European Child & Adolescent Psychiatry (2019) 28:1365–1373
https://doi.org/10.1007/s00787-019-01301-z

ORIGINAL CONTRIBUTION

Childhood methylphenidate adherence as a predictor of antidepressants use during adolescence

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Received: 25 September 2018 / Accepted: 25 February 2019 / Published online: 4 March 2019

Abstract

Methylphenidate (MPH) is a common and effective treatment for attention deficit hyperactivity disorder (ADHD), but little is known about the relationship between early childhood intake of MPH and onset of antidepressant treatment during adolescence. The study aimed to examine whether adherence to MPH during early childhood predicts the initiation of antidepressants during adolescence. This is a 12-year historical prospective nationwide cohort study of children enrolled in an integrated care system who were first prescribed MPH between the ages of 6 and 8 years ($N=6830$). We tested for an association between their adherence to MPH during early childhood (as indicated by medication possession ratio from MPH onset through the age of twelve) and the likelihood of being prescribed any antidepressant during adolescence (age 13–18). As all country citizens are covered by mandatory health insurance, and full services are provided by one of the four integrated care systems, data regarding patients' diagnoses, prescriptions, and medical purchases are well documented. Logistic regression analysis indicated that those with higher adherence to MPH had a 50% higher risk (95% CI 1.16–1.93) of receiving antidepressants during adolescence when controlling for other comorbid psychiatric conditions and parental use of antidepressants. In this large-scale longitudinal study, MPH adherence during early childhood emerged as a predictor for antidepressant treatment during adolescence, which may reflect increased emotional and behavioral dysregulation in this group. The highly adherent patients are at higher risk and should be clinically monitored more closely, particularly into adolescence.

Keywords Attention deficit hyperactivity disorder · Methylphenidate · Antidepressants · Adherence · Depression · Anxiety · Longitudinal analysis

Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common psychiatric diagnoses among children and adolescents worldwide, with an estimated prevalence of 3.4–7.2% across countries [1, 45]. The standard of care for ADHD typically includes long-term treatment with stimulants such as methylphenidate (MPH)-based medications [42], and their use is effective in symptoms control [43]. Yet, adherence to MPH is low as child and adolescent patients often discontinue the treatment, mostly as a result of emotional and social adverse side effects, such as loss of appetite or social stigma [7, 17, 46], as well as negative parental attitudes toward medical treatment of ADHD [8]. The mean 12-month medication possession ratio (MPR) of MPH among children and adolescence is merely 37% [17] and approximately 21% of patients completely terminate

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the medical treatment [46]. Even young children (below 9 years), who are considered more adherent than adolescents [18], have been found to have relatively medium to low levels of adherence (MPRs 73–67%, respectively). Researchers still endeavor to generate novel formulas that will increase children and adolescence adherence [10]. In the current study, the focus was on the long-term predictions of adherence to MPH. Specifically, we asked whether adherence to MPH in early childhood is a significant predictor of antidepressants use later in adolescence. The following brief review of the current literature will lead to the rationale to hypothesize that adherence will be negatively associated with antidepressants use (i.e., high adherence during early childhood will predict lower likelihood of antidepressants use).

A worldwide escalation in MPH-based medication prescriptions for treating ADHD has been reported in the last few decades, particularly among children and adolescents [48]. As a result, the long-term effects of exposure to MPH have become a major public health interest, particularly given the high prevalence, long duration, and early age of MPH treatment onset [21]. There is also an important distinction between ADHD clinical onset in early childhood and later during adolescence, considering recent findings indicating different age-related effects; while early onset of MPH treatment can protect from substance abuse [31], it was found to be unrelated to the development of mood disorders among males [29]. Other studies have also revealed age-dependent neurobiological effects of MPH; whereas children aged 10–12 had cerebral blood flow increase following MPH consumption, older patients did not [39]. Similar findings were consistently found among non-human subjects [47].

An association between ADHD and mood disorders, learning disabilities, antisocial behaviors, substance use, and other clinical conditions has also been fairly well established [5]. Recent large-scale population study indicated that a relatively large portion of children and adolescents (6%) is treated with a combination of MPH and antipsychotic medications [37]; however, depression and anxiety are the most common comorbidities. Recent findings suggest that among individuals with ADHD, there is a 14% point prevalence of concurrent severe depressive symptoms, compared to 1% among all children and adolescents [23]. Although the comorbidity of ADHD and depressive symptoms in the general population may range from 5% [36] to higher than 20% [26], about 15% of medicated ADHD children and adolescents are also prescribed antidepressant medication (ADM), which is the most common comorbidly prescribed medication for this population [3]. In one study, adolescents who attempted suicide had high prevalence of ADHD (65%), but only 22% were diagnosed before the suicidal attempt and merely 13% received pharmacological treatment [30]. Furthermore, the use of MPH was not found to be associated with long-term risk of suicide behaviors [28]. Studies also indicated that MPH may be effective in treating depressive/anxiety symptoms, especially among patients with traumatic brain injuries [24]. Copeland et al. recently demonstrated that the relationship between ADHD and depression is still poorly understood; a high comorbidity between the two diagnoses, with an odds ratio of 8 to carry both diagnoses (compared with only one of them) and became insignificant when controlling for other comorbidities (e.g., conduct disorder and oppositional defiant disorder), thus suggesting an indirect link [13]. In other words, ADHD may be associated with other behavioral and emotional states, which in turn lead to higher risk of depression.

The current literature has not addressed several key aspects and possible long-term outcomes including the occurrence of a depression/anxiety comorbidity, which is highly prevalent, and therefore, it remains important to review empirical evidence, indicating the antecedents and consequences of medication use and adherence among the school-age population. The previous reports suggest that consistent medical treatment of ADHD may be protective against later onset of depression [4, 35] and anxiety [6, 14]. A 12-week MPH treatment regimen prescribed to ADHD-diagnosed children with depressive symptomatology significantly improved the severity of depressive symptoms in children and adolescents [19]. However, the duration of all of these studies range from 1 to 12 months (with an average of 3.2 months). Furthermore, it often relied on retrospective assessments [15], did not included duration of MPH use [35], followed participants for a shorter time period [19], or relied on a small sample size [4, 15, 19]. Recent studies that had followed participants for a longer duration included participants with an ADHD onset at a wide age range [25, 49].

The current study

The aim of the current study was to determine the relationship between adherence to MPH, among children diagnosed with ADHD and prescribed MPH in early childhood (i.e., before the age of eight), and future dispensed prescriptions of ADM, addressing the current gaps in the literature, i.e., focus on early childhood MPH onset, using a large sample and longitudinal research design. Our study encompassed a large general population-derived sample, using a historical prospective, longitudinal research design (12-year follow-up). We tested the hypothesis, which was based on the previous research on MPH adherence [38, 39, 47], that high adherence to MPH during childhood would be associated with lower risk of dispensed prescription for ADM during adolescence.

Methods

Setting

Clalit Health Services is the largest of four integrated payer–provider healthcare organizations in Israel, covering over 4 million members, which is more than 50% of the national population. There is universal healthcare coverage in Israel [11], and despite some minor sociodemographic differences between the healthcare organizations and standardized basic services provided by each, Clalit is the largest and covers all municipals districts across Israel [12]. Furthermore, the coverage of the health services is very wide, and therefore, the vast majority of medical treatments are well-documented within the organization database. For instance, when purchased through the basic medical insurance that is provided to all citizens, a monthly treatment with regular methylphenidate-based medication would cost approximately 8$ (USD), while the average annual income is 33,000$ per working person (other methylphenidate-based medications, such as Ritalin-LA or Concerta, would cost approximately 30–60$ a month pending individual insurance coverage). Access to the data warehouse and the analyses were approved for this study by the Clalit Health Services Review Board .

Participants

The study included members of Clalit Health Services born between January, 1990 and December, 1996 who were *first* prescribed with continuous MPH treatment (all formulations, standard, and extended release) between the age of 6 and 8 years (i.e., January, 1998 through December, 2002), and who were not prescribed any ADM before age 12. According to the Israeli Health Ministry directives, mandatory for all physicians, continuous MPH treatment is prescribed only following comprehensive evaluation for ADHD by a certified child psychiatrist or child neurologist. All participants were followed through the age of 18 (December, 2014) (see Fig. 1 for flow chart).

Adherence

Adherence was calculated using MPR [16], with the numerator reflecting the number of dispensed MPH monthly purchases and the denominator reflecting the number of months from first prescription (index date) through age 12 (see Eq. 1). It is important to note that in the Israeli health system, most of the MPH medications are covered by the national basket of health services and that both the prescription and purchase of these medications are strictly regulated and documented [12]. Empirical data support the notion and the MPR reliably indicates actual exposure [44]. Adherence was then divided into two levels: high (MPR $\geq$ 50%) and low (MPR < 50%) for the purpose of all analyses, based on the previous research on MPH adherence that often found an average adherence of < 70% among various population [10, 17] and, therefore, regarded 50% as a cutoff for poor adherence [33]:

Equation 1. Calculation of adherence as MPR.

$$\text{Adherence}(\%) = \frac{\text{Number of dispensed MPH monthly purchases}}{\text{Time (months) from index date through age 12}} \times 100. \quad (1)$$

Outcome

Our primary outcome of interest was the occurrence of at least one dispensed prescription of any ADM (ATC N06A) between the ages of 12–18. According to the Israeli Health Ministry directives, mandatory for all physicians, antidepressant treatment at this age group is prescribed only following comprehensive evaluation by a certified child psychiatrist.

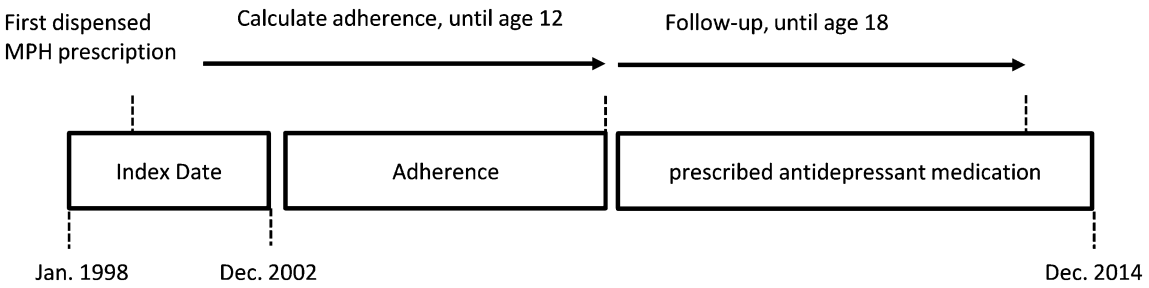

Fig. 1 Flowchart of the study design

Covariates

We included the following demographic characteristics as covariates: age at first prescription (6–8 years), sex, immigrant status, country of birth, ethnicity (defined as Jewish, Non-Jewish, or missing at the clinic level based on the clinic's catchment area), and socio-economic status (defined as low, medium, high, or missing based on clinic catchment area). All variables were extracted as of the index date, with two exceptions (ethnicity and socio-economic status) which were extracted at age 12, to improve the completeness of the data set.

We also included clinical characteristics at index date that might be associated with depression/anxiety: BMI category [27] (underweight—BMI < 18.49, normal weight—BMI 18.5–24.9, overweight—BMI 25.0–29.9, and obese—BMI > 30.0), history of comorbidity (head injury, neoplasm, diabetes, thyroid disease, and epilepsy), history of having been prescribed psychoactive medication (antipsychotics, antiepileptics, mood stabilizers, and anxiolytics), and having a parent with a at least one prescription for an antidepressant medication. Participants who had at least one prescription of any ADM before or at index date were excluded from the sample.

Statistical analysis

We present the clinical and demographic characteristics of the cohort by adherence group at the index date, as well as by the outcome during the follow-up period. We then performed logistic regression to test for the association between childhood adherence to MPH and adolescent prescription of ADM. We initially tested univariate association using logistic regression and then created a set of features for adjusted models. Imputation was not performed as there were insufficient variables for the beginning of the period. We removed variables whose shared variance with the outcome was less than 1%. Multicollinearity was tested using variance inflation factor (VIF) and we sequentially removed terms, whose score was above 4. We then performed backwards stepwise logistic regression based on minimizing the Bayesian information criterion (BIC) score. In addition, we tested the interaction between age and adherence.

We analyzed the proportion of patients purchasing an ADM by deciles and quintiles of adherence, to test whether indeed the 50% cutoff of adherence was suitable. We further performed this process by age. We used the Hosmer–Lemeshow test to establish calibration (goodness of fit p value = 0.96), as well as inspecting calibration plots, and tested discrimination using ROC plots.

Table 1 Demographic and clinical characteristics at index

	MPR < 50%	%	MPR ≥ 50%	%
Total, *N*	5094	74.5	1740	25.5
Age (years)				
6	1204	23.6	507	29.1
7	1872	36.7	650	37.4
8	2018	39.6	583	33.5
Sex				
Male	3977	78.1	1,512	86.9
Female	1117	21.9	228	13.1
Immigrant status				
Yes	296	5.8	94	5.4
No	4798	94.2	1,646	94.6
Country of birth				
Israel	4798	94.2	1646	94.6
Western	63	1.2	23	1.3
Eastern Europe	50	1.0	17	1.0
Africa	4	0.1	1	0.1
Other	179	3.5	53	3.0
Ethnicity*				
Jewish	4705	92.4	1689	97.1
Non-Jewish	355	7.0	48	2.8
Unknown	34	0.7	3	0.2
SES*				
Low	1536	30.2	457	26.3
Medium	2317	45.5	838	48.2
High	1093	21.5	399	22.9
Unknown	148	2.9	46	2.6
BMI				
Underweight	33	0.6	13	0.7
Normal weight	331	6.5	167	9.6
Overweight	75	1.5	32	1.8
Obese	132	2.6	66	3.8
Unknown	4523	88.8	1462	84.0
Comorbidity				
Head injury	22	0.4	4	0.2
Neoplasm	19	0.4	2	0.1
Diabetes	3	0.1	3	0.2
Thyroid disease	5	0.1	6	0.3
Epilepsy	99	1.9	27	1.6
Psychoactive drugs				
Antipsychotics	377	7.4	222	12.8
Antiepileptics	170	3.3	66	3.8
Mood stabilizers	162	3.2	61	3.5
Anxiolytics	138	2.7	47	2.7
Parents with any ADM				
Yes	2551	50.1	954	54.8
No/Unknown	2543	49.9	786	45.2

MPR medication possession ratio, *ADM* antidepressant medications
*$p < 0.05$

Table 2 Demographic and clinical characteristics by outcome

	No ADM age 12–18	%	ADM age 12–18	%
Total, *N*	6264	91.7	570	8.3
Age (years)				
6	1555	24.8	156	27.4
7	2295	36.6	227	39.8
8	2414	38.6	187	32.8
Sex				
Male	5049	80.6	440	77.2
Female	1215	19.4	130	22.8
Immigrant status				
Yes	336	5.4	54	9.5
No	5928	94.6	516	90.5
Country of birth				
Israel	5928	94.6	516	90.5
Western	76	1.2	10	1.8
Eastern Europe	53	0.8	14	2.5
Africa	5	0.1	0	0.0
Other	202	3.3	30	5.3
Ethnicity*				
Jewish	5850	93.4	544	95.4
Non-Jewish	377	6.0	26	4.6
Unknown	37	0.6	0	0.0
SES*				
Low	1833	29.3	160	28.1
Medium	2879	46.0	276	48.4
High	1373	21.8	119	20.9
Unknown	179	2.9	15	2.6
BMI				
Underweight	43	0.7	3	0.5
Normal weight	448	7.2	50	8.8
Overweight	94	1.5	13	2.3
Obese	176	2.8	22	3.9
Unknown	5,503	87.8	482	84.5
Comorbidity				
Head injury	22	0.4	4	1
Neoplasm	18	0.3	3	1
Diabetes	6	0.1	0	0
Thyroid disease	10	0.2	1	0
Epilepsy	113	2	13	2
Psychoactive drugs				
Antipsychotics	468	7	131	23
Antiepileptics	211	3	25	4
Mood stabilizers	198	3	25	4
Anxiolytics	162	3	23	4
Parents with any ADM				
Yes	3289	53	396	69
No/Unknown	2975	47	174	31

MPR medication possession ratio, *ADM* antidepressant medications
*$p < 0.05$

Results

Most children (74.5%) in the cohort had MPH adherence below 50% (average MPR was 34.4%). There were only two covariates that were associated with both MPH adherence (Table 1) and ADM prescription (Table 2): prescribed antipsychotic drugs ($\chi^2(1) = 46.56$, $p < 0.001$; $\chi^2(1) = 157.19$, $p < 0.001$, respectively) and having at least one parent with ADM use ($\chi^2(1) = 11.71$, $p < 0.001$; $\chi^2(1) = 60.53$, $p < 0.001$, respectively). Children who had been prescribed antipsychotic drugs or those with known parental use of ADM were more likely to have high MPH adherence during childhood and were in greater risk for later ADM usage. None of the other covariates was significantly associated with both index (i.e., adherence) and outcome (i.e., ADM between age 12–18) and, therefore, were not included in further analyzes.

Within the ADM users group, approximately 31% were from the high adherence group, which is higher than their proportion in the population [25.5%; $\chi^2(1) = 14.88$, $p < 0.001$]. The primary multivariable regression analysis indicated that children with high adherence were at higher risk to be prescribed an ADM during adolescence (OR 1.50 [95% CI 1.16–1.93]). Parental use of ADM (OR 1.98 [95% CI 1.65–2.39]) and use of other antipsychotic medications (OR 3.41 [95% CI 2.73–4.25]) also significantly predicted the ADM usage during adolescence (see Appendix A for unadjusted coefficients).

Sensitivity analyses

The sensitivity analyses yielded non-significant change of effect size. We repeated tests stratifying the population by age and brain injuries, a factor that may indicate more severe symptomology, to refute alternative explanations to the association between MPH and ADM; however, none of the sensitivity analyses significantly altered any of the findings. Therefore, there is no reason to assume that the findings are moderated by age or other indicators of severity, available in the data.

Discussion

This 12-year historical prospective study aimed to address the relationship between adherence to MPH during childhood and the onset of antidepressant treatment during adolescence. The primary finding is that children with high MPH adherence had a 50% higher likelihood for first ADM prescription during adolescence when controlling for the use of other non-ADM psychiatric medications or parental use of ADM. Although a correlation between ADHD and emotional dysregulation has been consistently documented [40],

our results do not support some previous findings which reported negative association between MPH adherence and depression/anxiety diagnoses [4, 14, 15, 19, 25, 35]. Recent large-scale prospective studies of a Taiwanese cohort which indicated that children with ADHD are at higher risk for major depression disorder compared to non-ADHD children [25, 49]. However, within the ADHD children cohort, those who were more adherent to MPH treatment throughout childhood had lower risk for major depression disorder [25] and bipolar disorder [49] later during early adulthood. A recent comprehensive review suggested that MPH treatment reduces the risk of anxiety among children with ADHD [14], and similar findings were found regarding state-anxiety symptoms among adults [6], in contrast to our findings.

Whereas the previous research included wide age ranges for the initial diagnosis of ADHD, most commonly at any time during childhood or adolescence, our study examined a more selected population of children who were first prescribed MPH in earlier childhood. This means that for ADHD patients diagnosed in this age group, those with higher adherence to MPH have a higher risk to develop depression/anxiety symptoms that require treatment with antidepressants during adolescence. Pediatricians, child psychiatrists, and other mental health professionals should be aware of this risk during follow-up of this younger pediatric population age group.

There are several possible mechanisms that may explain why high adherence to MPH during early childhood is associated with increased risk for depression/anxiety medication use later during adolescence. First, it is possible that children who need persistent treatment for ADHD during early childhood suffer from more severe dysregulation, which first appear as deficits in attention, hyperactivity, and poor behavioral regulation, and are later manifested also by emotional regulatory dysfunctions (i.e., depression/anxiety). This explanation is in line with the increased rate of children medicated concurrently with antipsychotics in the high adherence group (12.8% vs. 7.4%, OR 3.41 [95% CI 2.73–4.25]). It has been recently suggested that early users of MPH may be prone to other brain function deficits, as found in a study that examined impaired cerebral activity among those who first received treatment before age 16 compared to adults who were never prescribed MPH or who had their first prescription given after the age of 23 years [38].

Second, there is growing attention given to the differences between children and adolescents in the presentation of mood and anxiety disorders. It had been established that some depressive symptoms may appear as irritability among children and adolescents [1] and, therefore, be misdiagnosed as ADHD [9]. For these children, MPH treatment would be ineffective and may lead to earlier onset of clinical mood/anxiety symptoms that may necessitate ADM pharmacotherapy. It is possible that the high adherence group in our study included more misdiagnosed children and that may have confounded the results. However, since MPH treatment is usually ineffective for misdiagnosed patients, one would expect a consequential low MPH adherence in this group. Therefore, this explanation seems less likely to explain our findings.

Third, it is possible that relatively more persistent consumption of MPH initiated at an early age has an effect on the onset of depression or anxiety. Although numerous studies demonstrated the effectiveness and safety of MPH treatment, mainly up to 2 year duration [20], more research in needed to understand the implications of longer term MPH treatment among young children. For instance, recent studies suggested that in terms of scholastic achievement among children and adolescents, controlled pauses in medical treatment can even become beneficial [2]. Furthermore, although continuous MPH treatment predict major decrease in ADHD symptoms, it led to only minor improvement in math-related domains and had no effect on language-related (e.g., reading comprehension) domains [22].

Finally, one of the novelties in the current study is focusing on early childhood; therefore, it important to consider developmental aspects as well. Specifically, in this early developmental stage, parents play a significant role in MPH adherence, as they regulate the medical supervision, purchase, and consumption of these medications [33, 48]. In our data, we controlled for parental use of any ADM, which may indicate both genetic risk for depression/anxiety, as well as inclination or awareness to search and use medical therapy. Similarly, research has shown that aversive side effects or dissatisfaction from the impact of medical treatment are important factors in adherence as well [7, 17, 46]. Either the parent's or the child's satisfaction with the effects of MPH in childhood may increase the likelihood to seek other medical treatment when needed. Therefore, these individual factors should be considered in future research (i.e., parental attitudes and positive response to medication).

The prevalence of ADM usage in our sample (8.3%) is higher than the 1–2% prevalence that is commonly found in general population of adolescents worldwide [34, 41]. Considering the comorbidity of ADHD and depression or anxiety [5], we would expect to find higher rates of ADM; however, we have no reason to assume that ADM was less accessible for the low-adherence group.

The findings of our study should be interpreted in light of its limitations. First, we have limited ability to assess additional covariates, including medication effectiveness, school performance, side effects, and ADHD severity, despite our attempts with sensitivity analyses. Second, although continuous MPH treatment in Israel is prescribed only after comprehensive assessment for ADHD by a certified child psychiatrist or child neurologist, especially in such a young age group, future research should include

assessment of different modalities of ADHD severity for control. Furthermore, our findings do not establish causal relationship, and ADM prescription may represent other medical conditions beyond depression or anxiety, for instance, obsessive–compulsive disorder, which is less prevalent. Therefore, we do not suggest that MPH adherence is a cause of depression or anxiety onset, or that medical practitioners should change the guidelines for MPH treatment during childhood. Finally, although all of the residents in Israel are covered by law with medical health insurance, which includes both ADHD and ADM treatments, some might still prefer to purchase these medications from private providers (e.g., avoiding the stigma of ADM treatment; preference to non-MPH medications such as amphetamines or Strattera). This consideration is important within the Israeli context, as some might wish to avoid documentation of ADM usage that might affect their mandatory army service positions. In such cases, the information would not be documented in our data.

Conclusions

This historical prospective study is the first to follow a large representative sample of children ($N = 6830$) who commenced treatment with MPH at early age (6–8 years) over a span of 12 years. Counter-intuitively, the results indicate that those who were highly adherent to MPH had %50 higher likelihood to be prescribed ADM during adolescence. These findings highlight the importance of systematic follow-up for all children who initiated MPH treatment at an early age and persist in their treatment; while greater adherence is likely associated with a greater beneficial effect on ADHD symptoms, the underlying emotional and behavioral dysregulation among symptomatic children may still present during adolescence, as reflected by ADM prescriptions. This study also emphasizes the need for further large-scale prospective research initiatives such as Attention Deficit Hyperactivity Drugs Use Chronic Effects (ADDUCE) project, which is a collaborative longitudinal study of the long-term effects of MPH use among children and adolescence currently conducted in Europe [21, 32].

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Appendix A

Variables included in the final model predicting dispensed prescription of ADM (unadjusted).

Variable	Coefficient	95% CI
MPH adherence	1.26	1.04–1.52
Antipsychotics	1.98	1.65–2.39
Parental ADM use	3.51	2.81–4.36

MPH methylphenidate, *ADM* antidepressant medications.

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