Medication use in children and adolescents

KIKI CHEUNG

Studies using different information sources

THESIS

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Kiki Cheung

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Medication use in children and adolescents

Studies using different information sources

Medicatiegebruik bij Kinderen en Adolescenten

Studies op basis van verschillende informatiebronnen

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To my loving parents,
both of whom I always look up to

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1 General Introduction

BACKGROUND

Many medications that are used nowadays have only been studied in adults. For this reason, these are not prescribed to children and adolescents, or prescribed off-label, where prescribing doctors adjust the dosage of a medication that was approved for adults on the basis of dose estimations and pharmacokinetic- and dynamic properties. However, children and adolescents cannot be considered as small adults and with the limited information available, it is not known whether the drug will be effective and safe. In 2006, the Pediatric Regulation [1] was introduced, leading to children being included in well-controlled pediatric clinical trials, in which the efficacy and safety of these medicines can be studied. Even though such clinical trials are nowadays conducted, there are still a large number of medications which have not been studied in children. For these medications there may be some supportive information available in the literature or in other information sources such as the Dutch Child Formulary (kinderformularium). The doctor will have to make the decision whether or not to prescribe a medication based on the available evidence [2]. However, for a number of medications, it is known that these can be harmful to the patients of certain age groups. These are considered to be contraindicated for use in certain age groups and use of these medications is therefore strongly discouraged. Despite this, GPs or specialists may still decide to prescribe these medications if it is deemed necessary, and if the benefits outweigh the risks. In this thesis we have discussed many types of medication that can be used in children and adolescents, but most studies are focused on the psychotropic medications such as methylphenidate and antidepressants.

Methylphenidate

Although many medications are contraindicated for use in children, the opposite may also occur. For example, the sympathomimetic psychostimulant methylphenidate was registered for use in children but not in adults. Nevertheless, methylphenidate was still largely prescribed despite the known contraindication in adults until December 2017 when it was finally registered for use in adults. Methylphenidate is one of the most commonly prescribed drugs for the treatment of attention deficit/hyperactivity disorder (ADHD), which is a psychiatric disorder affecting approximately 5% of the children and adolescents worldwide [3]. This drug was contraindicated (until recently) for use in patients of 18 years and older because of the cardiovascular risks associated with use of these drugs [4, 5]. This was also one of the reasons why this drug was not approved for use in adults as previous studies have shown that they may increase heart rate and blood pressure, leading to an increased risk of myocardial infarction, stroke and sudden cardiac death [5]. Patients may continue treatment with methylphenidate beyond the age of 18 years if they started using it during their childhood. However, previous studies have also shown that the use of methylphenidate in younger patients has decreased, and that methylphenidate is currently more often prescribed to patients of 18 years and older than to children [6, 7].

The prescribing behavior has changed over the past years and this leads to the question on which grounds prescribers decide to start treatment with medication such as methylphenidate. There are clear guidelines with regard to ADHD treatment where symptom severity and functional impairment may be one of the reasons for medication treatment initiation [8]. However, other factors such as age and sex may also be related to treatment initiation with methylphenidate. Methylphenidate is known to be more often prescribed to boys than girls, which can partly be explained by the fact that ADHD is more often diagnosed in boys than girls due to the differences in ADHD symptoms (such as hyperactivity) [9, 10]. Apart from the child characteristics, there may also be other factors contributing to treatment initiation with medication. The decision to start treatment with medication or even to visit a GP is often made by their parents, especially when the children are still young. It usually depends on the parents' knowledge of, and perceptions about ADHD, which may vary across different ethnic and socioeconomic groups [11]. However, the influence of parental factors in treatment initiation with methylphenidate in children is understudied. Thus, studies are needed to investigate the different factors that may influence the decision to start treatment with methylphenidate, especially when other treatment options such as behavioral therapy are also available. Even if treatment is started, it also depends on the parents to make sure that these children follow the prescribed treatment regimen. Most studies focusing on treatment adherence and persistence are done in adults and limited information is available about adherence and persistence in children. For this reason, the persistence and adherence in different patient groups (depending on child characteristics) warrants further studies. Additionally, the influence of family characteristics should also be taken into account.

Antidepressants

Other commonly used drugs in children and adolescents are the antidepressants, which were first developed in the 1950s. Antidepressants are used to help relieve symptoms of depression or anxiety disorders, as well as other conditions. The SSRIs are the most commonly prescribed antidepressants as they have fewer adverse effects than other antidepressants [12]. However, SSRIs should also be prescribed with caution because of the increased risk of suicide in young people for which a black-box warning was released in 2004 [13]. Depression is a mental health disorder of which the frequency has increased over the years from childhood to adolescents and adulthood [14]. It may have a significant impact when diagnosed during childhood, such as impaired school performance and an increased risk of other mental health disorders [14]. Thus, early intervention is important to treat these patients. Although a black-box warning was released, it is still not clear whether use of antidepressants may lead to an increased risk of suicide as the existing literature provides contradictory evidence on this issue [15, 16]. Therefore, studies are needed to investigate the risks associated with use of these drugs in order to support the GPs and other healthcare professionals in the decision making on whether or not to treat patients with antidepressants.

Information sources

For the work presented in this thesis, various information sources have been used of which an overview is provided in table 1.

Table 1. *Information sources used in this thesis*

	Source	Type	Setting	Size	Year
2.1/4.1/ 4.2	The Generation R Study	Population-based prospective cohort study	Rotterdam area, Netherlands	9,778 participants	2002-2006
3.1	SFK	Community pharmacy dispensing data	Netherlands	~15.8 million people	1990
4.3/ 5.1	IPCI	Electronic medical records; primary care	Netherlands	~2.5 million patients	1989

**SFK indicates Dutch Foundation for Pharmaceutical Statistics; IPCI, integrated primary care information database*

The first mentioned source is the Generation R Study, which is a large prospective population-based cohort in which children are followed from fetal life onwards. For this study, all pregnant women who were resident in Rotterdam and who had a delivery date between April 2002 and January 2006 were asked to participate in the study. Over the years, detailed and extensive data has been collected such as questionnaires, interviews, detailed physical and ultrasound examinations, but also behavioral observations of children and their parents [17]. These questionnaires also contain questions about the medication that have been used by the mothers during pregnancy. In addition, (hard copies of) pharmacy record data were retrieved to determine the medications that were dispensed to mothers by pharmacies during pregnancy. The medication use by children is partly covered by questionnaires filled out by their parents. Furthermore, electronic pharmacy record data were retrieved from pharmacies which include all medication that have been dispensed from birth until the age of 15 years in the children. Secondly, we have used the database of the Dutch Foundation for Pharmaceutical Statistics (Stichting Farmaceutische Kengetallen, SFK), which contains data from more than 97% of all community pharmacies in the Netherlands [18]. These data have been collected since 1990 and include the following information: sex and year of birth, product name, active substance according to the Anatomic Therapeutical Chemical code (ATC code) [19], dispensing date, total number of drug units per prescription, prescribed daily number of units, dosage regimen, type of prescriber (general practitioner, specialist or other) and the first two digits of the postal code indicating the region of the pharmacy. Lastly, data for studies in this thesis were retrieved from the Integrated Primary Care Information database, which is a longitudinal observational dynamic database containing medical records from more than 450 general practitioners (GPs) throughout the Netherlands [20]. This database contains medical records such as information on demographics, symptoms and diagnosis which is based on the International Classification of Primary Care (ICPC) codes and free text, referrals, laboratory findings, discharge letters and

medication prescriptions. These prescriptions contain details on product name, daily dosage, the ATC code, and duration of use.

AIMS AND OUTLINE OF THIS THESIS

This thesis aims to present an overview of the use of medication in children and adolescents using different information sources, where we evaluated factors related to the prescribing, dispensing and taking of medication, and its associated events.

This thesis is divided into seven chapters. The first chapter provides a general introduction to the various information sources that are used to study medication use in children and adolescents. Besides, the use of methylphenidate and antidepressants by children and adolescents are also briefly discussed, but are covered in more detail in the consecutive chapters.

In **chapter 2**, we evaluated the concordance between two information sources: self-reported medication use by pregnant women and pharmacy record data, which can both be used for drug utilization studies. In **chapter 3**, we aimed to determine the medications that are contraindicated for use in certain age groups and to what extent these are still dispensed to children. In **chapter 4**, we aimed to determine the different factors associated with treatment initiation and continuation with methylphenidate. In **chapter 4.1**, we studied the maternal factors that may be associated with methylphenidate initiation in children as parents play an important role in the decision making of treatment in children. Moreover, in **chapter 4.2**, we determined the persistence and adherence to methylphenidate in children of school–going age and we studied potential determinants that were associated with adherence. Children who started treatment with methylphenidate, may also need to stop at some point, but it can also be decided to continue their treatment. Until recently, the use of methylphenidate beyond the age of 18 years was contraindicated due to the cardiovascular risks associated with methylphenidate use [21]. In **chapter 4.3**, we aimed to determine the percentage of patients who continued treatment beyond the age of 18 years and the different factors associated with continued treatment. In **chapter 5**, we investigated the risk of suicide in current antidepressant users compared to past antidepressant users.

Finally, a general discussion and future perspective for upcoming research is presented in **chapter 6**, followed by a summary of all findings in **chapter 7**.

2 Evaluation between self-reports and pharmacy records

2.1 The concordance between self-reported medication use and pharmacy records in pregnant women

Cheung K, El Marroun H, Elfrink ME, Jaddoe WVW, Visser LE, Stricker BHCh

Pharmacoepidemiol Drug Saf. 2017;26(9)1119-1125.

ABSTRACT

Background and objectives: Several studies have been conducted to assess determinants affecting the performance or accuracy of self-reports. These studies are often not focused on pregnant women or medical records were used as a data source where it is unclear if medications have been dispensed. Therefore, our objective was to evaluate the concordance between self-reported medication data and pharmacy records among pregnant women, and its determinants.

Methods: We conducted a population-based cohort study within the Generation R study, in 2,293 pregnant women. The concordance between self-reported medication data and pharmacy records was calculated for different therapeutic classes using Yule's Y. We evaluated a number of variables as determinant of discordance between both sources through univariate and multivariate logistic regression analysis.

Results: The concordance between self-reports and pharmacy records was moderate to good for medications used for chronic conditions, such as selective serotonin reuptake inhibitors or anti-asthmatic medications (0.88 and 0.79, respectively). Medications that are used occasionally, such as antibiotics, had a lower concordance (0.51). Women with a Turkish or other non-western background were more likely to demonstrate discordance between pharmacy records and self-reported data, compared to women with a Dutch background (OR Turkish: 1.63, 95%CI: 1.16-2.29); OR other non-western: 1.33, 95%CI:1.03-1.71).

Conclusions: Further research is needed to assess how the cultural or ethnic differences may affect the concordance or discordance between both medication sources. The results of this study showed that the use of multiple sources is needed to have a good estimation of the medication use during pregnancy.

INTRODUCTION

Maternal medication use has increased over the past years with approximately 80% of women receiving at least one prescription medication during pregnancy [22, 23]. Knowledge about the medications used during pregnancy is crucial as it may affect the birth outcome. The risk of adverse perinatal outcomes or birth defects from medication exposure is often evaluated in observational studies, as pregnant women are often not enrolled in clinical trials. These studies mostly rely on exposure data collected by a self-reporting tool, as pharmacy records are often not available [24-26]. Self-reported data are considered to be an important source of information as it may also include over-the-counter medication data, which is not consequently registered in the pharmacy. However, patient self-reported data can be subject to errors caused by recall bias or social desirability bias, awareness and knowledge [27, 28]. Researchers of a previous study found that only 43% of the dispensed prescription medications were reported as actually used by pregnant women, but the factors that may have influenced this are not clear [29]. Another study showed that pregnant women may be more likely to recall and report medication use, because of their increased awareness of potential teratogenic effects of certain medications [30]. This may be different for women from ethnic minority groups as the literature shows that Hispanic and black women are less likely to seek for information about their health on the internet, but also cultural differences and language barriers may play a role [31, 32]. Other factors that may influence the accuracy of recalling the prescribed medications include age, educational level, alcohol use and general health [28, 33-35].

Currently, there is no 'golden standard' to assess maternal medication exposure, as each source is prone to bias, which may lead to misclassification of exposure. A number of studies have been conducted to assess the determinants that may affect the performance or accuracy of self-reports. However, these studies are often not focused on pregnant women in particular or the concordance is calculated with medical records and health insurance databases where it is not clear if medications have been dispensed [36-39]. Although pharmacy dispensations do not reflect patient compliance, a high medication possession ratio in case of chronic use is a good proxy indicator of compliance. Moreover, pharmacy records are not affected by patient recall. Therefore, pharmacy records can be used as an indicator of the validity of self-reported medication data.

In this study, we used self-reported data and pharmacy records collected from a population based cohort study in pregnant women to evaluate the concordance of medication use between self-reported data and pharmacy records for different therapeutic classes among pregnant women, and its determinants.

METHODS

Study population

This study was conducted within the Generation R study, a population-based prospective birth cohort in Rotterdam, the Netherlands [40]. The cohort included 9,778 mothers and their children who were born between April 2002 and January 2006. Of these mothers, 8,880 (91%) were enrolled in the study during pregnancy and 898 (9%) at birth of their child. Mothers were selected based on the availability of pharmacy records in our database. Dispensing records were obtained from pharmacies after permission to contact their pharmacy was given, which was obtained for the large majority (n=4,930). Furthermore, women with either no pharmacy records or self-reported data of the studied therapeutic classes were excluded (n=2,293). The flowchart for women included in the current study (n=2,637) is shown in Figure 1. The Generation R study was approved by the Medical Ethics Committee of the Erasmus Medical Centre, Rotterdam. Written informed consent was obtained from all parent-participants.

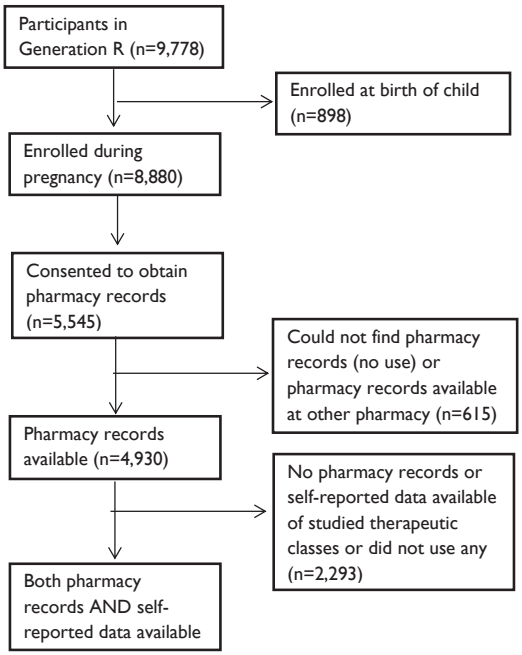

Figure 1. *Selection of mothers with both pharmacy records and self-report data available. The Generation R Study.*

Pharmacy records

All printed pharmacy records were stored and for each research hypothesis, the relevant drugs from each record were entered manually into an automated database. The following therapeutic classes were available electronically: Selective Serotonin Reuptake Inhibitors (SS-

RIs), benzodiazepines, folic acid, antibiotics, anti-asthmatics, antihistamines and non-steroidal anti-inflammatory drugs (NSAIDs), as used in earlier studies [41-45]. The medications were limited to 'prescription-only' medications, but folic acid and antihistamines were also included as these medications were relatively more often recorded at pharmacies compared to other medications which can also be obtained 'over-the-counter' (e.g. NSAIDs).Therefore, we did not include NSAIDs in our study. Details of dispensing date, product, number of units, daily prescribed number and strength were all available. Use of medication from other therapeutic classes was considered as 'no medication use' in our study as we focused on these six prescribed therapeutic classes.

Self-reported maternal medication use

Data on maternal medication use was collected using self-reported questionnaires that were sent by post to the mothers at each trimester: early pregnancy (gestational age < 18 weeks), mid-pregnancy (gestational age 18-25 weeks) and late pregnancy (gestational age >25 weeks). In the first trimester, we asked them to fill in the medicines that they had taken in the preceding six months. In the second and third trimester we asked which medications they had used in the preceding three months [40]. The questionnaires were available in Dutch (also comprehensible for Surinamese women), English and Turkish. If needed, women with a Moroccan ethnicity were assisted in the filling out of the questionnaires by Moroccan speaking research assistants.

Socioeconomic determinants

Other factors including maternal age at intake, alcohol use, smoking, ethnicity, education level, marital status and household income were also obtained using these questionnaires. Ethnicity of participating mothers was defined according to the classification of Statistics Netherlands [46]. All lifestyle and medication related questions included the question as to whether they were exposed to these factors before and/or during pregnancy to assess the period of exposure.

Statistical analysis

The concordance between self-reported medication data and pharmacy record data was calculated for different therapeutic classes using Yule's Y. This is a measure of agreement for dichotomous variables and is less dependent on the prevalence than kappa [47]. It has the same possible range of values as kappa (-1 to 1) and are interpreted as follows: <0 no agreement; 0.01-0.20 slight agreement; 0.21-0.40 fair agreement; 0.41-0.60 moderate agreement; 0.61-0.80 substantial agreement and 0.81-0.99 almost perfect agreement [48]. In addition, we calculated the sensitivity and specificity for self-reported medication use compared to pharmacy data. We calculated the Odds Ratio (OR), with 95% CI, as the chance of having discordance between self-reported data and pharmacy record data (presence pharmacy record/absence self-report or absence pharmacy record/ presence self-report). We evaluated the following

variables as determinant of discordance (yes/no) between both sources through univariate logistic regression analysis: maternal age at intake, alcohol use and smoking during pregnancy, ethnicity, maternal education, marital status, net household income and the number of prior pregnancies. In addition, a multivariate analysis was performed. On average, 15.6% of data across these variables was missing. To avoid the bias of complete case analysis, we accounted for missing information on these determinants (data of self-reports and prescription records were not imputed) by using multiple imputation methods (n= 10 imputations). Results were considered statistically significant at $p < 0.05$. Finally, in a non-response analysis, we investigated whether any of the determinants was associated with non-response. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.

RESULTS

Characteristics of the study population

A total of 2,637 women used medication during pregnancy according to their pharmacy records, self-reported data or both (Table 1). Mean maternal age was 29.8 years and the majority of the group never smoked during pregnancy (73.4%) or used alcohol while pregnant (48.3%). Furthermore, half of the study population was Dutch (50.5%) and only a small proportion of these women had a low educational level (5.2%). In addition, only a small percentage of the study population did not have a partner (16%) and almost half of these women were married (47.9%). The proportion of women with an average income (€900-€2200) was the same as the proportion of women with a high income (>€2200, 44.8%) and for the majority of women it was their first pregnancy.

Yule's Y, sensitivity and specificity

Table 2 shows the concordance between self-reported data and pharmacy records for different therapeutic classes. Among all classes reported, SSRIs showed the highest rate of concordance (0.88), whereas folic acid had the lowest concordance (0.48). Benzodiazepines, anti-asthmatics and antihistamines showed a substantial concordance (0.79; 0.68 and 0.61 respectively) and for antibiotics, the concordance was considered moderate (0.51). Overall, the specificity levels among these therapeutic classes are considered to be high (>90%), with the exception of antibiotics (83.9%). The sensitivity levels on the other hand, showed some greater differences among the different therapeutic classes. The sensitivity of SSRIs, benzodiazepines, antibiotics and anti-asthmatics ranged from 60.7% to 74.3%, indicating a moderate sensitivity. For the other therapeutic classes the sensitivity was somewhat lower (folic acid:36.4% and antihistamines:40.6%).

Table 1 *Characteristics of the mothers included in our study*

Characteristic	Mothers included in the study (n=2,637)
Age in years, mean (SD)	29.8 (5.2)
Alcohol use	
Never during pregnancy	48.3
Until pregnancy was known	13.9
Continued during pregnancy	37.8
Smoking	
Never during pregnancy	73.4
Until pregnancy was known	9.0
Continued during pregnancy	17.6
Ethnicity	
Dutch	50.5
Turkish	9.4
Surinamese	8.9
Moroccan	6.8
Other western	16.3
Other non-western	8.0
Maternal education [a]	
Primary education	5.2
Secondary education	46.8
Higher education	48.0
Marital status	
Married	47.9
Living together	36.1
No partner	16.0
Net household income	
<€900	10.4
€900-2200	44.8
>€2200	44.8
Number of prior pregnancies	
0	56.0
1	29.2
2 or more	14.8

All numbers are given in percentages or mean (SD). [a] *Highest education followed. Abbreviations: n; number of women, SD; standard deviation*

Table 2 *Concordance between self-reported data and pharmacy record data of maternal medication use, by therapeutic class (n=2637)*

Therapeutic class	Yule's Y [a]	FN rate, %	FP rate, %	Sensitivity [b], %	Specificity [b], %
SSRIs	0.88	33.3	0.8	66.7	99.2
Benzodiazepines	0.79	39.3	2.2	60.7	97.8
Folic acid	0.48	63.6	6.4	36.4	93.6
Antibiotics	0.51	34.9	16.1	65.1	83.9
Anti-asthmatics	0.68	25.7	9.5	74.3	90.5
Antihistamines	0.61	59.4	3.7	40.6	96.3

[a] Calculated using the following formula: Y=(√ad- √bc)/(√ad+√bc), a=pharmacy and self-report; b=only self-report; c=only pharmacy record; d=no pharmacy record and self-report. [b] Sensitivity and specificity of self-reported medication use compared to pharmacy records. Abbreviations: FN; false negatives, FP; false positives, n; number of women, SSRI; Selective Serotonin Reuptake Inhibitors

Factors associated with discordance between self-reported data and pharmacy records

Table 3 shows the results of the univariate analysis where discordance between both sources is associated with an age of 24 years and younger (OR:1.40, 95%CI: 1.05-1.85), a non-Western background (OR Turkish:1.91, 95%CI: 1.44-2.54; OR Surinamese:1.52, 95% CI: 1.13-2.04; OR Moroccan:1.66, 95%CI: 1.20-2.30 and OR other non-Western:1.49, 95%CI: 1.18-1.88), a lower education (OR primary:1.53, 95%CI: 1.05-2.21 and OR secondary:1.43, 95%CI: 1.20-1.70), a lower net household income (OR <€900:1.64, 95%CI: 1.19-2.25) and having two or more prior pregnancies (OR:1.34, 95%CI: 1.06-1.70). The results of the multivariate analysis only shows a significant association with a Turkish background (OR:1.63, 95%CI: 1.16-2.29), another non-western background (OR: 1.33, 95%CI:1.03-1.71) and having one or more prior pregnancies (OR 1 prior pregnancy:1.22, 95%CI: 1.00-1.49 and OR 2 or more prior pregnancies:1.32, 95%CI: 1.00-1.74).

Table 3 *Determinants that are associated with discordance between self-reported data and pharmacy records (n=2,637)*

		Univariate analysis		Multivariate analysis	
Characteristic	N (%)	OR	95% CI	OR	95% CI
Age				0.98	0.96-1.00
<25 years	533 (20.2)	1.40	1.05-1.85	-	
25-35 years	1711 (64.9)	1.01	0.79-1.29	-	
>35 years	393 (14.9)	1 (ref)		-	
Alcohol					
Never during pregnancy	1279 (48.5)	1 (ref)		-	
Until pregnancy was known	359 (13.6)	0.80	0.61-1.03	0.99	0.75-1.31
Continued during pregnancy	1001 (37.9)	0.76	0.63-0.91	1.00	0.81-1.23

Table 3 *Determinants that are associated with discordance between self-reported data and pharmacy records (n=2,637)* (*continued*)

		Univariate analysis		Multivariate analysis	
Smoking					
Never during pregnancy	1939 (73.5)	1 (ref)		-	
Until pregnancy was known	234 (8.9)	0.78	0.57-1.07	0.79	0.57-1.10
Continued during pregnancy	465 (17.6)	1.11	0.89-1.38	1.01	0.80-1.29
Ethnicity					
Dutch	1332 (50.5)	1 (ref)		-	
Turkish	249 (9.4)	1.91	1.44-2.54	1.63	1.16-2.29
Surinamese	236 (8.9)	1.52	1.13-2.04	1.30	0.94-1.79
Moroccan	180 (6.8)	1.66	1.20-2.30	1.38	0.94-2.01
Other non-western	429 (16.3)	1.49	1.18-1.88	1.33	1.03-1.71
Other western	212 (8.0)	0.59	0.41-0.86	0.58	0.39-0.84
Maternal education [a]					
Primary education	152 (5.8)	1.53	1.05-2.21	0.96	0.63-1.46
Secondary education	1207 (45.8)	1.43	1.20-1.70	1.10	0.88-1.36
Higher education	1280 (48.5)	1 (ref)		-	
Marital status					
Married	1268 (48.1)	1 (ref)		-	
Living together	948 (35.9)	0.82	0.68-0.99	0.98	0.79-1.20
No partner	422 (16.0)	1.17	0.92-1.47	1.03	0.77-1.38
Net household income					
<€900	414 (15.7)	1.64	1.19-2.25	1.21	0.84-1.73
€900-2200	864 (32.8)	1.16	0.90-1.49	0.93	0.72-1.21
>€2200	1360 (51.6)	1 (ref)		-	
Number of prior pregnancies					
0	1479 (56.1)	1 (ref)		-	
1	768 (29.1)	1.19	0.99-1.44	1.22	1.00-1.49
2 or more	391 (14.8)	1.34	1.06-1.70	1.32	1.00-1.74

[a]*Highest education followed. Abbreviations: CI; confidence interval, n; number of women , OR; odds ratio, P; p-value*

DISCUSSION

Pharmacy records are often used as the source of medication exposure information [49-51]. However, not all medications are dispensed through pharmacies and therefore, questionnaire data are also an important source of information. In this study, we compared the self-reported information on prescribed medication use during pregnancy with the presence of medication use in pharmacy records for different therapeutic classes of medications. In addition, we

evaluated the potential factors that are associated with discordance between self-reported medication use and pharmacy records.

Overall, we found that medications required for managing chronic conditions (SSRIs and anti-asthmatics) had a good or substantial concordance between maternal self-reports and pharmacy records. This finding is in line with the results of another study where the authors compared self-reports with prescription data in medical records [52]. However, a higher concordance for benzodiazepines was observed in our study compared to the results of a study in older adults (0.58), which can be explained by age as studies have shown that older people are less likely to recall their medication use [38, 53]. Medications taken for acute conditions (antibiotics, folic acid, antihistamines) had a substantial to moderate concordance. Sarangarm et al. observed similar results for the concordance of antibiotics, but for folic acid and antihistamines we found a lower concordance in the available literature [37, 52, 53]. This can be explained by recall bias, which is less likely to occur in chronic medication than in acute medication use [29, 54]. Furthermore, the number of drugs that were used during pregnancy may also contribute to discordance between both sources. However, we were not able to study this as the number of women who used more than one drug during their pregnancy was very small (n=97). Another possible explanation of the low concordance of folic acid and antihistamines is that these medications are available over the counter. Therefore, the use of these medications is not always captured in the pharmacy databases and thus contributing to discrepancy between both sources.

The sociodemographic and economic characteristics may have influenced the probability of concordance. In our study, the number of prior pregnancies was associated with discordance between both medication sources, which is not in line with a previous study [37]. The group of women with no prior pregnancies was larger (57.1%) compared to those who had 1 to 2 (28.6%) or more prior pregnancies (14.3%) when it comes to 'not reporting' medication use. However, the number of women who did not report medication use in the concerning study was quite low (n=7) which may explain these differences compared to our study. Furthermore, the concordance was lower in women with a Turkish and other non-western background. The ethnic differences between self-reported data and data based on medical records from general practitioners has been examined in a previous study by Uiters E. et al [39]. They report that the level of concordance did not differ between the ethnic groups, implying that the validity of self-reported data and medical records did not differ among different ethnic groups. However, another study, based on data from a survey and health insurance register, found lower concordance rates on health care utilization (including prescription medication) for immigrants [55]. This finding is in line with the current results, where women with a non-western background were more likely to have a discordance between self-reported and pharmacy data. Other studies showed that adherence to medication may be lower in the ethnic minority groups, which means that the prescribed medications are not always taken by these patients [56-58]. Non-adherence and lack of persistence should therefore also be taken into consideration.

Moreover, the question remains as to how much this discordance between self-reported data and pharmacy data is due to cultural or religious factors as they may have different beliefs about the use of medication during pregnancy. Finally, a possible explanation is that ethnic minorities may face language barriers as Dutch is not their native language and potentially did not understand all questions. However, the questionnaires in our study were also available in Turkish, which means that language barrier should not have hampered these women completing the questionnaires. Further research is needed to assess how the cultural or ethnic differences may affect the concordance or discordance between both medication sources.

Strengths and Limitations

One of the strengths of this study is that maternal medication use was determined based on pharmacy record data, which is more accurate than prescribed medication according to medical records, because medication can be prescribed but never collected from pharmacies [59]. Furthermore, our study population comprises almost 50% of women with a non-Dutch ethnic background, thus we were able to study the patterns of concordance among women with different ethnic backgrounds. Despite the strengths of our study, we also had some limitations. First, the period of recall was three months, which can be considered as long. Therefore, it is likely that women do not recall all medications that have been used in that period. However, we believe that pregnant women are more likely to remember what they have used as they may be more aware of the risks and safety of medication use during pregnancy [30, 60]. Second, the time frames of pharmacy records and self-reported data did not perfectly overlap for all participants as there was no possibility to fill out the exact dates of use in the questionnaire. Participants who were enrolled in the study during the third trimester of pregnancy may have used medications in the first trimester and discontinued medication use during the third trimester of pregnancy. Therefore, these women may not have reported use of medications during pregnancy. However, given that the specificity is high for all therapeutic classes and the proportion of women enrolled at this stage was low (~10%), this scenario is unlikely. Third, the majority of our study population was highly educated, which may have affected our results in terms of external validity, showing higher concordance rates compared to the general population. However, in our study we were not able to see a significant association between maternal education and discordance. Finally, for a large number of women information on medication use of both sources was not available, which may increase the likelihood that these women did not complete the questionnaire or did not give consent to obtain pharmacy records for certain reasons that are related to the demographic and socio economic factors. The results of the non-response analyses did not show significant differences between both groups for ethnicity, net household income, number of prior pregnancies, smoking and alcohol. However, for marital status (p-value:0.03) and education (p-value:<0.001) we did see some differences between both groups. Despite these differences, we did observe similar results in our study compared to the existing literature showing an association between marital status and education as deter-

minants and discordance between both sources [37, 55, 61, 62]. There is also a possibility that the pharmacy records were not available, because the medication was dispensed at another pharmacy. Furthermore, some mothers did not receive one or more questionnaires due to a variety of logistical reasons and were therefore not able to complete the questionnaires [40]. These data are missing completely at random and therefore it does not influence our results.

Conclusion

In conclusion, the results of our study indicate that the concordance between self-reports and pharmacy records was moderate to good for medications used for chronic conditions, such as antidepressants or anti-asthmatic medications. Medications that are used occasionally, such as antibiotics had a lower concordance. The concordance could be explained by the accuracy of recall, which may be influenced by factors such as the level of education and prior pregnancies. Furthermore, as some of the investigated medications (e.g. folic acid) are also available over the counter, the pharmacy records may represent a selection and this may also influence the concordance and should be taken into account. Finally, we found that ethnic background may play a role in self-reporting the use of medications. Different cultural beliefs about medication use during pregnancy, non-adherence and lack of persistence may be an explanation of the observed discrepancy among the different ethnic groups. Further research is needed to assess how the cultural or ethnic differences may affect the concordance or discordance between both medication sources. The results of this study showed that the use of multiple sources on medication use is needed to have a good estimation of the medication use during pregnancy.

3 Contraindicated drugs in children

3.1 Filled prescriptions of age-related contraindicated drugs in children: an on-year nationwide cohort study in the Netherlands

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ABSTRACT

Background and objectives: Children are still prescribed age contraindicated drugs, but information about the number and type of these drugs delivered to children in the Netherlands is limited. The objective of this study was to determine the incidence and prevalence of contraindicated drugs that were dispensed to children.

Methods: The study was conducted in the Netherlands with routinely collected data from 95% of all community pharmacies. We performed a one-year nationwide observational study where all patients aged 17 years or younger who have received at least one prescription in 2016 were included. Contraindicated drugs were selected, according to the 5th level of ATC code, using different information sources. The main outcome measure in this study was the proportion of (newly) contraindicated drugs that were dispensed to children.

Results: In total, 3.9% of all children received at least one drug that was contraindicated for age. The highest percentage of contraindicated drugs that were dispensed was observed in patients aged 1 to 2 years and 13 to 17 years (7.0% and 5.7%, respectively) and the percentage of contraindicated drugs that were dispensed was higher in female patients than in male patients (4.3% and 3.6%, respectively; p-value <0.001).

Conclusions: The results of this study showed that a substantial percentage of children received a contraindicated drug, which is more common in females than in males. Furthermore, the information about contraindications is limited and inconsistent.

INTRODUCTION

Many drugs are prescribed off-label as they were not approved for use in children[63],[64]. GPs and other prescribers make decisions based on the available evidence, which can be very limited. Drugs used for treating children are often insufficiently documented with regard to dosing, efficacy, and safety in this group. When off-label use is associated with a safety hazard or a risk of serious adverse drug reactions, it is described as a contraindication, which means that there is sufficient evidence that the drug is or might be harmful and use of these drugs is not advised. [65]. In some circumstances there is insufficient information available about the use of drugs in children. In this case, it is acceptable to prescribe these drugs if the benefits outweigh the risks (warning). Contraindications are always described in the labels of the products concerned and should be strictly followed to ensure safe use of these drugs in a specific population[66]. One of the recent examples is the label revision for products containing codeine and tramadol which states that these drugs are contraindicated for the treatment of pain in children younger than age 12. Adverse event reports showed that the use of codeine was associated with respiratory depression and death, with the majority of cases involving children under the age of 12[67]. This contraindication shows that it is important for healthcare professionals to know that prescribing these drugs to children from this particular age group should be avoided and alternatives should be used instead. However, in some cases, contraindicated drugs are still prescribed when there is a great burden of disease and no alternatives are available[68]. In other cases it is also possible that prescribers were not aware of the contraindications in the drug labelling[68].

Numerous studies have described the contraindication of medication use in relation to specific diseases or patient characteristics, but the focus on age and sex in children in these studies is very limited [69-71]. Moreover, these studies are often based on information from prescription data and it is not always clear if these drugs were actually dispensed by the pharmacists. Therefore, we performed a one-year nationwide observational study to determine the incidence and prevalence of contraindicated drugs that were dispensed to children with routinely collected data from community pharmacies in the Netherlands.

METHODS

Setting

Data were obtained from the Dutch Foundation for Pharmaceutical Statistics (Stichting Farmaceutische Kengetallen). This database contains dispensing data from 95% of all community pharmacies in the Netherlands that has been collected since 1990[72]. In the Netherlands, the community pharmacies dispense the vast majority of all out-patient prescriptions. For each dispensing, the following information is available: a unique anonymous patient code, sex and year

of birth, product name, active substance according to the Anatomic Therapeutical Chemical code (ATC code)[19], dispensing date, total number of drug units per prescription, prescribed daily number of units, dosage, regimen, type of prescriber (GP, specialist or other healthcare professional) and the first two digits of the postal code indicating the region.

Cohort definition

All patients aged 17 years or younger who have received at least one prescription during the study period between 1 January 2016 and 31 December 2016 were included. Patients with an unknown sex were excluded.

Measures

Drugs that are contraindicated in children were selected according to the 5th level ATC code of the World Health Organisation[19]. The prescription codes (PRK code) were used if products had to be selected on substance level. The primary reference source that was used to determine the contraindication status in children was the Farmacotherapeutisch Kompas 2016 (a national formulary provided by the National Health Care Institute) because it contains information of all drugs and most details about the topic of interest. The descriptions in the Farmacotherapeutisch Kompas are written based on the information in the summary of product characteristcs (SmPC), which is considered as a legal document that was approved by the Medicines Evaluation Board or the European Medicines Agency. The alternative source of information was the SmPC of the products concerned, which was used in case of conflicting information from different sources. Furthermore, the Kinderformularium (national formulary for children) was used when the information about the contraindication was not clearly described[2]. The following drugs that are contraindicated in children below 6 months of age were excluded from the analysis as only the year of birth was available: atazanavir, cotrimoxazol, fluticasone, hydrocortison (systemic), methylprednisolone, nandrolone, sodium polystyrene sulfonate, pethidine, prilocaine, somatropin, sulfadiazine, tocofersolan and vitamine B complex (parenteral).

Analysis

For all patients, we determined the number of drugs dispensed between 1 January 2016 and 31 December 2016. In our study, a person was identified as user of a contraindicated drug when having at least one contraindicated drug dispensed during the study period. In the analyses, we have calculated the cumulative 1-year incidence as the proportion of the total cohort to which a contraindicated drug was dispensed in the year 2016 for the first time since birth. In addition, the cumulative 1-year prevalence was determined by the proportion of children with a contraindicated drug dispensed in the study period, including those who had started before 1 January 2016. This was also stratified according to age, which was classified into five groups: <1 year, 1-2 years, 3-6 years, 7-12 years and 13-17 years. In addition, we investigated the sex differences and we calculated the number of contraindicated drugs that were dispensed per

region and per type of prescriber. The analyses included almost the entire Dutch population and therefore the calculation of confidence intervals for the incidence and prevalence were not deemed necessary. We also investigated the information available in the Farmacotherapeutisch Kompas, SmPC, Kinderformularium about the reasons for a drug to be contraindicated, which are classified into the active ingredient, high/unknown dosage, formulation, lack of information about efficacy or safety and the presence of excipients. Finally, we have calculated the number of patients, the number of drugs that were dispensed and mean age for the most commonly dispensed contraindicated drugs.

RESULTS

Patients with an unknown sex (n=122,144) were excluded from the analysis. The remaining 1,527,021 patients received at least one drug in 2016 where 3.9% of these patients received a drug that was contraindicated for age (table 1). The cumulative prevalence was significantly higher in females compared to males (4.3% and 3.6%, respectively; p-value <0.001) and highest in patients aged 1 to 2 years (7.0%). The majority of patients received only one type of drug that was contraindicated for age in the study period (1 drug: 58,597 (6.0%); 2 or more: 1,496 (0.3%)).

Table 1 *Children aged 0-17 years who were prescribed contraindicated drugs in 2016*

	Number of children who received drugs	**Number of children who received a contraindicated drug (%)**	**Number of dispensed drugs**	**Number of dispensed contraindicated drugs (%)**
Overall	1,527,021	60,093 (3.9)	4,454,048	105,106 (2.3)
Sex				
Male	769,903	27,604 (3.6)	2,370,735	48,481 (2.0)
Female	757,118	32,489 (4.3)	2,083,313	56,625 (2.7)
Age				
<1 year	59,163	2,289 (3.9)	129,022	2,901 (2.2)
1-2 years	214,506	15,114 (7.0)	277,841	21,295 (7.6)
3-6 years	336,202	3,093 (0.9)	762,978	5,198 (0.7)
7-12 years	429,485	11,731 (2.7)	1,253,424	20,456 (1.6)
13-17 years	487,665	27,866 (5.7)	2,030,783	55,256 (2.7)
Number of different drugs[a]				
1 drug	972,451	58,597 (6.0)	-	-
2 or more	554,570	1,496 (0.3)	-	-

[a]*The number of different drugs was determined based on the ATC7-codes.*

The number of new users of a contraindicated drug in 2016 was 43,206 (2.8%), which was significantly higher in females (3.1%) than in males (2.6%) (p-value <0.001). The cumulative incidence was highest in the age categories 1 to 2 years (5.5%) and 13 to 17 years (4.2%), followed by the age categories 0 to 1 (2.3%), 7 to 12 years (1.8%) and 3 to 6 years (0.6%). The postal code information available for each patient indicated that the number of patients who received a contraindicated drug in the Netherlands is fairly equally distributed (North 4.0%; East 3.9%; West 3.9% and South 4.0%). The majority of patients received the contraindicated drugs from their GP (n=1,256,213), followed by medical specialists (n=314,836) and other healthcare professionals (n=206,563) but the contraindicated drugs were nevertheless relatively more often prescribed by medical specialists than by GPs (GP 3.4%, specialist 4.2% and other 3.6%). The most common drugs that were relatively more often prescribed by specialist than GPs or other healthcare professionals are hydrocortisone/neomycin/polymyxin B (specialist: 1.26%, GP: 0.48% and other healthcare professionals: 0.37%), atropine (specialist: 0.26%; GP:0.003% and other healthcare professionals: 0.03%) and dimetindene (specialist: 0.23%; GP:0.06% and other:0.08%).

Overall, the number of patients who received a contraindicated drug was significantly higher in females than in males (4.3% and 3.6%, respectively; p-value <0.001) (table 2). Higher percentages were observed for female patients in the higher age groups (7-12 years:3.0%, 13-17 years:6.5%) compared with male patients (7-12 years:2.5%, 13-17 years:4.6%). For male patients, higher numbers were observed in the lower age groups (<1 year:4.1%, 1-2 years:7.7%) than in female patients (<1 year:3.6%, 1-2 years:6.2%). Cholecalciferol (females: 2.5% and males 1.5%) and metoclopramide (females: 0.5% and males: 0.3%) were relatively more often prescribed to females than males. Hydrocortisone/neomycine/polymyxine B (males: 0.8% and females: 0.5%) and dimetidene (males: 0.13% and females: 0.08%) were relatively more often prescribed to male patients.

Table 2. *Children who were prescribed contraindicated drugs per age group, stratified by sex*

	Male		**Female**	
Age	*Total*	*Contraindicated (%)*	*Total*	*Contraindicated (%)*
All ages	769,903	27,604 (3.6)	757,118	32,489 (4.3)
<1 year	33,201	1,357 (4.1)	25,962	932 (3.6)
1-2 years	116,332	9,007 (7.7)	98,174	6,107 (6.2)
3-6 years	177,066	1,668 (0.9)	159,136	1,425 (0.9)
7-12 years	232,991	5,812 (2.5)	196,494	5,919 (3.0)
13-17 years	210,313	9,760 (4.6)	277,352	18,106 (6.5)

One of the most common contraindications is due to the active pharmaceutical ingredient, which is seen in 49 types of drugs and in 25,875 patients (table 3). Drugs that are contraindicated due to the formulation (e.g. difficulty swallowing) was only observed in one type of drug and in 180 patients.

Table 3. *Different type of reasons for age-related contraindications*

Reason for contraindication	Number of different types of drugs with a contraindication for age (n=63)* n (%)	Number of patients receiving a contraindicated drug (n=60,093) n (%)
Active ingredient	49 (77.8)	25,875 (43.1)
High dosage or unknown dosage	7 (11.1)	32,323 (53.8)
Formulation	1 (1.6)	180 (0.3)
Lack of information about efficacy or safety	3 (4.8)	1,675 (2.8)
Presence of excipients	3 (4.8)	40 (0.1)

**Only contraindicated drugs that were dispensed to children by community pharmacies in the Netherlands in 2016 were included. Abbreviations: n:number.*

Figure 1 shows that cholecalciferol is one of the most frequently dispensed drugs that is contraindicated for age. The combination of hydrocortisone/neomycin/polymyxin b, doxycycline, dimetindene, atropine and clobetasol were also in the top ten of the most commonly dispensed contraindicated drugs, but these drugs were relatively less dispensed to children with an age that is within the contraindication age limit. The other 15 most commonly dispensed drugs were: fludrocortisone/neomycine/polymyxin B/lidocaine, lidocaine, promethazine, etoricoxib, meloxicam, levodopa/benserazide, temazepam, zolpidem, insulin, zopiclone, rhubarb extract/salicylic acid, loperamide, scopolamine, norfloxacin (systemic) and sodium phosphate (rectal) (results not shown due to low numbers).

Table 4 shows more detailed information from the most commonly dispensed drugs with a contraindication for age. For a number of drugs the actual number of contraindicated drugs dispensed is lower than the group that was selected based on the ATC codes. Cholecalciferol was dispensed to 30,301 children, where 15,988 children (53%) received the oral suspension which is contraindicated because of its high dose of vitamin D. Metoclopramide was dispensed to 6,253 patients where 110 patients (1.8%) were below the age of 1. The metoclopramide suppositories which are contraindicated in children and adolescents less than 18 years, were dispensed to 3,559 children (57% of the total number). Doxycycline was dispensed to 2,670 children with an age lower than 12 years, of whom 305 were less than 8 years (11.4%). Furthermore, 268 patients received the drug with the ATC code N04BA02 which not only includes levodopa/benserazide, but also levodopa/carbidopa. The contraindicated drug levodopa/benserazide was dispensed to 93 patients (35%). Other commonly dispensed drugs that are contraindicated in children below the age of 2 years are dimetindene, levomenthol, promethazine, loperamide, fludrocortisone/neomycin/polymyxin B and lidocaine. Temazepam and zoplicon are contraindicated for age because the effectiveness and safety of use in children have not been studied yet.

Table 4. *Additional information on the most commonly prescribed contraindicated drugs*

Name of drug (ATC code)	Children[a]	Dispensings[b]	Mean age (SD)	Potential risk, reason for contraindication
Cholecalciferol (A11CC05)[c]	30,301	60,034	13.3 (4.0)	The oral suspension of cholecalciferol and the combination with calcium carbonate is contraindicated in children aged 17 years and below because it contains a high dose of Vitamin D.
Calcium carbonate /cholecalciferol (A12AX)	2,518	6,434	12.7 (3.9)	
Metoclopramide (A03FA01)	6,253	7,056	12.0 (4.8)	Contraindicated in children below the age of 1. Metoclopramide suppositories are contraindicated in children aged 17 and below because of the high risk of extrapyramidal disorders.
Doxycycline (systemic) (J01AA02)	2,670	2,904	10.4 (1.8)	Contraindicated in children below the age of 8 (infections) and 12 years (facial rosacea), because of the risk of tooth staining.
Dimetindene (R06AB03)	1,560	2,106	0.8 (0.4)	Contraindicated in children below the age of 1, because the sedative effect can be associated with episodes of sleep apnoea.
Levomenthol (R05X)	904	936	0.9 (0.7)	Contraindicated in children below the age of 2, because substances containing menthol have been reported to cause instant collapse or laryngospasm.
Fludrocortisone/ neomycin/ polymyxine B/ lidocaine combination (S02CA07)	800	891	1.4 (0.6)	Contraindicated in children below the age of 2 because of the possibility of increased absorption of neomycine and the kidney function may not be fully developed. There is also a potential risk of nephrotoxicity and ototoxicity due to neomycin.
Promethazine (R06AD02)	643	696	1.9 (0.4)	Contraindicated in children below the age of 2, because promethazine may lead to severe respiratory depression and apnea. A potential association of promethazine use with the sudden infant death syndrome has also been reported.
Levodopa/ Benserazide combination (N04BA02)	268	496	11.4 (4.8)	Contraindicated in children and adolescents aged 24 years and below. Animal studies have suggested that benserazide may cause skeletal abnormalities if administered before skeletal development is complete.
Temazepam (N05CD07)[c]	226	352	7.0 (3.4)	Contraindicated in children aged 11 years and below because the safety and effectiveness in children have not been established.
Zoplicon (N05CF01)	171	283	14.4 (3.9)	
Loperamide (A07DA03)	112	129	1.3 (0.8)	Contraindicated in children below the age of 2 because use of loperamide has been associated with fatal episodes of paralytic ileus.

[a]The number of patients are counted based on the ATC codes. The numbers of patients who have received the medication within the age limit for contraindication are shown. Patients outside the age limit were excluded. [b]The number of drugs dispensed are counted based on the ATC codes. The number of drugs dispensed are shown of drugs that are contraindicated for age. [c]Cholecalciferol and the combination with calcium carbonate have been compiled on one line. Temazepam and Zoplicon have been compiled on one line. Abbreviations: ATC: Anatomical Therapeutic Chemical; SD: Standard Deviation.

DISCUSSION

It is not always clear why a drug is contraindicated and how many of these drugs are prescribed to children despite their contraindication for age. In this nationwide study, we have calculated the incidence and prevalence of drugs with a contraindication for the age groups to which they were nevertheless dispensed. In our study we observed that 3.9% of all children received at least one drug that was contraindicated for age, which are mainly newly prescribed drugs (2.8%). These results are almost similar to the results observed in the study by Bensouda-Grimaldi L. et al. (3.2%)[68]. Our results also showed that male patients received more overall prescriptions than female patients, but contraindicated drugs were relatively more often dispensed to female patients. The difference in drug use may partly be explained by sex differences such as the variation in disease prevalence or severity, but the differences in health care may also explain this observation[73] [74-76]. Further research is needed to address the sex differences in prescribing drugs to children.

Alternatives are available for many contraindicated drugs, but in some circumstances the contraindicated drug is needed. Prescribing an on-label drug does not always have to be accurate, whereas prescribing a contraindicated drug does not have to be considered bad practice either. One of the examples is the oral suspension cholecalciferol which is contraindicated because of the high dose of vitamin D. These drugs are necessary for children with an impaired vitamin D absorption such as cystic fibrosis or serious vitamin D deficiency in rachitis. However, it is not clear if they were all prescribed for these type of indications, as we observed a large number of patients who received the high dose of Vitamin D in our study. The increase of vitamin D use since the global recognition of vitamin D deficiency in the general population has also led to an increase in vitamin D intoxications, which were partly due to inappropriate prescribing[77]. This may also be explained by the differences between information sources that was observed as the oral suspension with a high dose of vitamin D was only mentioned in the Farmacotherapeutisch Kompas, but not mentioned or described in the Kinderformulary. Specialists, GPs or other healthcare professionals may use different information sources as we also observed that not only specialist were more likely to prescribe contraindicated drugs, but also the type of drugs between specialists and GPs together with other healthcare professionals were slightly different.

Metoclopramide is still prescribed for chronic use for the indication symptomatic gastro-esophageal reflux as the substantial need is not met by other medications[78]. However, the contraindication of metoclopramide suppositories in higher age groups is not very clear as it is described as a contraindication, but was also described as a warning according to the same information source[20]. Another commonly prescribed drug that is contraindicated in children is doxycycline, which should be avoided because of its known adverse effect; tooth staining[79]. It is possible that doxycycline is still prescribed despite the label warning as it is considered as

one of the most effective treatments for tick borne diseases or because recent studies showed no visible dental staining in children [80],[81],[82].

Strengths and limitations

One of the strengths of our study is that we used a population-based dispensing database which registers drugs that were dispensed in more than 95% of all community pharmacies in the Netherlands. Pharmacists play an essential role in drug safety and it is likely that the number of contraindicated drugs is higher in prescription data than in our study as we have used dispensing data. Detailed information was available of all drugs that were dispensed to children. The relatively long history available also enabled us to study any drugs that were dispensed since birth to determine the 1-year cumulative incidence and prevalence. Our study also has several limitations. Our data does not include the drugs that were dispensed by hospital pharmacies where the numbers of contraindicated drugs that were dispensed may be higher. No information about the month of birth was not available. Therefore, we only included drugs in our analysis where the contraindication for age was based on the number of years and not months. Also, no information was available with regard to the indication of the drugs prescribed.

Conclusion

The results of this study showed that a substantial percentage of children received a dispensed drug which is contraindicated for that age, which is more common in females than in males. Sex differences in disease prevalence or healthcare may explain this observation. We also observed that the information about the contraindication (contraindication or warning and the reason) is limited and not consistent between the different information sources. Since prescribing an on-label drug can be inaccurate, as much as prescribing an contraindication drug can be good practice, it is important that all prescribers and healthcare professionals are informed sufficiently about the contraindications. Further research is needed to investigate the sex differences and the reasons for prescribing particular drugs despite their contraindication for age.

4 Methylphenidate use in children

4.1 Maternal sociodemographic factors are associated with methylphenidate initiation in children in the Netherlands: a population-based study

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Submitted for publication

ABSTRACT

Background and objectives: Methylphenidate is widely used to treat children with attention deficit hyperactivity disorder (ADHD). Apart from the indication, multiple factors may contribute to the decision to initiate treatment such as maternal sociodemographic factors of which relatively little is known. Therefore, the objective was to investigate the association between these factors and child methylphenidate initiation.

Methods: The study population included 4,243 children with pharmacy dispensing records from the Generation R Study in the Netherlands. Maternal sociodemographic characteristics were tested as determinants of methylphenidate initiation through a time-dependent Cox regression analysis with date of first prescription as event date. Subsequently, we stratified by mother-reported clinically relevant ADHD symptoms.

Results: Methylphenidate was less likely to be prescribed to girls (adjusted hazard ratio (HR):0.34,95%CI:0.24-0.49) and to children born to a mother with a non-western ethnicity (adjusted HR:0.41,95%CI:0.28-0.60) compared to mothers of Dutch-Caucasian ethnicity, and more likely if mothers completed secondary education compared to a higher education (adjusted HR:1.52,95%CI:1.09-2.12). After stratification on ADHD symptoms, the associations remained similar, except for maternal education where no association was found in children with ADHD symptoms. Children without ADHD symptoms were more likely to receive methylphenidate when their mother completed a low (adjusted HR:2.29,95%CI:1.10-4.77) or secondary (adjusted HR:1.71,95%CI:1.16-2.54) education.

Conclusion: The current study showed that even when there are no reported ADHD symptoms, boys and children born to a mother of Dutch-Caucasian ethnicity or a low maternal education were more likely to receive methylphenidate treatment. Treatment initiation in children without ADHD symptoms should be further investigated.

INTRODUCTION

Worldwide, 5% of children will develop or have symptoms of attention deficit hyperactivity disorder (ADHD) [83]. Stimulant medication is widely used for the treatment of ADHD of which methylphenidate is considered the first choice of pharmacological treatment [84]. However, not all children eligible for methylphenidate treatment receive the medication and conversely some children may receive methylphenidate when it is not needed [85]. Even though, there are clear guidelines with regard to ADHD treatment, symptom severity and functional impairment are not the sole determinants of treatment initiation. Numerous studies have explored other factors that might contribute to the use of stimulant medication in children diagnosed with ADHD [86, 87]. One of the factors known to be related to initiation with stimulant medication is the patient's sex. Stimulants are more often prescribed to boys than girls, which can partly be explained by the fact that ADHD is more often diagnosed in boys than in girls and this may reflect differences in ADHD symptoms between boys and girls [88-90]. Apart from child characteristics, the prescribing behavior of physicians as well as the availability of non-pharmacological treatment options to the family are important [91-93].

Not every child diagnosed with ADHD receives pharmacological treatment[94]. While symptom's severity as well as non-response to non-pharmacological interventions play an important role in the initiation of pharmacological treatment [94], there may be other factors contributing to a family's decision to visit a general practitioner or specialist, a child psychiatrist or to start medication [95]. Children often rely on caregivers for support and management of chronic conditions involving taking medications, where mothers are mostly considered as the primary caregiver [96]. However, the importance of the mothers, notably maternal characteristics in determining methylphenidate treatment initiation should be studied further [97-99]. Previous studies showed that the utilization of ADHD medication may be influenced by sociodemographic factors such as ethnicity and socioeconomic status [89, 100]. However, these studies do not address the presence or absence of any ADHD related symptoms in these children, which may also vary across the different sociodemographic groups [11, 101].

The objective of our study was to investigate the association between maternal sociodemographic and prenatal lifestyle factors in relation to child methylphenidate treatment initiation. Subsequently, we performed analyses stratified by the presence of maternal reports of clinically relevant ADHD symptoms in children using the determinants that were significantly associated with child methylphenidate prescription.

METHODS

Design & study population

The study was conducted within The Generation R Study, which is a large prospective population-based cohort study investigating children's health from fetal life onwards in Rotterdam, the Netherlands [17]. Pregnant women who were resident in Rotterdam and who had a delivery date between April 2002 and January 2006 were asked to participate in the study. In this cohort, detailed and extensive data collection has been conducted, which include questionnaires, interviews, and behavioral observations of children and their parents [17]. In addition, we retrieved pharmacy records from community pharmacies throughout Rotterdam, depending on where the child resided and collected their prescription-only drugs. In total, 9,778 mothers were enrolled in the study and gave birth to 9,749 live born children (Figure 1). Of this group, 7,896 children and their parents were invited to participate in the follow-up study (56 died; 1,086 withdrawn from study; 639 lost to follow-up). Children were excluded from the study if their parents chose to later withdraw from the study (n=74). They were also excluded if

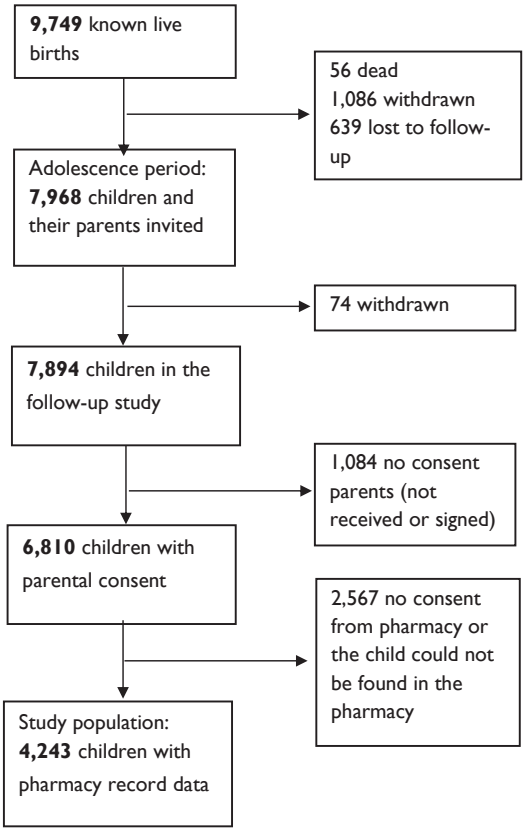

Figure 1. *Selection of the study population*

no consent by their parents was provided (n=1,084) or because no consent was given by the pharmacist or the child could not be found in the pharmacy (n=2,567). Pharmacy records could be obtained from 4,243 children. The Medical Ethics Committee of the Erasmus Medical Center approved all study procedures, and parents provided written informed consent.

Child Methylphenidate prescription

Pharmacy records of Generation R participants were collected based on the living area of their mothers (northern, southern, western of eastern part of Rotterdam). This information was used to determine at which pharmacies they may collect their medication. Pharmacists were contacted and asked for consent to retrieve the pharmacy records. Children may collect their medication at more than one pharmacy and these pharmacy records were all linked to one particular child. Pharmacy records of children may not be available because either their pharmacy or their parents did not give consent to retrieve these records or because the child's pharmacy could not be found.

For 4,243 individuals in The Generation R Study, all prescriptions which were filled at their pharmacy during the entire study period were gathered starting at birth. For each prescription we had the product name, anatomical therapeutic chemical (ATC) code [102] , date of filling, number of delivered tablets/capsules, and prescribed daily number of doses. All study participants were followed from date of birth until a first prescription of methylphenidate or end of the study period at 1 September 2017, whichever came first. Information about the use of ADHD medication (N06BA) was obtained from the collected pharmacy dispensing records. Furthermore, information about the type of prescriber of the first methylphenidate prescription (e.g. general practitioner, specialist or at the hospital) was available, which was retrieved from the electronic pharmacy records as well.

Child ADHD symptoms

The Child Behavior Checklist (CBCL/1.5-5 and CBCL/6-18) was used to obtain information about behavioral and emotional problems in children [103]. The CBCL is a questionnaire that was filled out by mothers when children were 1.5, 3, 5 and 9 years of age. The CBCL/6-18 was only used at the 9 years assessment. The CBCL contains items on the child's behavioral and emotional problems during the preceding 2 months which were scored on a 3-point scale; 6 of the items make up de attention-deficit/hyperactivity problems scale. Children were classified as having ADHD symptoms in the borderline clinical range, when the cut-off score was above the 93rd percentile. It has been reported that these DSM-oriented scales provide accurate and supplementary information on clinical diagnosis with a good reliability and validity for the CBCL [103, 104]. For the statistical analysis, we used the last questionnaire that was filled out by the mother prior to date of first methylphenidate prescription. The average time between the completion of the last CBCL and first prescription of methylphenidate was 2.9 years (SD: 3.6).

Child and maternal characteristics

The following maternal lifestyle and demographic characteristics were considered as potential determinants for starting treatment with methylphenidate: maternal age at intake, ethnicity (Dutch-Caucasian or other Western, non-western, defined according to the classification of Statistics Netherlands [105]), household income (<€1200, >€1200 and <2000, >€2000 per month), educational level (primary, secondary, higher), marital status (married, living together, no partner), alcohol use (yes/no), caffeine intake (yes/no) and smoking during pregnancy (yes/no) [106]. Maternal psychopathology in mid-pregnancy was assessed, using the Brief Symptom Inventory (BSI) which is a validated self-report questionnaire which includes a spectrum of psychiatric symptoms. A weighted sum score above 0.75 means that clinically relevant psychopathology symptoms were present [107, 108]. In addition, the use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy (the most frequently used antidepressant in our study), which was obtained from pharmacy records and self-reported information [109]. This information from mothers was collected during pregnancy or at birth of their child. Finally, we also considered child's sex as a potential determinant.

Analysis

Child and family characteristics were presented for all children with pharmacy records, which also included the type of prescriber, age of first methylphenidate prescription and the life style factors of the mothers. Second, we investigated which maternal lifestyle and demographic characteristics were related to methylphenidate initiation. For the main analyses, we calculated the hazard ratio (HR), with 95% confidence interval (CI) for each determinant associated with initiation of methylphenidate using a time-dependent Cox regression model, where non-methylphenidate users can serve as a control more than one time [110]. A time-dependent model was used, because the CBCL questionnaires were completed at different points in time (1.5, 3, 5 and 9 years). For this analysis, we considered the presence of clinically relevant ADHD symptoms based on the CBCL questionnaire data completed prior to the date of first methylphenidate prescription. As determinants of methylphenidate treatment initiation, we considered all above-mentioned maternal and child characteristics in the univariate analysis. Second, a multivariable Cox regression analysis was performed with the variables that were univariably associated. Separately, we tested the interaction between maternal education and ethnicity in the post-hoc analysis with an interaction term. Finally, we performed analyses stratified by clinically relevant ADHD symptoms (above 93rd percentile) using the factors that were associated with child methylphenidate prescription in the main analysis.

First, we performed complete-case analyses. In the non-response analysis, we explored differences between mothers and children of responders and non-responders. In the sensitivity analysis, we performed the same analysis using multiple imputation of the covariates (where less than 30% was missing) using the expectation maximization algorithm to deal with miss-

ing data. Results were considered statistically significant at p<0.05. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY).

RESULTS

Child methylphenidate prescription

Pharmacy records were available for 4,243 children. A total of 295 children were prescribed an ADHD medication, where 291 (99%) received methylphenidate. Due to the small number of other ADHD medication (dexamphetamine n=3 and atomoxetine n=1) prescribed, we only analyzed data of children who started their treatment with methylphenidate. In total, 291 children received a methylphenidate prescription. The average age of receiving their first methylphenidate prescription was 9.4 years. Of the children who received methylphenidate, 207 children received their first methylphenidate prescription from a specialist (71%) and they were more often boys (n=221, 75.9%).

Demographic and lifestyle characteristics

In Table 1, the characteristics of the study population are shown. Half of the children who were included in our study were girls (n=2,066, 48.7%). Of those children whose mother filled in the CBCL questionnaires (n=2,070), 179 (8.6%) had ADHD symptoms above the cut off score. Furthermore, 1.621 (38.2%) mothers had a non-western background, 2,016 (47.5%) had a relatively high monthly household income (€>2000) and only a small percentage had a low educational level (n=361, 8.5%).

Table 1. *Maternal and child characteristics of study population*

Characteristic	N (%), n=4,243
Sex, girl	2,066 (48.7)
ADHD symptoms present (CBCL by mother)[a]	
No	1,891 (44.6)
Yes	179 (4.2)
Age of first methylphenidate prescription, mean (SD)*	9.4 (2.2)
*Type prescriber **	
No methylphenidate prescription	3,955 (93.2)
Specialist	209 (4.9)
General Practitioner	37 (0.9)
Hospital	10 (0.2)
Maternal age (at intake) in years, mean (SD)	30.6 (5.2)
Parity	
1	2,260 (53.3)
>1	1,983 (46.7)

Table 1. *Maternal and child characteristics of study population* (*continued*)

Characteristic	N (%), n=4,243
Ethnicity mother	
Dutch-Caucasian and other western	2,480 (58.4)
Non-western	1,621 (38.2)
Household income	
<€1200	570 (13.4)
€1200-2000	571 (13.5)
€>2000	2,016 (47.5)
Maternal education level	
No education/ primary education	361 (8.5)
Secondary education	1,708 (40.3)
Higher education	1,747 (41.2)
Marital status	
Married	1,921 (45.3)
Living together	1,418 (33.4)
No partner	484 (11.4)
Smoking during pregnancy	
No	3,056 (72.0)
Yes	596 (14.0)
Alcohol use during pregnancy	
No	1,991 (46.9)
Yes	1,322 (31.2)
Caffeine intake during pregnancy	
No	2,105 (49.6)
Yes	1,468 (34.6)
Maternal psychopathology (BSI)	
<0.76	2,770 (65.3)
0.76 and higher	485 (11.4)
SSRI use during pregnancy	
No	1,798 (42.4)
Yes	36 (0.8)

*Numbers are given in numbers (percentages) unless stated otherwise. The numbers of the missing values are not shown in this table, but are as follows: type prescriber 22 (0.5%); reported ADHD symptoms 2,173 (51.2%); ethnicity 142 (3.3%); household income 1,086 (25.6%); maternal education 427 (10.1%); marital status 420 (9.9%); smoking during pregnancy 591 (14%); alcohol use during pregnancy 930 (21.9%); caffeine intake during pregnancy 670 (15.8%); maternal psychopathology 988 (23.3%) and SSRI use during pregnancy 2,409 (56.8%). *The information about the type of prescriber was only provided of children who received methylphenidate (n=291).* [a] *Clinically relevant ADHD symptoms: Children were classified as having ADHD symptoms in the borderline clinical range when their cut-off score was above the 93rd percentile. BSI indicates Brief Symptom Inventory; N, number of children; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors. All numbers are given in percentages or mean (SD).*

Determinants of methylphenidate treatment initiation

In the multivariable analysis (Table 2), we found that girls were less likely to be treated with methylphenidate than boys (adjusted HR: 0.34, 95%CI: 0.24-0.49). As expected, children were more likely to receive a methylphenidate prescription when mothers reported clinically relevant child ADHD symptoms (adjusted HR: 8.67, 95%CI: 6.25-12.02). We observed that children were more likely to start treatment with methylphenidate when mothers completed secondary school (adjusted HR: 1.52, 95%CI: 1.09-2.12) compared to mothers with a higher educational level. Furthermore, a non-western ethnicity of mothers was associated with a lower likelihood of methylphenidate treatment (adjusted HR: 0.41, 95%CI: 0.28-0.60) compared to a Dutch-Caucasian or other western background. Finally, the interaction between maternal education and maternal ethnicity was found to be significant (P: 0.001). Children whose mother received a secondary education as compared to a higher education in the western group were more likely to receive methylphenidate (HR:1.93, 95%CI: 1.45-2.58). In the non-western group, no significant association was found (no/ primary education HR: 0.70, 95%CI: 0.36-1.38; secondary education HR: 0.71, 95%CI: 0.42-1.20).

Table 2. *Maternal and child factors associated with methylphenidate treatment initiation*

Characteristic	Cases, N (%) (n=291)	Crude HR, 95%CI	Adjusted HR, 95%CI (cases, n=180)
Sex child			
Boy	221 (75.9)	Ref	Ref
Girl	70 (24.1)	*0.31 (0.24-0.41)*	*0.34 (0.24-0.49)*
ADHD symptoms present (CBCL by mother)[a]			
No	128 (44.0)	Ref	Ref
Yes	78 (26.8)	*9.06 (6.71-12.23)*	*8.67 (6.25-12.02)*
Maternal age at baseline, years			
<25	44 (15.1)	Ref	
25-30	85 (29.2)	0.87 (0.59-1.27)	
31-36	123 (42.3)	0.77 (0.54-1.10)	
>36	39 (13.4)	0.81 (0.52-1.27)	
Parity			
1	154 (52.9)	Ref	
>1	137 (47.1)	1.02 (0.80-1.29)	
Ethnicity mother			
Dutch-Caucasian and other western	201 (69.1)	Ref	Ref
Non-western	82 (28.2)	*0.60 (0.46-0.79)*	*0.41 (0.28-0.60)*

Table 2. *Maternal and child factors associated with methylphenidate treatment initiation (continued)*

Characteristic	Cases, N (%) (n=291)	Crude HR, 95%CI	Adjusted HR, 95%CI (cases, n=180)
Household income			
<€1200	29 (10.0)	0.67 (0.44-1.00)	
€1200-2000	38 (13.1)	0.89 (0.61-1.28)	
€>2000	150 (51.5)	Ref	
Maternal educational level			
No education/ primary	20 (6.9)	0.91 (0.56-1.49)	1.04 (0.52-2.06)
Secondary	138 (47.4)	*1.37 (1.06-1.78)*	*1.52 (1.09-2.12)*
Higher	106 (36.4)	Ref	ref
Marital status			
Married	113 (38.8)	Ref	
Living together	106 (36.4)	1.29 (0.98-1.70)	
No partner	40 (13.7)	1.44 (0.99-2.10)	
Alcohol use during pregnancy			
No	124 (42.6)	Ref	
Yes	100 (34.4)	1.23 (0.94-1.62)	
Smoking during pregnancy			
No	196 (67.4)	Ref	Ref
Yes	55 (18.9)	*1.48 (1.09-2.03)*	1.02 (0.70-1.48)
Caffeine intake during pregnancy			
No	143 (49.1)	Ref	
Yes	97 (33.3)	1.04 (0.80-1.35)	
Maternal psychopathology (BSI)			
<0.76	178 (61.2)	Ref	
0.76 and higher	33 (11.3)	1.06 (0.72-1.56)	
SSRI use during pregnancy			
No	132 (45.4)	Ref	
Yes	4 (1.4)	1.58 (0.55-4.53)	

A time-dependent model was used where the ADHD scores of the last completed CBCL questionnaire prior to methylphenidate prescription was considered. In the adjusted model we included all univariably associated determinants. The number of non-methylphenidate users are not presented in the table due to the time component of the model where non-methylphenidate users can serve as a control more than once. [a] Clinically relevant ADHD symptoms: Children were classified as having ADHD symptoms in the borderline clinical range when their cut-off score was above the 93rd percentile ADHD indicates attention deficit hyperactivity disorders, BSI, Brief Symptom Inventory; CBCL, Child Behavior Checklist CI, confidence interval; HR, hazard ratio; N, number of children; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor.

Stratification by ADHD symptoms

Absence of ADHD symptoms

Table 3 shows that girls without clinically relevant ADHD symptoms were less likely to receive a methylphenidate prescription than boys (adjusted HR: 0.25, 95%CI: 0.16-0.39). Children with

mothers of a non-western background were less likely to receive a methylphenidate prescription than those with a Dutch-Caucasian background (adjusted HR: 0.42, 95%CI: 0.26-0.68). Furthermore, we found that children were more likely to receive a methylphenidate prescription when mothers completed lower education than those who completed high education (no education/ primary education adjusted HR: 2.29, 95%CI: 1.10-4.77 and secondary education adjusted HR: 1.71, 95%CI: 1.16-2.54).

Table 3: *Maternal and child factors associated with methylphenidate treatment initiation stratified by the presence and absence of clinically relevant ADHD symptoms*

CBCL filled out by the mother	Characteristic	Cases, N	Crude HR, 95% CI	Adjusted HR, 95% CIb
ADHD symptoms absent	*Sex*			
	Boy	101	Ref	Ref
	Girl	27	*0.26 (0.17-0.39)*	*0.25 (0.16-0.39)*
	Ethnicity			
	Dutch Caucasian and other western	94	Ref	Ref
	Non-western	32	*0.51 (0.33-0.77)*	*0.42 (0.26-0.68)*
	Maternal education			
	No education/ primary	11	1.20 (0.61-2.35)	*2.29 (1.10-4.77)*
	Secondary	57	1.33 (0.90-1.95)	*1.71 (1.16-2.54)*
	Higher	48	Ref	Ref
ADHD symptoms present[a]	*Sex*			
	Boy	58	Ref	Ref
	Girl	20	*0.54 (0.32-0.89)*	*0.53 (0.32-0.90)*
	Ethnicity			
	Dutch Caucasian and other western	55	Ref	Ref
	Non-western	23	*0.41 (0.25-0.68)*	*0.45 (0.26-0.77)*
	Maternal education			
	No education/ primary	5	0.38 (0.14-1.03)	0.60 (0.21-1.70)
	Secondary	44	0.92 (0.55-1.54)	1.10 (0.65-1.86)
	Higher	26	*Ref*	*Ref*

A time-dependent model was used where the ADHD scores of the last completed CBCL questionnaire prior to methylphenidate prescription was considered. In the adjusted model we included all determinants. The number of non-methylphenidate users are not presented in the table due to the time component of the model where non-methylphenidate users can serve as a control more than one time [a] Clinically relevant ADHD symptoms: Children were classified as having ADHD symptoms in the borderline clinical range when their cut-off score was above the 93rd percentile. [b]Corrected for time between completion of CBCL and first methylphenidate prescription. ADHD indicates attention-deficit hyperactivity disorder; CBCL, child behavior checklist; CI, confidence interval; HR, hazard ratio; N, number of children.

Presence of ADHD symptoms

When child ADHD symptoms above the cut-off were reported, we found that girls were less likely to receive a methylphenidate prescription than boys (adjusted HR: 0.53, 95%CI: 0.32-0.90) (Table 3). Children of non-western mothers were less likely to receive a methylphenidate prescription compared to those of mothers with a Dutch-Caucasian or other western background (adjusted HR: 0.45, 95%CI: 0.26-0.77).

Sensitivity analyses

In the multivariable analysis with imputed data we found similar results: direction and size of the effect estimates overall did not change much. We found that girls were less likely to receive methylphenidate (adjusted HR: 0.31, 95%CI: 0.21-0.47) or when they had a mother with a non-western background (adjusted HR: 0.48, 95%CI: 0.31-0.75). Children were more likely to receive a methylphenidate prescription when they had ADHD symptoms above the cut-off reported by their mothers (adjusted HR: 10.12, 95%CI: 6.95-14.74). However, the association between methylphenidate initiation and a low maternal education was non-significant (no/primary education adjusted HR: 2.01, 95%CI: 0.94-4.28; secondary education adjusted HR: 1.37, 95%CI: 0.94-2.01).

Non-response analyses

For the variables that were included in the analyses, less than 30% were missing, except for SSRI use during pregnancy (56.8%) and the reported clinically relevant ADHD symptoms (51.2%). The non-response analysis showed no significant differences between children with and without information for the maternal characteristics. However, we found that 2,173 women did not complete the CBCL questionnaires at all or did not complete the questionnaire prior to the first prescription of methylphenidate. A dropout analysis on this variable showed that the missing of the CBCL questionnaire was not significantly associated with sex, but it was associated with ethnicity (P<0.001), maternal education (P<0.001) and methylphenidate initiation (P<0.001).

The analysis in the group without information on ADHD symptoms (missing information) showed similar results for sex and ethnicity (girls adjusted HR 0.49, 95%CI: 0.30-0.83 and non-western background (adjusted HR 0.61, 95%CI 0.36-1.03). For maternal education, we found that a lower education was significantly associated with a decreased risk of methylphenidate use compared to higher education (no education/ primary HR 0.31, 95%CI 0.11-0.91).

Pharmacy records were not available for half of the cohort participants (results not shown in table). For children of whom no pharmacy records were available, we found that their mothers were significantly younger (maternal age 29.6 vs 30.6, P<0.001), had a lower household income (20.6% <1200 vs 18.1%, P<0.02), were lower educated (12.0% no education/primary education vs 9.5%, P<0.001), more often did not have a partner (15.6% no partner vs 12.7%, P0.001), used less alcohol during pregnancy (35.4% vs 39.9%, P<0.001), smoked more during pregnancy (19.7% vs 16.3%, P<0.001) and used less caffeine during pregnancy (61.9% vs 58.9%).

DISCUSSION

Main findings

In the current study, we found that several child and maternal sociodemographic factors were related to methylphenidate treatment initiation. In our study we were able to study these determinants stratified by the presence and absence of clinically relevant ADHD symptoms. Our findings show that methylphenidate was more frequently prescribed to boys than girls. It also shows that children of mothers with a non-western background were less likely to receive methylphenidate treatment than those of mothers with a Dutch-Caucasian or other western background. These findings are both in line with results that have been shown in previous studies [89, 90, 111]. However, the previous studies as described above only addressed the association with sociodemographic factors in patients with an ADHD diagnosis. In our study, we found that even when no ADHD symptoms were reported by mothers, boys and children born to mothers with a western ethnic background were still more likely to receive methylphenidate. Furthermore, we found that a low and secondary maternal education was associated with methylphenidate prescription in children without reported symptoms. A previous study of Russel et al., found no significant association between maternal education and medication use in children in a UK population [88]. This could also be explained by the differences in the educational system of the Netherlands and the UK. It is also possible that they did not find the association as they only explored the sociodemographic factors of medication use among children with ADHD.

Explanations for these findings

First, sex differences with regard to use of methylphenidate or other stimulants is probably related to the diagnosis of ADHD, which is more common in boys than girls [9]. Moreover, boys with clinically ADHD, present more outwardly signs of ADHD, such as hyperactive and impulsive behavior, while girls present more inwardly signs, such as inattentiveness and low self-esteem [112]. In addition, girls may express their difficulties differently; for example emotional problems are more common in girls with ADHD than in boys. Also, boys tend to show more hyperactivity, than girls [10, 113]. This may both lead to boys being diagnosed with ADHD more often as well as earlier initiation of pharmacological treatment as shown previously [88]. However, in our study we observed that girls are still less likely to be treated with methylphenidate irrespective of the presence of ADHD symptoms. It is possible that girls may be less qualified as their symptoms are not considered severe enough [114]. However, it could also imply that girls with ADHD symptoms are undertreated while on the other hand boys without ADHD may be overtreated [115]. Parents may find it more difficult to cope with the hyperactive and impulsive behavior which is more prevalent in boys and this could also be the reason why boys are more likely to be treated with medication.

Second, we showed that children without clinically relevant ADHD symptoms with mothers who only had limited education (no education, primary and secondary education) were more likely to receive a methylphenidate prescription. On the other hand, no significant association with maternal education was observed in children with ADHD symptoms. This finding might be interpreted that as long as the child has ADHD, there is no problem with inequity. When it comes to children without a diagnosis, there is inequity in treatment. Nevertheless, a previously published study showed that a low maternal education was associated with less involvement in the decision-making of medication initiation in children. Parents may not have sufficient knowledge about ADHD and feel that it is necessary to initiate methylphenidate when this is not thoroughly discussed with them [116]. Furthermore, we found that children whose mother had a western ethnic background who received a lower education, were more likely to receive methylphenidate than children whose mother received a high education. It may seem that only mothers with a western ethnic background with a low education are less likely to be involved. This association was not found in the non-western group. This may suggest that mothers with a non-western background, irrespective of educational level, are treated differently than mothers with a western ethnic background.

Third, children with ADHD problems and their parents from ethnic minority groups may have less access to healthcare or less communication with healthcare professionals due to a language barrier [101, 117-121]. They may also receive less appropriate diagnoses or treatments as the symptoms observed for these disorders may differ across ethnic groups, and may differ from what clinicians are trained to expect [122, 123]. ADHD problems are also often recognized by teachers when children are more hyperactive than others. However, not all parents may consider hyperactivity as a behavioral problem as some parents may have a positive attitude towards a child with high energy [124]. This view and recognition of ADHD related problems may vary across different ethnic groups. Furthermore, ethnic minority families may also be less likely to recommend medication and may prefer behavioral therapy over stimulant medication as found in previous studies [125, 126]. The findings of the current study may reflect cultural differences, knowledge and perceptions about ADHD and its pharmacological treatment.

Strengths and limitations

Strengths of our study are the relatively large population-based cohort, its prospective design, independent registration of dispensed medicines, and the multi-ethnic nature of the sample which limit the chance of selection and information bias. Treatment initiation was based on pharmacy dispensing records, which is more accurate in terms of dispensation date than information on prescription medication from medical records or questionnaires as medication can be prescribed but not collected at pharmacies. However, our study also has some limitations. One of the limitations is that we had to rely on questionnaires filled out by mothers to assess the presence of ADHD symptoms. These mother reports are considered valuable as they provide more insight into the perspective of the mothers with regard to their child's behavior

as ADHD symptoms are not always recognized as such across different demographic groups. However, not all mothers completed the CBCL questionnaire, which is also considered as an important limitation as we were not able to assess the presence of ADHD symptoms in these groups. Information bias may have occurred if the association between maternal characteristics or sociodemographic factors and treatment initiation is different for responders and non-responders, but this is difficult to ascertain. Nevertheless, the stratified analysis in the group without information on ADHD symptoms showed similar results for sex and ethnicity, except for maternal education. Another limitation is that pharmacy records were not available for half of the participants of The Generation R study as not all pharmacists provided consent to obtain the dispensing records from their pharmacies. As shown in the results, we found that mothers of children without pharmacy records differed on several aspects. Despite this selection bias, we observed similar results in our study compared to the available literature showing an association between initiation of methylphenidate and ethnicity, maternal educational level and smoking during pregnancy [116, 127]. Furthermore, no information about other treatment (e.g. behavioral therapy) was available. Therefore, we were not able to assess if specific demographic groups were not receiving therapy or were treated with behavioral therapy. Finally, information about maternal characteristics were not available for each child, but the non-response analysis showed no significant differences between both groups.

Conclusion

In conclusion, the current study showed that even when there are no reported ADHD symptoms, boys and children born to a mother of Dutch-Caucasian ethnicity or a low maternal education were more likely to receive methylphenidate treatment. This may suggest overtreatment. Considering these findings, it is important for healthcare professionals to be aware of these differences and take these into account when deciding on initiating treatment with methylphenidate. Reasons for treatment initiation in children without ADHD symptoms should be further investigated.

4.2 Persistence and adherence to methylphenidate in children in the Netherlands

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ABSTRACT

Background and objectives: Several studies have examined factors that may contribute to adherence and/or persistence to methylphenidate, but these were mainly conducted in adults and not in children. In children, determinants of adherence and are probably different from adults. However, information about the family and child characteristics in relation to adherence and persistence to methylphenidate treatment in children is limited. Therefore, the objective was to study determinants of adherence to and persistence of methylphenidate in children.

Methods: The study population included a subset of 307 children, from the population-based Generation R Study in the Netherlands, who all had at least one dispensing record of methylphenidate from birth up to the age of 16 years. Adherence was defined as a medication possession ratio (MPR) ≥ 0.80. Persistence was defined as duration of methylphenidate use until a discontinuation period ≥ 6 months. Family and child characteristics were tested as determinants of adherence with multivariable logistic regression analysis. Persistence was evaluated using a Kaplan Meier analysis.

Results: Children of a nulliparous mother (adjusted OR: 2.31, 95%CI: 1.17-4.54) or a mother with an average household income (compared to high) were more likely to be adherent (adjusted OR: 3.45, 95%CI: 1.43-8.31). Girls were more often non-persistent than boys (adjusted HR: 1.44, 95%CI:1.07-1.95) and children who started treatment at age 12-16 were more often non-persistent than children who started before 12 years of age (adjusted HR: 3.55, 95%CI:2.54-4.98).

Conclusion: In conclusion, the results of our study showed that both child and family characteristics may play a role in methylphenidate treatment adherence. Furthermore, sex and age at start of the treatment was found to be associated with non-persistence. These findings may be important for healthcare professionals when initiating methylphenidate treatment in children.

INTRODUCTION

Methylphenidate is the first line pharmacological treatment option for attention deficit hyperactivity disorder (ADHD) as it is considered an effective pharmacological treatment in children[84]. However, for medication to be effective, compliance to treatment is crucial. Two important aspects of compliance are reflected by adherence and persistence. Adherence refers to the extent to which patients take medications as prescribed and persistence refers to continuing treatment for the prescribed duration . Various studies have shown that adherence and persistence to stimulant medication in children and adolescents is only 40 to 50% [128, 129]. Many studies investigating adherence and persistence to methylphenidate were performed in adolescents and adults, whereas limited information is available in children [130, 131]. A previous study in adults, examined different sociodemographic factors that may contribute to adherence and persistence to methylphenidate treatment, and showed that male gender and a lower educational level were associated with discontinuation [132]. To investigate treatment adherence and persistence in children, it is important to consider also parental involvement as there are many parental factors that may contribute, such as socio-economic status and ethnicity [133]. A previous study that followed children with attention deficit hyperactivity disorder (ADHD) for 3 years, showed that pharmacological treatment was not accepted by all families [134], which may influence adherence and persistence to methylphenidate as parents are supposed to encourage children to continue to take their medication. However, the number of patients included in that study was small [134] and family or patient characteristics were not investigated. For example, the age at treatment initiation may play a role as adolescents usually manage their own medication intake and could be more likely to forget or abstain from medication [135]. For school-aged children, parents usually make treatment decisions and have a greater influence on adherence and persistence to medication. Studies also showed that medication adherence was greater when both children and parents felt that symptoms improved with treatment. The adherence and persistence may also be dependent on the dosage and the number of pills they have to take on a daily basis [130, 133, 136]. Finally, many studies have assessed adherence and persistence separately [135, 137-139]. However, it is important to assess adherence together with persistence, as they both are important aspects of adequate pharmacotherapy. For this reason, the objective of our study was to determine adherence to and persistence of methylphenidate treatment in children and to study potential determinants that were associated with these outcomes.

METHODS

Study population

This study was conducted within the Generation R Study, a large population-based cohort study investigating children's health from fetal life onwards in Rotterdam, the Netherlands [17]. All pregnant women from Rotterdam with a delivery date between April 2002 and January 2006 were asked to participate in the study. Detailed and extensive data have been collected over the years which included interviews, questionnaires and behavioral observations of children and their parents [17]. In addition, pharmacy records of the children from community pharmacies from Rotterdam were retrieved. In the current study, all children (n=7,986) and their parents were invited to participate in the follow-up. Children were excluded if parents withdrew from the study (n=74), if no consent by parents was provided (n=1,084) or if the pharmacy did not consent to retrieve the pharmacy records, or because no pharmacy records were available in the pharmacy database (which may include non-users) (n=1,742). For 5,068 individuals in The Generation R Study, all prescriptions which were filled at their pharmacy during the entire study period were gathered. Of these, 6% (n=307) of children received at least one methylphenidate prescription and formed the study population (Figure 1 for flowchart). All methylphenidate-using individuals were followed as of their first prescription until a) the end of the study period at 30 October 2018, b) loss to follow-up or c) end date of the last methylphenidate prescription, whichever came first.

Pharmacy records

Linkage between pharmacy records and Generation R participants was done at the community pharmacies in Rotterdam, but the information on methylphenidate use was extracted from automated pharmacy records, which was provided by the Dutch Foundation for Pharmaceutical Statistics [18]. For each dispensation, we collected the product name, Anatomical Therapeutic Chemical (ATC) code [102], date of filling, number of delivered tablets/capsules, and prescribed daily number. A methylphenidate dispensation was selected based on the ATC code N06BA04.

Methylphenidate use

Adherence was measured by the Medication Possession Ratio (MPR). The MPR measures the percentage of time a patient has access to medication and was calculated when children received at least 2 prescriptions of methylphenidate. The MPR is the sum of days' supply of methylphenidate during the follow-up period divided by the number of days in the that time period, i.e. between the first and end of the last prescription. According to international literature, a good adherence is set at an MPR of 0.80 or higher [129, 140]. Persistence of methylphenidate was calculated for all children who received at least one prescription of methylphenidate. Currently, there is no clear definition of non-persistence of methylphenidate treatment. In general, as previous studies used a gap period of 15 to 180 days as non-persistence [138, 139].

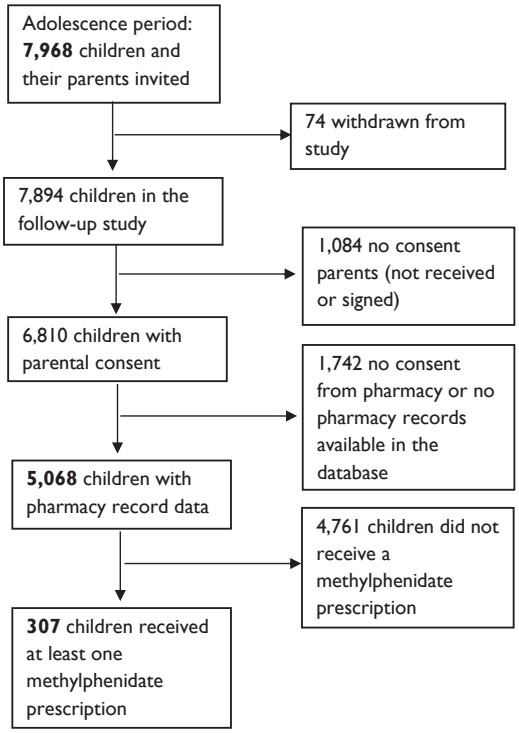

***Figure 1**. Selection of study the population*

Prescriptions for methylphenidate in the Netherlands are generally filled for 3 months. To ensure that no methylphenidate was dispensed after that, a gap period of 6 months (without prescription) was chosen for non-persistence. Non-persistence was calculated starting from the calculated end date of the last prescription. Additionally, we collected information on the type of methylphenidate prescriber (specialist, general practitioner), as well as prescriptions of other psychotropic medication prior to the first methylphenidate dispensation, including anti-epileptics, antipsychotics, anxiolytics, hypnotics and sedatives, antidepressants or other ADHD medications (ATC code N06BA). We included the number of times the prescription was switched from short-acting methylphenidate to long-acting methylphenidate or vice versa and the number of prescriptions of short- or long-acting methylphenidate (number of long-acting prescriptions greater than short-acting or number of short-acting greater than long-acting).

Child characteristics and other determinants

Child characteristics that were considered as determinants of adherence, include age at first methylphenidate prescription (5-11 and 12-16 years), sex, ethnicity (Dutch , non-Dutch western, and non-Dutch non-western) [105], and the presence of ADHD symptoms and other emotional and behavioral problems as reported by mothers using the Child Behavior Checklist

[103]. The Child Behavior Checklist (CBCL/1.5-5 and CBCL/6-18) was used to obtain information about behavioral and emotional problems in children [103]. The CBCL questionnaire has been filled out by the mother when the child was 3, 5 and 9 years old. The CBCL/6-18 was only used at the 9-years of age assessment. For the analyses, we used the most recently completed questionnaire prior to the first methylphenidate prescription. The CBCL contains items on the child's behavioral and emotional problems which are scored on a three-point scale (0=not true, 1=somewhat or sometimes true, 2=very or often true) during the preceding 2 months. There are five Diagnostic and Statistical Manual of Mental Disorders (DSM)-oriented scales: affective problems, anxiety problems, pervasive developmental problems, ADHD and oppositional defiant problems. It has been reported that these DSM-oriented scales provide accurate and supplementary information on clinical diagnosis with a good reliability and validity for the CBCL [104, 123]. We also measured the level of ADHD symptoms using the revised Conner's' Parent Rating Scales, (CPRS-R), which was filled out by primary caregiver at the age of 7-8 years. The CPRS-R consisted of 27 items that yielded several subscales: ADHD combined, ADHD Inattentive, ADHD Hyperactive-impulsive and Oppositional Defiant Disorder Scale [141]. The score ranges from 0-18 for the ADHD inattentive, hyperactive-impulsive and oppositional defiant disorder and a possible score between 0-36 for the ADHD combined. Higher scores indicate more problems. Autistic traits were assessed using the Social Responsiveness Scale (SRS) short form [142]. Each item is rated from 0 to 3 (never true to almost always true), covering social, language, and repetitive behaviors. We used a cut-off defined as the upper 15% for the presence of autistic traits.

Family characteristics

We considered several family characteristics as potential determinants for adherence in children: parity (1, >1), marital status (married, living together, no partner), maternal education (no/primary, secondary and high) and household income (low: ≤€2000, moderate: €2100-4000, high: €>4000). The demographic data was obtained using self-reports.

Analysis

Baseline characteristics were presented for all methylphenidate users with regular summary statistics.

First, determinants for methylphenidate adherence (MPR ≥0.80) at 2 years of follow-up (after receiving their first prescription) were assessed using logistic regression analyses to calculate odds ratios (OR) and their 95% confidence interval (CI). For all determinants, we tested their independent association with adherence. Then, a multivariable logistic regression model was performed with all relevant determinants and confounders based on the literature (age, sex, ethnicity, type of prescriber, other psychotropic medication, number of short-acting and long-acting methylphenidate, number of switching, parity, marital status, maternal education

and household income) [136, 138, 143] to assess the association with the 2-years adherence. The MPR was only calculated for children who received at least 2 prescriptions.

Second, to evaluate the extent of medication non-persistence between a low (MPR lower than 0.50), moderate (MPR between 0.50 and 0.79) and a high MPR (MPR of 0.80 and higher), we used unadjusted Kaplan-Meier curves. Statistically significant differences in methylphenidate persistence among children with a MPR<0.50, a MPR 0.50-0.80 and a MPR≥0.80 were identified using Wilcoxon tests. An extended Cox proportional hazards model was used to assess the risk of non-persistence adjusting for determinants.

Missing data of the determinants (ethnicity, type of prescriber, parity, marital status and household income) were imputed using multiple imputation (n=5)[144]. Missing data were only imputed if less than 30% of the specific variable was missing. Data of the child's behavioral characteristics (CBCL, SRS and CPRS-R) were not imputed. Results were considered statistically significant at p<0.05. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY).

RESULTS

Baseline

The characteristics of the study population and information about the dispensed medications are shown in Table 1. The mean age of first methylphenidate prescription was 9.7 years and the majority of children receiving methylphenidate were boys (74.6%). Children were more often

Table 1. *Baseline child and family characteristics of children who have received a methylphenidate (MPH) prescription (n=307)*

Child characteristic	
Age at first methylphenidate prescription (years), mean (SD)	9.7 (2.4)
Sex	
Boy	229 (74.6)
Girl	78 (25.4)
Ethnicity	
Dutch and other western	226 (73.6)
Non-western	81 (26.4)
Type of prescriber of first methylphenidate prescription	
Specialist	274 (89.3)
General practitioner	33 (10.7)
Other psychotropic medication prior to the first methylphenidate dispensation[a]	
No	276 (89.9)
Yes	31 (10.1)

Table 1. *Baseline child and family characteristics of children who have received a methylphenidate (MPH) prescription (n=307)* (*continued*)

Child characteristic	
Short- and long-acting MPH	
Number of short-acting MPH per child, mean (SD)	9.7 (21.1)
Number of long-acting MPH per child, mean (SD)	14.0 (22.7)
Number of times of switching between long- and short-acting stimulants	
0	174 (56.7)
1	60 (19.5)
2 or more	73 (23.8)
Affective problems (CBCL)[b] , mean (SD)	3.6 (4.4)
Anxiety problems (CBCL) [b], mean (SD)	2.0 (3.7)
Pervasive developmental problems (CBCL) [b], mean (SD)	2.1 (4.0)
Attention deficit/ hyperactivity problems (CBCL) [b], mean (SD)	2.5 (4.3)
Oppositional defiant problems (CBCL) [b], mean (SD)	2.1 (3.7)
Presence of autistic traits (SRS)[c]	
No	149 (48.5)
Yes	58 (18.9)
Attention deficit hyperactivity disorder (CPRS)[d], mean (SD)	15.6 (8.2)
Cognitive problems/ inattention (CPRS)[d], mean (SD)	7.5 (4.7)
Oppositional defiant disorder (CPRS)[d], mean (SD)	5.1 (3.6)
Hyperactivity (CPRS)[d], mean (SD)	5.0 (4.1)
Family characteristics	
Parity	
1	169 (55.0)
>1	138 (45.0)
Marital status	
Married, living together	249 (81.1)
No partner	58 (18.9)
Maternal education	
No/ primary education	11 (3.6)
Secondary education	145 (47.2)
Higher education	151 (49.2)
Household income	
Low	61 (19.9)
Moderate	125 (40.7)
High	78 (25.4)

*Values are given in numbers (%), unless stated otherwise. *Number of missing values are not shown. [a]anti-epileptics, anti-depressants, antipsychotics, anxiolytics, hypnotics and sedatives and melatonin. [b]CBCL indicates Child Behaviour Checklist (CBCL/1.5-5 and CBCL/6-18) [c]SRS indicates Social Responsiveness Scale short form. [d] CPRS indicates Conner's Parent Rating Scale. Abbreviations: MPH indicates methylphenidate; N, number; SD, standard deviation.*

Dutch or had a western ethnic background (73.6%) compared to non-wester and the majority of our children received their first methylphenidate prescription from a specialist (89.3%). 10.1% of the children received other psychotropic medications prior to their first methylphenidate prescription. Finally, 18.9% of the children had autistic traits above the cut-off score.

Determinants of adherence

Table 2 shows determinants that were associated with adherence (MPR ≥0.80) to methylphenidate treatment. Of the 264 children with more than one prescription, 63 were adherent 2 years after treatment initiation. In the univariable analyses, we found that children more likely to be adherent when they mainly received long-acting methylphenidate during the follow-up

Table 2. *Determinants associated with adherence (MPR ≥0.80) to methylphenidate treatment at 2 years after treatment initiation (n=264)**

Characteristics	Adherent at 2 years (n=63), n (%)**	Univariable, OR (95% CI)	Multivariable, OR (95%CI)
Child characteristics			
Age at first methylphenidate prescription, years			
5-11	50 (79.4)	Ref	Ref
12-16	13 (20.6)	0.66 (0.33-1.30)	0.75 (0.34-1.64)
Sex			
Boy	52 (82.5)	Ref	Ref
Girl	11 (17.5)	0.58 (0.28-1.19)	0.54 (0.24-1.21)
Ethnicity			
Dutch and other western	54 (85.7)	Ref	Ref
Non-western	9 (14.3)	*0.39 (0.18-0.85)*	0.50 (0.21-1.21)
Type of prescriber of first MPH prescription			
Specialist	60 (95.2)	Ref	Ref
General practitioner	3 (4.8)	0.39 (0.11-1.34)	0.38 (0.10-1.49)
Other medication before first MPH prescription[a]			
No	54 (85.7)	Ref	Ref
Yes	9 (14.3)	1.80 (0.76-4.28)	1.78 (0.66-4.81)
Short-acting and long-acting MPH			
Mainly short-acting	20 (31.7)	ref	ref
Mainly long-acting	43 (68.3)	*2.50 (1.37-4.54)*	*2.01 (0.99-4.11)*
Number of switching between long- and short-acting MPH			
0	23 (36.5)	Ref	ref
1	11 (17.5)	1.12 (0.51-2.48)	1.15 (0.46-2.88)
2 or more	29 (46.0)	*3.15 (1.65-6.03)*	*2.35 (1.08-5.09)*

Table 2. *Determinants associated with adherence (MPR ≥0.80) to methylphenidate treatment at 2 years after treatment initiation (n=264)** (*continued*)

Characteristics	Adherent at 2 years (n=63), n (%)**	Univariable, OR (95% CI)	Multivariable, OR (95%CI)
Affective problems (CBCL)[b]	45 (71.4)	0.96 (0.89-1.04)	
Anxiety problems (CBCL) [b]	58 (92.1)	0.92 (0.80-1.05)	
Pervasive developmental problems (CBCL) [b]	58 (92.1)	1.05 (0.95-1.15)	
Attention deficit/ hyperactivity problems (CBCL) [b]	57 (90.5)	1.00 (0.93-1.08)	
Oppositional defiant problems (CBCL) [b]	58 (92.1)	1.03 (0.93-1.14)	
Presence of autistic traits (SRS)[c]			
No	31 (49.2)	Ref	
Yes	18 (28.6)	1.74 (0.86-3.51)	
Attention deficit hyperactivity disorder (CPRS)[d]	42 (66.7)	1.01 (0.96-1.05)	
Cognitive problems/ inattention (CPRS)[d]	42 (66.7)	1.00 (0.93-1.08)	
Oppositional defiant disorder (CPRS)[d]	42 (66.7)	1.02 (0.92-1.12)	
Hyperactivity (CPRS)[d]	42 (66.7)	1.07 (0.99-1.16)	
Family characteristics			
Parity			
1	42 (66.7)	*2.00 (1.10-3.66)*	*2.31 (1.17-4.54)*
>1	21 (33.3)	Ref	Ref
Marital status			
Married, living together	59 (93.7)	Ref	Ref
No partner	4 (6.3)	*0.26 (0.09-0.77)*	0.26 (0.06-1.07)
Maternal education			
No/ primary education	2 (3.2)	1.04 (0.19-5.59)	1.83 (0.24-13.77)
Secondary education	29 (46.0)	0.95 (0.50-1.81)	0.91 (0.42-1.97)
Higher education	32 (50.8)	Ref	Ref
Household income			
Low	8 (12.7)	0.79 (0.28-2.23)	2.25 (0.46-11.05)
Moderate	42 (66.7)	*2.49 (1.20-5.17)*	*3.45 (1.43-8.31)*
High	13 (20.6)	Ref	Ref

*Values are given in numbers (%), unless stated otherwise. * The MPR was only calculated when more than 2 prescriptions was received. **Number of missing values are not shown. ***The multivariable model included all variables except for the behavioural characteristics. Determinants were selected based on the literature. [a]anticonvulsants, antidepressants, antipsychotics, anxiolytics, hypnotics and sedatives and melatonin. [b]CBCL indicates Child Behaviour Checklist (CBCL/1.5-5 and CBCL6-18). We corrected for the time between the date the questionnaire was completed and the date of first prescription [c]SRS indicates Social Responsiveness Scale short form. [d] CPRS indicates Conner's Parent Rating Scale. Abbreviations: CI indicates confidence interval; N, number; OR, odds ratio; SD, standard deviation.*

period (OR: 2.50, 95%CI: 1.37-4.54). However, this association did not remain present in the multivariable analysis (adjusted OR: 2.01, 95%CI: 0.99-4.11). Also, children who switched their medication multiple times from short-acting to long-acting (and vice versa) were more likely to be adherent than those who did not switch (adjusted OR: 2.35, 95%CI: 1.08-5.09).

Further, children of nulliparous mothers (adjusted OR: 2.31, 95%CI: 1.17-4.54) were more likely to be adherent. Compared to those with a high household income, we observed an association between a moderate household income and methylphenidate treatment adherence (adjusted OR: 3.45, 95%CI: 1.43-8.31). For the remaining determinants, including age of first treatment, sex, type of prescriber of first prescription, dispensation of other medications prior to the first methylphenidate prescription, maternal education and behavioral characteristics, no significant associations were found in the univariate or multivariate analysis.

Persistence

In total, 264 children were included in the survival analyses as they received more than one prescription for which the MPR could be calculated (43 children only received one prescription). In the study population, 67 children had an MPR below 0.50 (25.4%), 125 children had an MPR between 0.50 and 0.79 (47.3%) and 74 children had an MPR of 0.80 or above (28.0%). The overall mean treatment duration until discontinuation was 2.7 years (SE: 0.14). In patients with an MPR <0.50, the mean treatment duration was 2.6 years (SE: 0.24), the mean treatment duration in patients with a MPR between 0.50 and 0.79 was 5.6 years (SE: 0.17), and the mean treatment duration in patients with a good adherence (MPR≥0.80) was 3.1 years (SE: 0.33).

Figure 2 shows the survival curves of persistence in children with a low, (MPR <0.50), intermediate (MPR 0.50-0.70) and a high adherence (MPR≥0.80). We found that children with a low or intermediate MPR had a higher persistence in the first 2.7 years of methylphenidate treatment (P<0.001). After 2.7 years, persistence was higher in children with a good adherence (P<0.001). Differences in survival curves between the three MPR groups were observed (p= 0.03).

Table 3 shows the risk of non-persistence in children who started methylphenidate treatment. Only 4 children (1.3%) were persistent during the entire follow-up period. Girls were more likely to discontinue treatment than boys (adjusted HR: 1.44, 95%CI: 1.07-1.95). The risk of non-persistence increased with age (adjusted HR: 3.55, 95%CI: 2.54-4.98). Children who were more often prescribed short-acting methylphenidate than long-acting methylphenidate were more likely to be non-persistent (number of short-acting higher than long-acting, adjusted HR: 1.49, 95%CI: 1.13-1.96).

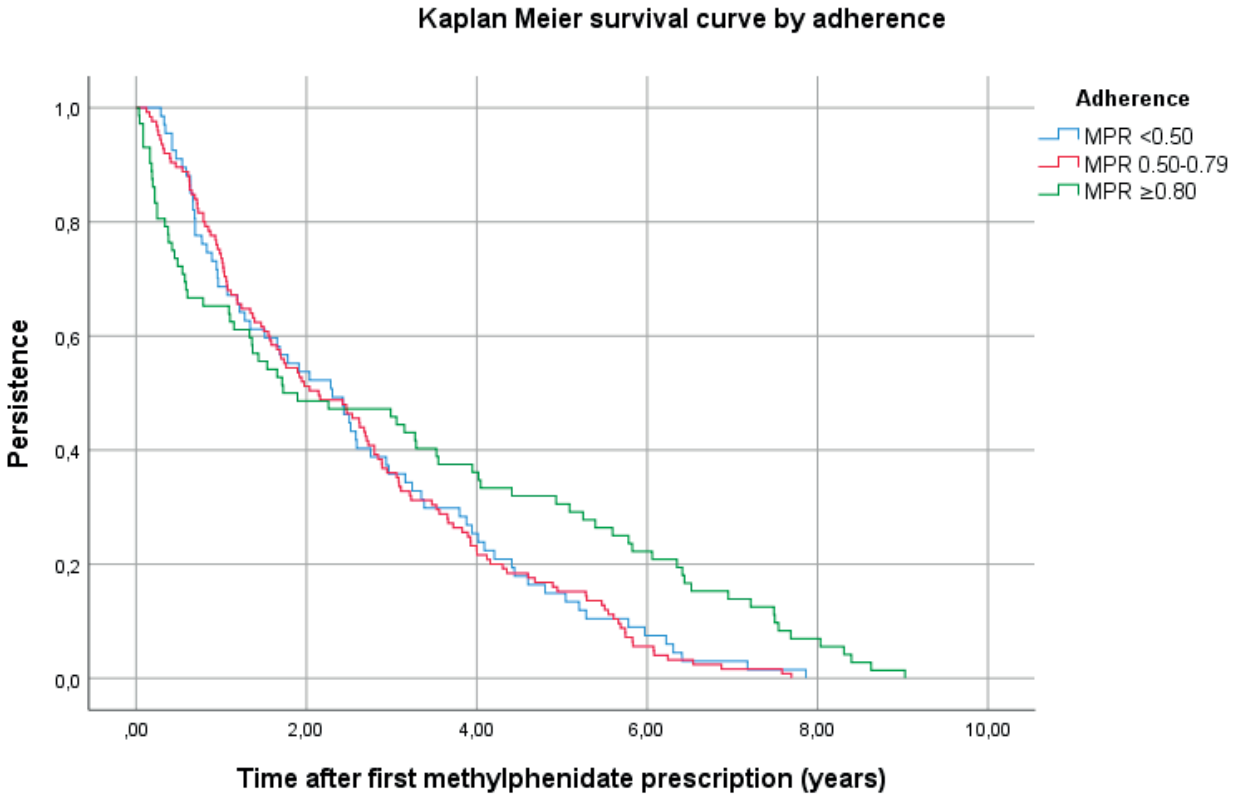

Figure 2. *Kaplan Meier curve for persistence by adherence (n=264)*

The Kaplan Meier curve was presented for persistence where children were censored when having a gap period without prescriptions for 6 months or more (non-persistence). This curve shows the probability of persistence of methylphenidate treatment in three adherence groups (low, intermediate and high) over a time interval with a maximum of 9 years after the first methylphenidate prescription. Abbreviations: MPR indicates medication possession ratio; n, number.

Table 3. *Risk factors for medication discontinuation (non-persistence) (n=307)*

Variable	Adjusted HR (95% CI)
MPR	
<0.50	ref
0.50-0.79	1.01 (0.74-1.38)
≥0.80	0.82 (0.56-1.19)
Sex	
Boy	ref
Girl	*1.44 (1.07-1.95)*
Age of first prescription	
5-11 years	ref
12-16 years	*3.55 (2.54-4.98)*
Ethnicity	
Dutch and other western	ref
Non-western	1.13 (0.83-1.53)
Type of prescriber of first MPH prescription	
Specialist	ref
General practitioner	1.26 (0.82-1.92)
Other medication before first MPH prescription[a]	
No	ref
Yes	0.91 (0.60-1.40)
Short-acting and long-acting MPH	
Mainly short-acting	*1.49 (1.13-1.96)*
Mainly long-acting	ref
Number of switches between long- and short-acting MPH	
0	ref
1	1.05 (0.75-1.47)
2 or more	*0.77 (0.56-1.06)*

**Adjusted for MPR, Sex, age of first prescription, ethnicity, type of prescriber, other medications prior to the first MPH prescription, number of short-acting and long-acting methyphenidate and the number of switches between long-acting and short-acting. [a]anticonvulsants, antidepressants, antipsychotics, anxiolytics, hypnotics and sedatives and melatonin. Abbreviations: CI indicates confidence interval; MPH, methylphenidate, N, number; OR, odds ratio; SD, standard deviation.*

DISCUSSION

Main findings

This study aimed to investigate the adherence and persistence of methylphenidate treatment and their associated determinants. The current findings show that children who switched their medication multiple times from short-acting to long-acting (and vice versa) were more likely to be adherent than those who did not switch. Also, a number of family characteristics played a

role in the treatment adherence of children. We found that children whose mother had given birth to more than one child had a lower adherence and children from families with a moderate household income were more adherent than those with a high household income.

We found that girls were more likely to discontinue treatment than boys and that the risk of discontinuation increases with age. Furthermore, we found that children who were mainly using long-acting methylphenidate, were less likely to discontinue.

Explanation of these findings

First of all, it is important to emphasize that adherence in children is, unlike adolescents and adults, not only based on child determinants but also on parental factors. Parents play an important role in the medication adherence of children as they usually depend on them. We found that children whose mother gave birth to more than one child, were less likely to be adherent. As these children are mostly reliant on their parents, it is possible that mothers who have more than one child may find it difficult to make sure that their child follows the prescribed treatment regimen due to an overload of responsibilities and tasks (as they have to take care of more than one child) [145]. Furthermore, we found that children from families with an average household income were more likely to have a good adherence than those from families with a higher household income. Whether this is due to a higher household income where both parents are working and therefore have less time to monitor medication use in children, could not be studied. Further research is needed to investigate this observation. It is also possible that mothers with a higher household income are more ambivalent towards this type of pharmacotherapy [146].

Second, we found that after the 2.7 years, the persistence was higher in children with a good adherence compared to the lower ones. Children may stop using their medication due to adverse effects (e.g. problems with sleep or loss of appetite) or contra-indications and only take it when needed, resulting in discontinuity of treatment and thus a lower adherence [147]. They may also stop taking methylphenidate if they feel that the treatment does not work. Children who do not take their medication as prescribed (non-adherence) may eventually discontinue treatment as shown previously [137].

However, the question of whether patients are non-persistent or non-adherent may also be influenced by the fact that children are advised to have a medication-break (of one to two weeks) at least once a year. The Dutch Guidelines for General Practitioners describes that these breaks should be initiated to determine whether or not the pharmacological treatment should be continued, preferably during a representative period. However, in some cases it may only be possible to have these breaks during vacations and weekends [8].

Third, the results of our study show that girls were more likely to be non-persistent than boys, which was previously reported [138]. One of the possible reasons is that the effectiveness of methylphenidate is easier to measure in boys in terms of symptoms improvement than girls, because boys more often show hyperactivity while girls more often have concentration

problems. When these symptoms improve, parents will probably encourage their children to take their medication according to prescribed treatment regimen [10, 113]. It is important to conduct further research to investigate the differences in non-persistence to methylphenidate treatment among boys and girls.

Finally, we found that children who started methylphenidate treatment at an older age were more likely to be non-persistent than those who started at a young age. This is in line with a previously published study where a younger age (0-8 years vs 10-19 years) was associated with greater persistence [138]. A possible explanation is that they may have used methylphenidate (often short-term) for other reasons than treating ADHD symptoms, such as increasing school performance and are therefore less persistent [148]. However, the number of prescriptions of short-acting stimulants in the young and older children was not significantly different. Another possible reason is that methylphenidate was prescribed for other indications such as oppositional defiant disorder (ODD), where methylphenidate may be less effective.

When considering long- and short-acting methylphenidate, our finding shows a greater persistence in children who mainly received long-acting methylphenidate, which is in line with a previous study [149]. Also, children who switched medication multiple times from long-acting to short-acting and vice versa, were more likely to be adherent than those who did not switch at all. It may be possible that they switch based on the severity of the disorder, but also the symptom improvement and adverse events may have played a role. This group may be more willing to try and find the best possible treatment and therefore are more likely to be adherent to treatment [150].

Strengths and limitations

One of the strengths of this study is the population-based cohort of young children with up to 16 years of follow-up and the multi-ethnic nature of this population. This long follow-up duration enabled us to investigate potential factors associated with adherence at 2 years (rather than 6 months as in previous studies)[135, 136]. Pediatric patients who started with methylphenidate may stop and restart again. Therefore, it is important to examine adherence at least 1 year after treatment initiation. Also, extensive information about the children and parents was collected prospectively since birth, which made it possible to assess numerous factors that are associated with a good treatment adherence. Furthermore, adherence and persistence were calculated based on dispensing records which is more accurate in terms of dispensation dates than information on prescription records as these medications may have been prescribed but not collected from pharmacies.

However, our study also has several limitations. We did not have information on clinical diagnoses and relied on maternal reported questionnaire data on emotional or behavioral problems in the child. Furthermore, we did not have information about other treatment such as behavioral therapy, which may have also influenced the persistence and adherence to methylphenidate. Also, the number of children in the older age groups is lower as for most children

in our study, they were followed until the age of 16 years. Therefore, the follow-up after treatment initiation in the older children was shorter. However, persistence was only calculated in children when at least 7 months of follow-up was available after starting treatment to ensure a gap-period of 6 months (which is needed to measure non-persistence). Finally, we did not have sufficient power to assess the association between several determinants, such as child ethnicity and marital status with adherence as the numbers were too low. Further research in a larger population is needed to assess if and how ethnicity or marital status would affect adherence to methylphenidate in children.

Conclusion

In conclusion, the results of our study showed that both child and family characteristics may play a role in treatment adherence. Furthermore, child sex and start of treatment was found to be associated with persistence. Considering these findings, it is important for healthcare professionals to take these into account when initiating methylphenidate treatment.

4.3 Methylphenidate initiated during childhood is continued in adulthood in half of the study population

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ABSTRACT

Background and objectives: Until the beginning of 2018, methylphenidate was only approved in the Netherlands for children between 6 and 18 years old, because of the cardiovascular risk in adults. Despite the fact that it was not approved for use in adults, there was a considerable degree of off-label use in this group. Therefore, the objective of this study was to estimate the number of patients who started methylphenidate during childhood and continued treatment beyond the age of 18 years and to study the determinants that may be associated with continuing treatment.

Methods: Patients aged 17 years and younger who have received at least one prescription of methylphenidate were identified in the Integrated Primary Care Information (IPCI) database (1996-2017). Logistic regression analyses were performed to assess the association between potential determinants and continuation with methylphenidate treatment at the age of 18 years.

Results: Fifty-three percent of all methylphenidate users (n=1,020) continued their treatment after the age of 18 years. Patients were more likely to continue treatment with methylphenidate if they started treatment at the age of 15 to 17 years compared to patients of 11 years and younger (adjusted OR: 5.74, 95%CI: 1.48-22.31), if they had a medication possession ratio (MPR) between 0.80 and 1.00 compared to a low MPR (adjusted OR: 2.18, 95%CI: 1.23-3.85) and if they lived in an area with a medium level of urbanization (adjusted OR: 1.98, 95%CI: 1.06-3.69). Furthermore, a relatively high number of patients had a MPR greater than 1.0 (MPR > 1.0: 24.8%,) of whom 91.3% started their treatment when they were between 15 and 17 years old.

Conclusion: Methylphenidate treatment initiated during childhood was continued in half of the study population when reaching the age of 18 where adolescents were more likely to continue treatment than young children. We also found that ~25% of our study population had a MPR greater than one, which may suggest misuse or abuse of methylphenidate.

INTRODUCTION

One of the most common neurobehavioral disorders is attention-deficit/hyperactivity disorder (ADD/ADHD), affecting approximately 5% of children worldwide and persisting into adulthood in the majority of the patients[3]. Stimulant medication such as methylphenidate is mostly prescribed as treatment for ADHD and the use of these drugs has increased over the past years[151]. Until the beginning of the year 2018, methylphenidate was only approved in the Netherlands for children between 6 and 18 years old because of the cardiovascular risk in adults[4]. This is also one of the most important reasons that this drug was not approved for use in adults as previous studies have shown that they may increase heart rate and blood pressure and subsequently may lead to a slightly increased risk of myocardial infarction, sudden cardiac death, and stroke [5]. Despite the fact that it was not approved for use in adults, there was a considerable degree of off-label use in this group[21, 152]. Patients who have started ADHD drugs during childhood often continue treatment during adulthood, especially if they still suffer from symptoms and when the drug remains effective[137]. Previous studies have shown that approximately 60% of children with ADHD demonstrated persistence of symptoms into their mid-20's [153, 154]. In 2015, there were more than 57,000 patients aged 25 and older who were using methylphenidate in the Netherlands [155]. A previous small study by McCarthy et al showed that almost half of the study population in UK (n=610) who started treatment in childhood were still on treatment at the age of 18 years or older[156]. They also found that the probability of persistence was lower in females than in males when methylphenidate was initiated at a younger age, but the opposite was observed when treatment was started in adolescence. However, the numbers in this study were low and it is not clear if there are also other determinants that might be associated with persistence.

Because of the cardiovascular risks in adulthood, it is important to investigate the determinants of off-label use. Therefore, the objective of this study was to estimate the number of patients who started methylphenidate during childhood and adolescence and continued treatment beyond the age of 18 in the Netherlands in the period before it was approved for use in adults. In addition, we studied the determinants of continuing treatment with methylphenidate at the age of 18 years.

METHODS

Setting

Data were obtained from the Integrated Primary Care Information (IPCI) database, a longitudinal observational dynamic database containing medical records from more than 450 general practitioners (GPs) throughout the Netherlands. The study population is representative of the Dutch population and contains medical records of approximately 2,500,000 patients, including

longitudinal data on demographics, symptoms and diagnosis based on ICPC codes (International Classification of Primary Care) and free text, referrals, laboratory findings, discharge letters and drug prescriptions. All general practices in IPCI are fully automated and prescriptions contain details on product name, daily dosage, Anatomical Therapeutical Chemical (ATC)-code [19], and duration of use. Details of the database have also been published elsewhere[20, 157].

Study population

The study population consisted of all patients with active follow-up during the study period between 1 January 1996 until 1 January 2017 having at least one year of medical records available and a prescription for methylphenidate during the study period. Patients were only included if they started methylphenidate before the age of 18 years and if they reached the age of 19 years (to guarantee at least 1 year of follow-up during adulthood) before the end date of the study. The flowchart for children and adolescents included in the study is shown in figure 1. All patients were followed from study entry until the end date of the study.

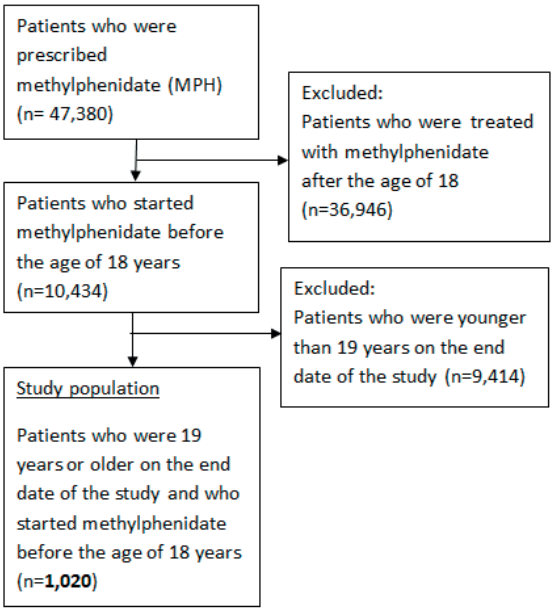

Figure 1 *Selection process of the study population*

Case definition

In this nested case-control analysis in a cohort of methylphenidate users, cases were defined as users of methylphenidate who continued use beyond the age of 18 years while controls were users who had used methylphenidate during childhood or adolescence but discontinued treatment before the age of 18 years.

Covariates

For each patient, we retrieved information from the IPCI database on covariates such as sex and age of first prescription of methylphenidate, the duration of use which was calculated from the start date of methylphenidate treatment until the end date of treatment or age of 18 years (whichever came first), the number of different types of ADHD drugs that were prescribed (such as dexamphetamine and modafinil) and the use of other psychotropic drugs before the age of 18. Furthermore, we also included the presence of any potential contraindications for use of methylphenidate namely the presence of cardiovascular and cerebrovascular disease (CVA, heart failure, myocardial infarction) and psychiatric disorders, such as alcohol and drug abuse, somatization disorder, psychotic symptoms, depression, anorexia nervosa, compulsory disorder, anxiety or suicide attempt. This comorbidity was assessed via disease specific ICPC code searches. We also considered medication adherence as a potential determinant which was measured by the medication possession ratio (MPR). The MPR was calculated by dividing the sum of the day's supply of methylphenidate during the study period by the difference between the first and end date of the last. According to international literature, a good adherence is set at a MPR of 0.80 or higher [129, 140]. The MPR was only calculated if patients received at least 2 prescriptions of methylphenidate. Finally, we considered demographic information such as the living area: socially deprived area and the urbanization level as potential determinants.

Analysis

Within the study population, we conducted a case-control analysis. As potential determinants, we included sex, age of first prescription (<12 years, 12-14 years and 15-17 years), MPR, number of different types of ADHD drugs before reaching the age of 18 years, use of other psychotropic drugs before the age of 18 and the presence of any potential contraindications in the database before starting treatment with methylphenidate. We also included demographic information where we also considered the living area as potential determinants: socially deprived area (yes/no) and urbanization level (very high: >2,500 addresses per km2, high: 1,500-2,500 addresses per km2, medium: 1,000-1,500 addresses per km2, low: 500-1,000adresses per km2 and not urban/rural: <500 addresses per km2). For the main analyses, we calculated the odds ratio (OR), with 95% confidence interval (CI) for each determinant associated with continuation of methylphenidate at the age of 18 years. We evaluated the potential determinants of continuation of methylphenidate at the age of 18 years through univariable logistic regression analysis. In addition, a multivariable logistic regression analysis was performed including all univariably associated determinants. For those patients who continued treatment at the age of 18 years, we also determined the age when they will stop using methylphenidate. Results were considered statistically significant at $P< 0.05$. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY).

RESULTS

In total, 47,380 patients were prescribed methylphenidate during the study period where 78% of these patients were older than 18 years (prevalent users or patients starting methylphenidate beyond the age of 18). This group was excluded together with those who were younger than 19 years on the end date of the study (younger than 19 years, n=9,414). Overall, we identified 1,020 patients who were prescribed methylphenidate before the age of 18 years of whom there were more males than females (males: 64.8% and females: 35.2%) (table 1). The majority of the study population received their first methylphenidate prescription when they were between 15 and 17 years (86.9%). The majority of patients have been using methylphenidate for less than 6 months (55.5%), received one type of ADHD drug (90.9%), did not use any other psychotropic drugs before the age of 18 (87.3%) and did not have a contraindication before the start of treatment with methylphenidate (82.2%). Furthermore, the majority of patients lived in areas with a medium to high level of urbanization (very high: 12.2%, high: 24.6%, medium: 18.4%, low: 7.4%, not urban/rural: 4.3%) and in a non-socially deprived area (yes: 5.5%, no: 89.3%). We also observed that a relatively high number of patients had a MPR greater than 1.0 (24.8%) compared to the number of patients with a MPR of 1.0 and lower (<0.50: 21.3%, 0.50-0.79:21.2% and 0.80-1.00:13.9%). Of the patients with a MPR above 1 (n=253), the majority had a MPR between 1.01 and 2.00 (n=209) and a small part had a MPR greater than 2 (n=44). When stratified for age, we observed that 91.3% of these patients with a MPR above 1 started their treatment when they were between 15 and 17 years old.

In the multivariable analyses, we found that patients who started treatment at the age of 15 to 17 years were more likely to continue treatment with methylphenidate at the age of 18 years (adjusted OR: 5.74, 95%CI: 1.48-22.31) (Table 2). People with a MPR between 0.80 and

Table 1 *Characteristics of patients who attained the age of 18 years and were prescribed methylphenidate (n=1,020)*

Characteristic	Patients (n=1,020)
Sex	
Male	661 (64.8)
Female	359 (35.2)
Age[a]	
<12 years	13 (1.3)
12-14 years	121 (11.9)
>14-17 years	886 (86.9)
Duration of use	
<6 months	566 (55.5)
6-24 months	336 (32.9)
>2 years	118 (11.6)

Table 1 *Characteristics of patients who attained the age of 18 years and were prescribed methylphenidate (n=1,020)* (*continued*)

Characteristic	Patients (n=1,020)
MPR[b]	
<0.50	217 (21.3)
0.50-0.79	216 (21.2)
0.80-1.00	142 (13.9)
>1.00	253 (24.8)
Number of different ADHD drugs[c]	
1	927 (90.9)
2 or more	93 (9.1)
Use of other psychotropic drugs before age 18	
No	890 (87.3)
Yes	130 (12.7)
Potential contraindication before start ADHD drug	
No contraindication	838 (82.2)
Cardiovascular diseases	25 (2.5)
Psychiatric disorders[d]	157 (15.4)
Urbanisation level	
Very high	124 (12.2)
High	251 (24.6)
Medium	188 (18.4)
Low	75 (7.4)
Not urban/ rural	44 (4.3)
Missing	338 (33.1)
Socially deprived area	
No	911 (89.3)
Yes	56 (5.5)
Missing	53 (5.2)

All numbers are given in numbers (%), unless stated otherwise. [a]Age of first prescription of methylphenidate. [b]MPR was only calculated for patients who received at least 2 prescriptions (n=828). [c]The number of different ADHD drugs is based on the ATC7 codes. [d]Psychiatric disorders include alcohol and drug abuse, somatization disorder, psychotic symptoms, depression, anorexia nervosa, compulsory disorder, anxiety or suicide attempt. Abbreviation: MPR: medication possession ratio, n:number

1.00 were also more likely to continue treatment compared to those with a MPR below 0.50 (adjusted OR: 2.18, 95%CI: 1.23-3.85). We also found that patients living in a medium level of urbanization were also more likely to continue use of methylphenidate beyond the age of 18 years (adjusted OR: 1.98, 95%CI: 1.06-3.69). Patients who continued treatment beyond the age of 18 (n=542) received their last prescription for methylphenidate before the age of 21 (36.3%) and a small group stopped using methylphenidate when reaching the age of 25 (2.2%). For the majority of patients who continued treatment, it is not known at what age they received their

Table 2 *Determinants that are associated with continued use of methylphenidate at the age of 18 years (n=4,050)*

Characteristic	Stopped	Continued	Univariable analysis	Multivariable analysis
	N (%) (n=478)	**N (%) (n=542)**	**OR (95% CI)**	**OR (95% CI)***
Sex				
Male	318 (66.5)	343 (63.3)	Ref	Ref
Female	160 (33.5)	199 (36.7)	1.15 (0.89-1.49)	1.39 (0.94-2.06)
Age[a]				
<12 years	10 (2.1)	3 (0.6)	Ref	Ref
12-14 years	74 (15.5)	47 (8.7)	2.12 (0.55-8.09)	2.43 (0.60-9.93)
15-17 years	394 (82.4)	492 (90.8)	4.16 (1.14-15.23)	5.74 (1.48-22.31)
MPR[b]				
<0.50	104 (29.1)	113 (24.0)	Ref	Ref
0.50-0.79	93 (26.1)	123 (26.1)	1.22 (0.83-1.78)	1.30 (0.80-2.09)
0.80-1.00	52 (14.6)	90 (19.1)	1.59 (1.03-2.46)	2.18 (1.23-3.85)
>1.00[b]	108 (30.3)	145 (30.8)	1.24 (0.86-1.78)	1.22 (0.75-1.97)
Number of different ADHD drugs[c]				
1	430 (90.0)	497 (91.7)	Ref	
2 or more	48 (10.0)	45 (8.3)	0.81 (0.53-1.24)	
Use of other psychotropic drugs before age 18				
No	417 (87.2)	473 (87.3)	Ref	
Yes	61 (12.8)	69 (12.7)	1.00 (0.69-1.44)	
Potential contraindication before start ADHD drugs				
No contraindication	396 (82.8)	442 (81.5)	Ref	
Cardiovascular diseases	11 (2.3)	14 (2.6)	1.14 (0.51-2.54)	
Psychiatric disorders[d]	71 (14.9)	86 (15.9)	1.09 (0.77-1.53)	
Urbanization level				
Very high	65 (13.6)	59 (10.9)	Ref	Ref
High	105 (22.0)	146 (26.9)	1.53 (0.99-2.36)	1.40 (0.79-2.49)
Medium	68 (14.2)	120 (22.1)	1.94 (1.23-3.08)	1.98 (1.06-3.69)
Low	36 (7.5)	39 (7.2)	1.19 (0.67-2.12)	0.98 (0.47-2.03)
Not urban/ rural	19 (4.0)	25 (4.6)	1.45 (0.73-2.90)	1.35 (0.56-3.24)
Socially deprived area				
No	409 (85.6)	502 (92.6)	Ref	Ref
Yes	34 (7.1)	22 (4.1)	0.53 (0.30-0.92)	0.76 (0.33-1.80)

*All numbers are given in numbers (%), unless stated otherwise. *Sex and variables with P<0.05 in the univariable analysis were included in the multivariable analysis. [a]Age of first prescription of an ADHD drug (N06BA). [b] The MPR was only calculated if patients received at least 2 prescriptions of methylphenidate (n=828). [c]The number of different ADHD drugs is based on the ATC7 codes. [d]Psychiatric disorders include alcohol and drug abuse, somatization disorder, psychotic symptoms, depression, anorexia nervosa, compulsory disorder, anxiety or suicide attempt. Abbreviation: CI: confidence interval, MPH: methylphenidate, MPR: medication possession ratio, n:number*

last prescription of methylphenidate as the follow-up ended at the age of 19 years (and we do not know if they received a methylphenidate prescription after that) (61.4%).

DISCUSSION

In this study, we found that a remarkably high percentage of patients older than 18 years were using methylphenidate. We also found that fifty-three percent of all methylphenidate users continued their treatment after the age of 18 years despite the fact that this was a relative contraindication as the drug was not licensed for use in adults during this study period. Previous studies have described concerns about cardiovascular safety in adult patients who are treated with methylphenidate [4, 158]. This drug was associated with an increased heart rate and blood pressure and previous studies have shown that even small increases in blood pressure and heart rate were associated with an increased risk of cardiovascular events [159-161] [162]. Furthermore, we observed that the majority of patients started treatment with methylphenidate at the age of 15 to 17 years and were more likely to continue their treatment at the age of 18. This observation could be explained by the small number of patients who initiated methylphenidate at a younger age. However, previous studies showed that the number of users in the Netherlands aged 16 years or older was increasing [163, 164]. It may appear that more severe, later onset youth were treated in our study. However, it is more likely that the first choice of long-acting stimulants in adults as opposed to the first choice of short-acting treatment in children may explain these findings as the long-acting stimulants are associated with increased adherence [165]. Despite the results where methylphenidate is more likely to be continued at 15 to 17 years of age, we also observed that the majority of patients who continued treatment at the age of 18 (within the study period), stopped using methylphenidate when reaching the age of 21 and the remaining group stopped before the age of 25. Similar findings were observed in a previous study, where they stopped treatment by age 21[166]. Patients may stop treatment when they experience less ADHD symptoms when reaching this age or because it was the patient's decision to discontinue medication (dislike of taking medications or the feeling of being able to cope without pharmacological treatment) [137, 167, 168].

Methylphenidate treatment is mostly initiated during childhood and some patients continue to use it in adulthood as they may still suffer from ADHD symptoms [169]. In our study, we observed that methylphenidate was continued in 53% of all methylphenidate users which is higher than the number found in the study by McCarthy et al. (~40%) [156]. This may be explained by the differences in drug prescribing between both countries as the results of the study by McCarthy et al. also described higher estimates of ADHD drug prescribing in the Netherlands than UK. In this study they also found that the probability of persistence in females was lower compared to males when starting treatment at a younger age, however the opposite was observed in patients who started their treatment in adolescence [156]. In our study, relatively

more women were included compared to the previous study, but we did not find a significant association with continued use for the different age groups and gender.

The results of our study also showed that more than half of the patients stopped treatment within 6 months which is also the moment that patients have to see their physicians as part of the regular monitoring process (cardiovascular status or worsening of psychotic symptoms) for those who started treatment with methylphenidate [8]. At that moment, patients may stop their treatment due the adverse events or because the drug was ineffective [170] [171]. Another possibility is that they may be misdiagnosed as having ADHD. Even though it is a condition that has been studied extensively, the causes of ADHD remain poorly understood, which makes it difficult to make a correct ADHD diagnosis [172].

It is not clear if the cardiovascular risks of these drugs are considered when deciding to stop or continue treatment with methylphenidate. We only found a small number of patients with cardiovascular disease in their medical history, but no significant associations were found.

In our study, we observed a relatively high number of patients with a MPR greater than 1.0, especially in patients aged 15 to 17 years. A MPR above 1.0 may indicate that patients are taking more than the prescribed dose, but it may also indicate stock piling due to early refills or vacation supplies[173]. However, it is also important to emphasize the possibility that methylphenidate was used for other reasons than for the treatment of ADHD [174]. A previous study has shown that the potential for abuse or misuse has increased along with the increase in prescribing frequency of methylphenidate [175]. Reasons for misuse of ADHD medication that were frequently reported are to improve attention, concentration and alertness, to improve academic performances and they are misused recreationally [174, 175]. This may also be one of the explanations of the short-term use of methylphenidate in this age group as described earlier which may be related to the need for treatment in alleviating difficulties in education instead of taking methylphenidate to treat ADHD related symptoms [176]. These findings were also observed in a previous study conducted in Sweden [177] . Furthermore, a previous study showed that misuse of short-acting methylphenidate is also more common than with the long-acting methylphenidate [178]. The fact that only the short-acting methylphenidate is fully reimbursed in the Netherlands may have also influenced this. These data suggest close monitoring of methylphenidate use and dispensation of these drugs, in particular to patients aged 15 years and higher.

The main strength of our study is that we had access to a large real life population-based cohort with detailed information on drug prescriptions and co-morbidities over a long period of time. Furthermore, selection bias in our study is not likely as almost all inhabitants in the Netherlands are registered with one GP where data are collected as part of routine patient care, irrespective of a research question. However, our study also has several limitations. Firstly, there was no information available on dispensing by the pharmacy nor on actual drug intake. Secondly, we do not have (complete) information about the severity of the disease and therefore we may have included the less severe cases of depression or other disorders where the use

of methylphenidate is contraindicated. Furthermore, the database may miss the prescriptions that are directly written by medical specialists. This database mainly contains GP prescriptions and also prescriptions that are initiated by the specialist and continued by the GP, but it is possible that not all prescriptions by medical specialists are captured in the database. However, in the Netherlands it is common practice for GPs to continue prescriptions when initiated by medical specialists, especially if it concerns drugs for chronic use. There is also the potential of selection where especially older children are selected as the median active follow-up time in IPCI is relatively short (mean: 6.8 years, SD: 2.0 years) as our study only selected children who were followed until at least the age of 19 years. Previously published articles showed that the number of methylphenidate dispensations among people of 15 years and older have increased in the Netherlands and in other European countries (UK, Denmark and Germany) [6, 179, 180]. Furthermore, the lack of objective measures of ADHD and the changes over time may have influenced the findings as we did observe a higher percentage of patients continuing treatment beyond the age of 18 years in the period 2012-2016 compared to the previous 5 years. This can be explained by the increased ADHD recognition and treatment and the change in different prescribing patterns among different age groups and gender [180, 181]. Because these changes also occurred in other western countries, we think that our results can be generalized to many of these countries. ADHD diagnosis and treatment with medication may be more accepted in the future by the general population as the attitude of parents and children towards ADHD has also changed. Treatment with medication can be considered by parents as a way to improve their child's achievements and performance at school. Also the children themselves may feel the need to use psychostimulants to improve their performance at school [182]. Furthermore, it is possible that treatment in girls may also increase in the future as ADHD diagnosis in this gender group may improve over time [10].

Conclusion

About half of the patients who were prescribed methylphenidate during childhood and adolescence continued their treatment in adulthood which was considered as off-label use until recently. The majority of this population started their treatment in adolescence, which may explain the reason for continuing treatment at the age of 18 years. We also found that ~25% of our study population had a MPR greater than one, which may suggest misuse or abuse of methylphenidate.

5 Antidepressant use

5.1 Antidepressant use and the risk of suicide: a population-based cohort study

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ABSTRACT

Background and objectives: The existing literature provides contradictory evidence on antidepressant use and risk of suicide. Some studies have shown that the use of Selective Serotonin Reuptake Inhibitors (SSRIs) is associated with an increased risk of suicide, especially during the first months of treatment, whereas other studies did not confirm this association. For this reason, our objective was to investigate the association between antidepressant use and risk of suicide in incident antidepressant users in relation to time since starting therapy.

Methods: We conducted a population-based cohort study within the Dutch Integrated Primary Care Information (IPCI) database, in incident users of antidepressant therapy between 1994 and 2012 (n=27,712). Cox proportional hazard models were used to study the association between current use of SSRIs, tricyclic antidepressants (TCA) and other antidepressants and risk of suicide or attempted suicide.

Results: During follow-up, a total of 280 incident antidepressant users attempted or committed suicide. Current use of SSRIs (hazard ratio (HR): 0.78, 95% CI: 0.57-1.07), TCAs (HR: 0.82, 95% CI: 0.48-1.42) or other antidepressants (HR: 0.75, 95% CI: 0.47-1.18) was not statistically significantly associated with suicide compared to past use of any of the antidepressants.

Conclusions: This study did not indicate an increase in risk of suicide after starting treatment with SSRIs, TCAs or other antidepressants compared with past antidepressant use.

INTRODUCTION

Suicide accounts for almost one million deaths worldwide each year and is therefore a major problem in many countries [183]. Depression is the most important risk factor [184]. From the various treatments that are available to treat depression, Selective Serotonin Reuptake Inhibitors (SSRIs) are prescribed most frequently [185]. This preference to prescribe SSRIs, compared to tricyclic antidepressants (TCAs), is due to their milder adverse effect and toxicity profile [186]. Compared to non-use as well as compared to TCAs and other antidepressants, SSRIs were associated with an increased risk of suicidal behaviour, especially in children and adolescents [187-189]. The risk seems to be increased especially during the first month of therapy [188, 190]. As a causal pathway, it is hypothesized that SSRIs may cause agitation and subsequently potential ill-considered behaviour, before their beneficial effect relieves depression [191]. However, others could not confirm the increased risk of suicide during use of SSRIs [192-194]. It therefore remains controversial whether SSRI use is associated with suicidal behaviour. For studies comparing SSRIs and TCAs, findings might be influenced by confounding by indication, as indications for prescribing TCAs and SSRIs are different [195, 196].

Because of the lack of consistency between studies and the limitations of some of these, our objective was to investigate the association between incident use of antidepressants and the risk of suicide or suicide attempts in a large population-based study with prospectively gathered healthcare information, under the hypothesis that the risk of suicide would be higher during the first weeks of treatment with SSRIs, TCAs or other antidepressants.

METHODS

Setting

Data from the Integrated Primary Care Information (IPCI) database were used. The IPCI database contains computer-based patient records of more than 600 Dutch General Practitioners (GPs). In the Dutch healthcare system, the GP acts as the gatekeeper of all individual healthcare information and all inhabitants are registered with a GP. The IPCI database currently contains patient information of 1.5 million subjects, including age, sex, date of birth, symptoms, diagnoses, laboratory results, summaries of specialist letters and drug prescription data. Drug prescription data, included product name, quantity prescribed and dosage regimen. The International Classification of Primary Care (ICPC) coding system is used to code diagnoses [20, 157, 197]. We used the Anatomical Therapeutic Chemical (ATC) classification scheme to classify drugs that were prescribed to patients. The IPCI database follows the European Union guidelines on the use of medical data for medical research and has been validated to be used for pharmacoepidemiological research. The scientific and ethical advisory board of the IPCI project approved the study design and use of the data (project number: 07/49).

Study population

The study population comprised all patients with an incident antidepressant prescription between 1994 and 2012 who had ≥1 year of data registered in the database before entering the study. Patients were followed from the date of first antidepressant drug prescription (baseline) until their first attempted suicide, completed suicide or end of the study period on 1 February 2012 whichever came first. We excluded patients under the age of 10, patients with a recorded diagnosis of a psychotic disorder (ICPC code P71) and patients who had multiple different antidepressant drug classes dispensed on the same day. Patients who received an antidepressant prescription 6 weeks prior to the end of the study period were excluded, to ascertain that everybody had at least 6 weeks of follow-up.

Outcome measures

The study outcomes were defined as a notification of either a completed suicide or as an attempted suicide, either coded as P77 (ICPC code 'suicide') or p77.01 (ICPC code 'suicide attempt'), or as similar free text through automated text search. All cases identified with the automated text search were validated manually using the electronic medical records. The first date of suicide or suicide attempt served as the index date.

Exposure definition

The exposure of interest was antidepressant drug use. We categorized these drugs into three classes based on ATC code (4th level): TCAs (N06AA), SSRIs (N06AB) and other antidepressants (N06AG, N06AF and N06AX). Throughout the follow-up time, each individual could provide person-time to one or more periods of current or past exposure over the course of the study period. Patients were classified as currently or previously exposed to an antidepressant, based on the exposure status on the index date. If the date of event fell between the start date and end date of an antidepressant prescription, these patients were considered as current users. If the index date was after the last date of prior antidepressant use, the patient was considered a past user.

Co-variables

Several co-variables were considered as potentially confounding factors: year of first antidepressant prescription, indication for antidepressant use (at date of first antidepressant prescription and at index date), age, sex, history of previous suicide attempts, history of self-harm (both within 1 year prior to the date of first antidepressant prescription), psychotropic drug use at index date (antipsychotics: ATC-code N05A, anxiolytics: N05B, hypnotics and sedatives: N05C) and sequential use of different antidepressants (switching). The latter was considered as a potential risk factor, as some patients may be resistant to antidepressant medications possibly indicating a more severe depression. The indication for antidepressant drug use was identified through the diagnoses in the medical records and includes the following indications:

depression (ICPC code P76 and P03), anxiety (P01 and P74) and depression and anxiety combined. We used the ICPC codes and corresponding free text to identify patients with depression using an automated text search. When the indication was not grouped in the above mentioned categories, the indication was stated as 'other indication'. A subsample was validated manually to determine whether the automated text search correctly identified 'depression' and 'anxiety' as the indications for antidepressant use.

Statistical analyses

A Cox proportional hazards model was used to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs) for the associations between the use of different antidepressants and suicide or suicide attempt [110]. Use of antidepressants was included in the model as a time-varying determinant. Co-variables were included in the multivariable model if they changed the point estimate of the association between antidepressant use and suicide > 10 percent or were considered clinically relevant. Sub-analyses were performed to investigate whether the risk varied in relation to time since starting therapy (1-14 days, 15-28 days and >28 days). To evaluate potential confounding by indication, we investigated current antidepressant use in depressed patients and current use for other (unknown) indications separately. Dose response analyses were performed to assess whether the risk varied between high and low dose of antidepressant use. A low dose was defined as the median dose or less and a dose higher than the median dose was defined as a high dose. Analyses with regard to the duration of past use were performed to assess whether this influenced the risk of suicide in our population. In the analyses, we took less than 1 year and more than 1 year past use as separate reference groups. In another sub-analysis potential effect modification by age and sex was tested, stratified analyses were presented accordingly. All analyses were performed using SPSS version 21.0 (IBM Corporation, Armonk, NY). P-values below 0.05 were considered statistically significant.

RESULTS

Baseline characteristics

Table 1 describes the baseline characteristics of the study population. A total of 27,712 patients were identified as having received an antidepressant drug prescription, of whom the majority were women (61.2%). SSRI users tended to be younger (median: 44 years, IQR: 42.0 – 70.0) than those prescribed TCAs (median: 55 years, IQR: 28) and SSRI users comprised the largest group of patients for whom a diagnosis of depression was registered (37.6%) compared to TCAs (7.3%) and other antidepressant types (19.4%).

Antidepressant use

Table 1 *Characteristics of study population at baseline according to first antidepressant type prescribed*

Characteristic	All anti-depressants (n= 27,712), N (%)	TCAs (n=7,732), N (%)	SSRIs (n=12,686), N (%)	Other anti-depressants (n=7,294), N (%)
Age, years				
10-24	2,169 (7.8)	399 (5.2)	1,305 (10.3)	465 (6.4)
25-40	7,388 (26.7)	1,364 (17.6)	4,082 (32.2)	1,942 (26.6)
41-55	8,442 (30.5)	2,179 (28.2)	3,721 (29.3)	2,542 (34.9)
56-70	5,187 (18.7)	1,953 (25.3)	1,820 (14.3)	1,414 (19.4)
>70	4,526 (16.3)	1,837 (23.8)	1,758 (13.9)	931 (12.8)
Mean age (SD)	49.6 (17.9)	55.3 (18.3)	46.7 (18.5)	49.1 (16.9)
Sex, female	16,970 (61.2)	4,916 (63.5)	8,001 (63.1)	4,053 (55.6)
Indication of use				
Depression	6,752 (24.4)	564 (7.3)	4,774 (37.6)	1,414 (19.4)
Anxiety	1,103 (4.0)	191 (2.5)	655 (5.2)	257 (3.5)
Depression and anxiety	706 (2.5)	54 (0.7)	511 (4.0)	141 (1.9)
Other (unknown) indication	19,151 (69.1)	6,923 (89.5)	6,746 (53.2)	5,482 (75.2)
History of self-harm [a]	257 (0.9)	24 (0.3)	173 (1.4)	60 (0.8)
Use of psychotropic drugs				
Antipsychotics	484 (1.7)	83 (1.1)	264 (2.1)	137 (1.9)
Anxiolytics	2069 (7.5)	381 (4.9)	1190 (9.4)	498 (6.8)
Hypnotics and sedatives	1523 (5.5)	388 (5.0)	733 (5.8)	402 (5.5)

Values are given in numbers (percentages) unless stated otherwise. [a] Referred to as self-injury or previous suicide attempts, prior to date of first antidepressant prescription. Abbreviations: n; number of antidepressant users, TCAs; tricyclic antidepressants, SSRIs; Selective Serotonin Reuptake Inhibitors

Associations between known risk factors and suicide

In the total population with 280 cases, we found that a history of self-harm (HR: 6.94, 95% CI: 4.53-10.64) and psychotropic drug use (HR antipsychotics: 6.42, 95% CI: 4.19-9.85, HR anxiolytics: 5.07, 95% CI: 3.78-6.79, HR hypnotics and sedatives: 4.33, 95% CI: 3.05-6.15) were the strongest factors associated with the risk of a suicide (attempt) (table 2). Age, in particular between age 10 to 24 years (HR: 6.41, 95% CI: 3.76-11.06), was also found to be strongly associated with the risk of a suicide attempt. Other factors that were significantly associated with suicide were different antidepressant prescriptions (switching antidepressants) (HR: 2.38, 95% CI: 1.69-3.34) and depression (HR: 2.53, 95% CI: 1.82-3.50). A higher risk was observed for patients diagnosed with both depression and anxiety at the same time (HR: 4.40, 95% CI: 1.92-10.1).

Table 2 *Hazard ratios of potential risk factors for suicide and suicide attempt*

Variable	Cases, N	HR (95% CI) [c]	P
Age, years			
10-24	50	6.41 (3.76-11.06)	<0.001
25-40	90	2.87 (1.73-4.76)	<0.001
41-55	107	2.68 (1.62-4.41)	<0.001
56-70	38	1.58 (0.90-2.76)	0.11
>70	18	1 (ref)	
Sex, female[b]	182	0.92 (0.73-1.16)	0.47
Indication for antidepressant			
Depression	54	2.53 (1.82-3.50)	<0.001
Anxiety	7	1.66 (0.78-3.56)	0.19
Depression and anxiety	6	4.40 (1.92-10.06)	<0.001
Unknown/other indication	236	1 (ref)	
History of self-harm [a,b]	23	6.94 (4.53-10.64)	<0.001
Concurrent use psychotropic drugs [b]			
Antipsychotics	23	6.42 (4.19-9.85)	<0.001
Anxiolytics	59	5.07 (3.78-6.79)	<0.001
Hypnotics and sedatives	38	4.33 (3.05-6.15)	<0.001
No. of antidepressant types prescribed during follow-up			
1	253	1 (ref)	
>1	50	2.38 (1.69-3.34)	<0.001

[a] Referred to as self-injury or previous suicide attempts, prior to date of first antidepressant prescription. [b] Reference group: male, no history of self-harm and non-use for psycholeptics. [c] Adjusted for age and sex. Age was adjusted for gender and gender was adjusted for age only. Abbreviations: HR; Hazard rate ratio, CI; confidence interval, n; number of cases with completed suicide or suicide attempt, P; p-value

Association between antidepressant treatment and suicide (attempt)

Table 3 shows the association between current antidepressant use and suicide (attempt). We observed no significant associations with suicide in patients who were prescribed SSRIs (HR: 0.78, 95% CI: 0.57-1.07), TCAs (HR: 0.82, 95% CI: 0.48-1.42) or other antidepressants (HR: 0.75, 95% CI: 0.47-1.18), compared to past use, after adjustment for the known risk factors (age, sex, indication of use, antipsychotic use, anxiolytic use and number of different antidepressants prescribed). We also found no evidence of a higher suicide risk in patients prescribed TCAs currently (HR: 0.89, 95% CI: 0.26-3.06), SSRIs (HR: 0.56, 95% CI: 0.31-1.09) or other antidepressants (HR: 0.54, 95% CI: 0.20-1.45) when restricted to the indication of depression. When stratified by age or gender, no significant differences for the different strata was observed (results not shown). Patients treated with TCAs receiving a high dose compared to low dose were at a higher risk of suicide (HR: 3.52, 95% CI: 1.04-11.93, p-value: 0.043). In patients treated with

SSRIs, no significant differences were observed between high and low dose (HR: 1.44, 95% CI: 0.61-3.39, p-value: 0.409). We did not observe differences in suicide risk between the analyses where we took a reference group of less than 1 year and more than 1 year past use (results not shown).

Table 3 *Risk of suicide in patients prescribed SSRIs, TCAs and other antidepressants*

	Total population			Depression only		
Exposure	**Cases, N**	**Adjusted HR (95% CI)[b]**	**Adjusted HR (95% CI)[c]**	**Cases, N**	**Adjusted HR (95% CI)[b]**	**Adjusted HR (95% CI)[d]**
Past use [a]	202	1 (ref)	1 (ref)	27	1 (ref)	1 (ref)
Current use of TCAs	15	1.01 (0.58-1.76)	0.82 (0.48-1.42)	3	1.07 (0.32-3.59)	0.89 (0.26-3.06)
Current use of SSRIs	63	1.19 (0.88-1.62)	0.78 (0.57-1.07)	19	0.63 (0.34-1.19)	0.56 (0.31-1.09)
Current use of other antidepressants	23	1.18 (0.75-1.85)	0.75 (0.47-1.18)	5	0.61 (0.23-1.63)	0.54 (0.20-1.45)

Suicide risk by indication. [a] Includes use of all antidepressant types. [b] Model 1: adjusted for age and sex. [c] Model 2: adjusted for sex, age, antipsychotic use at index date, anxiolytic use at index date, indication at index date and the number of different antidepressants prescribed during follow-up. [d] Adjusted for all the above mentioned risk factors except for the indication at index date. Abbreviations: HR; Hazard rate ratio, CI; confidence interval, n; number of cases with completed suicide or suicide attempt, P; p-value, TCAs; tricyclic antidepressants, SSRIs; Selective Serotonin Reuptake Inhibitors

Analyses by duration of antidepressant use

Figure 1 shows the association between SSRIs and suicide risk in relation to time since starting therapy. Although a higher risk was observed in patients who recently started therapy with SSRIs (HR 1-14 days, adjusted for age and sex: 1.44, 95% CI: 0.96-2.17), this did not reach

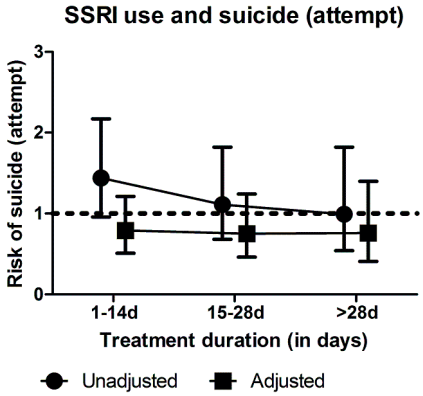

Figure 1 *SSRI treatment duration and risk on suicide (attempt)*
Current treatment with SSRIs compared to past use of all antidepressant types. Model 1: adjusted for age and sex. Model 2: adjusted for sex, age, antipsychotic use at index date, anxiolytic use at index date, indication at index date and the number of different antidepressants prescribed during follow-up. Abbreviations: SSRIs, Selective Serotonin Reuptake Inhibitors; d, days.

statistical significance. After adjustment for the other factors, we observed no increased risk in patients who recently started SSRIs (HR 1-14 days: 0.79, 95% CI: 0.51-1.21, HR 15-28 days: 0.75, 0.46-1.24 and HR >28 days: 0.76, 0.41-1.40). Similar results were observed for patients who were prescribed TCAs or other antidepressants, but with wider confidence intervals due to low numbers of cases (results not shown).

DISCUSSION

The objective of the current study was to assess the association between the use of different antidepressant drug classes and the risk of suicide or suicide attempt during the first weeks of treatment. The results of our study did not show an association between the different antidepressant drug classes and suicide (attempts) overall nor during the first weeks of treatment. In addition, we did not observe an increased risk in the initial treatment period nor did we find an increased risk when restricting analyses to specific indications. We also found no significant effect modification by age and gender. Previous studies yielded similar results [6, 21]. Patients receiving a high dose of TCAs compared to low dose were at a higher risk of suicide. A possible explanation is that these patients suffer from a more severe depression, which is associated with an increased risk of suicide [198]. Also, depressed patients use TCAs for self-poisoning or suicide [199].

In line with currently available literature, we found that classical risk factors, such as young age, depression, a history of self-harm, antipsychotic use (as a crude measure of a psychotic indication) and sequential use of different antidepressants were associated with a higher risk of suicide (attempts) [187, 191, 195, 200-202]. Previous researchers observed an increased risk of suicide with SSRI use in young individuals [187, 203, 204]. Although it might therefore be speculated that the risk of suicide in SSRI users is age dependent, age did not act as an effect modifier in our study, suggesting that risk was similar between low and high age. However, our study population consisted largely of patients aged 25 and over (92.2%), leaving only a limited number of patients aged 25 years or younger. In contrast to our results, another study observed an increased risk of suicide in patients with depression prescribed SSRIs, TCAs or other antidepressants compared with no current treatment [205]. A possible explanation for the lower risk of suicide is that 'no current treatment' may indicate no depression or less severe depression than being under treatment. Confounding by indication in the previous studies might underlie this difference in observation, as these studies did not adjust for the indication of treatment [195, 205].

Previously, an increased risk of suicidal behaviour during the first month of SSRI therapy compared with other antidepressants was found [195]. However, others could not confirm this, as the risk was found to be highest in the month before the initial prescription (because suicide attempt may prompt initiation of antidepressant treatment) and a decline in risk after initiation

of treatment [206]. In our study, estimates for the first weeks of use did not differ significantly from longer durations of use. Although it is likely that the duration of past use may influence the risk of suicide, this did not change the risk in our study population. We did not find an increased risk in current users compared with past users of less than one year nor did we find an increased risk in current users compared with past users of more than one year. Therefore we suggest that the risk is similar in both reference groups. A possible biological mechanism that might explain the phenomenon of increased suicidal risk in the first weeks after start of SSRIs may be the slow onset of drug action in patients with severe depression [207]. The serotonin levels may increase before the depression is relieved, presumably by down regulation of the postsynaptic receptor population [208]. Therefore, patients may transiently become extremely agitated and restless and commit suicide before the drug treatment starts to relieve depression [191, 207, 209]. Patients may also become more anxious following onset of SSRI treatment, which is also associated with an increased risk of suicide [210]. Our results did not support the findings of these previous studies [188, 190], as we did not find evidence or differences in risk of suicide in relation to time since starting therapy. A possible explanation for this finding is that the population used in this particular analysis, where we stratified by treatment duration, was not restricted to patients with depression only. The number of cases was too small to make precise estimates in this analysis.

Strengths and limitations of the study

An advantage of our study is the large number of GPs participating in the IPCI project, providing us with complete medical information of at least 1.5 million patients. In the Dutch healthcare system, the GP acts as the gatekeeper of all individual healthcare information. Consequently, there was information on drug use and potential confounders available. With this information we were able to assess the use of antidepressants and the potential confounders at different time points. A key advantage of this cohort design is that we were able to include all eligible incident antidepressant users, which minimizes the risk of selection bias. Also, in our opinion, the information bias is minimal as we used prescription records as the source of medication data [28, 211]. However, patients whose antidepressant treatment was initiated by a specialist (prior to cohort entry) may have been misclassified as the IPCI database largely consists of GP prescription data and it does not include information about whether prescribed medications are actually taken by the patient. However, we expect that the actual intake of antidepressant drugs will be non-differential between the different drug classes. We manually validated all potential suicide cases and grouped those who did not have a recorded suicide or suicide attempt in the control group and therefore minimizing the risk of misclassification of the outcome. Our study also has several limitations. Several studies have demonstrated that patients with a greater risk of suicide or self-harm (often with a recorded history of self-harm) are preferably prescribed SSRIs, since this antidepressant class is safer when taken in overdose than TCAs [196, 212]. As the number of history of self-harm cases in our study was low, it is likely that we were

not able to extract all cases of self-harm prior to start of therapy. Another observation is the relatively high number of patients with an indication for antidepressants other than depression or anxiety. We assumed that not all patients with depression were recognized as such, because we restricted only to synonyms for depression, and not for keywords of symptoms in the automated text search. We manually validated a subsample to determine whether the automated text search correctly identified 'depression' and 'anxiety' as the indication for antidepressant use. We found similar results for depression (47.3%) and anxiety (10.3%) as was found earlier [213]. It could be speculated that the change in the prescribing practices over the last 20 years may have affected our results. However, we believe that this is not an issue in our study as the majority of our study population received their first antidepressant prescription after 1 January 2000 (90.5%). We also included the year of first antidepressant prescription in the model as a confounding factor, but this did not change the risk of suicide (attempt). A recently published study showed that the number of cases of suicide and self-harm that was not reported in the UK health care database was relatively high, which may also be considered as a limitation in our study [214]. However, we expect that under-reporting of suicide attempts between different antidepressant drug classes will be non-differential.

Conclusion

In summary, we did not find evidence for an increased risk of suicide or suicidal attempts in the first weeks of treatment in patients who were treated with SSRIs, TCAs or other antidepressants in comparison to patients who have previously been treated with antidepressants.

6 General discussion

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Over the past years, we have been conducting observational research using different databases with data collected over the years. Such databases have become larger over the past decade thanks to the increasing computerization of healthcare, containing more detailed information about medication use and diseases in individuals and over longer periods of time. Many databases can nowadays be linked to each other to study specific associations between exposures and outcomes, such as the linkage between health registers containing data on persons with diseases or health-related events and pharmacy record databases. Of course, only when linking takes into account current legislation and individual privacy. These observational studies using big databases are becoming more and more important as they are able to answer questions which could not be answered by clinical trials due to the homogeneous population and small sample sizes in these trials. These observational studies also enable us to investigate when and why certain medications are prescribed.

In this chapter, key findings will be discussed as well as how it relates to the existing knowledge and the currently available literature. The following two main topics will be further elaborated, where the clinical relevance of the findings in this thesis will be discussed:

1. Information captured in the different databases
2. Pharmacological treatment, is it always the best solution?

INFORMATION CAPTURED IN THE DIFFERENT DATABASES

Pharmacy records vs medical records vs reported data – advantages and limitations

In observational studies, one can perform field studies but this approach is cumbersome and expensive. Therefore, we used many different types of databases. Databases can be different due to the type of population included or the information that is available. They each have their strengths and limitations, and the decision to choose one particular type is often based on the research question we intend to answer and the question whether the type of data that are needed, are available. For the results of this thesis, we have used different sources of information which are outlined below.

In chapter 3.1, information from the Dutch Foundation for Pharmaceutical Statistics was used, which contains dispensing data from more than 97% of all community pharmacies in the Netherlands. One of the main strengths of this database is its large size and the fact that it is population-based with detailed information about the medications dispensed, and the information including age and sex of patients. With these data, we were able to study the dispensation of the medications that are contraindicated in young individuals (chapter 3.1). For the identification of medication exposure, the Anatomical Therapeutic Chemical Classification (ATC)

of all medications were available [19]. Furthermore, we also had information on the dispensing date, the daily dosage and product name. Also, a relatively long history of this database was available (if born after 1990) which enabled us to study the medications dispensed since birth on the condition that they did not switch pharmacies. However, pharmacy record databases in itself are not suitable for investigating associations between medication exposure and health outcomes as the latter is unavailable. Also, there is no information about the indications for which the medications were prescribed. This collaborative pharmacy database is suitable for nationwide drug utilization studies for different types of medication. It may also give us an idea of any changes in prescription behavior compared to previous years as a relatively long history is available (since 1990) [18]. Furthermore, information about the type of prescriber and the postal code of the pharmacy are also available. This makes it possible to study the different prescription behaviors, also depending on the different regions. Another strength of this pharmacy database as opposed to prescription databases is that we have dispensing data instead of prescriptions as utilization data from GP databases, for instance, may overestimate actual drug use because not all prescriptions are filled at the pharmacy. However, one of the limitations is that it only covers the medication dispensed by community pharmacies and not the medications dispensed by hospital pharmacies, and no 'over-the-counter' drug use is registered. Also, we do not know if these medications are taken by patients. Therefore, it may not give us a complete overview of all medications that are used by patients.

In chapter 4.3 and 5.1, prescription data was used from the Integrated Primary Care Information database. This is a longitudinal observational dynamic database containing medical records from more than 450 general practitioners (GP) in the Netherlands [20]. In contrast to the pharmacy record database, the GP database contains detailed information about the diagnosis and co-morbidities based on ICPC codes (International Classification of Primary Care). This enabled us to study the associations between medication exposure and certain health outcomes. Furthermore, a long follow-up period (since 1996) of patients was available, which makes it possible to study long-term effects of medications and the association with certain outcomes. Moreover, GP data may give information about the indication for therapy which is not available in pharmacy databases. However, patients may also switch between GP practices where the follow-up period will end once they leave a participating GP practice. This may result in a shorter follow-up period for an individual. As mentioned earlier, this database only contains prescription data. In the Netherlands, pharmacists also act as a gatekeeper and they may decide that certain medications which are prescribed to them should not be given (e.g. because of a contraindication), of course only after discussing this first with the prescriber. Furthermore, lifestyle factors such as smoking or alcohol use may not always be captured in the database. Therefore, it will not be possible to adjust for these type of potential confounders.

The last database that was used in this thesis (chapter 4.1 and 4.2) is the database from the Generation R study. This study concerns a large prospective population-based cohort in which the health of children is investigated from fetal life onwards. Due to its prospective design,

detailed and extensive data have been collected, which includes questionnaires, interviews and behavioral observations. Also, information about their parents was collected such as certain lifestyle factors (smoking, alcohol use, caffeine intake), but also behavioral and demographic factors (ethnicity and education). Collecting information by conducting interviews is one way to gather important information in a consistent way. However, it was not be feasible to interview all parents included in the study, because these interviews can be very time-consuming. Nevertheless, questionnaires were also used to collect information. The limitation of using questionnaires is that there is always a chance that not all parents will complete the questionnaire, which may results in missing values. In this case it is possible that either parts of the questionnaires were not completed or the entire questionnaire has not been completed. When this information is missing completely at random (missing status not related to either exposure or outcome), the data sample may still be unbiased and representative of the population. However, when the missing status is not completely at random, it can have a strong effect on the results and the conclusions drawn from these data. Furthermore, the use of questionnaires may also be prone to information bias as parents may be completing the questionnaires incorrectly (they do not remember or misunderstand the question). For the collection of information about the medications that were used by mothers during pregnancy or medications used by children we also used questionnaires but for the mothers we also had a printout of the medication records from the pharmacy to verify. Also, pharmacy records of all children until November 2018 were collected recently which were linked to the other information that was obtained in the Generation R Study. This linkage enabled us to study the (long-term) effects of medications used by children and the association with health outcomes, of which both detailed information was available (such as the precise filling date, behavioral and demographic factors). In chapter 2.1, we have shown that the use of medications reported by mothers (questionnaires) may be as important as medications found in the pharmacy records to have a complete overview of all medications that were used.

Difficulties in obtaining information on medication use

In chapter 4.1 and 4.2, we have used pharmacy record data to determine the initiation of, as well as the persistence and adherence to methylphenidate. Electronic pharmacy records of participants in the Generation R study were obtained from the Foundation for Pharmaceutical Statistics (SFK), where we faced some challenges. In order to receive pharmacy records from the SFK, unique identification numbers of the Generation R participants were needed. These numbers could only be found in the computer systems of the community pharmacies. We used the postal code of the child's parents at study entry (between the years 2002 and 2006) and the postal code at the time of data collection (in 2017) to find the pharmacies of the children. All community pharmacies in the Rotterdam area (~80 pharmacies) were contacted and asked for consent to collect these identification numbers. The identification numbers of children were only collected when both parents gave consent. The recent change in the legislation where the

General Data Protection Regulation (GDPR) has replaced the Dutch Data Protection Act also affected the process of collecting pharmacy record data. This new European legislation has tightened the regulations and rules regarding the automatic processing of personal data. Due to this change, pharmacists were implementing measures to protect their data and limit the access, which was also one of the reasons that we were not able to collect pharmacy records of all children as some pharmacists were more reluctant to provide consent. Furthermore, there is the possibility that these children received their medication from other pharmacies. Until 5 years ago, patients were designated to one pharmacy but nowadays patients are free to choose any pharmacy. Although no longer obligatory, most patients simply chose the pharmacy nearest to their home. Fortunately, however, many pharmacies are on collaborative computer networks and patients are recognized if they go to the adjacent pharmacy in the same neighborhood. Finally, collecting the identification numbers of all Generation R participants is a time consuming process as these numbers all had to be found manually in the databases of the community pharmacies. Nevertheless, we were able to find the pharmacy record data of 5,068 children, which was 74.4% of all children whose parents gave consent to retrieve the pharmacy record data.

PHARMACOLOGICAL TREATMENT, IS IT ALWAYS THE BEST SOLUTION?

ADHD diagnosis in children and the influence of parents on the decision to initiate treatment and adherence

Behavioral and emotional problems have always been a challenge in terms of diagnosis and treatment as some people hide their symptoms and do not seek help. However, when we talk about children, the situation is much more complex. Children mostly rely on their parents as they can often not easily communicate their feelings, except for symptoms such as pain. The parents are usually the ones to notice any behavioral problems. These type of problems are, unlike other health outcomes (such as a high or low blood pressure), difficult to measure. It requires sufficient knowledge and experience to recognize behavioral problems, not only by general practitioners (GPs) but more importantly by parents, as they are the ones to visit the GP and experience the child's behavior during the whole day. Attention deficit hyperactivity disorder (ADHD) is one of the examples where the diagnosis can be difficult, because of the different symptoms that characterize this disorder. Usually the externalizing symptoms, such as hyperactivity and impulsivity are seen as the core symptoms of ADHD which is also more common in boys than in girls [10]. This is encountered by many parents as 'difficult behavior' and one of the reasons that relatively more boys are receiving pharmacological treatment than girls [88]. Not only is the disorder less often recognized in girls than in boys, but the internalizing symptoms (which are more often seen in girls) are also less likely to be qualified for

pharmacological treatment as their symptoms are not considered to be severe enough [114]. Consequently, parents may find it more difficult to cope with the behavior of boys, which may also increase the likelihood of initiating treatment in boys compared to girls. There are different pharmacological treatment options available, such as dexamfetamine or atomoxetine, but methylphenidate is considered as the first-line treatment for ADHD. Methylphenidate is a psychostimulant and acts by increasing the activity of dopamine and norepinephrine through inhibition on reuptake of these neurotransmitters. Before considering pharmacological treatment, lifestyle advices are given (such as a structured daily programme). If not enough, behavioral therapy is preferred and only in some (severe) cases it may be necessary to try a combination with medicines [8]. Even when pharmacological therapy is proposed by the GP or specialist, the final decision to initiate it in children should be supported by their parents. Parents are in the end also responsible for making sure that their children are taking the medication according to the prescribed treatment regimen. However, parents are not always entirely involved in the decision-making process with the healthcare professionals [215]. For most parents it is difficult to find help and discuss alternative treatment options [216]. They feel the pressure from school or other family members or friends to make the right decision [116, 118]. This may also be one of the reasons that parents accept the pharmacological treatment for their child, even if they do not fully support this decision. Parents may accept pharmacological treatment for several reasons: 1) they fully rely on the doctor's experience and knowledge as they want to do what helps most, 2) many children are using it nowadays so it is more or less socially accepted and considered worth trying [217]. These two reasons already show that parents are making decisions based on limited information. A previous study showed that some parents, in fact, prefer not to initiate medication because of the risks and because they do not like the idea of their child taking medication on a daily basis [146]. Therefore, it is important to understand and assess the attitude of parents towards initiating medication and consider their preferences in the decision-making process.

Parents will only be able to make the right decisions and follow the treatment schedule if they are fully aware of the risks and benefits of pharmacological treatment and understand the importance of adherence to treatment. Furthermore, information about the family characteristics (such as the ethnicity, education level of parents, household income and whether or not they have to raise their child alone) should also be considered when deciding to initiate medication as these factors may also be an important factor in terms of child's treatment adherence (chapter 4.2). After all, pharmacological treatment will not be effective if not taken according to the prescribed treatment regimen [218]. Therefore, the probability of non-adherence based on family characteristics should also be considered.

Undertreatment or overtreatment?

Earlier we discussed the differences between boys and girls in terms of initiating pharmacological treatment. This could mainly be explained by the differences in ADHD diagnosis which

depend on the symptom profile of boys (ADHD) and girls (attention deficit disorder, ADD). The failure to recognize symptoms in girls may result in undertreatment of the condition. However, in chapter 4.2 we showed that even when there are no reported ADHD symptoms, boys were still more likely to receive methylphenidate treatment. Thus, girls receiving less treatment than boys could imply that girls with ADHD symptoms are undertreated. However, there is also a possibility that boys without ADHD are being overtreated [115] [172] [219]. Apart from the indications and symptoms presented by these children, the current knowledge about ADHD diagnosis and treatment may also influence prescribers. Also, the effectiveness of methylphenidate in boys in terms of symptom improvement is easier to measure than in girls as the reduction of externalizing ADHD symptoms are more visible. [10, 113]. As our findings showed that medications were more often prescribed to boys irrespective of the presence of ADHD symptoms, it is suggested to conduct further research in a larger population. When conducting further research, the absence of ADHD symptoms should be further investigated in children who have already started treatment with medication. Also, the combination with behavioral therapy should be considered.

There are also other factors that may determine whether or not a child will receive medication. The results of our study showed that children born to mothers with a non-western ethnic background are less likely to receive methylphenidate treatment than those born to native Dutch mothers. This could be explained by cultural factors, such as their view on problematic behavior in children or medical approaches and beliefs [220]. In some cultures, a child with symptoms of hyperactivity or impulsive behavior can be seen as a child with high energy. Such parents may have a higher threshold for seeking help. Also, limited knowledge about ADHD or language barriers may be reasons that parents from certain cultures are less likely to visit their GP [220]. These challenges may lead to children with ADHD not receiving the treatment they need to alleviate their symptoms. Studies have shown that even when children with a non-western background are formally diagnosed with ADHD, their parents do not always accept medication and prefer behavioral therapy over pharmacological therapy [125, 126]. Although this has been reported as undertreatment in ethnic minorities in most studies, we might have to ask ourselves whether there is not the potential of (over diagnosis and) overtreatment in the western population [219].

The recognition of ADHD has increased over the years along with the increase in use of medication to treat this disorder [182]. Treatment with medication has proven to be effective by relieving ADHD symptoms [84] even more rapidly than with behavioral therapy alone. However, medications do not permanently cure the disorder and when diagnosed in childhood it tends to persist in up to 65% of adolescents and adults [221], while the long-term effects of the medications on the brain are not known [222-224]. At some point, these children have to cope with these symptoms without using medication, which may also be extremely difficult. They may experience rebound effects, leading to another problem to deal with [225, 226]. Although undertreatment of ADHD may still be a problem, there are also concerns of unneces-

sary medication use by children whose behavior may be managed through other means. It is important to focus on sufficiently informing parents on how to manage these behavioral problems by bringing more structure into their daily household. They should be informed, in the child's early years about the behavioral problems that may occur in children, such as the age these problems usually occur or other factors that may trigger these problems. Parents can therefore take these factors into account when raising their child and adapt their parenting style. However, further research is needed to determine what factors (in early childhood) may prevent these behavior problems. Finally, it should also be considered that parents may also have behavioral or emotional problems themselves. They should receive a different type of support and information about how to raise children with behavioral problems.

Based on our results and the existing literature, we may conclude that it is important for parents to be aware of the child's behavioral problems, but also to be informed as early as possible in order to timely recognize it. Pharmacological therapy may not always be necessary if parents are able to manage their child behaviorally (in early childhood) and avoid medication.

Contraindications

As previously discussed, not only the decision to start but also to discontinue treatment may be necessary as the long-term effects of medications are not always known. However, sometimes behavioral problems that were diagnosed during childhood may persist into adulthood. It is up to the specialist to determine whether continued treatment is necessary but then the risks should also be considered. Apart from the fact that the long-term effects on the brain are not known, methylphenidate was until recently also not approved for use in adults [21]. There were concerns about the cardiovascular risks when using methylphenidate, especially in the older population [4, 5]. Nevertheless, methylphenidate was still prescribed despite the potential risks, and this was allowed if prescribing followed the guidelines of the Dutch Society of Psychiatry [165]. Publications by the Foundation for Pharmaceutical Statistics (SFK) showed that the use of methylphenidate among the number of patients aged 6-15 years, has decreased since 2015. The other age groups showed an increase in the same period of time [6]. Although the increase in the older age groups has become less [7], a recently published study showed that ADHD among adults is increasing [227].

This is one of the examples where medications are prescribed despite the known potential long-term risks. However, in children age-related contraindications are common as many medications have not been tested in children for efficacy and safety. These medications are often prescribed off-label where the decision to prescribe medications is based on the need to treat and on experience and current knowledge about these medications. In some cases, healthcare professionals have to consult different information sources or the available literature about the use of certain medications in the different age groups. As prescribed earlier (chapter 3.1), the information sources provide inconsistent information about whether the medication can be used in a certain age group. In other cases, it is not clear why a medication is contraindicated

for a particular age group, which makes it difficult for a healthcare professional to make a decision to prescribe the medication. Furthermore, relative and absolute contraindications are also sometimes confused where 'off-label' is also branded as 'contraindications' in certain countries, such as in Korea where the lack of information on safety as well as efficacy is regarded as contraindications [228]. This can be misleading as off-label use can be implied as 'being harmful' where in fact the safety of the medication in certain age groups has not been established yet. Nevertheless, prescribing a contraindicated medication may sometimes be necessary and does not have to be considered bad practice. Therefore, further research is needed to assess the reason for prescribing particular medications despite their contraindication for age and if any of these contraindicated prescriptions has led to negative outcomes such as hospital admissions or serious adverse drug reactions. The Paediatric Regulation that came into force in the European Union in 2007, has already led to an improvement in the availability of information on the use of medicines for children [229]. Nevertheless, it remains a challenge to conduct the trials in children as there are some risks and pitfalls that need to be anticipated to ensure that children will benefit from this (such as a long approval process and complex ethical issues) [230].

When medications are used for other reasons than managing symptoms

Methylphenidate is considered safe when taken as prescribed and intended, but there is also a growing concern about potential misuse/abuse of prescription drugs [231]. A rise in methylphenidate use in adults may also come with a high potential of abuse or misuse, for instance, by students, but also professionals or athletes as the use of these medications may increase the feeling of energy and productivity [232]. Furthermore, young people may also take this medication for recreational purposes [233]. The concern of abuse among this population is that they are not aware of the risks of using this medication and without any healthcare professional monitoring their use, it may become a serious problem. They may experience the negative adverse effects, such as anxiety or insomnia [234]. Furthermore, repeated abuse of this medication may become a learned behavior and as a consequence they may keep continuing using this medication despite a desire to quit, which may again lead to other problems.

Another medication which has also been increasingly discussed in terms of safety, are the antidepressants, in particular the serotonin reuptake inhibitors (SSRIs). The SSRIs are known to cause agitation and activation, especially at the start of treatment. This is also known from some older tricyclic antidepressants such as nortryptiline [212]. Patients who are still in a depressed mood in combination with these new symptoms, may be at an increased risk of suicide [235]. This has led to concerns when using this medication to treat depression. Suicidal thoughts and acts may already be present in patients with depression and the use of antidepressants may or may not be associated with this risk. Thus, looking for an association still remains a challenge. However, undiagnosed bipolar disorder may also be present in patients with depression, where the use of antidepressants may even worsen their mood. As a consequence it may lead to psychosis and an increased risk of suicide [16]. These are rare cases where the

use of antidepressants should be discontinued and appropriate treatment should be started. However, as many other disorders, these are difficult to measure and clinicians should be careful when prescribing these medications. The currently available literature shows conflicting and inconclusive evidence [16] [205]. Despite of all this, care should still be taken to avoid harm in patients due to the use of particular medications, especially with these type of conditions.

FUTURE RESEARCH

The findings in this thesis show that more population-based research of drug effects is needed, especially in children and adolescents. Although clinical studies in children became more acceptable in the past years, there are still some challenges we may face such as the ethical considerations. Also, limited data is available about the real-life effects of medications in children once the drug is marketed. Apart from the fact that more research is needed to study the safety and efficacy in children, this lack of knowledge regarding pediatric specific drug use is still an ongoing area which need to be studied further in post marketing studies.

In our study, we have investigated the prescription of methylphenidate in children with and without mother-reported ADHD symptoms, which showed differences between children with a western and non-western ethnic background but also between boys and girls. Further research in a larger population is needed to investigate the potential of overtreatment and undertreatment in children with and without ADHD. When investigating this, it is also important to consider behavioral therapy, which may also vary across the different demographic groups as shown previously [125, 126].

Also, the potential of misuse or abuse could be addressed by studying the issue across different demographic groups (e.g. boys vs girls or western vs non-western). It could possibly give us more insight into the underlying reasons, which may hopefully lead to an improvement of the existing preventative measures.

Finally, we also discussed the age-related contraindicated medications which are sometimes still prescribed despite the contraindication. Therefore, the reasons for prescribing these age-contraindicated medications should be further investigated, where we want to know whether these are prescribed because the risks were unknown or because of other reasons. In addition, this could be studied further, where we may investigate the association between the use of these age-related contraindicated medications and serious adverse drug reactions or hospital admissions as the outcome. Most studies on contraindicated medications are focusing on the teratogenic effects or drug interactions [236-238], but studies investigating the age-related contraindications is limited [68, 239, 240].

7 Appendices

Summary

SUMMARY

This thesis comprises of studies where we used different information sources to answer questions related to the use of medication in children and adolescents.

Exposure to medication may already start at an early stage in the life cycle: the pregnancy period. Observational studies are often conducted to assess the risk of adverse perinatal outcomes, as pregnant women are not included in clinical trials due to obvious ethical reasons. In these studies, different information sources can be used to determine medication exposure during pregnancy. Within the Generation R Study (chapter 2.1), we compared the self-reported medication use and the dispensed pharmacy records for different therapeutic classes of medication. In this chapter, we showed that selective serotonin reuptake inhibitors (SSRIs) and anti-asthmatics, which are medications used for chronic conditions, have a substantial or good concordance between self-reported medication and dispensed pharmacy records. Medications taken for acute conditions, such as the antibiotics, folic acid and antihistamines, had a lower concordance when comparing both information sources. Several factors, such as the ethnic background may have played a role in the self-reporting of medication use.

Apart from pregnant women, inclusion of children is also not very common, although more accepted than in the past. Medications prescribed to children are often not approved for use for this particular age group as the safety and effectiveness have not been studied yet. Sometimes the risks are known, but even then, these medications may still be prescribed or dispensed. In chapter 3.1, we determined the incidence and prevalence of age-related contraindicated medications that were dispensed to children. The findings of this chapter show that a substantial percentage of children received a medication which was contraindicated for that age group. The results also indicated that information about the contraindication is not always consistent between different sources and that information about the risks is often limited.

The question to consider pharmacological therapy to treat ADHD symptoms in children has been discussed extensively. The decision to start treatment with medication does not only lie with the specialist or prescriber, but also their parents as children often rely on them for support and management of these chronic conditions. In chapter 4.1, we investigated the maternal sociodemographic characteristics as determinants of methylphenidate initiation, which shows that maternal education is an important determinant of methylphenidate treatment. Also, the child's sex and maternal ethnicity were found to be associated with initiating methylphenidate treatment, irrespective of the presence of clinically relevant ADHD symptoms.

Once children started treatment, several factors may influence adherence and persistence to treatment with methylphenidate. Chapter 4.2 shows that not only child's but also family characteristics play an important role in treatment adherence. These results also show that children starting at an older age and girls were more likely to be non-persistent than younger children and boys. Considering these findings, it is important for prescribers to take these into account when initiating methylphenidate treatment.

Drug treatment is often started during childhood, but it has also increasingly been prescribed at an older age. Chapter 4.3 of this thesis, indicates that methylphenidate, which was started during childhood, was continued in half of the study population when reaching the age of 18 years. The majority of this group started treatment at adolescence which may explain the reason for continuing treatment at this age. Furthermore, we found that ~25% of our study population had a medication possession ratio above one, suggesting misuse or abuse of methylphenidate. These data suggest close monitoring of methylphenidate use and dispensation of these medications, in particular to patients aged 15 years and higher.

Furthermore, we investigated the association between antidepressant use and the risk of suicide of which the results are presented in chapter 5.1. The results of this study did not indicate an increased risk of suicide after starting treatment with SSRIs, tricyclic antidepressants and other antidepressants when compared with past antidepressant use.

Finally, we have put results into perspective in the general discussion and give some future perspectives.

Nederlandse samenvatting

SAMENVATTING

Dit proefschrift bestaat uit hoofdstukken, waarbij we gebruik hebben gemaakt van verschillende informatiebronnen bij het beantwoorden van vraagstukken die gerelateerd zijn aan het medicatiegebruik bij kinderen en adolescenten.

Medicatiegebruik begint al in de vroege fase van het leven, namelijk tijdens de zwangerschap. Observationele studies worden vaak uitgevoerd om het risico op ongunstige perinatale uitkomsten te beoordelen, omdat zwangere vrouwen, omwille van ethische redenen, niet kunnen deelnemen aan klinische studies. Bij deze studies kunnen verschillende informatiebronnen worden toegepast om het gebruik van medicatie tijdens de zwangerschap te bepalen. Binnen de Generation R studie (hoofdstuk 2.1) hebben we informatie over het medicatiegebruik, die verkregen is middels vragenlijsten en apotheekgegevens, vergeleken tussen verschillende therapeutische groepen. In dit hoofdstuk, tonen we aan dat de concordantie tussen het medicatiegebruik op basis van vragenlijsten en apotheekgegevens voor de chronisch gebruikte middelen, zoals de selectieve serotonine heropnameremmers en de anti-astma middelen, vrij goed is. Medicijnen die gebruikt worden voor acute aandoeningen, zoals antibiotica, foliumzuur en allergiemiddelen, laten een lager concordantie zien wanneer we het medicatiegebruik op basis van beide informatiebronnen ook voor deze middelen vergelijken. Verschillende factoren, zoals etniciteit kunnen een rol hebben gespeeld bij het invullen van de vragenlijsten over het gebruik van medicatie tijdens de zwangerschap.

Naast zwangere vrouwen, komt het ook niet vaak voor dat kinderen aan klinische studies deelnemen, alhoewel dit tegenwoordig wel meer wordt geaccepteerd. Medicaties die worden voorgeschreven aan kinderen zijn vaak niet goedgekeurd voor het gebruik bij deze leeftijdsgroepen, omdat de veiligheid en effectiviteit nog niet zijn vastgesteld. In sommige gevallen worden deze geneesmiddelen toch wel voorgeschreven of afgeleverd, ondanks de bekende risico's bij het gebruik van deze middelen. In hoofdstuk 3.1 hebben we de incidentie en prevalentie berekend van de geneesmiddelen die bij verschillende leeftijdsgroepen gecontra-indiceerd zijn en toch aan de kinderen zijn afgeleverd. De bevindingen in dit hoofdstuk laten zien dat een aanzienlijk percentage kinderen een of meerdere geneesmiddelen hebben ontvangen die gecontra-indiceerd zijn voor de betreffende leeftijdsgroep. De resultaten geven ook aan dat de informatie over de contra-indicatie niet altijd consistent is tussen verschillende informatiebronnen. Tevens is de informatie over deze risico's vrij beperkt.

De overweging om medicaties voor te schrijven bij de behandeling van ADHD (aandachtstekort-hyperkinetische stoornis) symptomen bij kinderen is een veelbesproken onderwerp. De beslissing om te starten met medicatie ligt niet alleen bij de specialist of voorschrijver, maar ook bij de ouders. Kinderen zijn namelijk vaak afhankelijk van hun ouders en vertrouwen op hun steun en begeleiding bij dit soort chronische aandoeningen. In hoofdstuk 4.1 hebben we de socio-demografische karakteristieken van de moeder als determinanten bestudeerd bij het starten van methylfenidaat bij kinderen. De bevindingen in dit hoofdstuk tonen aan dat de

opleiding van de moeder een belangrijke rol speelt bij het starten van methylfenidaat. Tevens laten deze resultaten zien dat het geslacht van het kind en de etniciteit van de moeder ook gerelateerd zijn aan het starten van methylfenidaat bij kinderen, ongeacht de aanwezigheid van ADHD symptomen.

Op het moment dat kinderen met methylfenidaat zijn gestart, kunnen verschillende factoren van invloed zijn op de therapietrouw en de continuïteit van het gebruik van methylfenidaat (persistentie). Hoofdstuk 4.2 toont aan dat niet alleen de karakteristieken van het kind, maar ook van de familie een rol spelen bij therapietrouw. Deze resultaten laten ook zien dat meisjes en kinderen die op een later leeftijd zijn gestart, vaker stoppen dan jongens en kinderen die op een jonge leeftijd zijn gestart. Zodoende is het belangrijk dat voorschrijvers deze informatie meenemen bij de beslissing om met methylfenidaat te starten.

Methylfenidaat wordt vaak gestart op een jonge leeftijd (bij kinderen), maar het wordt ook in toenemende mate voorgeschreven aan ouderen. Hoofdstuk 4.3 van dit proefschrift geeft aan dat de helft van de studiepopulatie die op een jonge leeftijd met methylfenidaat is gestart, dit nog steeds gebruikt wanneer de leeftijd van 18 jaar is bereikt. De meerderheid van deze groep is op een late leeftijd gestart met methylfenidaat (15-17 jaar) en dat verklaart ook deels waarom deze patiënten het gebruik hiervan op de leeftijd van 18 jaar hebben voortgezet. Daarnaast geven de resultaten ook aan dat bij ongeveer 25% van de studiepopulatie meer geneesmiddelen bij de apotheek zijn afgeleverd dan zijn voorgeschreven (medication possession ratio boven 1.0). Dit suggereert dat methylfenidaat mogelijk voor andere redenen, dan voor de behandeling van ADHD symptomen, wordt gebruikt (misbruik). Gezien deze gegevens, is het belangrijk dat het gebruik en de aflevering van methylfenidaat goed in de gaten wordt gehouden, met name bij patiënten van 15 jaar en ouder.

Verder hebben wij ook de associatie tussen het gebruik van antidepressiva en het risico op suïcide bestudeerd, waarvan de resultaten zijn weergegeven in hoofdstuk 5.1. De resultaten van deze studie geven aan dat er geen verhoogd risico op suïcide is gevonden na het starten van de behandeling met antidepressiva. Hierbij hebben we de selectieve serotonine heropname remmers, tricyclische antidepressiva en de overige antidepressiva vergeleken met het gebruik van antidepressiva in het verleden.

Als laatst hebben we de resultaten in perspectief geplaatst in de discussie, waarbij ook een aantal toekomstperspectieven besproken wordt.

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PhD Portfolio

PHD PORTFOLIO

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PHD TRAINING

Research Skills

2011-2013	Master of Science in Epidemiology
2013	Scientific English writing course, Erasmus University, Rotterdam

Oral Presentation

2019	Methylphenidate treatment initiated during childhood is continued in adulthood in half of the study population 35th International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE) 24-28 August 2019, Philadelphia, PA, USA

Poster presentation

2019	Maternal sociodemographic factors are associated with methylphenidate initiation in children in the Netherlands: a population-based study 35th International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE) 24-28 August 2019, Philadelphia, PA, USA

TEACHING AND OTHER ACTIVITIES

2015-2017	Supervising practical Pharmacoepidemiology, Netherlands Institute for Health Sciences (NIHES), Rotterdam, the Netherlands

2016-2017	Supervising three students collecting pharmacy record data for the Generation R study
2015-2019	Coordinating assistant for the online Master European Programme in Pharmacovigilance and Pharmacoepidemiology
2018-2019	Supervising of two Pharmacy students Sümneyye Serife and Gulsum Çobanoğlu, 'Use of contra-indicated drugs in children', Leiden Academic Centre for Drug Research (LACDR)

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