drugs. Virtually all types of antidepressants act by increasing the amount of aminergic neurotransmitter in the synapse (5). Although greatest attention has been paid to the biogenic amines norepinephrine and serotonin, the action of some of the newer drugs has raised the possibility that dopamine may also play a role.

Each of the various types of antidepressants acts in different ways to increase the amount of aminergic neurotransmitter at the synapse. Tricyclics block the amine pump, the "off switch" of aminergic neurotransmission. Such an action presumably permits a longer sojourn of neurotransmitter at the receptor site. Monoamine oxidase inhibitors block a major degradative pathway for the amine neurotransmitters, which presumably permits more amines to accumulate presynaptically and more to be released. Sympathomimetics also block the amine pump, but are thought to act primarily by increasing the release of catecholaminergic neurotransmitters (6).

Most of the newer antidepressants also act by one or another of these mechanisms, as well as by acting as direct receptor agonists or antagonists. For

Table 2 The action of tricyclic antidepressants on various receptors in the brain [a]

Receptor	Effect of tricyclic antidepressant
Beta-2-adrenoreceptor	Down-regulation due to increased concentration of noradrenaline
Serotonin-1-receptor	Functional significance unknown
Serotonin-2-receptor	Down-regulation due to increased concentration of serotonin
Muscarinic acetylcholine receptor	Blocked Many anticholinergic side effects ? sedation
Alpha-1-adrenoreceptor	Blocked Orthostatic hypotension Sedation
Alpha-2-adrenoreceptor	Presynaptic down-regulation due to increased concentration of noradrenaline Less inhibiton of noradrenaline release
Histamine-1-receptor	Antagonized Sedation
Histamine-2-receptor	Antagonized ? consequences
Dopamine autoreceptor	Unknown; weak action

[a]Source: Potter W.Z. (5).

a long while the increase of aminergic neurotransmitter in the synapse was thought to increase postsynaptic responses in a deficient system. Such conclusions were based on short-term studies. Clinically, however, drugs are given long-term, which is deemed necessary for their full antidepressant action. When long-term administration of antidepressants is studied in animals, and the postsynaptic consequences are measured by the generation of cyclic AMP, a subsensitivity of the postsynaptic receptor is observed (7, 8). Thus, thinking about the consequences of increased aminergic neurotransmission produced by antidepressants has made a 180 degree turn. The evidence is now strong that the original theory was incorrect.

It appears that most classes of clinically effective antidepressants lead to decreased sensitivity of postsynaptic beta-adrenoreceptors. These include selective uptake inhibitors of both norepinephrine and serotonin, blockers of the uptake of both amines, monoamine oxidase inhibitors, and some drugs that block uptake of neither neurotransmitter. Electroconvulsive therapy likewise decreases receptor sensitivity. In addition, tricyclic antidepressants, the most widely studied class, act on a number of receptors, as shown in Table 2. More of these receptor actions elicit unwanted effects than contribute to the therapeutic actions (9).

As both serotonin and norepinephrine seem to be involved in depression, an

attempt has been made to reconcile the two-neurotransmitter theory of depression with the decreased sensitivity of β receptors. It is assumed that the final common denominator of antidepressant action is an augmentation of norepinephrine release with consequent down-regulation of beta-receptors. Serotonin, however, plays a permissive role in this process, acting at the level of the receptor. Block of serotonin synthesis in animals pretreated with parachlorphenylalanine (PCPA), a tryptophan hydroxylase inhibitor, negates the down-regulation of receptors that normally follows treatment with desipramine. PCPA also blocks the clinical effects of antidepressants. A similar distribution of norepinephrine and serotonin terminals in the cortex provides an anatomical basis for the interdependence of the two aminergic systems. Thus, the debate over which neurotransmitter is most involved in depression seems to have been resolved: both are involved, but norepinephrine represents the final common pathway (10).

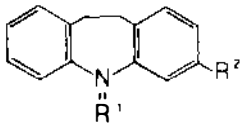
DRUGS FOR TREATING DEPRESSION

The number of drugs available for treating depression has been growing rapidly. The original group was exemplified by the tricyclic antidepressants, the monoamine oxidase inhibitors and, to a lesser extent, the sympathomimetic amines and lithium. This group might be referred to as "first-generation" antidepressants. During the past several years, a number of other drugs, usually chemically and sometimes pharmacologically different from these other classes, have been introduced. These drugs are often called "second-generation" antidepressants.

"First-Generation" Antidepressants

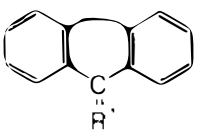
TRICYCLICS Chemical structures of some of the most commonly used tricyclics are shown in Figure 1. Slight modifications occur either in the ring structure or side chain. Even though slight, these chemical alterations provide pharmacological differences among the various tricyclics.

Imipramine This drug was the first antidepressant, discovered as such fortuitously in the clinic. Its pharmacokinetic properties, as well as those of some other antidepressants, are shown in Table 3. The major metabolic pathway is demethylation, which leads to formation of desipramine, an active metabolite. The amount of desipramine in steady-state conditions actually exceeds that of the parent compound in most patients. Desipramine may be further oxidized to active metabolites, but the extent of their contribution to therapeutic effects is uncertain (11). Imipramine blocks the amine pump both for norepinephrine and serotonin; desipramine specifically blocks uptake of norepinephrine. The net



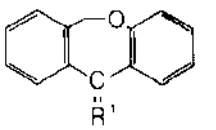
$R^1 = (CH_2)_3N(CH_3)_2$

imipramine



$R^1 = CH(CH_2)_2N(CH_3)_2$

amitriptyline



$R^1 = CH(CH_2)_2N(CH_3)_2$

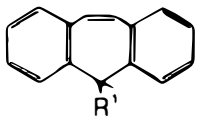
doxepin

$R^1 = (CH_2)_3NHCH_3$

desipramine

$R^1 = CH(CH_2)_2NHCH_3$

nortriptyline



$R^1 = (CH_2)_3NHCH_3$

protriptyline

$R^1 = Cl$

$R^2 = (CH_2)_3N(CH_3)_2$

clomipramine

$R^1 = CH_2CH(CH_3)CH_2N(CH_3)_2$

butriptyline

$R^1 = CH_2CH(CH_3)CH_2N(CH_3)_2$

trimipramine

Figure 1 Structural relationships among various tricyclic antidepressants. Major differences are in minor changes in the ring or side chain.

effect is that imipramine blocks uptake of norepinephrine more than of serotonin. Moderate sedative and anticholinergic effects may be troublesome to some patients. Alpha-adrenoreceptor blocking actions may be greater than those of most other tricyclics, which predisposes to orthostatic hypotension. Imipramine is a membrane-active local anesthetic (as are other tricyclics), which gives it both antiarrhythmic as well as arrhythmogenic actions. Usual doses of the drug are 75 and 300 mg/day.

Desipramine A metabolite of imipramine, this drug is used as a separate entity. A quicker onset of action than the parent drug was postulated, but that contention has been difficult to prove. Desipramine has fewer sedative, anticholinergic, and alpha-adrenoreceptor blocking actions than most other tricyclics. Patients who cannot tolerate the unwanted effects produced by these pharmacological actions may tolerate desipramine better. Doses are similar to those for imipramine.

Table 3 Pharmacokinetic parameters of various antidepressants

Drug	Bioavailability (%)	Protein binding (%)	Plasma $t_{1/2}$ (hr)	Metabolites in plasma	Volume of distribution (l/kg)	Therapeutic plasma concentrations (ng.ml)
Imipramine	29–77	88–93	6–20	Desipramine usually more; active	20–40	>180 total
Amitriptyline	31–61	82–96	31–46	Nortriptyline; usually less, active	—	>200 total
Nortriptyline	46–79	93	18–28	10-Hydroxy; 3–4 times as abundant; ? activity	21–57	50–150
Desiprimine	—	70–90	14–62	2-Hydroxy metabolite	22–59	145
Protriptyline		—	55–124	None active	19–26	70–170
Clomipramine	—	—	22–84	Desmethyl metabolite predominant; active	7–20	80–100
Doxepin	13–45	—	8–24	Desmethyl; active	9–33	—
Amoxapine	—	—	—	9-Hydroxy; 3–10 times as abundant; active	—	200–400
Alprazolam	—	65–75	6–27	? hydroxy	0.65–1.44	—
Maprotiline	66–75	88	21–25	Desmethylated, active	15–28	200–300
Trazodone	—	—	8	m-Chlorophenylpiperazine; active	—	—
Buproprion		85	11–14	? Active	—	25–100
Nomifensine		—	2–4	? Active	—	—

Amitriptyline This tricyclic was the most widely used until recently. A demethylated metabolite, nortriptyline, is generally not as abundant as the parent drug. Although amitriptyline in vitro has a selective action in blocking uptake of serotonin, nortriptyline has a mixed action. The net result is that amitriptyline has a mixed effect, predominantly on serotonin. Amitriptyline is probably the most sedative and most anticholinergic of all tricyclics; it is often used when sedation is desired (12). Doses are usually 75–300 mg/day.

Nortriptyline A metabolite of amitriptyline, this drug is also used as a separate entity. During the first pass through the liver it is extensively metabolized to 10-hydroxy-nortriptyline, which is far more abundant than the parent compound. The exact amount of activity contributed by the metabolite is unknown. Relatively fewer sedative and anticholinergic actions occur with nortriptyline than with the parent drug. Doses of nortriptyline have usually been lower than for the other tricyclics, although the basis of such conservatism has not been established.

Doxepin The strong sedative effects of this drug have been the basis for its promotion as an antianxiety as well as an antidepressant drug. A demethylated metabolite also contributes to its action. Doxepin itself has a relatively weak action in blocking the amine pump, despite the fact that it is generally thought to be equally effective as an antidepressant. Doses are similar to those of other tricyclics.

Protriptyline This drug has been one of the least popular tricyclics, and has not been widely promoted. Some clinicians believe that it has a stimulating action; it is certainly the least sedative tricyclic. Some anticholinergic action remains. Protriptyline may be a reasonable alternative for patients who become overly sedated by the other tricyclics. Doses are considerably lower than those of other tricyclics, generally 10–40 mg/day.

Others Butriptyline and trimipramine are isobutyl side-chain modifications of amitriptyline and imipramine, respectively. They differ little from the prototype drugs. Clomipramine is a chlorinated ring-substituted homolog of imipramine. Just why this modification provides a presumed specific efficacy for obsessive-compulsive patients is unclear. Doses of these drugs are similar to those of other tricyclics.

MONOAMINE OXIDASE (MAO) INHIBITORS MAO inhibitors are classified as hydrazides (-C-N-N-configuration) and nonhydrazides. The structures of some MAO inhibitors are shown in Figure 2.

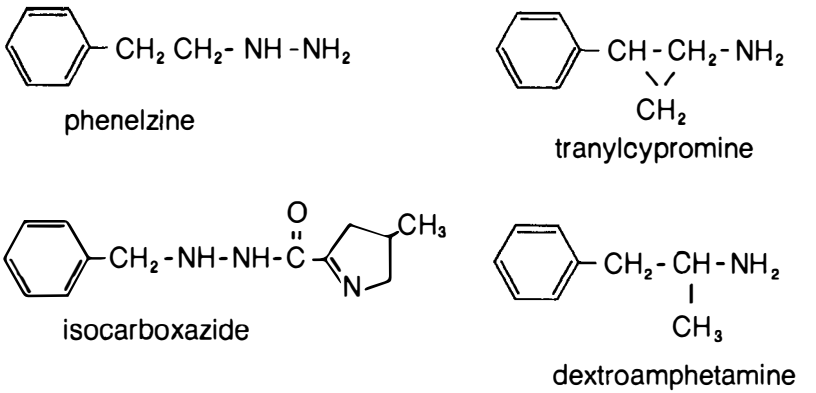


Figure 2 Structural relationships among MAO inhibitors. Note the close chemical relationship between tranylcypromine and dextroamphetamine.

Phenelzine This drug has been the most durable MAO inhibitor and is the only one currently promoted in the United States. At least 80% inhibition of monoamine oxidase must be obtained for optimal clinical effects. Doses of 1 mg/kg/day are usually necessary to obtain such inhibition, but the process takes time and so does the regeneration of the enzyme (13). Improvement in patients may not be evident until two or more weeks of treatment. When the drug is stopped, the enzyme is not regenerated for another two weeks. Tricyclics should not be added or replaced in the treatment program for at least that period. The converse sequence of the MAO inhibitor following tricyclics can usually be done with no delay. Usual doses of phenelzine are 45–90 mg/day.

Isocarboxazide This MAO inhibitor is neither widely used nor promoted and has been less well studied than the others. Usual doses are 20–50 mg/day.

Tranylcypromine The chemical structure of this nonhydrazide MAO inhibitor is similar to that of dextroamphetamine. It retains some of the sympathomimetic actions of the latter drug but is a much more potent inhibitor of monoamine oxidase. Usual doses are 10–30 mg/day.

SYMPATHOMIMETICS These drugs are used only in rare patients. Occasionally, they produce benefit in patients who have been resistant to the other antidepressants.

Dextroamphetamine The structure of this compound is shown in Figure 2. Insomnia and loss of appetite limit its use in some patients although stimulation and appetite suppression may be desirable effects for others. Some patients require substantial doses to obtain benefit but show little evidence of tolerance

or dependence with prolonged treatment. Usual doses are 10–30 mg/day, with some patients requiring as much as 60 mg/day. Methylphenidate, an amphetamine surrogate, is even less commonly used and has no special advantages.

LITHIUM Although lithium carbonate has been reported to be useful for treating acute depressions that appear not to be part of manic-depressive disorder, it is seldom used as a sole treatment. More likely it may be added to a tricyclic when the latter provides inadequate remission (14). Its use in preventing recurrences of depression, whether unipolar (endogenous) or bipolar (associated with manic episodes) is well documented. However, in a unipolar patient who has responded to a conventional antidepressant it is usually easier to continue or maintain the patient on that drug than it is to switch to lithium.

"Second-Generation" Antidepressants

The enthusiasm with which these drugs have been received stems from the several problems that remain with the "first-generation" drugs. First, only about 60–65% of depressed patients are helped and many do not attain a full remission of symptoms. Second, the clinical response to first-generation drugs may be delayed. This delay may be more a consequence of the slow induction of treatment mandated by the side effects of these drugs. Thus, it is more likely a pharmacokinetic than a pharmacodynamic phenomenon. Third, the numerous side effects of first-generation antidepressants may make it impossible to treat some patients with fully effective doses or may lead to noncompliance with treatment on the part of others. Finally, tricyclics in particular are potentially lethal when taken in overdose. The paradox is that one must prescribe such drugs to a group of patients with the highest risk of suicide.

Although it has not been claimed that the newer antidepressants are more effective overall than the tricyclics with which they are usually compared, they do assert three advantages: (*a*) a more rapid onset of action, (*b*) more tolerable side effects, (*c*) greater safety when taken in overdose (15).

Four of these drugs are currently on the market in the United States and more are expected soon. The variety of chemical structures of these drugs is shown in Figure 3.

Amoxapine Amoxapine is a demethylated metabolite of the antipsychotic, loxapine. It is further metabolized to hydroxy metabolites, which are 3–10 times as abundant as the parent drug and which probably account for the antidepressant activity (16). The net effect is more blockade of uptake of norepinephrine than of serotonin. The anticholinergic action is weak. The dopamine-receptor blocking action of loxapine is retained to a somewhat lesser degree in amoxapine, which also has some antipsychotic activity. This combined action may be especially suitable for patients with psychotic or agitated

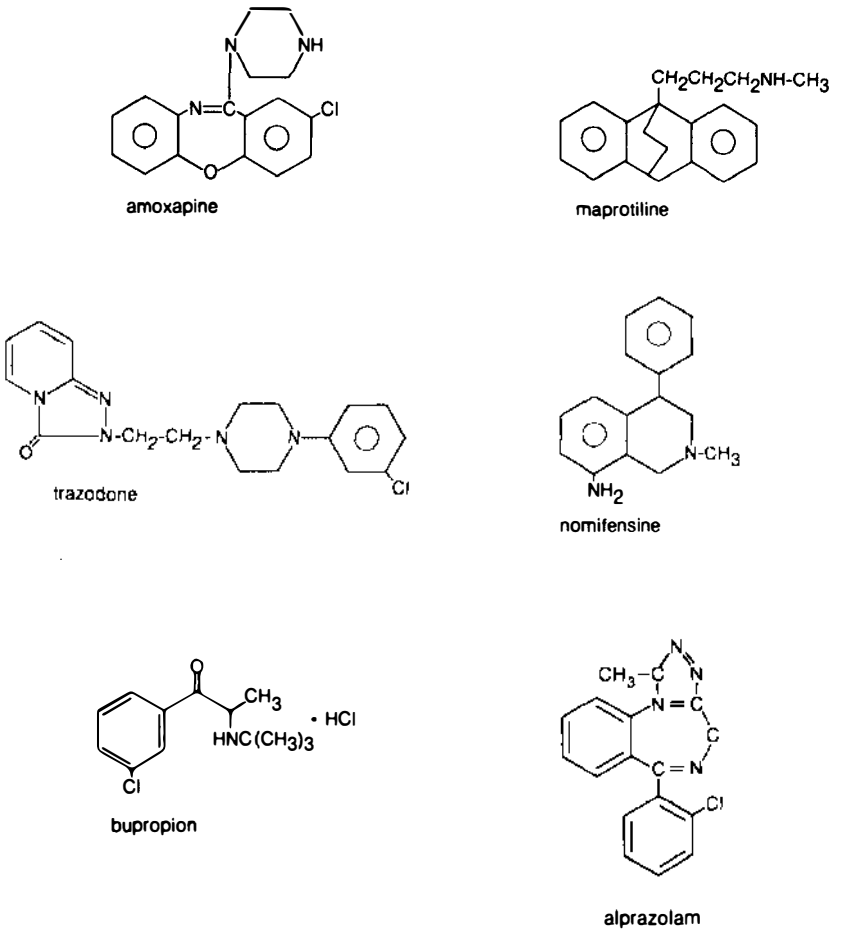


Figure 3 Structures of "second-generation" antidepressants. A variety of structures are involved.

depressions. However, it may also lead to extrapyramidal syndromes and hyperprolactinemia with sexual disturbances in men and amenorrhea-galactorrhea in women. Although the drug has less cardiotoxic action than tricyclics in overdoses, it produces seizures that are difficult to control, with an attendant fatality rate. Usual doses are 150–300 mg/day.

The claim for a more rapid onset of action is not substantiated and is further offset by an apparent tolerance to the therapeutic effects that may develop in some patients after an initial response. Not only are the usual sedative and anticholinergic side effects of tricyclics as common with this drug, but it also adds some of the side effects of antipsychotics. Severe neurotoxicity, which occurs after overdoses, makes it at least as dangerous as those tricyclics with predominant cardiotoxicity. In summary, amoxapine offers very little.

Maprotiline A two-carbon bridge across the central ring of the 6-6-6 three-ring structure of this drug creates a fourth ring, making it a tetracyclic compound (17). The side chain is the same monodemethylated aminopropyl sidechain found in desipramine, creating a rather similar structural geometry. The primary action of the drug is to block uptake of norepinephrine; it also has less sedative or anticholinergic action than amitriptyline, the drug against which it has most often been compared. Had it been compared with desipramine, which it resembles both in structure and in major mode of action, it is likely that no differences in these side effects would have been noted. The drug had a decade of use in other countries before arriving in the U.S. and was well recognized to cause seizures, even within the range of therapeutic doses. These are usually 100–300 mg/day.

Whether maprotiline has a faster onset of action has not been adequately tested. It seems to offer nothing new in its mechanism of action nor fewer sedative and anticholinergic side effects as compared with desipramine. Seizures occur at therapeutic doses far more often than with tricyclics. Skin rashes also seem to be more frequent. Overdoses are about as dangerous as with tricyclics. The drug offers little advantage over desipramine. Oxaprotiline, an active metabolite, is under clinical investigation but should not be much different.

Trazodone Although frequently described as a triazolopyridine compound, trazodone is more properly described as a phenylpiperazine. In this respect it resembles chemically oxypertine, a drug that has been used both as an antipsychotic and as an antianxiety agent. Pharmacologically, it is complicated (18). Some doses act as a serotonin receptor antagonist, while others act both as a serotonin agonist and as an uptake inhibitor. It may also increase release of norepinephrine by blocking alpha-2 adrenoreceptors. The exact mode of its therapeutic action is unknown, although presumably it works mainly as a serotonergic drug. An active metabolite, m-chlorophenylpiperazine, is formed; but it is not clear to what extent it may contribute to the antidepressant effect. Although clinically it has appeared to be as effective as the tricyclics against which it has been compared, results have often been spotty. Some patients obtain much relief, while others derive no benefit. The same dichotomy applies to its sedative effects. These limit doses in some patients while others are not at all bothered. Skin rashes seem to be more common than expected. Rare instances of short runs of ventricular tachycardia and priapism have occurred. The usual daily doses are 150–400 mg.

No claim is made for a more rapid onset of action, which is difficult to prove at best. The anticholinergic side effects of tricyclics are definitely fewer with this drug, but sedation can be troublesome. Overdoses have been managed easily with no apparent cardiotoxicity, despite the ventricular tachycardia

reported with therapeutic doses. If one were more confident about its therapeutic efficacy, which has been called into question, it might have some advantages (19).

Nomifensine A phenylisoquinoline derivative, nomifensine has been marketed in numerous countries around the world during the past several years and has been given to millions of patients. Despite this extensive clinical experience, it is a new drug in the United States. Abundant evidence suggests that nomifensine is a potent inhibitor of both dopamine and norepinephrine uptake (20). The neuropharmacological profile of the drug has been thought to lie between that of amphetamine and imipramine (21). In man, the EEG profile of the drug resembles that of desipramine (22). The latter observation is consonant with the fact that no amphetamine-like stimulation could be found in volunteer subjects given single doses (23). Almost every study agrees that nomifensine has little antimuscarinic action.

Most of the drug in plasma is in the form of a conjugate; numerous metabolites have been described. The $t_{1/2}$ of unchanged drug is 2–4 hours, but the clinical span of action is much longer, possibly due to an active metabolite.

The lack of effects of the drug on blood pressure, cardiac conduction times, and EKG in normal subjects, as well as the lack of significant cardiovascular complications following overdose, have made it more suitable than tricyclics for patients with cardiovascular disease (24). Another advantage over conventional antidepressants is a notable lack of psychomotor impairment (25). Side effects such as dry mouth, headache, and dizziness are so common that they are difficult to evaluate when reported for any drug. On the other hand, nausea, vomiting, or restlessness might be expected consequences of an increase in dopaminergic activity, whatever the mechanism. Excitation, delirium, stereotyped movements, and dyskinesia have been rarely reported but are plausible. In general, the drug has tended to produce fewer minor side effects than the tricyclics with which it has been compared. A sizable number of patients treated with the drug, perhaps as many as 1%, experience drug fever early in the course of treatment. The significance of this immune response to the drug remains to be seen.

No claim has been made for a more rapid onset of action. Clinically, the drug is as efficacious as the conventional antidepressants against which it has been compared, offering the notable advantage of a diminished number of the common side effects related to sedation and to anticholinergic actions. Overdoses of nomifensine have been marked by drowsiness, tremor, tachycardia, and obtunded consciousness. No convulsions, cardiac arrhythmias, or EKG changes have been noted. All side effects have been easily managed. If more experience with the drug in the United States confirms its efficacy and safety, nomifensine may represent a true advance in antidepressant drug treatment.

Several other new drugs may soon be available as treatments for depression.

Buproprion Buproprion has a phenethylamine structure that superficially resembles that of amphetamine or methoxamine. Chemical modifications on the ring and side chain have markedly changed its spectrum of pharmacological actions. The chlorine atom on the ring protects against rapid metabolism; the tertiary alkyl group is not readily dealkylated, avoiding pressor activity; the aminoketo group confers lipid solubility (26).

The exact mode of action of buproprion is unclear. It seems definitely to require the presence of intact dopamine neurons in the brain. An early study suggested that the drug acted primarily as a dopamine uptake inhibitor (27). It has little effect on norepinephrine uptake, no anticholinergic actions, and no inhibiting effects on monoamine oxidase. Chronic treatment produced neither down-regulation of beta-adrenoreceptors nor of dopamine receptors. It is possible that its major pharmacological effects may be mediated by an active metabolite.

Dry mouth is the most common side effect. Rashes may occur in 1–2% of patients. Anorexia and mild agitation may also be observed. Seizures have occurred with high doses (600–750 mg/day), which are no longer recommended; usual daily doses are 300–450 mg. Orthostatic hypotension or other cardiovascular effects have been notably absent during clinical drug trials.

Buproprion is of interest because it appears to work primarily through dopaminergic mechanisms, raising the possibility that this neurotransmitter may also be relevant to the pathogenesis of depression. A more rapid onset of action than that of conventional antidepressants has not been documented. The drug also lacks most of the sedative, anticholinergic, and cardiovascular side effects of tricyclic antidepressants, although it is equally effective. Overdoses of from 900–3000 mg have been easily managed without any cardiovascular problems. This drug will be exceedingly interesting to watch as it is used in clinical practice.

Alprazolam Alprazolam was one of a series of triazolobenzodiazepines synthesized in 1971. By 1973 the first report of its clinical use in anxious patients had appeared (28). Clinical observations suggested that it might also be useful for treating depression, and the first report on the use appeared in 1976. More recently, it has been thought to be useful for treating patients with panic attacks and agoraphobia.

Alprazolam exhibits the same profile of pharmacological activities as most other benzodiazepines (29). These actions would certainly justify its use as an antianxiety drug but do not explain why it should be different from other benzodiazepines in being an effective antidepressant. The efficacy of the drug in depression rests largely on a multiclinic trial that compared alprazolam (159 patients) with imipramine (146 patients) and placebo (131 patients). These patients met the standard research diagnostic criteria for depression. After 42 days of treatment, both active drugs produced more improvement in depression

than placebo but were not different overall. Drowsiness was more often found in alprazolam-treated patients and dry mouth in those treated with imipramine (30). Although the drug is not officially labeled for use as an antidepressant, many clinicians are using it. Clinical consensus at the moment is that the drug may be useful in mildly depressed patients who are outpatients but that it is not fully effective in severe depressives.

About the only side effects that have been noted with alprazolam relate to its action on the central nervous system. Drowsiness has been the most common complaint. Yet even the frequency and intensity of this side effect seem to be less than from comparable doses of other benzodiazepines. Some of the studies of the drug in depressed patients have used doses up to 10 mg/day (equivalent perhaps to 100 mg/day of diazepam). Thus, it is possible that should patients being treated with such doses be suddenly withdrawn from the drug, an abstinence syndrome would follow.

Alprazolam, if it really is a major antidepressant, would seem to have many advantages over the others. The major drawback is the slow withdrawal of the drug that may be needed to avoid abstinence syndromes.

CONCLUSIONS

The physician has available an increasing number of antidepressant drugs. None are clearly superior overall. Because some patients respond to one drug and not to another, however, the increasing selection of antidepressants provides additional opportunities for successful treatment. The problem for the pharmacologist is to reconcile apparent differences in the modes of action of these drugs with their common property of antidepressant effect. As we learn more about how drugs act in treating depression, we can postulate new theories about the condition's biological bases.

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