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Stimulant Medication Treatment of Target Behaviors in Children with Autism: A Population-Based Study

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Abstract

This study provides detailed information about stimulant medication treatment for the target symptoms of hyperactivity, impulsivity, disinhibition, and inattention in children with autism. In a previous study, 124 subjects fulfilling DSM-IV-based research criteria for autistic disorder were identified among all 0-21 year old residents of Olmsted County, MN from 1976-1997. For each of these 124 children with research-identified autism, information was abstracted on all prescribed psychopharmacological medications. Psychostimulants were used to treat 52.4% (N=65) of the 124 subjects. The median total duration of psychostimulant treatment was 4.0 years. There were 398 episodes of psychostimulant treatment. Favorable responses were associated with 69.4% of treatment episodes. Of the 398 episodes of stimulant treatment, 16.8% were associated with a documented side effect. At least one side effect was experienced by 66% of the children. These results indicate that psychostimulants are commonly prescribed for children with autism, and suggest that these medications may improve the target symptoms of hyperactivity, impulsivity, disinhibition and inattention.

Background

Autism is a developmental disorder characterized by impairments in social interaction, communication, and restricted patterns of behavior and interests.¹⁻⁴ In addition to these core symptoms, the additional symptoms of hyperactivity, impulsivity, disinhibition, and inattention are common among children with autism.⁴⁻¹¹ In one study using the High-Functioning Autism Spectrum Screening Questionnaire and the AD/HD Rating Scale-IV, children with pervasive developmental disorder scored as high as children with the diagnosis of AD/HD in the domains of inattention and hyperactivity/impulsivity.¹² These symptoms

interfere with learning in children with autism, and may be improved through pharmacotherapy.⁶⁻⁸

Previous studies have reported that 34 -55 percent of children with autism are being treated with psychotropic medications, including antipsychotics, antidepressants, and psychostimulants.^{6, 8, 9, 13- 15} Psychostimulants are the recommended treatment for AD/HD, with a positive response rate of 70-80%.^{5, 16-18} However, the use of psychostimulants to treat these symptoms in children with autism has not been as well studied.

Previous studies of psychostimulants in autistic children suggested some improvement in hyperactivity, inattention, and impulsivity.^{19, 20} A double-blind placebo crossover study by Quintana, et al, including only ten children, showed a statistically significant improvement in hyperactivity over placebo without significant side effects in children with autistic disorder.¹⁹ Beneficial effects of psychostimulants in children with autism were also seen in later studies, but there was concern that autistic children were more likely to have side effects^{20, 21}. Stigler, et al concluded that stimulants were not effective and were poorly tolerated in children with pervasive developmental disorders (PDD).¹¹ In a study of 13 children with PDD by Di Martino, et al, 5 had an increase in hyperactivity, stereotypies, dysphoria, and motor tics following a single dose of methylphenidate, suggesting decreased tolerance of psychostimulants in children with PDD.⁷

Recently, the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network studied the efficacy and safety of methylphenidate in children with autism in a double-blind, placebo-controlled, crossover trial.⁵ In this study, methylphenidate had a positive effect in 49% of subjects, while by comparison, 70-80% of children with AD/HD respond favorably to methylphenidate⁵. The study was discontinued in 18% of subjects due to side effects.⁵ The children enrolled in this study were recruited by the five academic outpatient clinics forming the RUPP Autism Network; therefore, these findings may not be representative of the broader population of children with autism.⁵

In this paper, we report the results of a population-based study of stimulant medication treatment provided throughout childhood to children with research-identified autism among all children ages 1-21 years, residing in Olmsted County, Minnesota, during the years 1976-1997²². We examine the rates of treatment with psychostimulants, effectiveness of treatment, and occurrence of side effects. We also report the age at initiation and duration of treatment, and address gender differences in response to treatment.

Methods

Study Setting and Subjects

Through the Rochester Epidemiology Project (REP), all inpatient and outpatient diagnoses are recorded and indexed for automated retrieval, for all patients seen at the Mayo Clinic and Olmsted Medical Center (Medical Diagnostic Index).²²⁻²⁴ Over 95% of residents of Olmsted County, MN receive their medical care locally at Mayo Clinic and Olmsted Medical Center.²⁴ The medical records contain complete information on all health care practices, including developmental, neurological, psychological, and psychiatric assessments, in addition to complete records of well-child visits.²² Therefore, complete medical records are available for 95% of the residents of Olmsted County, MN.²² All public and private school records, including notations related to developmental or learning problems, cognitive assessments, and special education services, are available through a contractual agreement.²²

The subjects of this study included all children with research-identified autism among residents of Olmsted County, age 21 years or younger, in each year from 1976-1997.²² The protocol was approved by the Institutional Review Board.

Ascertainment of Research-Identified Autism Incident Cases

In a preliminary study that employed the Medical Diagnostic Index, 182 patients with autistic disorder or pervasive developmental disorder, not otherwise specified (PDD, NOS) consistent with DSM-IV criteria, seen at Mayo Clinic between 1994 and 1998, were identified.²³ A list was then compiled of every single developmental, psychiatric or neurological clinical diagnosis ever given to each of these patients, which yielded 80 diagnoses. The medical records of these 182 patients were reviewed and every reference to symptoms of autism was transcribed. This list was used to create a 20 page glossary of phrases consistent with the symptoms of autism as specified in the DSM-IV.^{4, 22}

The Medical Diagnostic Index was then searched to identify all 3109 residents of Olmsted County 21 years or younger between 1976-1997 who ever received any of the 80 diagnoses previously mentioned (Figure 1). The medical records of these 3109 residents were then searched using the glossary of autism symptoms. This yielded 257 residents who had at least two symptoms of “impairments in reciprocal social interaction”.^{4, 22} The complete school and medical records of this sub-sample of 257 children were reviewed and each symptom from the glossary of DSM-IV symptoms was recorded.⁴ Those who fulfilled DSM-IV criteria for autism while they were residents of Olmsted County and were age 21 years or younger between January 1, 1976 and December 31, 1997 were included. Those with clinical diagnoses of Rett disorder, childhood disintegrative disorder, and those who were diagnosed with schizophrenia prior to fulfilling DSM-IV criteria for autism were excluded. Children with an IQ score of less than 35 were also excluded.⁴ These exclusion criteria are consistent with the DSM-IV guidelines for diagnosing autism^{4, 22}. This yielded a total of 124 children with “research-identified” autism among Olmsted County residents, ages 0 to 21 years, in the years 1976-1997. Additional details of this selection process are available in a previously published manuscript on the incidence of autism in Olmsted County.²²

In this cohort of 124 children, males (n=95) outnumbered females (n=29) by a 3.3 to 1 ratio. Comorbid clinical diagnoses included, among others, speech or language disorder (n=96; 77%) and epilepsy (n=17; 14%)²². The majority of our subjects (n=68; 61%) were cognitively impaired, as defined by an IQ or Developmental Quotient of 70 or less.²²

Psychopharmacologic Treatment Data Collected

A detailed chart review of the 124 subjects with research-identified autism was performed. We abstracted information about treatment with all psychopharmacologic medications ever prescribed, as documented in the medical record, including the names of the medications, doses, and dates when treatment was started and stopped. For each subject, we defined an *episode of treatment* with stimulants as a period of time during which a subject was treated with a specific medication at a specific dose.¹⁸ The dose of each stimulant was converted to methylphenidate equivalent units (MEUs). The conversion was as follows: 20 mg methylphenidate = 10 mg dextroamphetamine = 56.25 mg pemoline = 10 mg methamphetamine = 10 mg levoamphetamine plus dextroamphetamine combination (mixed amphetamine salts). The average daily dose of stimulant medication was calculated for each subject as a weighted average of each stimulant use by the duration of usage.¹⁸ We also recorded information about the child's response to the stimulant and the occurrence of side effects associated with each episode of treatment, based on explicit comments in the medical record. The response to treatment was described as favorable, if the target behaviors (hyperactivity, impulsivity, disinhibition, and inattention) improved, no response, and/or if

side effects were noted. We also recorded the specific side effects that were documented in each child's medical record. In addition, we abstracted the age at initiation of psychostimulant treatment for each child.

Statistical Analysis

The association between gender and psychostimulant treatment (yes vs. no) was assessed using the chi-square test. Continuously scaled outcomes (age at initiation of stimulant treatment, duration of treatment, and average daily dose) were each compared between boys and girls using the Wilcoxon rank sum test. On a per-episode basis, the association between nominal outcomes (response to treatment and occurrence of side effects) and gender were each evaluated based on fitting separate logistic models using generalized estimating equation methods for correlated binary data available in the GENMOD procedure in SAS. An exchangeable correlation structure was specified to model the correlation between multiple treatment episodes for each subject. Statistical analyses were performed using the SAS software package (SAS Institute, Cary, NC). All p-values were two-sided and p-values <0.05 were considered statistically significant.

Results

Psychopharmacologic Medication Use

In this population-based study, psychopharmacologic treatment of any class was used in 82 subjects (66%) at some point. Among these 82 subjects, 65 (79%), were treated with psychostimulants. Therefore, overall, among the 124 children with research-identified autism, 65 (52%) were treated with psychostimulants.

As summarized in Table 1, the median age at which treatment began was 7.6 years. The median duration of psychostimulant treatment was 3.1 years. The median duration of follow-up (from the date of the child's first medical visit to the date of their last medical visit prior to the earliest of either the date of data abstraction or age 21) was 12.4 years for all of the children in this sample (13.8 and 9.8 years, respectively, for the cases who were and were not treated with psychostimulants).

Methylphenidate was the most frequently prescribed psychostimulant, used in 80% of cases treated with psychostimulants, dextroamphetamine in 52%, mixed amphetamine salts in 20%, pemoline in 17%, and methamphetamine in 3% (Table 1). A single type of stimulant was used in 32 (49%) subjects, while 19 (29%) were treated with two different stimulants, and 14 (22%) with three different stimulants. The average daily dose of stimulant treatment was 23.4 mg MEUs overall [range, 2.5-75.2 mg MEUs (Table 1)].

There was no difference in overall psychostimulant treatment rates by gender (Table 1). Of the 95 males in our study, 50 (53%) were treated with psychostimulants. By comparison, 15 (52%) of the 29 females were treated with psychostimulants. Despite the small number of girls in this study, girls were more likely to have treatment initiated at a *later* age than boys (median age at initiation of treatment 10.5 years for girls versus 6.6 years for boys; $p<0.001$). Furthermore, girls were treated for a *shorter* duration than boys (median duration of 1.0 years for girls versus 3.4 years for boys; $p=0.030$; Table 1).

Response to Treatment

Among the 65 subjects treated with psychostimulants, there were 398 episodes of treatment. The median number of episodes per patient was 5 (range, 1-21). Favorable responses were associated with 276 (69%) episodes of stimulant treatment. This proportion was not significantly different for boys (68%; 235 of 345 episodes) versus girls (77%; 41 of 53 episodes)

($p=0.33$). There was no significant difference in rate of favorable response by stimulant used, specifically dextroamphetamine (73%) versus methylphenidate (69%) ($p=0.50$; Table 2).

Side Effects

Among the 65 patients treated with stimulants, 43 (66%) experienced at least one side effect. There was a trend for boys to be more likely to experience a side effect, with 36 of 50 (72%) boys experiencing at least one side effect, versus 7 of 15 (47%) girls, although this trend was not statistically significant ($p=0.069$). Of the 398 stimulant treatment episodes, 67 (16.8%) were associated with a side effect. There was no association between type of psychostimulant treatment (i.e., dextroamphetamine or methylphenidate) and the occurrence of side effects ($P=0.83$; Table 3). Documented side effects included tics, sleep disturbance, irritability, anxiousness, worsening of behavior, GI complaints/stomach aches, appetite changes, sedation/lethargy/sleepiness/drowsiness, and headache (Table 3).

Discussion

This study provides detailed information on the use of psychostimulants in a large, population-based cohort of children with research-identified autism. In this cohort, psychopharmacologic medications were used in 66.1% children with research-identified autism, a much higher rate than previously reported.^{13-15, 25} Furthermore, among those 82 children treated with psychopharmacologic medications, 65 (79%) were treated with psychostimulants. Overall, more than half (52.4%) of all children in this cohort were treated with psychostimulants. By comparison, in a previous population-based study of ADHD, 77.8% of children were treated with psychostimulants.¹⁸ While the use of psychostimulants in our study is higher than that reported in previous studies of children with autism, subjects in these studies were recruited from large treatment centers, or via mailed survey questionnaires to treatment providers or family members.^{11, 13-15} Therefore, results from these previous studies may not reflect the experience of the broader population of children with autism. Furthermore, the increased use of psychopharmacologic medications, especially psychostimulants, in our study population may reflect the long duration of follow-up of our subjects.

Methylphenidate was the most frequently used psychostimulant, as reported in previous studies examining the use of psychostimulants in children with autism.^{11, 14, 15} Thirty-three of sixty-five subjects in our study (51%) received more than one stimulant trial. This is far more than previously reported (31.3%) in a study of psychostimulant use in children with PDD.¹¹ The median average daily dose of stimulant treatment in our subjects was 23.4 mg MEUs, comparable to the methylphenidate doses reported in previous studies.^{5, 7, 19} While the type and dose of stimulant used in our subjects is similar to other reports, the greater number of stimulant treatment episodes in our sample may reflect the comprehensive information available to us, and long duration of our follow-up.

In a previous randomized, controlled, crossover trial of methylphenidate in children with autistic disorder, Asperger disorder, or PDD, NOS, there was an overall favorable response rate of 49%.⁵ However, those subjects were recruited from five large autism treatment centers, suggesting the potential for selection bias. In our population-based study, we found a higher favorable response rate of 69.4%. By comparison, the previously reported response rate in children with ADHD (having normal IQ) to psychostimulants is 70-80%.^{5, 18, 26} The favorable response rate in children with ADHD with borderline IQ and mental retardation was 67% in one, and 54% in another recent study.^{27, 28} Therefore, in our population-based cohort of children with research-identified autism (of which 60.7% were cognitively impaired), the favorable response rate to psychostimulants was closer to that of ADHD populations rather than for those cognitively impaired. More children with autism in our sample responded favorably than would be expected, given the prevalence of cognitive impairment in this cohort.

Side effects were experienced by 66% of the subjects treated with stimulants. However, only 16.8% of the treatment episodes were associated with a side effect. This suggests that, although the majority of children experienced at least one side effect, these side effects were not sustained throughout multiple treatment episodes. In a small study of the safety and efficacy of methylphenidate in children with PDD, five out of thirteen (37%) were considered to have an adverse response following a single dose.⁷ Of the remaining eight who then received twelve weeks of therapy, none experienced adverse effects.⁷ However, the five children who had side effects to the initial dose did not receive further doses to determine if the side effects would have been sustained. In a recent randomized, controlled, crossover trial of methylphenidate in children with PDD, 18% of study participants exited the study due to side effects, primarily irritability.⁵ This finding is consistent with our rate of side effects over all treatment episodes.

The rate of occurrence of side effects in our study population was higher than previously reported for children with AD/HD. In a previous population-based study of children with AD/HD, conducted in the same community with similar methodology, the overall frequency of side effects was 22%. However, only 8% of treatment episodes were associated with a side effect.¹⁸ By comparison, in two previous small studies of twelve and eleven children with developmental disabilities and ADHD, side effects were experienced by 50% and 45% of the children, respectively.^{29, 30} In a larger study of twenty-seven children with ADHD and mental retardation, there were no statistically significant differences between the active treatment and placebo in the number and intensity of side effects.²⁷ However, 22% of the children in this study discontinued their medication due to side effects.²⁷ In a more recent study of twenty-four children with mental retardation who were not autistic, there was a side effect frequency of 16-29%, comparable to our frequency of 16.3%.³¹ Furthermore, the side effect profile in our sample was consistent with the known side effects of psychostimulants, including tics, sleep disturbance, irritability and anxiousness, GI complaints, change in appetite, and headache.

The median duration of documented psychostimulant treatment was 3.1 years. This is longer than the mean duration of treatment reported in a previous retrospective study of psychostimulants in children with PDD.¹¹ Furthermore, the children in our study were followed for a median of 12.4 years overall, and 13.8 years for cases treated with psychostimulants.

In our study, we also explored differences in prescribing practices, response to treatment, and side effects based on gender. We found no difference in psychostimulant treatment rates between boys and girls. However, treatment was initiated at a significantly later age in girls than in boys. Furthermore, girls were treated for a significantly shorter duration. The proportion of girls who responded to treatment was not significantly different than the proportion of boys who responded. However, there was a statistically non-significant trend for boys to be somewhat more likely to experience a side effect. To our knowledge, this is the only data comparing methylphenidate treatment in boys and girls with autism, and suggests that girls with autism and hyperactivity, impulsivity, and/or inattentiveness may be under-treated. Alternatively, these findings may reflect differences in the rates of occurrence of these behaviors in boys and girls with autism.

Several potential limitations of our study should be noted. First, our study was retrospective. It is possible that we failed to detect all autism cases, or that medication treatment was incompletely documented in the medical records. Furthermore, we did not directly examine our subjects to verify their response to psychostimulants. However, our study design allowed us to apply current DSM-IV criteria for autism to the extensive information available for every child. Furthermore, complete medical and school records were available for all subjects, minimizing the possibility that information was missed.

This population-based study of children with research-identified autism indicates that psychostimulants are frequently prescribed to children, both boys and girls, with autism. The majority of these children (69.4%) showed improvement in the target symptoms of hyperactivity, impulsivity, disinhibition, and inattention. Although 66% of the children experienced at least one side effect, only 16.8% of the treatment episodes were associated with a side effect, suggesting these stimulant medications were well-tolerated. The findings from this study amplify recent reports, suggesting that stimulant medications may play an important role in the treatment of specific target symptoms in children with autism.

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Figure 1.

Flow diagram describing ascertainment of research-identified autism incident cases among residents of Olmsted County, Minnesota, age ≤ 21 years, during 1976-1997. IQ= Intelligence Quotient. DQ=developmental quotient.

* At least two unique symptoms of impaired reciprocal social interaction, at least one symptom of impaired communication, at least one symptom of unusual/repetitive behavior, and a total of at least six unique symptoms of autism.

Table 1
Type of psychostimulant usage, age at initiation of psychostimulant treatment, duration, and average daily dosage in children with research-identified autism in Rochester Minnesota from 1976-1997

Characteristic	Boys (N=50)	Girls (N=15)	Overall (N=65)
Type of psychostimulant, n (%)			
Methylphenidate	41 (82%)	11 (73%)	52 (80%)
Dextroamphetamine	29 (58%)	5 (33%)	34 (52%)
Mixed amphetamine salts	11 (22%)	2 (13%)	13 (20%)
Pemoline	9 (18%)	2 (13%)	11 (17%)
Methamphetamine	2 (4%)	0	2 (3%)
Age at onset of psychostimulant treatment (years)			
Median	6.6	10.5	7.6
Mean (SD)	7.0 (2.5)	10.8 (2.4)	7.9 (2.9)
Range	3.4-14.2	6.7-14.5	3.4-14.5
Duration of treatment with stimulants (years) [‡]			
Median	3.4	1.0	3.1
Mean (SD)	4.5 (4.0)	2.3 (2.8)	4.0 (3.9)
Range	3 days-14.1 yrs	1 day-6.9 yrs	1 day-14.1 yrs
Average daily dosage of stimulant treatment (mg MEUs) [‡]			
Median	23.3	27.0	23.4
Mean (SD)	25.4 (15.3)	34.1 (24.0)	27.3 (17.8)
Range	2.5-67.3	5-75.2	2.5-75.2

[‡]MEU=methylphenidate equivalent unit.

[‡]The results for duration and average daily dosage are based on 62 instead of 65 children. Three children (2 boys and 1 girl) had incomplete information on either dosages or start and stop dates of psychostimulant treatment.

Table 2

Frequency of treatment episodes with a favorable response to specific psychostimulants in children with research-identified autism in Rochester Minnesota from 1976-1997

Type of stimulant	Number of episodes	Favorable response N (%)
Methylphenidate	195	135 (69%)
Dextroamphetamine	143	105 (73%)
Mixed amphetamine salts	41	24 (59%)
Pemoline	16	11 (69%)
Methamphetamine	3	1 (33%)
Overall	398	276 (69%)

Table 3
Frequency of treatment episodes with a side effect to specific psychostimulants and the side effects experienced in children with research-identified autism in Rochester Minnesota from 1976-1997

Type of stimulant	Number of episodes	Side effects N (%)	Number of each type of side effect (<i>some episodes had more than one type of side effect</i>)
Methylphenidate	195	31 (16%)	4 episodes -Tics 6 episodes in 5 children-Appetite changes 6 episodes -Sleep disturbances 2 episodes -Headache 10 episodes in 9 different children-Irritability/anxiousness/worsening of behavior 4 episodes in 3 different children-Sedation/lethargy/sleepiness/drowsiness 2 episodes-Other
Dextroamphetamine	143	24 (17%)	3 episodes, with 2 in same child -Tics 5 episodes, with 3 in same child -Appetite changes 6 episodes in 4 different children-Sleep disturbance 10 episodes in 10 different children-Irritability/anxiousness/worsening of behavior 1 episode -Sedation/lethargy/sleepiness/drowsiness 1 episode-Other 1 episode-Unknown
Mixed amphetamine salts	41	7 (17%)	2 episodes, with both in same child-Tics 2 episodes -Sleep disturbances 3 episodes-Irritability/anxiousness/worsening of behavior 3 episodes, with 2 in same child-Other
Pemoline	16	4 (25%)	1 episode-Tics 1 episode-GI complaints/stomach aches 2 episodes-Other
Methamphetamine	3	1 (33%)	1 episode-Tics