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Stimulant ADHD medication and risk for substance abuse

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Abstract

Background—There are persistent concerns of long-term effects of stimulant ADHD medication on the development of substance abuse.

Methods—Using Swedish national registers, we studied all individuals born 1960–1998 and diagnosed with ADHD (26,249 men and 12,504 women). We investigated the association between stimulant ADHD medication in 2006 and substance abuse during 2009. Substance abuse was indexed by substance-related death, crime, or hospital visits.

Results—ADHD medication was not associated with increased rate of substance abuse. Actually, the rate during 2009 was 31% lower among those prescribed ADHD medication in 2006, even after controlling for medication in 2009 and other covariates (hazard ratio: 0.69; 95% confidence interval: 0.57–0.84). Also the longer duration of medication, the lower the rate of substance abuse. Similar risk reductions were suggested among children and when investigating the association between stimulant ADHD medication and concomitant short-term abuse.

Conclusions—We found no indication of increased risks of substance abuse among individuals prescribed stimulant ADHD medication; if anything, the data suggested a long-term protective effect on substance abuse. Although stimulant ADHD medication does not seem to increase the risk for substance abuse, clinicians should remain alert to the potential problem of stimulant misuse and diversion in ADHD patients.

Keywords

ADHD; Pharmacology; Substance abuse

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Introduction

Randomized controlled studies suggest that ADHD medication have beneficial short-term effects on symptoms of ADHD (Adler et al., 2009; Banaschewski et al., 2006; Findling, 2008; Findling et al., 2008; Koesters, Becker, Kilian, Fegert, & Weinmann, 2009; Kooij et al., 2010; Newcorn et al., 2008; Svanborg et al., 2009; Young, Sarkis, Qiao, & Wietecha, 2011). This is supported by a recent large study indicating significant associations between ADHD medication and reductions in criminality while under treatment (Lichtenstein et al., 2012). However, the possible beneficial effects on short-term behavior have to be carefully weighed against potential adverse effects (Graham & Coghill, 2008; Singh, 2008). Among these, there have been concerns over the long-term effects on the development of substance abuse (Humphreys, Eng, & Lee, 2013; Singh, 2008; Winhusen et al., 2011), where researchers and clinicians have proposed that risk for substance abuse might be particularly pronounced for youths who use stimulant ADHD medication during a sensitive developmental period (Fischer & Barkley, 2003; Mannuzza, Klein, & Moulton, 2003; Mannuzza et al., 2008).

Stimulant medications (e.g., methylphenidate) are the most commonly used pharmacological treatments for ADHD. One reason for the persistent concern for subsequent substance abuse derives from the fact that stimulant medications increase dopamine concentration in the nucleus accumbens (a brain region implicated in substance abuse and the proposed neural mechanism for ADHD treatment) (Wise, 2002; Volkow & Swanson, 2003). Behavior sensitization – a phenomenon of increased response to an addictive substance after repeated exposure - has been observed in humans (Boileau et al., 2008), and there have been reports of abuse and misuse of stimulant ADHD medication (Kollins, MacDonald, & Rush, 2001; Wilens et al., 2008). Although many studies seem to find no or possibly protective effects of ADHD medication on substance use (Barkley, Fischer, Smallish, & Fletcher, 2003; Biederman et al., 2008; Faraone & Wilens, 2007; Mannuzza, et al., 2008; Wilens, Faraone, Biederman, & Gunawardene, 2003), they have had limited sample sizes and data are as yet inconclusive. More evidence is critical for decisions about treatment among individuals with ADHD, their families, and clinicians. Additionally, such evidence is likely to influence societal acceptance of ADHD pharmacotherapy and media reporting on the disorder and its treatment, especially because ADHD by itself is associated with increased risk for substance abuse (Elkins, McGue, & Iacono, 2007; Klein et al., 2012).

We used Swedish population-based data to test the hypothesis that stimulant ADHD medication is associated with risk for long-term substance abuse.

Methods

Patients

Data were derived through linkage of several nationwide population-based registers in Sweden; unique personal identification numbers enabled accurate linkage (Ludvigsson, Otterblad-Olausson, Pettersson, & Ekbom, 2009). The National Patient Register (NPR) has nationwide coverage for psychiatric in-patient care and information on psychiatric out-patient visits to specialist physicians (not general practitioners) since 2001 with diagnoses

based on the International Classification of Diseases (ICD)(Organization, 1992). We identified all individuals born 1960–1998 in Sweden with at least one outpatient diagnosis of ADHD (ICD-10: code F90) between 2001 and 2009 in the NPR. We also used the Prescribed Drug Register, which includes information on all prescribed medical drugs since July 2005 (Wettermark et al., 2007). A non-ADHD general population sample, matched 1 to 10 on age, sex, and residential area at the time of the diagnosis was also used.

Substance abuse was identified through the national Patient, Cause of Death and Crime Registers (including convictions in all Swedish district courts since 1973) (BRÅ, 2011).

To account for socio-demographic information and migrations, we also linked to the Integrated Database for Labour Market Research (LISA), and the Migration Register.

Measures

Stimulant ADHD medication—The main exposure was stimulant ADHD medication at Jan 1, 2006 according to their Anatomical Therapeutic Chemical codes (ATC; methylphenidate-N06BA04, amphetamine-N06BA01 and dexamphetamine-N06BA02) (Zetterqvist, Asherson, Halldner, Langstrom, & Larsson, 2012).

Substance abuse—Several studies have used Swedish national registers to study substance abuse (Kendler et al., 2012). We employed the same definitions; that is (1) hospital visits with diagnoses of mental and behavioral disorders due to psychoactive substance use (ICD-10 codes: F11-F16, F19) identified from the Patient Register, or (2) deaths due to substance use (ICD-10 codes: F11–F16, F19) according the Cause of Death Register, or (3) convictions for a substance related crime according to the Crime Register (i.e., making, transfer, possession, or use of illegal substances). Substance abuse was treated as a time-to-event variable, and could occur repeatedly during the follow-up. We included only unplanned hospital visits to avoid misclassifying planned treatments (e.g., regular hospital visits in treatment programs) as events.

Covariates—We included five socio-demographic measures as covariates. Information on civil, employment and education status, as well as living in one of the three larger cities in Sweden (Stockholm, Göteborg, Malmö), and disposable family income in 2006 were retrieved from the LISA database. We also controlled for previous substance abuse, other psychiatric diagnosis (other than substance abuse and ADHD), criminal conviction (other than for substance abuse), and psychotropic medications other than ADHD medication.

Statistical Analyses

We used Cox-regressions with robust standard errors (to account for the correlations between periods within the same individual) and estimated the hazard of substance abuse during 2009, with stimulant medication status at Jan 1 2006 as the exposure. First we investigated associations while controlling for sex, and age and medication during follow up (as time-dependent covariates; Model 1). Second, we controlled also for the other covariates at baseline (i.e., in 2006; Model 2). To investigate if potential effects were mediated by non-substance (Model 3) and/or substance abuse related (Model 4) psychiatric or criminal events

during the time between baseline (2006) and follow-up (2009), such covariates for the time 2006–2008 were included in subsequent models.

To investigate whether time on treatment was important, we did separate analyses with the total number of years with ADHD medication 2006–2008 as the exposure.

We also performed a number of sensitivity analyses. First, we analyzed the association for those also on non-stimulant ADHD medication (atomoxetine-N06BA09). Second, some patients may have been not medicated because they were different (e.g., with comorbid conditions not suitable for stimulant medication) from those medicated; therefore, we analyzed a subsample of patients who had been on medication at least once during follow-up to rule out the potential confounding effect of such unmeasured conditions. Third, individuals with drug abuse at baseline might respond differently to treatment; a sensitivity analysis was performed with patients who had a drug abuse diagnosis before 2006 but not 2006–2008.

In addition, to test the effect on short-term abuse we studied the concomitant risk of substance abuse. Here we identified periods when individuals were on and off treatment; in accordance with previous studies an individual was defined as receiving treatment during the time interval between two dispensed prescriptions of ADHD medication, unless prescriptions occurred more than 6 months apart (Lichtenstein, et al., 2012; Zetterqvist, et al., 2012). “Within-individual analyses” were used to study the rate of substance abuse during stimulant ADHD medication compared to the same individual while untreated. Similar to our previous study (Lichtenstein, et al., 2012), this was done using stratified Cox regression, with medication and age as time-dependent covariates and with each individual entered as a separate stratum in the analysis. This method adjusts for all confounders that are constant within each individual during follow-up.

We also performed sensitivity analyses with individuals who were prescribed selective serotonin reuptake inhibitors (SSRIs; instead of ADHD medication). This analysis was one approach to deal with the possible non-specific beneficial effects of being prescribed medication, such as regular reviews by healthcare staff and links to other medical and social services.

The project was approved by the Ethics committee at Karolinska Institutet.

Results

We identified 26,249 men and 12,504 women who had ever received an outpatient diagnosis of ADHD and were alive on January 1, 2009. Of these, 16.0% of the males and 10.4% of the females were exposed to stimulant ADHD medication in January 1, 2006 (Table 1). Among males diagnosed with ADHD, 48.7% used stimulant ADHD medication and 6.2% had at least one substance abuse registration during follow-up (January-December 2009). Corresponding figures for matched general population controls were 0.4% and 0.6%. Among female ADHD patients, 53.0% had taken stimulant ADHD medication and 4.2% had at least one substance abuse registration, compared to 0.2% and 0.2% among controls, respectively. Large proportions had other (non-ADHD and non-substance abuse) psychiatric

diagnoses and had been convicted for other (non-substance abuse) crimes already before baseline (2006), and a large proportion also had diagnoses, convictions and other psychotropic medication in the time between baseline and start of follow-up (i.e., between 2006 and 2008). In both males and females, those taking stimulant medication were younger at start of follow-up, and less likely to be employed or married compared to non-users; these differences may be explained overall by stimulant users being younger than non-users.

We investigated long-term associations between stimulant ADHD medication and substance abuse by comparing patients on medication with those not on medication 1/1/2006. Those on medication did not have increased rates of substance abuse during follow-up; on the contrary, the rate of abuse during 2009 was lower for those on medication 1/1/2006 (Table 2). After controlling for age, sex and medication in 2009, the substance abuse rate was decreased 48% (Hazard Ratio [HR]=0.52, 95% confidence interval [95% CI]: 0.42–0.66). The association remained decreased at 31% when we controlled for other potential confounders (SES, substance abuse, psychiatric disorder, and criminal convictions before 2006; HR=0.69, 95% CI: 0.57–0.84).

Another issue is whether the findings reported above of less drug abuse among those on medication in 2006 are mediated by subsequent psychiatric disorders (including drug abuse). We therefore conducted mediation analyses with those covariates. The associations between medication in 2006 and drug abuse in 2009 were further reduced when controlling for non-substance psychiatric events and criminal convictions between 2006 and 2008 (HR=0.77, Table 2, Model 3) and substance abuse events (HR=0.87, Table 2, Model 4), suggesting that the association was partly mediated by both non-substance-related and substance-related psychiatric disorders and/or crimes.

For each year an individual was taking stimulant ADHD medication before follow-up there was a 13% (HR=0.87, 95%CI: 0.80–0.94) decrease in the rate of substance abuse registrations during 2009, after controlling for all confounders before 2006 (Table 2).

Decrease in substance abuse rates associated with ADHD medication were observed also when using different cohorts or exposures, that is, when we analyzed males and females separately (eTable 1), included non-stimulant ADHD medication, excluded individuals who were never treated, and did separate analyses for those with a drug abuse diagnosis already at baseline (eTable 2).

We performed analyses on a cohort of 17,328 children with ADHD who were 15 years old or younger 1/1/2006. There was no indication that stimulant ADHD medication increased the rate of abuse in this cohort but rather, there appeared to be an even stronger negative association (HR=0.38, 95% CI: 0.23–0.64; Table 2).

In addition to the long-term effects, we also investigated short-term associations between stimulant ADHD medication and concomitant substance abuse in the cohort of 26,393 men and 12,548 women with a ADHD diagnosis and alive in 2006. Concomitant substance abuse was less common during periods with stimulant ADHD medication according to the between-individual analyses; the hazard ratio was 0.57 (95% CI: 0.51–0.64; Table 3) suggesting that medication decreased the substance abuse rate 43%. Because patients

receiving medication might be different from non-medicated patients, the crucial test of a medication effect is when there are differences in substance abuse rate in the same individual in medication versus non-medication periods. The hazard ratio for this within-individual risk was 0.73 (95% CI: 0.68–0.77); thus even within individuals (i.e., after adjusting for confounders that do not vary with time, such as genes and childhood environment), stimulant ADHD medication reduced the concomitant substance abuse rate by about 27%. Similar results were evident regardless of the class of substance abused (eTable 3), and irrespective of the order of change in medication status (eTable 4). In contrast, there was no evidence of an association when we investigated SSRI instead of ADHD medication using stratified Cox regression (HR=1.04, 95% CI: 0.96–1.12).

Discussion

ADHD medication has been shown to have advantageous short-term effects on ADHD symptoms (Adler, et al., 2009; Banaschewski, et al., 2006; Findling, 2008; Findling, et al., 2008; Koesters, et al., 2009; Kooij, et al., 2010; Newcorn, et al., 2008; Svanborg, et al., 2009; Young, et al., 2011), and, similar to a study on drug related criminality (Lichtenstein, et al., 2012), our data suggest a concomitant association between stimulant ADHD treatment and lower rates of substance abuse. Even though short-term effects might be beneficial, there has been a persistent concern that treatment with stimulant medication could lead to long-term development of substance abuse (Singh, 2008; Winhusen, et al., 2011), and our previous study did not explore long-term associations with drug abuse and only addressed drug related criminality (i.e., not deaths or hospitalizations, which were more common than convictions). In this report, we have investigated almost 40,000 individuals with ADHD over 4 years, and found no indication of increased substance abuse at follow-up, which is consistent with a recent meta-analysis (Humphreys, et al., 2013). Rather the results suggested a decrease in substance abuse up to four years after medication and that the longer the duration of ADHD medication the lower the rate of substance abuse. Critics of ADHD medication have been specifically concerned about the risk for youth (Fischer & Barkley, 2003; Mannuzza, et al., 2003; Mannuzza, et al., 2008), but we found no indication of long-term increase in substance abuse in this group. Rather, consistent with a previous meta-analysis, we found a decrease in the abuse rate in youth (Wilens, et al., 2003), and also a decrease in adults.

ADHD medication can potentially have long-term effects on substance use problems for several reasons. One possible mechanism would be that ADHD medication leads to less exposure to substances and, thus, less chance of developing dependence or addiction. Another possibility could be that concomitant effects of treatment do not persist over a longer period. A third alternative is that there are concomitant effects, but when medication is discontinued, patients have developed substance use problems. We found significant associations between stimulant ADHD medication and lower rates of concomitant substance abuse in the within-individual comparisons (Table 3). Further, in the main analyses (Table 2), the significant association between stimulant ADHD medication and long-term substance abuse remained after controlling for the covariates (i.e., model 2). This association was partially mediated by direct effects on lower substance-related problems (model 4) and indirect effects through reduced psychiatric problems (model 3). Together these results are

most congruent with the first hypothesis; that is, the longer an individual takes the medication, the lower the risk for substance abuse, to some extent due to less chance of short-term substance-related and psychiatric problems.

An alternative explanation to the results is reverse causation, that is, that substance behavior before 2006 is correlated with substance abuse 2009 and that the earlier substance abuse (which may have been subclinical) decreased the likelihood of being prescribed ADHD medication in 2006. However, we do not think that our results are consistent with this hypothesis for the following reasons. We find similar results 1) when we control for substance abuse before 2006 (Table 2: model 2). 2) We identified similar effects in children (Table 2), who most likely were too young to have a substance abuse before medication. 3) When we restrict the analyses to individuals who had been medicated (eTable 2). Further, we get similar estimates (albeit non-significant due to limited sample size) when we restrict the analyses to patients with drug abuse already at baseline (eTable 2); thus, if it is reverse causation, the substance abuse was subclinical, mild, or did not influence the prescriber, as the physician had prescribed ADHD medication at least once. 4) We also noted the same effects when studying short-term effects (Table 3) and 5) regardless of the order of change in medication status (eTable 4) where this type of confounding is controlled.

This study is population-based and considerably larger than any other previous study on the association between stimulant ADHD medication and drug abuse. However, it has only 4 year follow-up, which limits its generalizability of effects over the life course. Nevertheless, it is reassuring that we found commensurate results when using duration of stimulant ADHD medication as the exposure, and that our findings are congruent with previous studies (Wilens, et al., 2003; Winters et al., 2011).

It should be noted that register based studies are liable to selection effects. In our analyses of short-term associations, we addressed this problem by within-individual analyses and found similar reduction in substance abuse rates, but this was not possible to do for long-term associations. To limit such bias in the long-term associations, we conducted sensitivity analyses on a subsample of patients that had indications for stimulant ADHD treatment at some point during the follow-up and found similar reduction in substance abuse rates and also investigated if the associations were mediated by behaviors between baseline and follow-up. The results suggest it is unlikely that a selection for ADHD-treatment in 2006 would be associated with drug abuse in 2009, without being mediated by drug abuse in 2006–2008. Because combined treatment provides only modest advantages over pharmacological treatment only (The MTA Cooperative Group, 1999), concurrent non-pharmacological treatments are an unlikely source of bias. To assess the potential confounding from concurrent drug treatments we analyzed concomitant substance abuse rates among individuals with ADHD diagnoses who discontinued SSRI (instead of ADHD medication); we found no evidence of an association with SSRI discontinuation. Further, the long-term association remained when we controlled for other common psychotropic drugs.

Nevertheless, unmeasured confounders can never be fully ruled out in this research design. Ideally, these results should be replicated in a randomized controlled trial, but a trial of long-

term effects of ADHD medication is unlikely to be feasible because of practical and ethical reasons.

These results should be interpreted in the context of other limitations. First, we used substance-related hospitalizations, deaths and convictions from medical and legal records to index substance abuse. While having the important advantage of not requiring accurate respondent recall and reporting, it included mainly severe cases of substance use outcomes. Thus, our results primarily concern severe drug abuse. Future research will need to explore whether the findings generalize to less severe substance use outcomes. Second, the findings were based on Swedish population data, and generalizations to other cultures/countries should be made with caution. Although the prevalence of ADHD diagnosis and medication varies between countries and over time, Sweden does not appear to be unusual in rates of ADHD and ADHD-medication (Scheffler, Hinshaw, Modrek, & Levine, 2007; Zoega et al., 2011). Alcohol is the major substance being abused in Sweden and alcohol sales per capita are similar to that in the US and Canada (National Institute of Public Health, 2008). Substance use also imposes social problems both in Europe (Rehm, Room, van den Brink, & Jacobi, 2005) and the US (Compton, Thomas, Stinson, & Grant, 2007). Compared to the US, however, the use of illegal drugs in Sweden is lower (National Institute of Public Health, 2008). Nevertheless, we cannot address whether the associations are the same in other cultures, and thus generalizations should be made with caution.

Conclusion

In summary, although we argue that concerns over long-term risks for substance abuse following ADHD medication probably have been overstated, the decision to prescribe stimulant ADHD treatment should, as in all clinical practice, take into account individuals factors and potential adverse effects. When considering ADHD medication, it is also important to acknowledge the risk for over-prescription; clinicians should remain alert to the problem of stimulant misuse and diversion (Wilens, et al., 2008).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- There are persistent concerns of long-term effects of stimulant ADHD medication on the development of substance abuse.
- ADHD medication was not associated with increased rates of substance abuse. Rather the results suggested a decrease in substance abuse up to four years after medication and that the longer duration of ADHD medication, the lower the rate of substance abuse.
- Concomitant substance abuse was less common during periods with stimulant ADHD medication according to the within-individual analyses.
- Although the present findings did not support long-term risks for substance abuse following ADHD medication, the decision to prescribe stimulant ADHD treatment should, as in all clinical practice, consider individual factors and potential adverse effects.

Table 1

Stimulant ADHD medication, substance abuse and other characteristics of patients diagnosed with ADHD.

	Men	Women
Number of patients at start of follow-up (2009)	26,249	12,504
Person-years at risk during follow-up (January–December 2009)	26,172	12,475
% on stimulant ADHD medication January 1, 2006	16.0%	10.4%
% on ADHD medication during 2009	48.7%	53.0%
% Registered at least once for substance abuse during 2009	6.2%	4.2%
% died with a substance abuse diagnosis	0.02%	0.01%
% Convicted at least once for a substance-related crime in the Crime Register	2.9%	1.2%
% Diagnosed at least once in the Patient Register for substance abuse	4.2%	3.6%
Age distribution in 2006		
8–15	49.3%	34.5%
16–25	29.7%	32.8%
26–35	11.6%	17.0%
36–46	9.4%	15.7%
Civil status in 2006*		
Unmarried	88.8%	76.7%
Married	6.2%	12.5%
Divorced	4.9%	10.6%
Widowed	0.1%	0.2%
Employed in 2006*	23.4%	25.2%
Studying in 2006*	32.6%	32.5%
Living in a metropolitan area in 2006	13.5%	13.8%
Non-substance psychiatric diagnosis before 2006	57.0%	68.5%
Non-substance criminal conviction before 2006	33.3%	23.4%
Substance abuse event before 2006	10.8%	7.5%
Non-substance abuse psychiatric diagnosis 2006–2008	25.4%	18.0%
Non-substance criminal conviction 2006–2008	19.7%	9.6%
Substance abuse event 2006–2008	11.9	8.0
Prescribed antipsychotics 2006–2008	12.9%	16.5%
Prescribed hypnotics/anxiolytics 2006–2008	29.9%	46.6%
Prescribed antidepressants 2006–2008	26.2%	48.1%
Prescribed drugs used in addictive disorders 2006–2008	5.1%	5.9%

Note:

* For individuals 16 years or older in 2006.

Table 2

Stimulant ADHD medication in 2006 and hazard ratio for substance abuse during 2009.

Medication	Hazard ratio for substance abuse during 2009							
	Confounder adjustment				Mediation analysis			
	Model 1: Adjusted for sex, age, and ADHD medication in 2009		Model 2: As in model 1 + other potential confounders before 2006		Model 3: As in model 2 + non-substance mediators 2006–2008		Model 4: As in model 3 + substance related mediators 2006–2008	
	Hazard ratio	95% Confidence interval	Hazard ratio	95% Confidence interval	Hazard ratio	95% Confidence interval	Hazard ratio	95% Confidence interval
All patients with an ADHD diagnosis								
Stimulant ADHD medication in January 1, 2006	0.52	0.42–0.66	0.69	0.57–0.84	0.77	0.65–0.93	0.87	0.74–1.03
Duration of treatment with stimulant ADHD medication 2006–2008 (in years)	0.80	0.73–0.88	0.87	0.80–0.94	0.89	0.82–0.96	0.95	0.88–1.02
All patients with an ADHD diagnosis and 15 years or younger in 1/1/2006								
Stimulant ADHD medication in January 1, 2006	0.33	0.20–0.56	0.38	0.23–0.64	0.42	0.26–0.70	0.45	0.27–0.74
Duration of treatment with stimulant ADHD medication 2006–2008 (in years)	0.72	0.61–0.86	0.76	0.63–0.90	0.77	0.65–0.92	0.80	0.68–0.94
All patients with an ADHD diagnosis and 20 years or older in 1/1/2006								
Stimulant ADHD medication in January 1, 2006	0.65	0.46–0.91	0.75	0.58–0.98	0.85	0.67–1.07	0.97	0.78–1.20
Duration of treatment with stimulant ADHD medication 2006–2008 (in years)	0.92	0.82–1.03	0.90	0.91–0.99	0.92	0.84–1.01	0.97	0.89–1.06

Note:
Model 1: Adjusted for sex, age and ADHD medication in 2009 as time-dependent covariates.
Model 2: In addition to model 1, adjusted for SES (civil status, employment, study, living in metropolitan area, income), non-substance abuse psychiatric diagnoses, non-substance-related criminal convictions, and substance abuse at baseline.
Model 3: In addition to model 2, adjusted for non-substance abuse psychiatric diagnoses, non-substance criminal convictions, and other psychotropic medications during follow-up (2006–2008).
Model 4: In addition to model 3, adjusted for substance abuse during follow-up (2006–2008).

Table 3

Short-term associations: Hazard ratios for substance abuse 2006–2009 during treatment periods compared to non-treatment periods in 38,941 patients with a diagnosis of ADHD.

Medication		Hazard ratio			
		Between-indivdual[1]		Within-individual[2]	
	Number of substance abuse diagnoses	Hazard ratio	95 % Confidence interval	Hazard ratio	95 % Confidence interval
Stimulant ADHD medication	20,335	0.57	0.51–0.64	0.73	0.68–0.77

Note:

[1]Hazard ratios were calculated with Cox regression (comparing periods when patients received medication with periods they did not).

[2]Hazard ratios were calculated with stratified Cox regression (comparing periods when patients received medication with periods they did not, within patients who changed their treatment status during follow-up).