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Lifetime Antipsychotic-Drug Exposure, Dyskinesia and Related Movement Disorders in the Developmentally Disabled

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STONE, R. K., W. F. ALVAREZ AND G. ELLMAN. *Lifetime antipsychotic-drug exposure, dyskinesia and related movement disorders in the developmentally disabled.* PHARMACOL BIOCHEM BEHAV **34**(4) 759–763, 1989.—The relationship between dyskinesia and related movement disorders was examined as a function of cumulative exposure to antipsychotic drugs (APD). Lifetime drug-exposure histories were obtained for 162 developmentally disabled (DD) persons; drug-exposed groups were compared to nondrug-exposed groups. There were no statistically significant relationships between dyskinesia and the amount of lifetime APD exposure, nor between dyskinesia and the number of long-term APDs, mean exposure, peak exposure, recency of exposure, duration of exposure, changes in medication levels, number of drug interruptions, age, gender, cerebral palsy, epilepsy, or IQ. Of the other movement disorders, a positive relationship was noted only between akathisia and long-term APD exposure; the increased prevalence of akathisia persisted beyond four years after APD withdrawal.

Antipsychotic drug Movement disorder Dyskinesia Mental retardation Dystonia Akathisia Parkinsonism

AN association between dyskinesia and antipsychotic drugs (APD) was first reported in 1957 (18); by that time, however, an association between APD and several other movement disorders had already been described, including parkinsonism, dystonia, and akathisia. The possibility of permanent, iatrogenic brain damage has made dyskinesia, more than other drug-induced movement disorders, the subject of a sizable literature and the target of considerable legislation and litigation (21).

The case for a causal relationship between APD and dyskinesia rests on correlation studies, with supporting evidence from drug-withdrawal and animal studies. Adequate prospective studies have yet to appear. For their part, drug-correlation studies have been largely retrospective and binomial (yes/no). Most of this literature derives from psychiatric populations where control groups have been uncommon. When such a group was recently reported, the prevalence of dyskinesia in non-APD-exposed persons was nearly identical to that of drug-exposed populations (7); subsequent evaluation of the same data revealed a slight correlation between APD and age (5). In a developmentally disabled (DD) population, another large study with a control group also found no more dyskinesia in the APD-exposed group, overall, than in the non-APD-exposed group (22); controlling for recency of exposure, this study did find significant relationships between APD and certain subgroups, notably age and gender. These relationships, however, accounted for only three percent of the variance.

Another type of correlation study uses cumulative drug-exposure data. In a comprehensive review of the literature between 1959 and 1979, Kane and Smith (15) reviewed 18 such studies, noting that four reported a positive relationship while fourteen did not. Since that time, two more studies have found no significant relationship between APD exposure and persistent dyskinesia (1,3), while one study did find such a relationship (12). It is often difficult to assure the integrity of life-long drug histories, and several studies have been reported which used less-precise drug data; one of these studies found a positive relationship (6) between APD and dyskinesia, while three did not (4, 10, 16).

Correlations between specific APD and dyskinesia have generally not been positive, with the possible exception of fluphenazine (9, 16, 17, 20). Duration of exposure to APD has sometimes been correlated with dyskinesia, but has not always been clearly distinguished from age, a generally accepted risk factor. Current dose (or recency of withdrawal) and polypharmacy are also potential complicating factors not addressed in all studies.

This study examines the relationships between movement

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disorders and cumulative APD exposure in a DD sample whose lifetime medication histories are known. Long-term (>6 months) and short-term (<6 months) drug-exposed subjects are compared with nondrug-exposed subjects

METHOD

Sample Selection

During a survey of the population of an institution (N = 1282), it was determined that the medication records of the older population were more likely to be incomplete. Initially, therefore, only those subjects were included who were 20 years of age or younger; the accuracy of 104/159 of these records could be assured and the remainder were rejected. To increase variability with regard to age, an older population was sampled with a stratified random-sampling technique, incorporating age (21–40 years) and gender; this resulted in another 58 complete records, for a total sample of 162.

Sample Characteristics

The mean age was 18.1 (SD = 7.0); 58% of the sample was male. The average IQ was 12.9 (SD = 11.6), ranging from 2 to 65; the majority of subjects were profoundly retarded. Seventy-nine percent were visually handicapped, and 39% were hearing impaired; 59% had cerebral palsy, and 64% (N = 103) had epilepsy.

Drug Histories

Drug reviews and symptom evaluations were performed by different groups with no knowledge of each other's results. Total drug exposure was calculated in terms of grams of each drug. Yearly body weights, extracted from the medical records, were used to calculate drug exposure in terms of grams per kilogram of body weight for each year. Antipsychotic drugs were converted to chlorpromazine equivalents to determine the combined dosage of multiple drugs; equivalency was calculated according to Davis (8). The maximum APD-exposure for any one-month period was the peak exposure. Any change in drug regimen was noted, and a temporary cessation of medication was recorded as a drug interruption. Noncontinuous or incomplete records were rejected. Institutional records were also rejected if preadmission records were incomplete. Seventy-five percent of the lifetimes of all subjects was accounted for by complete institutional records; the remainder had lived in the community prior to institutionalization, however, their preinstitutional records were complete.

Long-term exposure was defined as six or more months exposure, compared to short-term APD exposure which was defined as less than 6 months exposure. Long-term exposure is hereafter referred to simply as (drug/APD) exposure (or specified as such), whereas short-term exposure is specified as such. "Total" drug exposure specifies both short- and long-term exposure.

Evaluation of Symptoms

The method of examination (SIMAS) is discussed in detail elsewhere (23). Each subject was examined for dyskinesia, dystonia (DT), akathisia (AK), parkinsonism (PK), and paroxysms (PX). Each diagnostic category was further evaluated for severity and site of occurrence. Symptom categories were phenomenologic, i.e., there was no prejudgement of causality or pathogenesis. The word "dyskinesia" was used, rather than "tardive dyskinesia," to avoid the implication that the dyskinesias were known to be drug-induced prior to analysis.

The definition of dyskinesia was restricted to choreoathetoid-movement. Dystonia was defined as an abnormality of posture and/or the movement leading to an unsustained abnormal posture—as in torticollis or oculogyria. "Paroxysm" was chosen as a generic term, rather than myoclonus, to permit inclusion of all types of abrupt phenomena (duration <= one second), e.g., vocalizations, tics, and spasms. Akathisia was defined as motor restlessness. Parkinsonism was a constellation of symptoms which included bradykinesia, rigidity, and diminished spontaneity and associative movements.

Severity was graded on a scale ranging, in increments of 0.5, from 0 (not present) to 4 (most severe). Where severity was variable, the maximum observed-severity was reported. Each subject was examined for a minimum of 10 minutes; indirect and remote observations were made as well as direct physical examination, and activated examination where pertinent and possible. Questionable diagnoses were excluded.

Reliability

The reliability of SIMAS for assessing movement disorders is described more fully elsewhere (23). Among a group of physicians with six hours of standardized training, there was 95% agreement overall in distinguishing the five movement disorders. Akathisia and parkinsonism were the most reliably rated symptoms, and paroxysms the least. Intrarater agreement varied from 81% to 100%.

Analysis

Statistical analysis utilized chi-square and General Linear Model equations. Examination for nonlinear relationships was performed by entering squared terms into the equation. Interactions and multiplicative effects were evaluated by creating variables that were products of the factors.

RESULTS

The prevalence of movement disorders in the entire sample of 162 was 48% for dyskinesia, 19% for dystonia, 10% for akathisia, 5% for paroxysms, and 1% for parkinsonism. The five types of movement disorders were statistically distinct but not mutually exclusive.

Lifetime exposure to psychotropic drugs is presented in Table 1 (N = 87). Forty-four of these (51%) had been exposed to long-term APD; the most frequently used drugs were chlorpromazine, thioridazine, and haloperidol. While prochlorperazine was used by the greatest number of people, the actual exposure was relatively little; the usage consisted primarily of single-dose administrations, generally for nausea rather than behavior modification. Twenty-five (15%) persons had not been exposed to any psychoactive drugs whatsoever.

The cumulative duration of exposure to APD is also presented in Table 1. The values in Table 1 refer to drugs, rather than individuals; since the total drug exposure for an individual was the sum of multiple drugs, the exposure to any one drug could be considerably less than six months. The average duration of exposure for these individuals was 106.46 (SD = 70.86) months (ranging from six to 245 months), distributed over a period of time ranging from seven to 355 months (mean = 129.67, SD = 86.35).

On the average, there was a dosage-adjustment in APD regimens every three to four months. Fourteen people (33%) had no drug interruptions in their psychotropic regimen.

The relationship of APD exposure to prevalence of involuntary movement disorders is presented in Table 2. The only significant finding was a positive relationship with akathisia (Cramer's

TABLE 1

LIFETIME ANTIPSYCHOTIC-DRUG EXPOSURE (N = 87)

	Total Exposure (N = 87)					>6 Months Exposure (N = 44)				
		Duration (months)		Dosage (g/kg)			Duration (months)		Dosage (g/kg)	
Drug	N	Mean	(SD)	Mean	(SD)	N	Mean	(SD)	Mean	(SD)
Chlorpromazine	42	35.6	(45.1)	9.2	(19.5)	32	48.7	(46.7)	12.2	(21.6)
Thioridazine	41	51.2	(48.2)	7.3	(10.0)	37	56.7	(47.7)	8.1	(10.3)
Haloperidol	22	36.6	(33.0)	0.4	(0.9)	19	40.4	(32.5)	0.3	(0.5)
Trifluoperazine	12	34.2	(41.4)	0.3	(0.5)	12	34.2	(41.4)	0.3	(0.5)
Fluphenazine	7	31.9	(36.9)	0.1	(0.1)	7	31.9	(36.9)	0.1	(0.1)
Thiothixene	6	20.7	(26.1)	0.1	(0.1)	5	24.2	(27.6)	0.1	(0.1)
Piperacetazine	2	3.0	(2.8)	0.1	(0.2)	0	—	—	—	—
Prochlorperazine	43	3.4	(5.7)	0.0	(0.1)	11	7.7	(10.1)	0.1	(0.1)

TABLE 2

PREVALENCE OF MOVEMENT DISORDERS AS A FUNCTION OF ANTIPSYCHOTIC-DRUG EXPOSURE

	Drug Exposure							
	None (N = 75)		<6 Months (N = 43)		=>6 Months (N = 44)			
Movement Disorder	Prev	(N)	Prev	(N)	Prev	(N)	χ^2	$p<$
Dyskinesia	47%	(35)	58%	(25)	39%	(17)	—	NS
Akathisia	5%	(4)	7%	(3)	20%	(9)	7.68	0.02*
Dystonia	24%	(18)	19%	(8)	9%	(4)	—	NS

Prev = Prevalence.

*Collapsing categories "no APD" and "<6 months APD" yields $\chi^2 = 9.31$, $p<0.002$, phi = 0.26.

TABLE 3

LIFETIME APD EXPOSURE IN CHLORPROMAZINE EQUIVALENTS BY PRESENCE/ABSENCE OF MOVEMENT DISORDERS

	Total Sample (N = 87)			Long-Term APD Use (N = 44)		
	N	Mean APD Exposure, g/kg	(SD)	N	Mean APD Exposure, g/kg	(SD)
Dyskinesia						
Yes	77	6.39	(23.90)	17	30.67	(46.96)
No	85	7.35	(19.02)	27	22.32	(28.18)
Akathisia						
Yes	16	14.61	(28.01)	9	26.00	(35.30)
No	146	6.03	(20.42)	35	25.28	(36.12)
Dystonia						
Yes	30	6.33	(26.52)	4	45.79	(66.27)
No	132	7.01	(20.25)	40	23.34	(31.63)

TABLE 4

PREVALENCE OF MOVEMENT DISORDERS AND RECENCY OF LONG-TERM APD EXPOSURE

	Recency of Long-Term APD Exposure					
	Not Exposed N = 118*	Currently on APD N = 16	Off APD <=4 Years N = 15	Off APD >4 Years N = 13	χ^2	$p<$
Dyskinesia	51%	19%	53%	46%	6.05	NS
Akathisia	6%	19%	27%	15%	8.67	0.03
Dystonia	22%	12%	7%	8%	3.76	NS

APD = Antipsychotic drug.
*Includes short-term (<6 months) exposure.

V = 0.23, $p<0.02$). The number of persons with parkinsonism and paroxysms were insufficient to reach reliable conclusions. Two persons (1.2%) had parkinsonism as defined; both were female, and neither had received APD. Eight persons (4.9%) had paroxysms; two of these were exposed to APD, however, there was no statistically significant relationship.

Table 3 presents the amount of drug exposure in subjects with/without dyskinesia, akathisia, and dystonia. There were insufficient numbers of subjects with parkinsonism or paroxysms to reach reliable conclusions. There were no significant differences in mean APD exposure between groups with/without symptoms. The range (SD) of drug use was wide in all cases.

The relationship between movement disorders and the recency of APD exposure is presented in Table 4. At the time of examination for movement disorders, 16 (36%) of the long-term APD-exposure sample were currently receiving APD; 15 (34%) had been withdrawn from APD within the prior four years, and the remaining 13 (30%) had been withdrawn more than four years prior to examination. The average length of time from APD-withdrawal to examination was 34.80 months (SD = 47.88). With regard to dyskinesia, an inverted-V pattern emerged in which the lowest prevalence (19%) was found in the sample currently receiving APDs, with the prevalence peaking (58%) among those who had been withdrawn less than four years prior to examination, then diminishing to a value (39%) lower than the not-exposed group. The peak prevalence (53%), shortly after withdrawal, was similar to the prevalence of dyskinesia (51%) among those who had never been exposed to APDs.

By contrast, akathisia was more prevalent among those who had long-term APD exposure, and the increased prevalence was relatively persistent more than four years after withdrawal. Within the group who had been withdrawn from long-term APD exposure, there was a significant positive relationship between akathisia and the length of time they had been exposed to APD (r = .49, $p<0.01$).

Several other attributes of the population were examined; however, since no significant relations were revealed, the results are merely noted: among the APD-exposed group, overall, there were no significant relationships between dyskinesia and the number of APDs, amount of lifetime APD-exposure (either as grams, or grams/kg, calculated as chlorpromazine-equivalents), mean APD exposure, peak exposure, duration of exposure, recency of exposure, changes in medication levels, number of drug interruptions, age, cerebral palsy, epilepsy, or IQ. This was true for the examination of linear and nonlinear relationships as well as interactive and multiplicative effects tested by General Linear Model equations. Among those with only short-term APD exposure, dyskinesia was associated with epilepsy (phi = 0.22, $p<0.02$) and long-term anticonvulsant medication (phi = 0.26, $p<0.01$).

DISCUSSION

This study does not show a dose-dependent relationship between APD and dyskinesia in DD persons whose lifetime drug exposure is known; in this regard, it is concordant with the majority of such studies in psychiatric populations. Although dose-dependence is only one aspect of a causality argument, persistent failure to demonstrate such a relationship mitigates against the argument. There may be no such relationship, or there may be methodologic reasons for this apparent disparity. In a subpopulation, for example, Toenniessen reported a linear relationship which was apparent only in the first three years of exposure (24). Our data were insufficient to test this finding. In a study (12) which did find a positive relationship in a DD population, the finding accounted for 38% of the variance, but depended on a logarithmic transformation of the dosage. No such relationship emerged when our data were similarly transformed.

Other procedural factors must be considered: quantitative lifetime drug histories are difficult to obtain, and generally require some restriction of the population. In this study, only the records of relatively younger persons could be assured; had such histories been available for the entire population, different patterns may, or may not, have emerged. Although a few older persons were included, their numbers were insufficient to reach additional conclusions. The possibility of nonlinear relationships was examined but did not alter the conclusions. It has also been suggested that topographical regions (i.e., symptoms at different sites) may not be physiologically homogeneous (25), and should be distinguished on analysis. Controlling for site did not alter the conclusions, however there was insufficient spread of data to test this possibility vigorously. The effect of polypharmacy (multiple APDs) did not alter the conclusions; a negative correlation between dyskinesia and multiple drugs has been reported by others (14). Differing definitions of the movement disorders will certainly affect the results; unfortunately there is no universal consensus. Dyskinesia as choreoathetosis, however, is compatible with the AIMS scale (13), and with the original description of Schonecker.

More importantly, perhaps, is the well-known ability of APD to suppress dyskinesia. It is critical to consider the timing of the examination with regard to recency of drug exposure (22). For example, Aman and Singh reported a relationship between APD and dyskinesia which was present at three weeks after withdrawal, but was not significant at ten weeks (1). In our sample, persons currently on APD had the least dyskinesia (Table 2), while subjects withdrawn from APD within four years had the most dyskinesia (slightly higher than the non-APD-exposed group), and those off APD longer than four years had the least dyskinesia (less than the non-APD-exposed group). The Ns are small in our sample and, for dyskinesia, the relationships are not statistically significant; however, the inverted-V pattern of withdrawal parallels the findings of a larger qualitative study (22). As in that study, the prevalence of dyskinesia more than four years after withdrawal from APD was actually less than dyskinesia in nonexposed persons. Interestingly, persistent subsensitivity following APD exposure has been reported in animals (19).

The possibility of selective susceptibilities in DD subgroups was explored in the study mentioned above (22), where a relationship with APD, age, and female gender was noted when controlled for recency of exposure. Our drug data did not allow an extended analysis of this sort, however, the role of gender was

analyzed, and revealed no significant differences from the overall pattern. While the exposure/withdrawal pattern of dyskinesia followed the inverted-V shape described above, the same was not true of all movement disorders. For dystonia, the prevalence was less during APD exposure than prevalence in the nonexposed group, and it remained less during both early- and late-withdrawal phases. Only the prevalence of akathisia increased during exposure and remained relatively high during both phases of withdrawal. Of all the movement disorders analyzed, the akathisia pattern was most compatible with a causal relationship between APD exposure and movement disorder.

It is of some importance that this study, although retrospective, does have a control group. Moreover, the drug-exposure factor was calculated as both grams of drug over a lifetime of exposure, and as gm/kg of body weight; these permutations did not affect the conclusions. Length of exposure did not alter the outcome, nor did calculation of exposure in terms of mean values or peak values. Drug regimens were rarely monolithic, and multiple drugs were summed using the method of chlorpromazine-equivalents (2,8). The ultimate veracity of this method remains to be determined, however, it is common to virtually all such studies. Other schemes have been tried, based on chemical structure (11), but the translation of chemical structure into clinical effect is unproven. No specific APD could be determined to have more effect than any other. The same has generally been true in the literature, with the possible exception of fluphenazine.

The findings in this DD population may not generalize precisely to all groups. The prevalence of dyskinesia in this group, however, is very similar to prevalences reported in psychiatric and geriatric populations when adjusted for age (23). Although the prevalence of dyskinesia is high in the nonexposed group, APD exposure accounted for no additional predictability for dyskinesia in this sample.

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