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 socio-economic 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**.