

# Neuroleptic-Related Dyskinesias in Children and Adolescents

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**Background:** Few studies have investigated the comparative risk of neuroleptic-related dyskinesias in children and adolescents receiving typical versus newer, atypical antipsychotics. This prospective study was completed to test whether clinical use of atypical antipsychotics is associated with less risk for developing neuroleptic-related dyskinesias than clinical use of typical neuroleptics in an unselected heterogeneous population of seriously emotionally disturbed youths admitted to acute residential treatment. We also tested a novel model of predictive risk for neuroleptic-related dyskinesias in children and adolescents.

**Method:** 102 children and adolescents receiving typical neuroleptics, atypical antipsychotics, or the combination were studied. Youths developing neuroleptic-related dyskinesias were compared with youths free of dyskinesias over a 3-month study period on demographic, diagnostic, and treatment variables. Logistic regression was utilized to develop a novel model of predictive risk.

**Results:** Of neuroleptic-treated youths, 5.9% had probable tardive dyskinesia, a rate less than the prevalence of tardive dyskinesia in chronic neuroleptic-treated adults. Use of typical neuroleptics was significantly ( $p = .03$ ) associated with dyskinesia compared with use of atypical antipsychotics. Four variables including IQ, initial Abnormal Involuntary Movement Scale score, type of antipsychotic, and cumulative number of risk factors accounted for 35.8% of the variance when predicting dyskinesic status.

**Conclusion:** Use of atypical antipsychotics appears to be associated with less dyskinesia risk than typical neuroleptics in an unselected group of seriously emotionally disturbed children and adolescents. Results support a cumulative risk model of neuroleptic-related dyskinesia in youths. (*J Clin Psychiatry* 2001;62:967-974)

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Few studies have investigated neuroleptic-related dyskinesias in children and adolescents despite wide clinical acceptance of these medications in the pediatric age range. In youths, most studies of antipsychotic-related dyskinesias have investigated risk with typical neuroleptics.<sup>1-3</sup> Few studies have directly compared atypical neuroleptics with typical neuroleptics in the risk for dyskinesias in the child and adolescent population.<sup>4</sup> It is generally assumed among pediatric clinicians that atypical antipsychotics are safer in youths than typical neuroleptics, but this issue is not as well studied in children as in adults. With typical neuroleptics, reports indicate that between 12% to 33% of youths who receive antipsychotics develop dyskinesias.<sup>2,5,6</sup> The rate of withdrawal dyskinesia is higher (1% to 51%) than the rate of tardive dyskinesia in children and adolescents (1% to 4.8%), and withdrawal dyskinesia in youths is generally reversible.<sup>3-5</sup> In adults, approximately 25% of patients receiving extended neuroleptic treatment will manifest treatment-emergent tardive dyskinesia associated with varying degrees of social and/or functional impairment.<sup>7</sup> Youths receiving typical neuroleptics may have less risk for the development of emergent tardive dyskinesia than adults.<sup>8</sup>

Risk factors for antipsychotic-related dyskinesia development are better studied in adults than children and adolescents. In adults, it is well established that atypical antipsychotics such as olanzapine, risperidone, quetiapine, and clozapine are associated with less risk for dyskinesia than are typical neuroleptics.<sup>7,9,10</sup> The majority of studies support extrapyramidal side effects (EPS) as a risk factor in adults.<sup>11-13</sup> Other possible risk factors in adults include advanced age, use of concomitant anticholinergics, female gender, affective psychoses, cognitive difficulties, antipsychotic treatment variables (e.g., higher



potency, higher daily dose, typical neuroleptic exposure, intermittent neuroleptic exposure), and diabetes.<sup>12,14</sup>

In children, most studies have investigated populations with specific disorders, such as autism, mental retardation, or childhood-onset schizophrenia, as opposed to risk among heterogeneously diagnosed children in naturalistic treatment settings.<sup>2,5,6,15</sup> Findings are somewhat more contradictory in children and adolescents than in adults. Studies of autistic and mentally retarded children receiving typical neuroleptics have reported increased risk among this population for greater cumulative dose of drug and/or longer cumulative neuroleptic exposure, lower IQ, female gender, and presence of obstetrical complications at birth.<sup>1,2,15</sup> One study<sup>5</sup> of children with childhood-onset schizophrenia has also reported that longer duration of neuroleptic exposure is associated with increased risk of tardive dyskinesia. In contrast, one study<sup>6</sup> assessing antipsychotic-related dyskinesia risk in heterogeneous treatment populations of children and adolescents found no associations with dose level or cumulative exposure to drug.

Because even young children are treated with antipsychotics and because much less research has been completed to date assessing risk factors for antipsychotic-related dyskinesias in youths compared with adults, further studies are necessary. As atypical antipsychotic treatment in youths becomes more common,<sup>16</sup> studies addressing the comparative risk for dyskinesias between the newer atypical antipsychotics and older, typical neuroleptics are important to evaluate safety of use in children and adolescents.

We conducted a prospective, clinical study of antipsychotic-related dyskinesias in an unselected and heterogeneous population of 95 youths admitted to an acute residential treatment center. We hypothesized that treatment with a typical neuroleptic would be associated with significantly greater risk for developing an antipsychotic-related dyskinesia than treatment with the atypical antipsychotics risperidone or olanzapine. Additional aims are (1) to document the 3-month prevalence of antipsychotic-related dyskinesias in an unselected pediatric psychiatry treatment population, (2) to describe the topography of dyskinesias in the study population, (3) to compare youths who develop antipsychotic-related dyskinesias with youths who do not on a number of variables to identify correlates of risk in this population, and (4) to test a novel cumulative risk model of antipsychotic-related dyskinesias in children and adolescents.

## METHOD

### Subjects

The study population consists of all 95 evaluable subjects of 102 children and adolescents who were receiving antipsychotic medication at admission to an acute residential treatment facility, out of a total population of 291 con-

secutive admissions. The mean  $\pm$  SD age of the study population is  $13.7 \pm 2.6$  years (range, 7–21 years). There were 19 children (20%), age  $\leq 12$  years, and 76 adolescents (80%), age  $\geq 13$  years, in the study sample. Ethnic composition includes white, 75.8% (N = 72); African American, 13.7% (N = 13); Hispanic, 8.4% (N = 8); Asian, 1% (N = 1); and other, 1% (N = 1). Gender composition is 82.1% (N = 78) male and 17.9% (N = 17) female. Mean  $\pm$  SD full-scale IQ is  $80.4 \pm 16.5$  (range, 45–127). Data were collected beginning in 1993 and ending in 1999, a time when dosing practices with atypical neuroleptics for referred youths were rapidly changing. Written informed consent and child assent were obtained on all study subjects after procedures were fully explained.

### Medication

At admission, antipsychotic medications included typical neuroleptics in 48% (N = 49) and atypical antipsychotics in 45% (N = 46). Combined pharmacotherapy with both a typical and an atypical antipsychotic occurred in 7% (N = 7) of the study sample. Specific typical antipsychotics in study subjects included chlorpromazine in 5.9% (N = 6), thioridazine in 12.7% (N = 13), perphenazine in 14.7% (N = 15), haloperidol in 9.8% (N = 10), thiothixene in 2.9% (N = 3), pimozide in 1% (N = 1), and trifluoperazine in 1% (N = 1). Specific atypical antipsychotics included risperidone in 29.4% (N = 30) and olanzapine in 15.7% (N = 16). Most youths were receiving more than one psychiatric medication at admission, with a mean  $\pm$  SD number of medications of  $3.5 \pm 1.3$  (range, 1–8). Anticholinergics were present in 25.3% (N = 26), stimulants in 21.1% (N = 22), antidepressants in 54.7% (N = 56), anticonvulsants in 54.7% (N = 56), lithium in 11.6% (N = 12), clonidine in 16.8% (N = 17),  $\beta$ -blockers in 7.4% (N = 8), antihistamines in 7.4% (N = 8), and anxiolytics in 11.6% (N = 12).

Subjects were unselected for any psychiatric diagnosis, were seriously emotionally disturbed, and in all cases, had failed multiple previous outpatient and inpatient mental health interventions. Primary psychiatric disorders at admission included psychotic disorders in 28.4% (N = 27), affective disorders in 23.2% (N = 22), disruptive behavior disorders in 31.6% (N = 30), developmental disorders (e.g., autism and pervasive developmental disorder) in 6.3% (N = 6), tic disorders in 3.2% (N = 3), and others (e.g., intermittent explosive disorder, eating disorders) in 7.3% (N = 7).

### Diagnosis and Assessment

Subjects were assessed weekly by nursing staff using the Abnormal Involuntary Movement Scale (AIMS)<sup>17</sup> and scored according to the criteria of Munetz and Benjamin.<sup>18</sup> Neuroleptic-related dyskinesias were scored as present or absent using the criteria of Schooler and Kane.<sup>19</sup> To increase statistical power, a category of subthreshold

dyskinesia, defined as a total score of mild (AIMS  $\geq 2$ ) in one body area, was included in 5 subjects. Seven subjects concurrently receiving both a typical and an atypical antipsychotic could not be classified into mutually exclusive medication groups for the purposes of statistical comparison and were excluded from the analysis, leaving a total of 95 evaluable subjects. After admission, subjects continued or discontinued their antipsychotic medication according to the clinical decision of the treating child psychiatrist. Youths developing dyskinesias ( $N = 17$ ) were compared with children developing no dyskinesias ( $N = 78$ ) on demographic, diagnostic, and treatment variables over the first 3 months after admission.

AIMS examination was completed by nursing raters who were blind to study goals and hypotheses. However, in this clinical treatment setting, nurses could not be blinded to the clinical status of the patients. Nurse raters were trained by a child psychiatrist (D.F.C.) using didactic instruction, written material,<sup>18</sup> and videotaped practice to an item-by-item interrater agreement of 96%. Each child's treatment nurse and a child psychiatrist (D.F.C.) independently rated each AIMS. Good reliability was demonstrated between the psychiatry rater and multiple nurse raters with an intraclass correlation coefficient of .92 across 100% of ratings.

EPS were assessed by direct subject physical examination and clinical interview for akathisia and dystonia for each subject daily by nursing staff, weekly by the treating psychiatrist, and at admission using screening neurologic examination by the admitting pediatrician. Parkinsonian rigidity was assessed using question 5 (instruction 9) of the AIMS for extremity rigidity.<sup>18</sup> EPS were scored positive if symptoms were present and interfered with daily functioning.

Prior to AIMS ratings, demographic, diagnostic, and treatment variables were collected from extensive archival information available for each subject. These included age; gender; ethnicity; Tanner stage of sexual development as assessed by pediatric examination at admission; time since first neuroleptic use in months (as estimated from time of first appearance in the youth's medical record); known previous history of a movement disorder; any evidence at admission physical examination of a movement disorder, psychiatric diagnosis, or central nervous system (CNS) organicity (including abnormal neurologic screening physical examination, history of seizure, or abnormal electroencephalogram or CNS-imaging results); presence of EPS; neuroleptic potency (high vs. low); neuroleptic daily dose converted to chlorpromazine equivalents (CPZe); rapidity of taper for children discontinuing their antipsychotic defined as slow ( $\leq 25\%$  per month) or fast ( $> 25\%$  per month); history of multiple neuroleptic trials with different agents; and current polypharmacy at admission. IQ was assessed by psychologists using the Wechsler Intelligence Scale for Children (WISC-III)<sup>20</sup> for

children 6 through 16 years of age and the revised Wechsler Adult Intelligence Scale (WAIS-R)<sup>21</sup> for youths 16 years and older. All psychiatric diagnoses were made by a board-eligible or board-certified child psychiatrist using DSM-IV criteria.<sup>22</sup> The reliability of the rating procedure has been previously reported.<sup>23</sup>

On the basis of previous research, a composite total risk factor variable was created. This total factor is the sum of individual risk factors found important in previous neuroleptic dyskinesia research, including (1) total lifetime exposure to neuroleptics greater than 3 months,<sup>2,14,19</sup> (2) previous history of abnormal movement disorder that may indicate subtle abnormalities of the basal ganglia (baseline AIMS score  $\leq 2$  at admission, which may signify abnormality),<sup>8</sup> (3) CNS organicity,<sup>2</sup> (4) history of EPS,<sup>11-13</sup> (5) concomitant anticholinergic use,<sup>14</sup> (6) rapid taper of neuroleptic ( $> 25\%$  reduction in dose per month), (7) history of multiple neuroleptic trials,<sup>24</sup> (8) high neuroleptic dose defined as  $\geq 150$  CPZe per day,<sup>3,25</sup> (9) high-potency neuroleptic use,<sup>2,3</sup> and (10) use of a typical neuroleptic.<sup>5</sup>

### Statistics

The association between dyskinesia status and potential predictor variables was first investigated with bivariate analyses. For dichotomous variables, Fisher exact test was used. For most ordinal or continuous variables, t tests were conducted. However, if an ordinal or continuous variable deviated from normality, the nonparametric Mann-Whitney U test was used. All predictors that were found to be associated with dyskinesia status with a p value of at least .10 were entered into a forward stepwise logistic regression, with dyskinesia as the outcome.

## RESULTS

### Prevalence

Based on weekly serial AIMS examination, the 3-month prevalence of dyskinesia in the total admission population of 291 seriously emotionally disturbed youths is 5.8% ( $N = 17$ ). The 3-month prevalence of neuroleptic-related dyskinesia in the 95 evaluable subjects admitted on antipsychotic treatment is 17.9% ( $N = 17$ ). Of the 95 subjects admitted on antipsychotic treatment, 62 discontinued neuroleptics upon the recommendation of psychiatrists within 3 months after admission to acute residential treatment. Among these 62 children and adolescents, 9 (14.5%) developed a new neuroleptic-related dyskinesia that was not present at admission. These youths were discontinued from antipsychotic treatment because they did not have a psychiatric diagnosis consistent with neuroleptic treatment, were mostly treated for aggressive behaviors, and improved within the behavioral structure of residential treatment. Of the 33 youths who continued to take antipsychotics, all had developmental delay, a psychotic disorder, psychotic depression, bipolar disorder, or tic

disorder, disorders consistent with antipsychotic treatment as the current standard of care.

Of the 17 subjects experiencing a neuroleptic-related dyskinesia, 47% (N = 8) met criteria for withdrawal dyskinesia, 24% (N = 4) for probable tardive dyskinesia, and 29% (N = 5) for subsyndromal dyskinesia. Thus, 71% of dyskinesia subjects (N = 12) met full Schooler and Kane<sup>19</sup> criteria for withdrawal dyskinesia or probable tardive dyskinesia. Five subjects experienced subsyndromal dyskinesia symptoms rated as mild movements (AIMS score  $\geq 2$ ) in one body area. Of the 7 subjects receiving combined typical and atypical antipsychotic therapy who could not be classified into unique medication groups for the purposes of statistical comparison and were excluded from subsequent analysis, 2 patients (29%) had probable tardive dyskinesia at 3-month outcome. Counting the 2 subjects with combined neuroleptic-antipsychotic therapy and 4 subjects with monotherapy, 6 (5.9%) of 102 neuroleptic-treated subjects had probable tardive dyskinesia at 3-month outcome.

### Topography

The topography of dyskinetic movements for the 17 youths who developed dyskinesia includes 15 subjects (88%) who developed facial/oral dyskinesias, 10 subjects (59%) with extremity dyskinesias (usually of the fingers), 2 youths (12%) with truncal dyskinesias, and 1 youth (6%) with diaphragmatic dyskinesia characterized by repetitive grunting. Two affected body areas were present in 9 youths (53%), and 3 affected body areas were found in 2 youths (12%). The topography of dyskinesia in our study appears similar to that of adults and previous reports of children and adolescents.<sup>2,3</sup>

### Bivariate Analyses

**Demographic variables.** When demographic variables were examined, the dyskinetic group had significantly lower mean  $\pm$  SD full-scale IQ scores ( $72.2 \pm 16.6$ ) than did the nondyskinetic group ( $82.5 \pm 16.1$ ),  $t = 2.39$ ,  $df = 92$ ,  $p = .02$ . The mean  $\pm$  SD age of the dyskinetic group was  $13.6 \pm 2.7$  years, which did not differ significantly from the mean age of the nondyskinetic group ( $13.7 \pm 2.6$  years),  $t = 0.08$ ,  $df = 93$ , NS. The proportion of boys in the dyskinetic group (88.2%; N = 15) did not differ significantly from the proportion of boys in the nondyskinetic group (80.8%; N = 63), Fisher exact  $p = .73$ . The proportion of whites in the dyskinetic group (82.4%; N = 14) did not differ significantly from the proportion of whites in the nondyskinetic group (76.9%; N = 60), Fisher exact  $p = .76$ . When participants were identified as either prepubertal or postpubertal according to the method of Tanner, the 2 groups did not differ in the proportions who were identified as prepubertal (76.5% [N = 13/17] dyskinetic vs. 72.4% [N = 55/76] nondyskinetic, Fisher exact  $p = 1.0$ ).

**Diagnostic variables.** When diagnostic variables were examined, the proportion of subjects with dyskinesia with neuroleptic-induced EPS (47.1%, N = 8) was significantly higher than among the nondyskinetic group (14.1%, N = 11), Fisher exact  $p = .005$ . There was a trend for more participants in the nondyskinetic group to have been diagnosed with disruptive behavior disorders (35.9% [N = 28] vs. 11.8% [N = 2], Fisher exact  $p = .08$ ).

The groups did differ in their baseline total scores on admitting AIMS, with the dyskinetic group scoring  $0.53 \pm 1.12$  on average, and the nondyskinetic group scoring  $0.11 \pm .44$  on average, Mann-Whitney  $U = 545.5$ ,  $z = 2.25$ ,  $p = .03$ . No differences were found between groups in the proportion of psychotic, affective, developmental, tic, or other diagnoses. Groups did not differ on known previous history of movement disorder or on admitting examination evidence of an abnormal movement disorder.

**Treatment variables.** At admission, the mean  $\pm$  SD neuroleptic dose of subjects was  $271 \pm 315$  mg/day CPZe (range, 20–2500 mg/day). The mean  $\pm$  SD estimated lifetime duration of antipsychotic exposure in our sample was  $13.2 \pm 13.8$  months (range, 1–81 months). When treatment variables were examined, the dyskinetic group had a significantly higher number of subjects treated with typical rather than atypical neuroleptics (76.5%, N = 13) than subjects in the nondyskinesia group (46.2%, N = 36), Fisher exact  $p = .03$ . The dyskinetic group was significantly more likely to be receiving concurrent anticholinergic treatment (47.1% [N = 8] vs. 20.5% [N = 16]; Fisher exact  $p = .03$ ).

Of the 4 subjects receiving atypical antipsychotics who had a dyskinesia, all 4 were receiving risperidone (mean dose =  $3.75 \pm 3.1$  mg/day; range, 1–8 mg/day), and none were receiving olanzapine. Among subjects receiving atypical antipsychotics (N = 46), we compared the dyskinesia versus nondyskinesia group on a proportion of those using risperidone versus olanzapine. We found that 100% of those in the dyskinesia group were taking risperidone (N = 4) versus 61.9% (N = 26) in the nondyskinesia group. This difference was not significant (Fisher exact  $p = .28$ , NS).

The groups did not differ significantly on a history of multiple neuroleptic trials; other concurrent types of medications used including stimulants, antidepressants, anticonvulsants, lithium, clonidine,  $\beta$ -blockers, antihistamines, or anxiolytics; total number of concurrent daily medications; estimated lifetime exposure to neuroleptics, mean neuroleptic dose per day in CPZe; or rapidity of neuroleptic taper.

**Temporal variables.** The estimated time since first neuroleptic use did not differ between subjects with ( $15.3 \pm 17.6$  months) and without dyskinesia ( $12.1 \pm 12.3$  months) ( $t = .901$ ,  $df = 93$ , NS). A safe period of exposure since first starting neuroleptics could not statistically be identified in our sample. Subjects received olanzapine for

**Table 1. Significant Predictors of Dyskinesia Status in Stepwise Logistic Regression<sup>a</sup>**

Variable	B	SE (b)	p	OR	95% CI of OR	% Variance Accounted For
IQ score	-0.045	0.02	.04	0.96	0.91 to .999	9.7
Initial AIMS score	0.85	0.42	.04	2.34	1.02 to 5.37	10.8
Taking typical neuroleptic	2.22	0.80	.005	9.18	1.93 to 43.69	7.5
Number of risk factors	0.47	0.22	.03	1.60	1.05 to 2.44	7.8

<sup>a</sup>Abbreviations: AIMS = Abnormal Involuntary Movement Scale, CI = confidence interval, OR = odds ratio, SE = standard error of the mean.

a significantly longer period of time than subjects received risperidone (18.8 months,  $N = 16$  vs. 9.5 months,  $N = 30$ ;  $t = 2.25$ ,  $df = 44$ ,  $p = .03$ ). Although a direct comparison of dyskinesia in subjects receiving risperidone versus olanzapine was not significant, the fact that olanzapine subjects had a significantly longer period of time since first starting medication without developing any dyskinesias than risperidone subjects had suggests the possibility that olanzapine may be associated with less dyskinesia risk than risperidone during chronic antipsychotic treatment in our study sample.

In the 9 youths who developed a new-onset dyskinesia upon neuroleptic discontinuation, the follow-up AIMS showed a score in the dyskinetic range in a mean  $\pm$  SD  $3.1 \pm 2.3$  days (range, 1–8 days) after discontinuation.

### Outcome

At 3-month outcome, 13 (76.5%) of subjects with an initial score on the AIMS in the abnormal range had normal examinations, and 4 (23.5%) continued to have AIMS scores in the abnormal range. All 13 youths discontinuing their antipsychotic medication at 3 months attained a score on the AIMS within the normal range. The mean  $\pm$  SD time to disappearance of the movement disorder was  $3.5 \pm 3.8$  weeks (range, 1–3 weeks). Of the 4 subjects continuing neuroleptic medication (all were diagnosed psychotic), all continued to demonstrate scores in the abnormal range on the AIMS examination despite continuing antipsychotic therapy and were classified as having probable tardive dyskinesia. Thus, 23.5% ( $N = 4$ ) of youths with a dyskinesia met criteria for probable tardive dyskinesia.

### Risk Factors

A composite variable of the total sum of 10 risk factors was created and compared across the 2 groups. The mean  $\pm$  SD number of risk factors was  $4.53 \pm 1.72$  (range, 0–9). Those who developed dyskinesia had a significantly higher number of total risk factors ( $5.9 \pm 1.7$ ) than those who did not develop dyskinesia ( $4.7 \pm 1.8$ ) ( $t = 2.45$ ,  $df = 93$ ,  $p = .02$ ).

### Logistic Regression

All variables that distinguished the dyskinetic group from the nondyskinetic group at the .10 or lower level of significance were entered into a forward stepwise logistic regression: full scale IQ, baseline AIMS scores, typical versus atypical neuroleptics, presence of neuroleptic EPS, total risk factors, and diagnosis of behavior disorder. Current treatment with anticholinergics was not entered as a separate variable because it was included as one of the risk factors in the total risk factors score. IQ was forced to enter first. All other variables were free to enter at each step. The results can be seen in Table 1. Four variables accounted for 35.8% of the variance when predicting dyskinetic status (model  $\chi^2 = 23.22$ ,  $df = 4$ ,  $p < .001$ ): IQ (odds ratio [OR] = 0.96, 95% confidence interval [CI] = 0.91 to 0.999), initial AIMS score (OR = 2.34, 95% CI = 1.02 to 5.37), typical neuroleptic (OR = 9.18, 95% CI = 1.93 to 43.69), and total risk factors (OR = 1.60, 95% CI = 1.05 to 2.44). These 4 variables allow us to correctly classify 98.7% ( $N = 77$ ) of the nondyskinetic group and 47.1% ( $N = 8$ ) of the dyskinetic group, for an overall correct classification rate of 89.4%.

### DISCUSSION

Our hypothesis that treatment with typical neuroleptics would be associated with significantly greater risk for developing an antipsychotic-related dyskinesia than treatment with the atypical antipsychotics risperidone or olanzapine in an unselected heterogeneous population of seriously emotionally disturbed youths was supported. Previous studies in adults have reported less risk for antipsychotic-related dyskinesias in patients treated with atypical compared with typical antipsychotics.<sup>7,10</sup> Our results suggest that this may be true for children and adolescents as well.

Youths treated with typical D<sub>2</sub> dopamine-blocking neuroleptics were significantly more represented in the group diagnosed as having an antipsychotic-related dyskinesia than were youths treated with the atypical antipsychotics. The groups did not differ on daily antipsychotic dose or in estimated cumulative time of antipsychotic exposure in months. While their receptor affinities may differ, atypical antipsychotics all have the presence in the brain of a high serotonin-to-dopamine receptor blockade ratio of greater than one.<sup>10</sup> This property may play a role in the reported diminished dyskinesia risk with atypical in comparison with typical antipsychotics.

Although subjects receiving risperidone were not statistically more at risk for developing a dyskinesia compared with subjects receiving olanzapine, all of the dyskinesias developing in youths treated with atypical antipsychotics occurred in those receiving risperidone and none with olanzapine, despite olanzapine-treated subjects having almost twice the time since first neuroleptic use (18.8 months) as

subjects receiving risperidone (9.5 months). Although further research is required, this finding suggests the possibility of less dyskinesia risk with olanzapine than risperidone and is consistent with results from studies in adults that directly compare these 2 atypical antipsychotics.<sup>26</sup>

Our 3-month overall prevalence rate (including subsyndromal dyskinesia) of 17.9% and our 12.6% prevalence rate of youths meeting full research criteria for dyskinesia are similar to the 12% prevalence rate of antipsychotic-related dyskinesias reported in other clinical studies of unselected and heterogeneous antipsychotic-treated pediatric patients.<sup>6</sup> These prevalence rates are lower than rates up to 33% of neuroleptic-related dyskinesias reported for children with autism or mental retardation.<sup>2,4,15</sup> Dyskinesia rates for children with autism in previous studies may be higher because they may have been chronically treated with higher doses of neuroleptics than subjects in our sample. The unselected and heterogeneous composition of our population may explain these differences in prevalence rates. Prevalence rates of antipsychotic-related dyskinesias in clinical populations must take into consideration the baseline population rate of abnormal involuntary movements in youth. Our rates are elevated in comparison with the 4.1% baseline rate of abnormal involuntary movements reported for neuroleptic-naïve children in community samples.<sup>27</sup>

Of children admitted on neuroleptic therapy, 6 (5.9%) of 102 youths had probable tardive dyskinesia in the first 3 months after admission to acute residential treatment. This rate is less than the 20% to 25% rate of treatment-emergent tardive dyskinesia reported in adults chronically treated with neuroleptics<sup>7,12</sup> and suggests the possibility that in populations of seriously emotionally disturbed youths with high rates of long-term neuroleptic exposure, rates of tardive dyskinesia may perhaps be lower than in populations of antipsychotic-treated adults. Of youths developing a dyskinesia, 24% had probable tardive dyskinesia in our sample. This prevalence approximates the rates of tardive dyskinesia in adults and reinforces the need to carefully assess dyskinesia status and minimize risk factors for dyskinesia in populations of seriously emotionally disturbed children and adolescents with high rates of chronic neuroleptic exposure.

A novel composite risk factor summing 10 variables identified as important in previous research was successful in distinguishing between the dyskinetic and nondyskinetic groups. To our knowledge this has not previously been reported. The composite variable includes 4 drug factors (use of a typical neuroleptic, total time of exposure to antipsychotic, high dose  $\geq 150$  CPZe per day, high-potency neuroleptic), 3 diagnostic factors (previous history of abnormal movement disorder, CNS organicity, history of EPS), and 3 treatment variables (concomitant anticholinergic use, rapid taper of antipsychotic in those who discontinue, and a history of multiple antipsychotic

drug trials). The results of our study support a cumulative risk model of antipsychotic-related dyskinesias in children and adolescents wherein individual risk factors may not be significant but the total number of risk factors is significant across groups.

Results of logistic regression analysis suggest 4 risk factors that predict dyskinesia. Higher IQ decreases the risk; whereas higher baseline AIMS scores (which suggest the possibility of subtle CNS abnormalities), use of typical D<sub>2</sub>-blocking neuroleptics, and exposure to increasing numbers of risk factors all increase the risk of dyskinesia.

Lower IQ has been reported a risk factor for abnormal involuntary movements in neuroleptic-naïve children.<sup>27</sup> Our results suggest it is also a risk factor for antipsychotic-related dyskinesias in clinically referred youths. These results agree with the findings of previous studies which report that youths with mental retardation are more susceptible than others to antipsychotic-related dyskinesias.<sup>4</sup> Results showing a lower risk of antipsychotic-related dyskinesias with atypical agents suggest that these may be the antipsychotics of choice for persons with mental retardation.

Antipsychotic-induced EPS are thought to be caused by the blockade of postsynaptic nigrostriatal dopamine tracts, resulting in a relative increase in cholinergic-to-dopamine activity.<sup>11,12</sup> Antipsychotic-related dyskinesias are thought to be related to a supersensitivity response to chronic postsynaptic receptor dopamine blockade.<sup>10,12,13</sup> The supersensitivity theory would predict that patients who develop early antipsychotic-related EPS may also develop tardive dyskinesia. The appearance of EPS in the course of exposure to antipsychotics may be indicative of dopamine tract pathology that will eventually evolve into tardive dyskinesia.<sup>8,11</sup> Although not all studies agree,<sup>28</sup> the majority of studies in adults finds that EPS is a risk factor for tardive dyskinesia.<sup>11,12</sup> Our results, which found that the presence of EPS in antipsychotic-treated youths is significantly associated with antipsychotic-related dyskinesias, is in agreement with these investigations.

Our results differ from dyskinesia studies in adults suggesting that female gender and affective psychoses may be risk factors for tardive dyskinesia.<sup>12</sup> The small number of females and children with the diagnosis of affective psychosis in our study sample may account for this discrepancy. On the other hand, the greater plasticity of the immature and still developing brain in children and adolescents may also account for this difference in risk factors between the adult literature and our findings.<sup>8</sup>

A trend ( $p < .10$ ) exists for disruptive behavior disorders to be less associated with antipsychotic-related dyskinesias. Disruptive behavior disorders include attention-deficit/hyperactivity disorder (ADHD), conduct disorder, and oppositional defiant disorder.<sup>22</sup> This trend in the data set is not in agreement with other reports suggesting that ADHD may be a risk factor for treatment-

emergent tardive dyskinesia in patients receiving atypical antipsychotics.<sup>29</sup>

This study has several limitations. The 3-month study period is short in comparison with the 6-month to several-year length of other studies of antipsychotic-related dyskinesias in youths.<sup>2,5,6</sup> It is possible that had we extended our study length, prevalence rates would be higher. Nevertheless, despite the short study time, an appreciable prevalence of antipsychotic-related dyskinesias was found, suggesting that dyskinesias are not uncommon in heterogeneous and unselected populations of antipsychotic-treated seriously emotionally disturbed children assessed in naturalistic treatment environments. Another limitation is our inability to assess subjects before antipsychotic medication was started.<sup>2</sup> We could only evaluate youths at admission after ongoing exposure to antipsychotic agents. Because dyskinesias disappeared after antipsychotic discontinuation in all 13 subjects meeting criteria for withdrawal dyskinesia, and because abnormal involuntary movements continued in 4 of the 95 evaluable subjects classified as probable tardive dyskinesia despite ongoing antipsychotic treatment, it is unlikely that antipsychotics were simply suppressing preexisting abnormal movement disorders in our study population. Nurses completing AIMS rating scales were not blind to the typical/atypical antipsychotic treatment of their patients, which is a limitation of our study design that could not be overcome in a clinical treatment setting. A further constraint is the limited information available on total cumulative lifetime dose and duration of neuroleptic exposure. These could only be estimated from retrospective chart review and were not precise. In addition, our population had a borderline to low IQ (mean full-scale IQ = 80), increasing the possibility that our population may have increased rates of neurodevelopmental problems that might increase dyskinesia prevalence rates relative to populations of children and adolescents with IQs in the normal range. As such, our findings might not generalize to other samples of normal-IQ residential children and adolescents. Despite these limitations, our study has several strengths, including its prospective design, adequate number of subjects, and heterogeneous patient group.

In conclusion, our 3-month prospective study of neuroleptic-related dyskinesias in an unselected clinically referred population of seriously emotionally disturbed children and adolescents has several findings. First, use of atypical antipsychotics appears to be associated with less dyskinesia risk than typical neuroleptics. Our findings are consistent with studies in adults finding less dyskinesia risk with atypical antipsychotics and extend these results to the pediatric age range. Second, of the 102 youths who were treated with neuroleptics/antipsychotics, 5.9% had probable tardive dyskinesia at 3-month outcome. This rate suggests the possibility that in populations of seriously emotionally disturbed youths with high rates of

treatment with traditional neuroleptics, rates of tardive dyskinesia may be less than tardive dyskinesia rates in long-term, neuroleptic-treated adults. However, of youths developing a dyskinesia, probable tardive dyskinesia did occur in 24% and suggests the need for careful clinical vigilance and ongoing assessment. Finally, given the significant association of a composite variable summing 10 risk factors and antipsychotic-related dyskinesias in youths, it is important for clinicians to attempt to limit the total number of dyskinesia risk factors to which children and adolescents are exposed.

*Drug names:* chlorpromazine (Thorazine and others), clonidine (Catapres and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), perphenazine (Trilafon and others), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Navane), trifluoperazine (Stelazine and others).

*Disclosure of off-label usage:* The authors of this article have determined that, to the best of their knowledge, the following drugs have not been approved by the U.S. Food and Drug Administration for the treatment of developmental disorders and psychosis: chlorpromazine, clozapine, haloperidol, olanzapine, perphenazine, pimozide, quetiapine, risperidone, thiothixene, and trifluoperazine; and clonidine has not been approved for the treatment of ADHD, aggression, and tics.

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