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].