ADHD and atopic diseases

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Chapter 3

IS ATOPIC MEDICATION A RISK FACTOR FOR NON-ADHERENCE AND NON-PERSISTENCE OF METHYLPHENIDATE IN CHILDREN?

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ABSTRACT

Background Recent studies have found an association between atopic diseases and attention-deficit/hyperactivity disorder (ADHD). However, it is unclear what the effect is of atopic medication on the continuation of methylphenidate treatment of ADHD.

Objective To assess the association between atopic disease and the length of treatment with methylphenidate.

Methods A retrospective inception cohort study was conducted among methylphenidate user in a representative medication prescription database. The cohort inclusion criteria were children who received at least one methylphenidate prescription at age 4 – 17 years old. The atopic group was defined as children who had received a prescription for an atopic disease in the year before the start of the methylphenidate treatment. The non-atopic group was defined as those without any atopic prescription in the database. Non-adherence and non-persistence were based on the time deviation between two methylphenidate prescriptions from the dosing as recommended by the physician (non-adherence a at least 30 days but no longer than 6 months deviation and non-persistence a deviation of at least 6 months).

Result We identified 844 patients using methylphenidate with an history of atopic disease and 1794 patients using methylphenidate without an history of atopy. There was no difference in methylphenidate non-adherence between the atopic group and non-atopic group. The independent hazard ratio for a history of atopic medication and methylphenidate non-persistence was 1.15 (95% CI 1.02 – 1.29; p = 0.021) compared to controls, when adjusted for sex, age, antidepressant, antipsychotic, and melatonin prescription, and dosage formulation.

Conclusion Our study provides evidence that an history of an atopic disease increases the risk of methylphenidate non-persistence in children.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood-onset neurodevelopmental disorder with a worldwide prevalence between 3-7%.[1] The disorder is characterized by age inappropriate levels of inattention, hyperactivity, and/or impulsivity.[2] Treatment options for ADHD include behavioral therapy and parent training, and different types of medication.[3] Medication should only be considered in individuals with severe symptoms and impairment, or in those who did not respond sufficiently to psychological treatment.[3] Due to the chronic nature of ADHD, long-term therapy is often required. However, medication has only proven efficacy on the short-term (up to two years).[4] Nevertheless, clinical decisions regarding the length of treatment with ADHD medication should be based on the individual level.[5] If untreated or sub-optimally treated, ADHD can lead to significant impairment in academic, psychosocial, and professional development, but also problems with peer and family relationships.[6]

Compliance to medication is a common problem and the adherence to treatment is low especially on the long term.[7] It is estimated that 75% of the patients discontinue their medication within six months after initiation. After 12 months non-adherence or non-persistence is as high as 84%, indicating that non-persistence increases over time.[8,9] In general, non-persistence of methylphenidate, the most commonly used drug for the treatment of ADHD, can be explained by several reasons. ADHD symptoms may improve and therefore drug medication is no longer necessary; the response to methylphenidate may be disappointing; methylphenidate may have (serious) adverse events[10]; or non-persistence may be due to factors inherent to ADHD (e.g., lack of structure). Factors such as comorbidities can influence the non-persistence of ADHD treatment. Common comorbidities in patients with ADHD, like anxiety disorder, tic disorders, oppositional-defiant disorder (ODD) and/or conduct disorder (CD), are known for their association with decreased treatment adherence.[11-14]
Atopic diseases like asthma, allergic rhinitis, and atopic dermatitis have also been found to be associated with ADHD.[15-17] However, whether the presence of an atopic disease is a risk factor for ADHD medication non-persistence, similar as the risk of psychiatric comorbidities on non-persistence, is unclear. Therefore, the goal of this study was to assess the association between atopic medication and the non-adherence and non-persistence of methylphenidate treatment.

METHODS

Setting

This study was conducted using data from the IADB.nl database, a prescription database from the University of Groningen in the Netherlands and has been previously described in detail.[18] The IADB database contains prescription data, with information on users, prescribers, and costs of drug prescriptions. The data are collected from 60 community pharmacies in the Netherlands. The catchment population of these pharmacies is approximately 600,000 patients. Data from the pharmacies are available since 1999. Ethical approval for observational studies with anonymized data from IADB.nl is waived in the Netherlands. The University of Groningen IADB.nl prescription database collects and stores data according to the Dutch law on privacy.

Study population

The study population consists of all patients present in the IADB.nl database who met the inclusion criteria of the study. The following inclusion criteria were used for patient selection; (1) received at least one prescription of methylphenidate between January 1st, 1994 to December 31st, 2014, with no use of methylphenidate in the prior 365 days in order to only include starters of methylphenidate. The date of the first prescription was set as the index date; (2) age between 4 and 17 years at the index date; (3) followed-up at least 12 months after the index date to a maximum of three years; and (4) already in the database at least a year prior to the index date.

Definition of atopy

Presence of atopy was defined as being prescribed medication for asthma, atopic dermatitis, and/or allergic rhinitis in the period of 12 months prior to the index date. The prescription proxies that were used to define the atopic group in this study were defined according to the ATC classification system and based on a validation study by Mulder et al.[19], in which a positive predictive value was found for the medication proxies on predicting the corresponding atopic disease of up to 0.84. A history of asthma medication consisted of at least three prescriptions of inhaled anti-asthma drugs (ATC code R03) or at least two prescriptions of inhaled corticosteroid (ATC code R03AK and R03BA). For a history of atopic dermatitis medication least two prescriptions of dermal steroids (ATC code D07) were required. A history of rhinitis medication consisted of at least three prescriptions of systemic antihistamine (ATC code R06), or at least three prescriptions of nasal antihistamine (ATC code R01AC), or at least two prescriptions of nasal corticosteroid (ATC code R01AD). The non-atopic control group was defined as all children who did not receive any medication for asthma, atopic dermatitis, and allergic rhinitis as described above in the year before the index date.

Definition of outcome

Non-adherence and non-persistence were based on the time deviation between two methylphenidate prescriptions from the dosing as recommended by the physician or between the last methylphenidate prescription and end of follow-up. The difference between the outcomes depended on the length of the gap that was used. ***Non-adherence*** was defined as a minimum gap of 30 days (but no longer than 6 months) between two prescriptions of methylphenidate within the 3-year follow-up. ***Non-persistence*** was defined as a gap of at least of 6 months calculated by either a gap between two prescriptions of methylphenidate within the 3-year follow-up or between the methylphenidate prescription and the date when a patient left the database.

Confounding

Concomitant medication use was also recorded per patient. Medications which are potentially related to ADHD treatment or comorbidities included psychotropic medication (antidepressants, clonidine, antipsychotics, antiepileptics, anxiolytics, melatonin, and hypnotics), hypertension medication, diabetes medication, and dyslipidemia medication were included as potential confounding factors in our analyses. These comorbidities' prescriptions were measured during the whole period of the follow-up in the database. Other confounders that could contribute to methylphenidate non-persistence such as age (measured at index date), sex, and the drug's formulation for the first methylphenidate prescription was also recorded.

Statistical analysis

Descriptive statistic was conducted for variables within the atopy and non-atopy groups. We used student t-test and chi-square test to determine the differences between the atopic and non-atopic group in continuous and categorical variables respectively. A multivariate logistic regression was performed to obtain odds ratios (ORs) with their corresponding 95% confidence intervals (CIs) for the non-adherence of the atopic and non-atopic groups. Kaplan-Meier analysis was used to analyze the survival rate of methylphenidate non-persistence between the two groups. Additionally, Cox-regression analysis was used to calculate the hazard ratios (HRs). Multivariate regression was applied to explore the association between each covariate and methylphenidate non-persistence, and to control for confounding factors. HRs with 95% confidence intervals (CIs) were presented. SPSS version 23 was used for the statistical analyses.

RESULTS

In total, there were 2,638 patients included from the IADB.nl database. Among these patients, 844 patients were included in the atopic cohort and 1794 patients in the non-atopic cohort. The demographic characteristics of the patients in the atopic and non-atopic groups are shown in Table 1. In the atopic group, 525 patients (62.2%) received asthma medication, 247 patients (29.3%) received atopic dermatitis medication, and 192 patients (22.7%) received rhinitis medication. Furthermore, 737 patients (87.3%) had a prescription for one atopic disease, 94 patients (11.1%) for two atopic diseases and 13 patients (1.5%) for all three atopic diseases. The patients with a history of atopic medication use were younger when they started methylphenidate treatment than patients without use of atopic medication. Concomitant prescriptions such as antidepressant, antipsychotics, antiepileptic, anxiolytic, melatonin, other hypnotics, and hypertension medication were more common in the atopic group compared to the control group.

Table 1 Baseline characteristics of the atopic and non-atopic cohort of children on ADHD-medication in the IADB.nl database

	Atopic				P value
	Yes (n = 844)		No (n =1,794)		
	N	%	N	%	
Age at index date (mean (sd)	9.33 (3.47)		9.97 (3.46)		<0.001[a]
Sex (female)	209	24.8	433	24.1	0.726[b]
Concomitant prescription Psychotropic medication					
Antidepressant	91	10.8	147	8.2	0.030[b]
Clonidine	11	0.3	10	0.6	0.044[b]
Antipsychotics	217	25.7	352	19.6	<0.001[b]
Antiepileptic	29	3.4	33	1.8	0.012[b]
Anxiolytic	101	12.0	106	5.9	<0.001[b]
Melatonin	99	11.7	117	6.5	<0.001[b]
Other hypnotics	125	14.8	158	8.8	<0.001[b]
Hypertension medication	51	6.0	56	3.1	<0.001[b]
Diabetes medication	6	0.7	11	0.6	0.770[b]
Dyslipidemia medication	2	0.2	2	0.1	0.440[b]
Drug Formulation at therapy initiation					
Immediate release	792	93.8	1662	92.6	
Extended release	52	6.2	132	7.4	0.260[b]

[a] Student's t-test
[b] Pearson chi-square test

The logistic regression analysis showed that there was no difference in non-adherence between the atopic group and non-atopic group (ORs 1.0 (95% CI 0.8 – 1.3; p=0.8)) over the three year follow-up after controlling for sex, age, antidepressant prescription, melatonin prescription and dosage formulation. The rates of non-adherence with methylphenidate declined over the three years follow-up after the index date. The declining non-adherence rate among both groups was similar and did not differ significantly. More than half (>50%) of the patients in both groups were not persistently using methylphenidate within 6 months after the initiation of therapy.

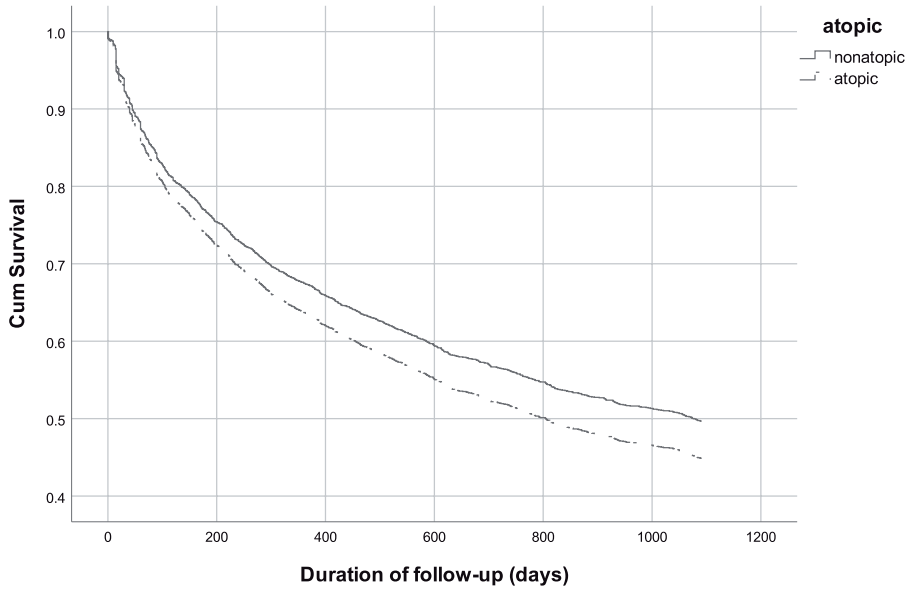
In our non-persistence analysis, the Kaplan–Meier survival curve estimated that children with atopic medication had a significantly higher risk of methylphenidate non-persistence compared to the control group ($p < .017$) (Figure 1). The crude hazard ratio was estimated to be 1.15 (95% CI 1.02 – 1.28; p=0.017). The adjusted hazards ratio of the multivariate analysis are shown in table 2.

Table 2 Risk of methylphenidate non-persistence in children during the 3-year follow-up

Variable	Hazard Ratio (95% CI)	p-value
Atopic medication	1.15 (1.02 - 1.29)	0.021
Sex (female)	1.21 (1.07 - 1.36)	0.003
Adolescence (13 – 17 years old at index date)	2.15 (1.72 - 2.68)	<0.001
Concomitant medication use		
Antidepressant	1.35 (1.14 - 1.60)	0.001
Antipsychotics	1.5 (1.31 - 1.70)	<0.001
Melatonin	0.67 (0.53 - 0.84)	0.001
Immediate release formulation methylphenidate	1.33 (1.07 - 1.66)	0.010

Abbreviations: CI, confidence interval

Figure 1 Survival curve of methylphenidate non-persistence in the atopic and non-atopic group during the 3-year follow-up



DISCUSSION

Our results show that atopic medication use does not significantly affect the non-adherence rate of methylphenidate use. However, having a history of atopic medication increased the risk of non-persistence of methylphenidate therapy.

To the best of our knowledge this is the first study looking into the association of atopic medication use and non-persistence of methylphenidate treatment. In general, non-adherence and non-persistence rates were high and comparable with literature.[8,9] There could be several reasons why individuals with a history of an atopic disease would have a higher risk to discontinue their methylphenidate treatment.

A first reasons may lie in the concomitant use of multiple drug regimens. It has been shown that multiple pill-regimens and comorbidities increase the risk of treatment non-adherence and treatment non-persistence.[12,20] In our study, medication use related to comorbid disorders, like antidepressants or antipsychotics, also increased the risk of methylphenidate non-persistence. When individuals with methylphenidate treatment also have to adhere to atopic treatment this could increase the likelihood of non-persistence in treatment, as a consequence of the multiple pill-regimens.

As a second reason for earlier non-persistence of methylphenidate, the association of atopic medication use and methylphenidate non-persistence could have occurred because of the interaction between concomitant atopic disease medication and methylphenidate. Several atopic medications have an interaction with methylphenidate, e.g., budesonide, and salmeterol. Both the atopic drugs and methylphenidate increase blood pressure and heart rate. Therefore, concomitant use can enhance the effects of both drugs on the cardiovascular system. Based on this interaction, we can assume that one reason why having a history of atopic disease drug prescription is associated with earlier methylphenidate non-persistence is because it enhances the adverse events of methylphenidate. However, this does not apply to all atopic drug prescriptions.

In addition to an effect of atopic medication on earlier methylphenidate non-persistence an increased risk was observed on methylphenidate non-persistence for sex and adolescence. Also the use of immediate release formulations of methylphenidate was associated with earlier methylphenidate non-persistence compared to the extended release formulations. Previous studies showed that older age is related to earlier treatment non-persistence due to an association with remission of symptoms and to an association with poor compliance.[14,21] Also multiple daily doses are often related to treatment non-persistence due to poor adherence and decrease in treatment effectiveness.[22] A large cohort study also found an association of female sex with the non-persistence of methylphenidate.[23]

Although this is the first study assessing the risk of methylphenidate non-persistence and the association with atopic medication, the results of this study must be considered in the context of its strength and possible limitations.

The strength of our study was the use of the IADB.nl database, which is a large population-based prescription database. Almost complete records of prescription are available because Dutch inhabitants normally only register at one pharmacy. The advantage of using the database is the absence of recall bias with respect to medication prescription use during childhood.

Despite this strength, potential limitations must be considered when interpreting the results. Because only prescription data are available, we did not have information about diagnosis or indications for the medication use. This makes the interpretation concerning the effect of either the medication use or the underlying comorbid disorder impossible. Moreover, the reason why patients discontinue their medication is not available, therefore we did not know whether non-persistence happened because of either positive or negative effects of the drugs. Consequently, the study-design restricts us to find out what the underlying mechanism of the association between the atopic medication use and methylphenidate non-persistence is.

Although we were able to control for potential confounders, we cannot exclude the possibility of other unmeasured confounding. In addition, there is a possibility that selection bias occurred in this study. According to Mulder ***et al,*** the proxies which are used to define the specific atopic disease have low sensitivity to include all atopic patients from the prescription database. This has resulted in the fact that a part of the methylphenidate users

with an atopic disease were not included in our exposed group and could have resulted in an underestimation of our results.

Since we defined the exposed time of atopic medication use within one year before the index date, the development of the atopic disease and the corresponding medication use after the initiation of methylphenidate therapy was unknown. Therefore, the results of this study only provide information about the association of an history of atopic medication use and methylphenidate non-persistence. Although a history of atopic medication is a prediction of current medication use, it is not possible to generalize our results to individuals with the concomitant medication use of both atopic drug and methylphenidate.

Concluding, our study provides evidence to support the hypothesis that atopic disease increases the risk of methylphenidate non-persistence in children. Based on these findings, physicians should be aware of a patients' history of an atopic disease in the management of ADHD. Further research is needed to investigate the underlying mechanism of having an atopic disease and the consequences for ADHD and the related methylphenidate use.

REFERENCES

1. Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. *J Child Psychol Psychiatry.* 2015;56(3):345-365.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, DSM-5. . 2013:947.
3. NICE. Attention deficit hyperactivity disorder: Diagnosis and management of ADHD in children, young people and adults. clinical guidelines CG72. http://guidance.nice.org.uk/CG72. Updated 2016. Accessed May/12, 2016.
4. The MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry.* 1999;56(12):1073-1086.
5. van de Loo-Neus GH, Rommelse N, Buitelaar JK. To stop or not to stop? how long should medication treatment of attention-deficit hyperactivity disorder be extended? *Eur Neuropsychopharmacol.* 2011;21(8):584-599.
6. Feldman HM, Reiff MI. Clinical practice. attention deficit-hyperactivity disorder in children and adolescents. *N Engl J Med.* 2014;370(9):838-846.
7. Gajria K, Lu M, Sikirica V, et al. Adherence, persistence, and medication discontinuation in patients with attention-deficit/hyperactivity disorder - a systematic literature review. *Neuropsychiatr Dis Treat.* 2014;10:1543-1569.
8. Lawson KA, Johnsrud M, Hodgkins P, Sasane R, Crismon ML. Utilization patterns of stimulants in ADHD in the medicaid population: A retrospective analysis of data from the texas medicaid program. *Clin Ther.* 2012;34(4):944-956. e4.
9. Setyawan J, Guerin A, Hodgkins P, et al. Treatment persistence in attention deficit/hyperactivity disorder: A retrospective analysis of patients initiated on lisdexamfetamine vs other medications. *J Med Econ.* 2013;16(11):1275-1289.
10. Hinshaw SP, Arnold LE, MTA Cooperative Group. Attention-deficit hyperactivity disorder, multimodal treatment, and longitudinal outcome: Evidence, paradox, and challenge. *Wiley Interdiscip Rev Cogn Sci.* 2015;6(1):39-52.
11. Palli SR, Kamble PS, Chen H, Aparasu RR. Persistence of stimulants in children and adolescents with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol.* 2012;22(2):139-148.
12. Toomey SL, Sox CM, Rusinak D, Finkelstein JA. Why do children with ADHD discontinue their medication? *Clin Pediatr (Phila).* 2012;51(8):763-769.
13. Barner JC, Khoza S, Oladapo A. ADHD medication use, adherence, persistence and cost among texas medicaid children. *Curr Med Res Opin.* 2011;27 Suppl 2:13-22.
14. Chen CY, Yeh HH, Chen KH, Chang IS, Wu EC, Lin KM. Differential effects of predictors on methylphenidate initiation and discontinuation among young people with newly diagnosed attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol.* 2011;21(3):265-273.
15. Hak E, de Vries TW, Hoekstra PJ, Jick SS. Association of childhood attention-deficit/hyperactivity disorder with atopic diseases and skin infections? A matched case-control study using the general practice research database. *Ann Allergy Asthma Immunol.* 2013;111(2):102-106.e2.
16. Tsai J-, Lue K-. Association between allergic diseases and attention-deficit-hyperactivity disorder in childhood: A population-based study. *Dev Med Child Neurol.* 2012;54:69.
17. Schmitt J, Buske-Kirschbaum A, Roessner V. Is atopic disease a risk factor for attention-deficit/hyperactivity disorder? A systematic review. *Allergy Eur J Allergy Clin Immunol.* 2010;65(12):1506-1524.
18. Visser ST, Schuiling-Veninga CC, Bos JH, de Jong-van den Berg LT, Postma MJ. The population-based prescription database IADB.nl: Its development, usefulness in outcomes research and challenges. *Expert Rev Pharmacoecon Outcomes Res.* 2013;13(3):285-292.
19. Mulder B, Groenhof F, Kocabas LI, et al. Identification of dutch children diagnosed with atopic diseases using prescription data: A validation study. *Eur J Clin Pharmacol.* 2016;72(1):73-82.
20. Schroeder K, Fahey T, Ebrahim S. How can we improve adherence to blood pressure-lowering medication in ambulatory care? systematic review of randomized controlled trials. *Arch Intern Med.* 2004;164(7):722-732.
21. Atzori P, Usala T, Carucci S, Danjou F, Zuddas A. Predictive factors for persistent use and compliance of immediate-release methylphenidate: A 36-month naturalistic study. *J Child Adolesc Psychopharmacol.* 2009;19(6):673-681.
22. Charach A, Fernandez R. Enhancing ADHD medication adherence: Challenges and opportunities. *Curr Psychiatry Rep.* 2013;15(7):371-013-0371-6.
23. Wang LJ, Yang KC, Lee SY, et al. Initiation and persistence of pharmacotherapy for youths with attention deficit hyperactivity disorder in taiwan. *PLoS One.* 2016;11(8):e0161061.