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Dyskinesia, Antipsychotic-Drug Exposure and Risk Factors in a Developmentally-Disabled Population

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STONE, R. K., W. F. ALVAREZ AND J. E. MAY. *Dyskinesia, antipsychotic-drug exposure and risk factors in a developmentally-disabled population.* PHARMACOL BIOCHEM BEHAV **29**(1) 45–51, 1988.—The relation between antipsychotic drug (APD) exposure and the prevalence of dyskinesia (DK) was examined in a large, developmentally-disabled (DD) population. Using qualitiative data in a cross-sectional, retrospective design, the drug-exposed group was systematically compared with a non-drug-exposed group, controlling for age and gender. When the population was evaluated with no regard to APD-exposure, age and female gender were significant risk factors, as in many prior studies. When APD-exposure was considered, it proved to be a complex variable dependent on the recency of exposure to APD, and the outcome depended on the method of analysis: when APD-exposure was considered as a binomial variable (yes/no), the relationship between APD and DK was not significant; when APD-exposure was controlled for recency of exposure, however, a significant relationship between APD and DK was demonstrated ($p<0.01$) although the relationship accounted for less than 3% of the variance. Analysis of the relation between DK-prevalence and recency-of-APD-exposure revealed a pattern of diminished prevalence during APD use and increased prevalence during early withdrawal.

Tardive dyskinesia Dyskinesia Antipsychotic drug Etiology Prevalence Withdrawal

TARDIVE dyskinesia is considered a major public health hazard of the modern era of psychiatry. The word "tardive," introduced to mean "belated onset" of symptoms [15], is sometimes used to mean "antipsychotic-drug induced" and the antipsychotic drugs (APD) are considered the preeminent risk factor for dyskinesia (DK). Of the other risk factors investigated, age is the most consistently supported [23], followed by female gender. While correlations between DK and APD have been demonstrated, evidence for a causal relationship is not conclusive. Evidence linking the two is largely nominal (yes/no) and retrospective although prospective studies have begun to appear [25,38]. Both animal [6, 14, 29, 44] and withdrawal [2, 16, 17] studies are said to support a causal relationship. On the other hand, withdrawal-emergent dyskinesia may differ from persistent dyskinesia, and the animal model may not be identical to human DK [41]. Where quantitative drug studies have been possible, a dose-dependent relationship has generally not been demonstrated—with the possible exception of fluphenazine [10, 35, 42]. Moreover, most epidemiologic studies have been done in psychiatric populations where control groups have been uncommon. Independent reports of spontaneous DK, however, have ranged from 0 to 38% [23], and the recent discovery of a non-APD-exposed [12] group has raised concern that the association between APD and DK may be largely coincidental.

Relatively few studies have been reported which examine the developmentally disabled (DD) where brain damage is a distinguishing characteristic, the prevalence of DK is high, and where APD use has been widespread [1, 19, 20, 31, 43]. Where brain damage has been specifically evaluated as a risk factor, the results have often been equivocal [23]. Still, those who appear to be more impaired often have more DK [13,45], and it is critical to determine whether the brain-damaged are vulnerable to commonly-used drugs. The problem is compounded by a relatively unrestricted definition of "tardive" which implies that the symptoms may appear at any time after the drugs have been discontinued, so that virtually any new symptom may be considered drug-related. Controls and quantitative data are obviously desirable, however, old medical records are not always available or accurate, and other classes of drugs, commonly used in DD hospitals, have also been reported to cause DK [3, 7, 5, 21, 26, 27, 30, 32, 36, 37, 47], suggesting the need for large-population, multi-variate analyses.

The present study provides such an analysis using qualitative data and control groups. The relationships between gender and age were examined, and compared in an APD-exposed and non-APD-exposed population.

METHOD

Subjects

The entire population of a large developmentally-disabled (DD) hospital (N=1282) was examined. The Sonoma Developmental Center is one of eight facilities for the developmentally disabled located in California. The age of the population ranges from infancy to senescence (1–98 years)

TABLE 1
EXPLANATION OF VARIABLES

Variable	Values	Definition
APD	0	No history of APD-exposure
	1	History of APD-exposure
Gender	1	Male
	2	Female
CP	0–3	No CP–severe CP
EP	0–8	No EP–severe EP
AUD	0–3	Normal–profound loss
VIS	0–6	Normal–total blindness
SC*	*t*-scores	High score=good behavior
PSS*	*t*-scores	High score=good PSS
DK, DT, AKA, PK, PX	0	No symptom
	1	Symptom present

APD=Antipsychotic drug, CP=Cerebral palsy, EP=Epilepsy, AUD=Auditory handicap, VIS=Visual handicap, SC=Self-control, PSS=Personal self-sufficiency, DK=Dyskinesia, DT=Dystonia, AKA=Akathisia, PK=Parkinsonism, PX=Paroxysm.
*Derived from analysis of California Client Development Evaluation Report (CDER) [46].

with a mean of 35.4 years. Mental retardation ranges from mild to profound with 73% listed as profoundly retarded and 18% as severely retarded. The gender distribution is 48% female, 52% male.

Evaluation

Each subject was rated for the presence of any of several types of movement disorder including dyskinesia, dystonia, akathisia, parkinsonism, and paroxysms. A rating scale, known as the Sonoma Involuntary Movement Assessment System (SIMAS), was created for use with the developmentally disabled although it is applicable to any population. The assessment utilizes a modified free examination to facilitate examination of non-compliant subjects. Inter-rater agreement ranged from 90% after two hours of training to 95% after 6 hours of training. The definition of dyskinesia is restricted to choreoathetoid movement while dystonia is defined as an abnormality of posture and/or the movement leading to a temporary abnormal posture—as in torticollis or oculogyria. "Paroxysm" is chosen as a generic term, rather than myoclonus, to permit inclusion of all types of abrupt phenomena, e.g., vocalizations. Both the severity and persistence of each symptom was rated although only the presence or absence of a movement disorder was evaluated in this part of the study. Questionable cases were excluded, however, the full range of severity (minimal to severe) was included. All subjects were examined by an experienced neurologist whose test-retest reliability ranged from 93–100%. Each subject was examined for a mimimum of 10 minutes; indirect and remote observations were made as well as direct physical examination and activated examination where pertinent and possible.

TABLE 2
DEMOGRAPHIC VARIABLES PREDICTING MOVEMENT DISORDERS

	DK (48%)[1]	DT (29%)	AKA (13%)	PK (3%)	PX (4%)
Age	0.12‡[2]	0.06†	−0.06†	0.20‡	NS
Sex	0.05*	−0.10‡	NS	−0.07†	NS
CP	NS	0.23‡	−0.09†	−0.09†	NS
EP	NS	−0.08‡	−0.08‡	NS	NS
Visual	−0.08‡	−0.06†	NS	NS	NS
Auditory	−0.05*	NS	NS	NS	NS
PSS	NS	−0.24‡	NS	NS	NS
SC	0.01†	0.1‡	−0.17‡	NS	NS
APD	NS	NS	0.10‡	NS	NS

[1]Prevalence of movement disorders in the entire population.
[2]Beta weights from multiple regression equations.
*$p<0.10$, †$p<0.05$, ‡$p<0.01$.
DK=Dyskinesia, DT=Dystonia, AKA=Akathisia, PK=Parkinsonism, PX=Paroxysm.
CP=Cerebral Palsy, EP=epilepsy, Visual=Visual Handicap, Auditory=Hearing Handicap, PSS=Personal Self-Sufficiency, SC=Self-Control, APD=Antipsychotic-Drug exposure=>1 continuous month.

Data Collection

APD-exposure was determined from three sources: (1) the hospital records of all patients were reviewed for four categories: (a) more than 1 month continuous exposure, (b) less than 1 month continuous exposure, (c) no exposure, and (d) insufficient information. Subjects in group b were incorporated into group c, and subjects in group d were excluded from further analysis. (2) Current drug usage was determined by review of the hospital pharmacy's data base of currently prescribed drugs. (3) Drug use during the previous four years was derived from a questionnaire sent to each subject's primary health-care provider. Only the presence or absence of a drug was evaluated. Drug-review and symptom-evaluation were conducted independently. APD included in the survey were: chlorpromazine, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, perphenazine, prochlorperazine, promazine, thioridazine, thiothixene, and trifluoperazine.

Epidemiologic data were derived from the Client Development Evaluation Report (CDER), an on-going data base which is updated annually on approximately 68,000 DD persons in California. An explanation of the epidemiologic variables is outlined in Table 1.

Analysis

Regression equations predicting each of the five abnormal movement symptoms were developed for the entire sample using APD-exposure, demographic factors, and measures of brain dysfunction as predictors. Subgroups defined by age, gender, and APD history were compared, and a totally drug-free subsample (N=51) was examined for prevalence of the movement disorders.

To further evaluate the relationship between APD-exposure and DK, two hypotheses were entertained: (a) APD-exposure places one at higher risk for DK, and (2) the timing of the sample is important with regard to the recency of APD-exposure. To test these hypotheses, while examining for the effects of age and sex, a series of multiple regression equations were created using DK as the dependent measure. Two

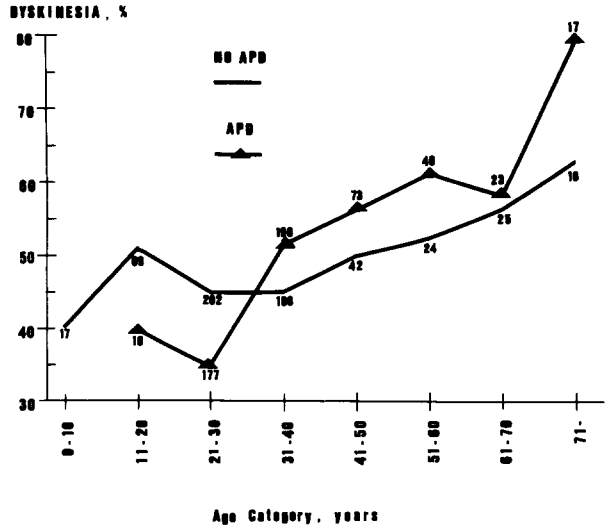

FIG. 1. Dyskinesia as a function of age and antipsychotic-drug exposure. Numbers at each point on the graph refer to numbers of subjects. APD=antipsychotic-drug exposure.

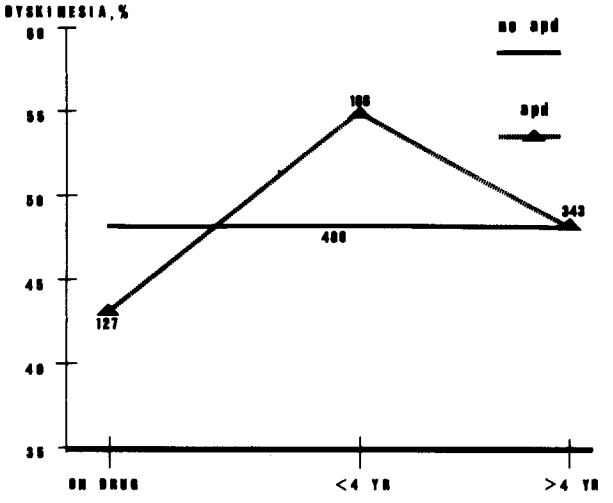

FIG. 2. Dyskinesia as a function of the recency of antipsychotic-drug exposure. Numbers at each point on the graph refer to numbers of subjects. APD=antipsychotic-drug exposure.

dummy variables for drug exposure were created in which the degrees of freedom were partitioned into two orthogonal planned comparisons—a linear comparison (APD-exposure vs. no APD-exposure) and, within the APD-exposed group, a quadratic comparison (current APD-exposure vs. APD-exposure=<4 years vs. APD-exposure >4 years). Interaction terms were tested in a backwards regression with non-significant interactions pooled into the error term.

RESULTS

The prevalence of dyskinesia in the entire sample of 1282 (submitted for publication) was 48%. Dystonia, akathisia, parkinsonism, and paroxysms occurred in 29%, 13%, 3%, and 4% of the population respectively. Many subjects (72%) had multiple symptoms—i.e., 28% had none of the five symptoms. The greatest prevalence of two coexistent symptoms occurred between dyskinesia and dystonia where 36% of those with dyskinesia also had dystonia (χ^2=28.9, p<0.0001).

Of 1310 medication records examined, 1097 records had sufficient information to determine their lifetime drug history. Fifty-two percent of the sample were exposed to APD for at least one continuous month while 45% had no history of APD use. The remaining 3% were exposed but for less than one month. Eleven percent of the total population are currently receiving APD and an additional 9% have been on these medications sometime in the last 4 years.

Results of the initial regression equations predicting the various movement disorders, using demographic factors, measures of brain dysfunction, and APD-exposure, are presented in Table 2. The various movement disorders were readily distinguished by differential patterns of predictors, however, APD-exposure was a significant (p<0.01) predictor only for akathisia. Other variables predicting akathisia imply that this movement disorder is prevalent among younger, relatively healthy individuals with poor self-control. DK was most closely associated with increased age, more often among females, and was not associated with behavioral problems, or with visual or auditory handicaps. Of the remaining three symptoms, there were no significant predictors of paroxysms, parkinsonism was positively correlated with age and male gender, and dystonia was associated with cerebral plasy—a redundancy in the California data base where cerebral palsy is equated with dystonic postures.

Based on the results of the regression analysis, the total sample was divided into appropriate subsamples for further analysis of drug exposure. Overall, there was no significant correlation of APD with DK (r=.00). Forty-eight percent of the population had DK in the APD-exposed group, and 48% of the population had DK in the non-APD-exposed group. Conversely, within the DK group, 54% had APD-exposure while 46% had none, a non-significant difference. In the subsample (N=51) who had never received psychoactive medications of any kind, the prevalence of DK was 49%, not significantly different from the total sample. The demographic characteristics of the three groups were similar.

When DK is plotted as a function of age (Fig. 1), a general increase in age-related incidence is apparent. After age 31 years, persons with APD-exposure have more DK than non-exposed persons. The slope of the APD-exposed population is slightly greater than the non-APD-exposed group, however the slope begins below the non-APD-exposed group. There are significant differences between the APD-exposed and no-APD groups in the 11–30 year categories where the APD-exposed group is older, has less self-control, and has a higher average IQ.

With regard to the planned comparisons of linear and quadratic components of APD-exposure, the regression equation yielded significant results (R^2=0.03, F(5,1045)=6.70, p<0.0001). Drug exposure was a significant factor in the linear (B=−0.20, F=6.28, p<0.01) comparison, and marginally so in the quadratic comparison (B=0.06, F=3.38, p<0.07). DK was predicted by increased age (B=0.18, F=25.22, p<0.001) with a tendency for DK to be more prevalent among females (B=0.06, F=3.33, p<0.07). The main effects of age and the linear comparison of APD-exposure were qualified by their significant two-way interaction (B=0.20, F=6.58, p<0.01). APD-exposure was not significantly different for either gender at any age category.

When APD-exposure was subdivided into three

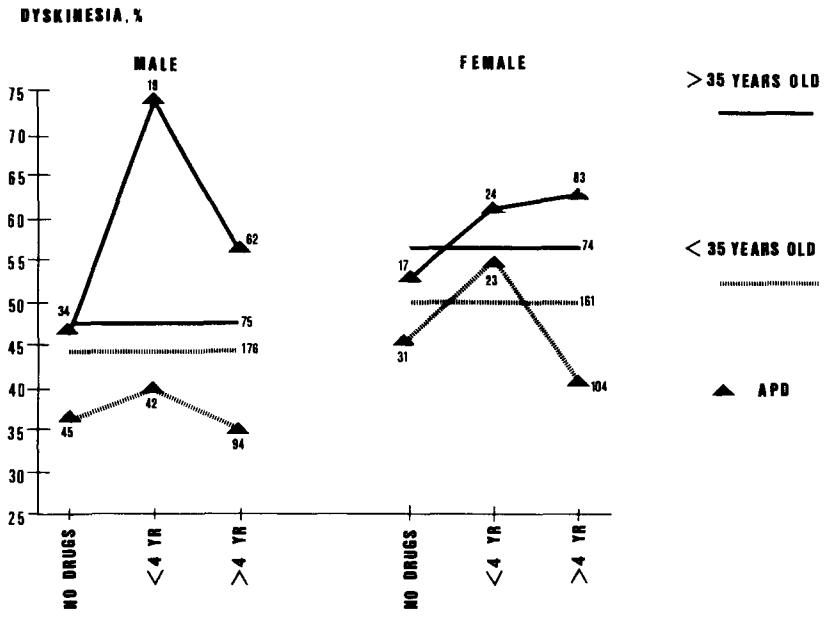

FIG. 3. Dyskinesia as a function of antipsychotic-drug exposure, age and gender. Numbers at each point on the graph refer to numbers of subjects. APD=antipsychotic-drug exposure.

categories based on recency of exposure to APD, DK prevalence in the group currently receiving APD (phase 1) was less than that in the no-APD group. DK prevalence was greatest in the group who had been withdrawn from APD within four years (phase 2). DK prevalence among subjects withdrawn more than four years age (phase 3) was similar to that in the no-APD group (Fig. 2). With minor variations, this inverted-V shaped curve was characteristic of all subgroups of the total sample divided on the basis of age (younger: <=35 years; older: >35 years), and gender (Fig. 3).

The younger male APD-exposed groups all showed less DK than non-APD-exposed males of comparable age. Demographic differences between APD and no-APD groups below age 35 years were greater than those between similar groups older than 35 years, probably due to recent admitting practices. Within the younger sample, the non-APD-exposed group was younger than the APD-exposed group, with lower IQ scores, less self-sufficiency, greater self-control, and more medical disabilities (epilepsy and cerebral palsy). Within the older sample, APD and no-APD groups differed significantly only in self-sufficiency, self-control, and cerebral palsy (Table 3).

DISCUSSION

The relationship between APD and DK has been founded on retrospective studies using nominal drug data—such as the present study. Studies using quantitative drug data have generally not supported a dose-dependent relationship. Even more crucial has been the rarity of control groups, leading to a circular logic where "tardive dyskinesia" has been regarded as "caused" by APD, and "tardive" defined as "exposed to APD." Without a control group, the association between APD and DK may be a coincidental correlation with a third factor, e.g., schizophrenia and/or brain damage.

In the present study, which does have a non-APD-exposed group, the outcome depended on the method of analysis. When the recency of APD-exposure was considered, a significant ($p<0.01$) relationship between APD and DK was determined, however the linear relationship accounted for only 3% of the variance. When APD-exposure was considered as a binomial variable, there was no correlation between DK and APD. Fortuitous exposure to other psychoactive medications probably did not influence the no-APD group, since there was as much DK in persons not exposed to any psychoactive drugs as there was in persons who were exposed to APD. A large British study [12] with a control group also found no correlation between APD and DK; when corrected for age [9], a slight correlation with APD was noted, however the majority of patients appeared to have DK related to their primary illness, chronic schizophrenia. Studies of tardive dyskinesia in the DD have generally pre-judged the relationship between DK and APD. In two small (N=95) studies, Gualtieri *et al.* [17] reported a 33% prevalence but included no APD-control group. In a larger study [40] (N=211) with mean age and inclusion criteria similar to the present study, the prevalence was 30% but, again, no non-APD-exposed group was included. In a study of a DD population which did evaluate non-APD-exposed persons [22], the control group had consistently more DK than the APD-exposed group. Another small study (N=24) with a control group [2] found no significant relationship between APD and DK.

Absence of a control group, due to widespread use of a medication, is not unique to studies of APD. The same situation probably obtains with long-term levodopa therapy in parkinsonism [33]. Without such a control group, it is difficult to know whether the dyskinesias which often appear after years of levodopa therapy are related to the drug, or to the progress of the underlying disease [28, 33, 34]. In a study [39] which is analogous to this problem, the relationship was examined between tics and central-nervous-system stimulants in several monozygotic-twin pairs. Tardive tics did appear after drug treatment, however the unexposed twins de-

TABLE 3

COMPARISON OF DRUG/NO DRUG POPULATION FOR AGE CATEGORIES <=35 YEARS AND >35 YEARS

		Age <=35 Years				Age >35 Years			
Variable	APD	N	Mean	t	$p<$	N	Mean	t	$p<$
Age	No	337	24.3	−9.5	0.0000	149	50.9	1.25	NS
	Yes	339	28.5			239	49.1		
EP	No	334	2.2	5.18	0.0000	149	1.2	0.11	NS
	Yes	338	1.4			239	1.2		
CP	No	337	1.9	11.55	0.0000	149	1.8	7.97	0.0000
	Yes	339	0.9			239	0.7		
PSS	No	337	36.7	−11.77	0.0000	149	41.5	−5.45	0.0000
	Yes	339	43.7			239	46.3		
IQ	No	328	10.3	−4.95	0.0000	146	19.7	−0.01	NS
	Yes	322	14.7			221	19.8		
SC	No	337	49.5	14.05	0.0000	149	51.8	11.22	0.0000
	Yes	339	37.7			239	41.7		

APD=history of antipsychotic drug use; EP=epilepsy; CP=cerebral palsy; PSS=personal self-sufficiency; IQ=intelligence quotient; SC=self control.

veloped the same symptoms, arguing that the etiology was the underlying neuropsychiatric disability for which the stimulants were prescribed rather than the stimulants themselves. Indeed, the same conclusion has been suggested for the relationship between APD and tardive dyskinesia [9], and anecdotal reports suggest that such involuntary movements were conspicuous in institutionalized psychiatric populations in the pre-APD era [8, 9, 11].

The effect of age and gender on the prevalence of DK has often been reviewed [23]. The former is generally supported, the latter less so. Significant variables have not always been controlled, however, and different methodologies have led to different conclusions. When the present population was evaluated with no regard for drug exposure (submitted for publication), a significant relationship was demonstrated between DK and age, as in many prior studies. The age-related increase was attributed largely to females over forty years, a finding which also finds support in the literature. When the same populations were reevaluated with regard to APD-exposure, the APD-exposed elderly (age as a categorical variable) had significantly more DK than the non-exposed elderly ($p<0.01$). The APD-related increase in DK is seen in Fig. 1 where, however, there is acutally less DK in the APD-exposed age-groups between 11–30 years. The interaction may be the result of the cross-sectional analysis and population differences (the result of changing admission practices). In the 11 to 30-year age groups (Table 3), the no-APD group is more medically and developmentally disabled, which may account for the higher prevalence of DK, while the APD-exposed group has less self-control—presumably the reason for the use of APD. The difference between APD-exposed/no-APD females persisted only as a non-significant trend. Similar findings were reported in an on-going prospective study (in a psychiatric population) [24] which demonstrated a positive correlation with age but failed to find a significant interaction of sex by age—although the same non-significant trend was noted for older females to be at greater risk; the study did not report APD-control values. In a small study (n=40) of elderly DD females (mean age=65 years) [4], also using nominal drug data, APD-exposed persons appeared to be at greater risk: of the 9 elderly DD females who had received APD, 100% had dyskinesia compared to 80.6% (25/31) of those who had not. In the recent study by Richardson and associates, the DD population [40] was selected on the basis of exposure to APD. Within this all-APD-exposed group, "tardive dyskinesia" was correlated positively with age, however correlation with female gender depended on the method of analysis: the association with female gender was significant only in a bivariate comparison and failed to reach significance in the multivariate analysis where age was highly significant.

When APD-exposure was sub-divided into three categories defined by the recency of exposure, the inverted-V shape, created by the three phases of recency-of-exposure, was characteristic of all groups, lending credence to its authenticity. Although the results of this (quadratic) analysis are only marginally significant ($p<0.07$), the trends are interesting and may be clarified by future research. Phase 1, current exposure, probably represents the masking effect of APD. The peak effect (phase 2) is compatible with withdrawal-emergent effects. Both effects have been often reported in the psychiatric literature, although a distinction between "masking" and "treatment" may be biased. Withdrawal-emergent DK has also been reported [2,18] in the DD, as well as apparent masking [22]; conversely, one study noted relatively more DK in persons currently receiving APD [40]. The shape of the final limbs of the inverted-V (phase 3) suggests that the older population does not recover as well as the younger, and females less so than males. However, although the shape of the plot suggests longitudinal progression, the data are acutally cross-sectional, and population differences may exist between the groups in each phase. The failure of the younger males to reach control values while still displaying the characteristic inverted-V probably refelcts heterogeneity within the younger group due to recent differences in admission policies—although it is not clear why this difference exists for males but not for females. These differences were not significant between the older APD-exposed group and its control.

Within the 4-year period after APD withdrawal defined in this study, the time of the peak value of withdrawal-

emergent enhancement is unknown; the numbers of subjects in sub-categories within this period were too few to provide reliable information. In one study, withdrawal-emergent effects had resolved by 10 weeks [2], while, in another [22], DK was still increasing 9 months after withdrawal.

Overall, the combined effect of APD, age, and gender accounted for only 3% of the variance, suggesting that these variables are less important than other, unidentified variables. Of those unidentified factors which most account for the variance, brain damage must be considered. The prevalence of DK in this DD population is clearly higher than the non-DD population and is, presumably, related to nonspecific encephalopathy, or brain damage—the factor which obviously distinguishes the DD from the non-DD population. Since all the movement disorders were described well before the APD era, a high prevalence would certainly be expected in any large brain-damaged sample—with or without APD exposure. On the other hand, the prevalence of DK in this DD population, when adjusted for age and inclusion criteria, was very similar to the schizophrenic control group noted above (60% vs. 67%), suggesting that markers of overt brain damage are greater in schizophrenic populations than is generally believed, or that only selected encephalopathic features, shared by both groups, are necessary for DK. Where brain damage has been specifically evaluated as a risk factor for DK, the results have often been equivocal [23]. In the study by Richardson *et al.* [40], DK was not significantly associated with any of the diagnostic categories indicative of neurological deficit. The same is true in this study, where there was no significant correlation between DK and putative measures of brain damage, i.e., I.Q., cerebral palsy, epilepsy—however the sample represents a very compressed range of encephalopathy even among the DD population, and the independent variables are imperfect measures of differences in this range.

In this study, the outcome depended on the method of analysis: in the total sample, no relationship was demonstrated between APD and DK when APD-exposure was considered as a binomial variable—the method used in most prior analyses. When the recency of APD-exposure was considered, statistically significant relationships were demonstrated, however the relationships accounted for only 3% of the variance. Of those unidentified factors which do account for most of the variance, brain damage must be suspected but was not confirmed by this study; the failure to do so may be due to inadequate measures of brain damage. This study benefits from its large population and control groups; it is retrospective and cross-sectional, however, and future studies may profit from prospective, longitudinal designs with appropriate controls. The timing of the examination for DK, with regard to the recency of drug exposure, will affect the outcome and may have contributed to differences among some studies, e.g., short-term withdrawal effects, such as withdrawal-emergent DK, must be distinguished from long-term effects, such as persistent DK. As in most prior studies, this study does not use quantitative data for actual dosage, duration of therapy, or for the severity or persistence of symptoms; the discrepancies of the qualitative-data design are partially offset by the relatively large population, however the use of quantitative data will add an important dimension to future investigations.

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