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Age of Methylphenidate Treatment Initiation in Children with ADHD and Later Substance Abuse: Prospective Follow-Up into Adulthood

Salvatore Mannuzza, Ph.D., **Rachel G. Klein, Ph.D.**, **Nhan L. Truong, M.A.**, **John L. Moulton III, Ph.D.**, **Erica R. Roizen, B.A.**, **Kathryn H. Howell, B.S.**, and **Francisco X. Castellanos, M.D.**
From the New York University Child Study Center, NYU Department of Child and Adolescent Psychiatry, New York, NY (all authors), and the Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY (Drs. Mannuzza and Castellanos).

Abstract

Objective—Animal studies report that age at stimulant exposure is positively related to later drug sensitivity. This study was designed to examine whether age at initiation of stimulant treatment in children with attention deficit hyperactivity disorder (ADHD) is related to subsequent development of substance use disorder (SUD).

Method—Prospective longitudinal study of 176 methylphenidate-treated white boys (6–12 years) with ADHD but without conduct disorder, evaluated at mean ages 18 (94% retention) and 25 (85%), and 178 comparisons diagnosed by blinded clinicians. The Cox proportional hazards model included childhood predictor variables: age at initiation of methylphenidate treatment, total cumulative dose, treatment duration; IQ; severity of hyperactivity; socioeconomic status; also lifetime parent mental disorder. Separate models tested for four lifetime outcomes: Any SUD, Alcohol SUD, Non-Alcohol SUD, and Stimulant SUD. Other outcomes included antisocial personality disorder, mood and anxiety disorders.

Results—There was a significant positive relationship between age at treatment initiation and Non-Alcohol SUD. None of the predictors accounted for this association. Post-hoc analyses showed that the development of antisocial personality disorder explained the relationship between age at first methylphenidate treatment and later SUD. Even when controlling for SUD, age at stimulant treatment initiation was significantly and positively related to the later development of antisocial personality disorder. Age at first methylphenidate treatment was unrelated to mood and anxiety disorders.

Conclusion—Early age at initiation of methylphenidate treatment of children with ADHD does not increase risk for negative outcomes, and may have beneficial long-term effects.

Numerous studies have shown that childhood attention deficit hyperactivity disorder (ADHD) is significantly associated with adolescent and adult substance use disorders (SUD) (1–8). Additionally, stimulants are considered first-line treatments for children with ADHD (9,10). Animal studies have raised concern about stimulant treatment through findings of sensitization to the effects of drugs. The sensitization hypothesis, a neuroadaptional model, posits that exposure to stimulants results in dopamine system alterations which, in turn, increase sensitivity to the reinforcing effects of the previously experienced substance. Behavioral sensitization has been demonstrated in numerous mammalian species, including nonhuman

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primates, and has been found to be long-lasting (11,12). Consistent with this model, some have suggested that there may be a causal link between stimulant treatment in childhood and later SUD (13,14). The potential role of stimulants in the pathogenesis of SUD is a major public health concern since stimulant use is widespread, and these medications are increasingly prescribed to young children (15). Of relevance to this controversy, some animal studies have reported developmental effects on stimulant sensitization. Specifically, later preference for cocaine in rats is decreased by early, compared to later methylphenidate administration (16, 17), suggesting that age at exposure may modulate long-term drug effects on the brain, at least in rats.

Over a dozen studies have examined the association between stimulant treatment of ADHD and SUD (18–20) and, with one exception (21), have failed to find a significant positive relationship. In non-ADHD children treated with methylphenidate or placebo, we also failed to find a relationship between exposure to methylphenidate and SUD in adulthood (22). To our knowledge, no study has examined the association between age at first exposure to stimulants and later SUD. The purpose of this study is to examine possible relationships between age at initiation of methylphenidate treatment and the later development of SUD. We report on a clinic sample of boys with ADHD who were prospectively followed and systematically assessed by blind clinicians in late adolescence (3,4) and adulthood (5,6). Stimulant treatment began as early as age 6 for some children, and as late as age 12 for others.

METHOD

Participants

Participants were 6–12 year old white boys of middle socioeconomic status, referred to a no-cost child psychiatric research clinic in New York between 1970 and 1977 (23,24). Criteria were: referral by schools because of behavior problems; elevated ratings on standard scales of hyperactivity by teachers and parents; behavior problems in settings other than school; a diagnosis of DSM-II hyperkinetic reaction by a child psychiatrist based on interviews with mother and child, and school information; no previous significant treatment with stimulants (defined as more than 10 mg/day of methylphenidate for more than a month); IQ $\geq$ 85 (25, 26); no evidence of psychosis or neurological disorder, and; English-speaking parents and a home telephone. The exclusion of previously treated children did not incur any appreciable loss of cases since stimulants were not used in the community in the 1970's.

Children were excluded if the referral involved aggressive or other serious antisocial behaviors, or if the psychiatric assessment with parent and child revealed a pattern of antisocial activities. This exclusion was implemented to rule out children with conduct disorders (CD) because of the controversy over the diagnostic distinction between hyperactivity and CD. To determine whether conduct problems were successfully excluded, we examined the ratings on two measures, the Conners Teacher Rating Scale (CTRS) (27) and the Conners Parent Rating Scale (CPRS) (28), whose scoring ranges from 0 (Not at All), to 3 (Very Much). The overall mean of combined parent and teacher ratings on items corresponding to DSM-IV CD behaviors (bullying, lying, stealing, truancy, etc.) was very low (mean, 0.7; SD, 0.4), documenting that frequency of conduct problems was extremely scarce.

Probands would have met criteria for DSM-IV ADHD combined type since: cross-situationality of hyperactivity was required; all subjects were clinically impaired by ADHD; relatively severe hyperactivity was required; mean ratings on the CTRS items of restless/overactive, inattentive/distractible, and excitable/impulsive [rated 0 to 3] were 2.8, 2.6, and 2.4, respectively, and; classroom observation ratings made by blind observers showed highly significant differences between index and “normal” children on items related to hyperactivity (“out of chair”), inattention (“off task”), and impulsivity (“interference”) (29).

Of 207 ADHD probands in the entire childhood cohort, 182 were treated with methylphenidate, administered bid. The remaining 25 either refused treatment or were noncompliant. Six of those treated (3%) refused participation in the follow-ups (described below). Therefore, this report includes the 176 probands (97%) who were treated with methylphenidate in childhood, and who participated in the follow-up assessments.

A non-ADHD white male comparison group (n = 178) matched for age, social class, and geographic residence was recruited at adolescent follow-up (3,4).

Prospective Follow-Ups

Participants were evaluated in late adolescence (mean age ± SD, 18.4 ± 1.3 years; 94% retention) and adulthood (mean age ± SD, 25.3 ± 1.3 years; 85% retention). At both follow-ups, ADHD probands and non-ADHD comparisons were systematically interviewed by clinicians who were blind to childhood status [details in Gittelman et al. (3) and Mannuzza et al. (4) regarding adolescent follow-up, and in Mannuzza et al. (5,6) regarding adult follow-up]. For both follow-ups, written informed consent was obtained after the study purpose and procedures had been fully explained.

At late adolescent follow-up, subjects were administered a modification of the Diagnostic Interview Schedule (30), the Teenager Or Young Adult Schedule, a systematic clinical interview which includes DSM-III attention deficit, conduct, substance use, mood, anxiety, and psychotic disorders. Parents were administered the Parent Interview (3). Diagnoses were considered present if they were made on the basis of either the informant or the self assessment. Inter-rater reliability was excellent for both self and informant assessments [kappas: ADD = .85 and .91; Conduct Disorder = .93 and .75; Substance Use Disorder (SUD) = .81 and .88; Any DSM-III disorder = .79 and .83, respectively] (4).

At adult follow-up, subjects were administered the Schedule for the Assessment of Conduct, Hyperactivity, Anxiety, Mood, and Psychoactive Substances (31), which includes lifetime DSM-III-R antisocial personality disorder (APD), ADHD, SUD, mood, anxiety, and psychotic disorders. Inter-rater reliability was good to excellent for all major disorders [kappas: ADHD = .70; APD = .69; SUD = .80; Mood disorder = 1.00; Any DSM-III-R = .67] (5).

Parent Diagnostic Assessments

At the first follow-up, parents were administered the Diagnostic Interview Schedule (30) by independent blind clinicians. Attempts were made to interview both parents directly. However, when one parent was not available (e.g., deceased, estranged), the spouse was administered the Spouse Informant Schedule (SIS), a semi-structured interview derived from the DIS for this study. The SIS includes sections on DSM-III alcohol and non-alcohol substance use disorders, antisocial personality disorder, and attention deficit disorder. Diagnostic interviews were obtained for the parents of 146 (83%) of the 176 participants. Of these, nearly all mothers (97%) were directly interviewed, but informant interviews were obtained for two-thirds (65%) of fathers.

Data Analyses

Model Employed—The Cox proportional hazards model (32) was used to assess the relationship between age at methylphenidate treatment initiation in childhood and later development of SUD. Substance use disorder was considered present if it was diagnosed at either late adolescent or adult follow-up (i.e., lifetime SUD).

Four survival analyses were conducted with the following non-mutually exclusive outcome measures: Any SUD, Alcohol SUD, Non-Alcohol SUD (cannabis, opiates, cocaine, etc.), and

Stimulant SUD (cocaine, amphetamines, etc.). The rationale for including these outcome variables was as follows. It was of interest to determine whether the relationship between age at initiation and later Stimulant SUD differed from other SUD categories since subjects were treated with stimulants in childhood. Separate categories for Alcohol and Non-Alcohol SUD were included since our late adolescent and adult follow-ups showed that, compared to controls, probands were at significantly increased risk for Non-Alcohol SUD, but not for Alcohol SUD (3–6). Age at most recent interview was used as the time of censoring for non-cases (i.e., cases with no SUD diagnosis). Similar post-hoc analyses examined the relationship between age at first methylphenidate treatment and later APD, anxiety and mood disorders.

Alternative Explanations—Since age at first exposure to methylphenidate treatment was not a random characteristic, we considered whether other factors might account for the development of substance use disorder. The following were included in the analyses:

1. Characteristics of Methylphenidate Treatment: Treatment exposure (dosage and duration) might have varied as a function of children's ages. To address this possibility, the effects of total cumulative dose of methylphenidate treatment (mg) and duration of treatment (months) were assessed.

2. Characteristics of Participants: Childhood IQ was entered since a significant relationship between IQ and SUD has been reported (33). In addition, severity of childhood hyperactivity, as measured by the Hyperactivity Factor of the CTRS (28), was included.

3. Other Variables possibly related to SUD: In addition to treatment and subject characteristics, socioeconomic status and parent psychopathology have been related to SUD in offspring (34–36). The Hollingshead and Redlich 2-factor index (37) was used to assess SES. We also examined the effects of lifetime DSM-III diagnoses of parents.

Building and Testing the Model—In summary, the following 9 predictor variables initially were included: child's age (in years) at initiation of methylphenidate treatment, total cumulative dosage (mg), and duration of treatment (months); childhood Full Scale IQ; severity of childhood hyperactivity (28); SES in childhood (37); and lifetime mental disorder in the mother, father, or either parent (entered separately, and rated dichotomously). As described by Hosmer and Lemeshow (38), the following data analytic strategy was employed. Step 1: univariate analyses were conducted for all continuous (using proportional hazards analyses) and dichotomous (using Kaplan-Meier analyses) predictor variables with each of the four outcome variables (Any SUD, Alcohol SUD, Non-Alcohol SUD, and Stimulant SUD). Step 2: variables showing $p < .20$, 2-tailed, in the univariate analyses were entered together, into the proportional hazards analyses. Step 3: variables with $p > .05$, 2-tailed, were discarded, and proportional hazards analyses were rerun with the remaining variables and their interactions. Proportional hazards assumptions also were tested in the final model.

RESULTS

Predictor Variables (Table 1)

The distribution of the 176 participants by age at initiation of methylphenidate treatment was as follows: age 6 years, 25 children (14%); 7 years, 49 (28%); 8 years, 29 (16%); 9 years, 28 (16%); 10 years, 23 (13%); 11 years, 19 (11%); 12 years, 3 (2%). Mean ± SD daily dosage of methylphenidate was 41.7 mg ± 12.4 mg. The means ± SDs for the 9 predictor variables are shown in Table 1. Participants were middle-class, of average intelligence, and had relatively severe ratings of hyperactivity (mean, 2.3 out of possible 3.0). One-third of mothers, one-third of fathers, and half of either parent had a lifetime mental disorder.

Outcome Variables

Among the 176 treated participants, 80 (45%) fulfilled criteria for SUD at some time in their lives. Of those, 49 (28%) had an Alcohol SUD, 65 (37%) met criteria for a Non-Alcohol SUD, and 43 (24%) of those individuals in the latter category fulfilled criteria for Stimulant SUD.

Building and Testing the Model

First, univariate analyses were conducted for the 9 predictor variables with each of the four outcome variables.

Any SUD—Two predictor variables had p-values less than .20: age at initiation of treatment (Wald $\chi^2 = 3.47$, $p < .06$) and socioeconomic status (Wald $\chi^2 = 2.47$, $p < .12$).

Alcohol SUD—Only one predictor variable had a p-value less than .20: treatment duration (Wald $\chi^2 = 1.75$, $p < .19$).

Non-Alcohol SUD—Two predictor variables had p-values less than .20: age at initiation of treatment (Wald $\chi^2 = 4.92$, $p < .03$) and socioeconomic status (Wald $\chi^2 = 2.86$, $p < .09$).

Stimulant SUD—Only one predictor variable had a p-value less than .20: age at initiation of treatment (Wald $\chi^2 = 3.33$, $p < .07$).

Since only one variable was associated with Alcohol SUD and Stimulant SUD, and p-values were greater than .05, no further analyses were conducted for these outcomes. For Any SUD and Non-Alcohol SUD, the two predictor variables showing promise (age at initiation and SES) were entered together, and rerun in the proportional hazards analyses. The only predictor variable that remained significant ($p < .05$) was age at initiation of stimulant treatment, and only for the Non-Alcohol SUD outcome (Wald $\chi^2 = 4.24$, $p < .04$). Participants who developed Non-Alcohol SUD (n = 65) were treated at a significantly later age than those who never developed Non-Alcohol SUD (n = 111) [means ± SDs = 9.10 ± 1.74 years vs. 8.52 ± 1.55 years, $t(174) = 2.31$, $p = .02$].

We also examined how rates of Non-Alcohol SUD in probands compared to those in the 178 non-ADHD controls. ADHD probands were classified as early-treated (methylphenidate treatment began at age 6 or 7) and late-treated (methylphenidate treatment began at ages 8–12). The division was made at age 8, since this was the sample mean and median. Lifetime rates of SUD were significantly greater among late-treated probands than among early-treated probands (44% vs. 27%, Wald $\chi^2 = 5.38$, $p < .02$) and non-ADHD comparisons (44% vs. 29%, Wald $\chi^2 = 6.36$, $p < .02$), with no difference between the latter groups (27% vs. 29%, Wald $\chi^2 = 0.12$, $p > .10$).

We also considered that perhaps the persistence of ADHD was accounting for the relationship between age at stimulant initiation and the development of SUD. To examine this possibility, we conducted a survival analysis with age at initiation and age at ADHD offset as predictor variables, and Non-Alcohol SUD as outcome. Results showed that age at stimulant initiation significantly predicted SUD outcome when controlling for offset of ADHD (Wald $\chi^2 = 3.78$, $p = .05$), but age at offset of ADHD did not predict development of SUD when controlling for age at stimulant initiation (Wald $\chi^2 = 2.51$, $p > .10$). In other words, age of desistence of ADHD did not matter; only age at which stimulant treatment started predicted SUD.

Finally, we examined the specificity of the relationship, i.e., does age at initiation of methylphenidate treatment predict only SUD, or also the development of other disorders? Separate survival analyses were conducted for the following lifetime diagnoses: antisocial

personality disorder, mood disorder, and anxiety disorder. Results showed that only antisocial personality disorder was significantly and positively associated with age at stimulant initiation (Wald $\chi^2 = 14.87$, $p < .001$). Mood disorders (Wald $\chi^2 = 1.35$, $p > .10$) and anxiety disorders (Wald $\chi^2 = 0.40$, $p > .10$) were not.

Post-Hoc Analyses of Antisocial Personality Disorder and Substance Use Disorder

It is not surprising that age at initiation was significantly associated with both SUD and antisocial personality disorder since follow-ups of this sample consistently showed substantial comorbidity between SUD and antisocial disorder (3–6). This finding raised the possibility that antisocial personality disorder (APD) was accounting for the SUD-treatment initiation relationship. Therefore, two additional survival analyses were conducted, one with APD as outcome and Non-Alcohol SUD as covariate, and the other with SUD as outcome and APD as covariate. The first analysis showed that age at first methylphenidate treatment remained significantly associated with APD when SUD was covaried (Wald $\chi^2 = 7.67$, $p < .01$). However, when APD was controlled for, the relationship between treatment initiation and SUD was no longer present (Wald $\chi^2 = 0.09$, $p = .76$).

This finding raised the possibility that children referred relatively later for treatment had higher levels of conduct problems than children referred earlier. If so, conduct problems in childhood could account for higher subsequent rates of both APD and SUD, and age at methylphenidate initiation would be irrelevant to later SUD. Such a possibility seemed viable since, even in this sample with very low conduct problems, we found that severity of such problems predicted later antisocial personality disorder (39). However, there was no relationship, not even a trend, between age at first methylphenidate treatment and severity of conduct problems (measured by teacher ratings) [$r(176) = .05$, $p = .49$).

A second possibility was that parents with APD or SUD were relatively less diligent about bringing their child for treatment, perhaps accounting for the apparent relationship between age at first stimulant treatment and the later development of SUD and APD in the child. This possibility was examined in three ways. First, age at first methylphenidate treatment was compared for offspring of parents with and without these disorders. Mean ± SD of stimulant initiation (years) was 8.3 ± 1.6 for offspring of APD parents vs. 8.7 ± 1.6 without APD [$t = 0.61$, $p = .54$]. Mean ± SD of stimulant initiation (years) was 8.5 ± 1.7 for offspring of SUD parents vs. 8.8 ± 1.6 without SUD [$t = 0.75$, $p = .45$]. Mean ± SD of stimulant initiation (years) was 8.5 ± 1.7 for offspring of parents with APD or SUD vs. 8.8 ± 1.6 without APD and SUD [$t = 0.75$, $p = .45$]. Point biserial correlations for age at first methylphenidate treatment (years) with presence/absence of mental disorder were: $r(176) = -.05$, $p = .54$ for parent APD; $r(176) = -.06$, $p = .45$ for parent SUD; and $r(176) = -.06$, $p = .45$ for parent APD or SUD. Finally, we compared early-treated and late-treated cases on the rates of APD and SUD in parents. For APD, 3% vs. 5%, $p = .37$. For SUD, 25% vs. 18%, $p = .69$. For APD or SUD, 25% vs. 18%, $p = .69$. In summary, we found no relationship between APD or SUD in the parents, and age at initiation of stimulant treatment.

DISCUSSION

To our knowledge, this is the first prospective follow-up study to examine the relationship between age of initiation of methylphenidate treatment for ADHD and subsequent development of SUD, as well as other disorders. Risk of developing SUD was significantly associated with age at methylphenidate treatment, specifically, the later the treatment, the greater the chances of developing SUD. The principal value of the finding is in disconfirming that early exposure to stimulants presents special risk to children with ADHD, at least with regard to SUD and antisocial personality disorder.

Unexpectedly, the development of antisocial personality disorder accounted for the association between age when first treated with methylphenidate and substance abuse. This association was not due to age-related differences in early conduct problems. Although findings are consistent with animal data that later preference for cocaine in rats is relatively decreased by exposure to methylphenidate early rather than late in development (16,17), the relevance of animal neurodevelopmental models of stimulant exposure is not straightforward. The relationship between age at first stimulant exposure and later SUD has to take account of the observation that the relationship is mediated by the development of antisocial personality disorder.

It is unclear why age at initiation of stimulant treatment and the later development of SUD and APD appear related. Castellanos and colleagues (40) reported that unmedicated children with ADHD had smaller brain white matter volume than medicated children with ADHD and non-ADHD comparisons. Early stimulant treatment might increase brain functional reserve by increasing (or normalizing) brain white matter volume during a developmental period of greatest plasticity, and greater brain functional reserve may be associated with decreased risk of SUD. We are presently conducting an adult follow-up study on the current sample, now age 40, in which MRI scans will examine whether there are structural differences in early-treated and late-treated cases.

The major limitation of this study is that it is an experiment of nature which relied on a referred clinical sample. The age at referral was not experimentally controlled, so that unidentified non-random factors related to treatment initiation, other than those examined, may have contributed to the relationship between age first treated and SUD and APD. For example, perhaps parenting-family factors mediated this association, such that failure to attend to the needs of the child led parents to delay treatment for their child. Parent psychopathology, in general, and parent APD and SUD, in particular, did not explain this relationship, but other features related to child rearing may be relevant. Therefore, replication is essential. Other limitations include the sample's ethnic homogeneity, exclusion of females, and the minimum age of 6, thus restricting generalizability of results to clinic referred 6–12 year old white males. Furthermore, we do not know whether findings apply to early stimulant exposure or to early referral for treatment, independent of methylphenidate administration. It could be that timing of interventions, regardless of their nature, affect long-term outcome. Thus, the duration of untreated ADHD in childhood, rather than stimulant treatment *per se* might the important variable. Put otherwise, we cannot differentiate presumed effects of stimulant medication from effects of age at referral, independent of stimulant exposure.

The use of stimulants in young children has generated considerable controversy. At the least, the study findings do not indicate that treatment relatively early in childhood increases risk for negative outcomes.

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TABLE 1

Methylphenidate Treatment History, Childhood Characteristics, and Parent Mental Status of 176 ADHD Participants

Category/ Predictor Variable	Mean (SD)	Category/ Predictor Variable	N (%)
Methylphenidate Treatment		Parent Lifetime Mental Disorder[4] (yes, no)	
1. Age (years) at Initiation	8.7 (1.6)		
2. Total Cum. Dose (mg)	30,016 (26,791)	7. Mothers	49 (34)
3. Duration (months)	23.2 (18.6)	8. Fathers	44 (30)
Childhood Characteristics		9. Either Parent	75 (51)
4. Socioeconomic Status[1]	3.3 (1.0)		
5. Full Scale IQ[2]	104 (12)		
6. CTRS Hyperactivity[3]	2.3 (0.5)		

[1] Hollingshead and Redlich (1958) index, ranging from 1 (upper class) to 5 (lower class)

[2] Wechsler Intelligence Scale for Children (Wechsler, 1949, 1974)

[3] Conners Teacher Rating Scale Hyperactivity Factor Score, ranging 0 to 3 (most severe)

[4] Diagnostic interviews were obtained for the parents of 146 (83%) of the 176 participants