Summary and discussion
Outline

This thesis described several studies on the use of stimulant medication among children in the Netherlands using qualitative as well as quantitative methods and parents, physicians, and pharmacy data as data sources. In this closing chapter the main results will be summarized and all results will be taken into consideration to answer and discuss the following four research questions raised in the introduction:

1) Is concern about stimulant use among children justified for the Dutch situation?
2) Is stimulant medication part of a multimodal treatment program?
3) What is the use of psychotropic co-medication among stimulant users?
4) Are pharmacy data useful in child psychiatry research?

Finally, I will reflect on recent developments in the field of ADHD treatment and give recommendations for future research.

Summary

In the first chapters of this thesis (chapter 2-5) several aspects of current practice of stimulant treatment among children in the Netherlands were described. Chapter 2 described how pharmacies were used to recruit parents of stimulant-treated children for a questionnaire survey and how the prescribing physician was approached. Also, response and consent rates were analyzed with respect to characteristics of the stimulant-treated children and physicians. We found that the community pharmacy can be a valuable starting point for recruiting parents and physicians of users of prescription drugs for survey research, yielding high response rates and low consent refusal rates.

From the questionnaire survey held among parents of stimulant-treated children we described the current practices around the initiation and follow-up care of stimulant treatment among children (chapter 3). We found that 91% of the stimulant-treated children were diagnosed with ADHD. In 77% of the cases the child or the parents received non-pharmacological therapy besides stimulants. One out of five children received psychotropic co-medication; melatonin (11%) and antipsychotics (7%) were mentioned most frequently. Stimulant treatment was initiated by child psychiatrists and pediatricians in 51% respectively 32% of the cases, but GPs provided the repeat prescriptions for 61% of the children. Almost 20% of the children did not receive follow-up care concerning the treatment with stimulants. The odds of not receiving follow-up care was increased when the prescribing responsibility
was transferred between physicians, mostly from specialist to GP. Children who visited pediatricians for follow-up were more likely to undergo physical examinations than children who visited child psychiatrists and GPs. From the results of this survey we concluded that major concern about the injudicious initiation of stimulant treatment by GPs appears unnecessary for the Dutch situation. However, our study did demonstrate cause for concern about the follow-up care for stimulant-treated children.

There has been increasing awareness that ADHD is often accompanied with other psychiatric disorders that warrant special consideration in the treatment. Therefore, we investigated whether the presence of psychiatric co-morbidity in stimulant-treated children with ADHD was associated with the use of psychotropic co-medication and receiving non-pharmacological treatment, using data from the survey among stimulant-prescribing physicians (chapter 4). Among the stimulant-treated children diagnosed with ADHD, pervasive developmental disorder (PDD) and oppositional defiant disorder/conduct disorder (ODD/CD) were the most frequently reported co-morbid psychiatric disorders (both 10%). We found statistical significant associations between the presence of co-morbidity and the use of antipsychotics and the use of melatonin. Antipsychotics were, with 17%, most frequently used among stimulant-treated children with ADHD and co-morbid PDD. Melatonin was mainly used among children with co-morbid ODD/CD (16%). The presence of psychiatric co-morbidity was also associated with higher use of non-pharmacological treatment. In the ADHD-only group 74% of the children or their parents received or had received any non-pharmacological treatment. This percentage was 92% for ADHD and co-morbid PDD, 90% for ADHD and co-morbid ODD/CD and 82% for children with ADHD and other co-morbidity. Children with co-morbid PDD or ODD/CD received more intensive behavioral interventions and day treatment than the other children and were more often treated in an inpatient clinic. Also counseling was most frequently offered to parents of children with ADHD and co-morbid PDD or ODD/CD. Home-based interventions were especially applied when co-morbid PDD was present, as it was provided in 23% of these families, and in no more than 10% of the other families. We concluded that stimulant-treated children with ADHD and psychiatric co-morbidity received more psychotropic co-medication and non-pharmacological treatment than children with ADHD-only. Moreover, the type of psychotropic co-medication and non-pharmacological treatment received by the children and the parents, depended on the specific co-morbid psychiatric disorder being present.

The chronic course of ADHD and the pharmacokinetic parameters of short-acting stimulants make the double-blind, placebo-controlled, randomized N-of-1 trial very suitable for assessing the effectiveness of stimulants in individual patients. In chapter 5 we examined the use of N-of-1 trials among children in the Netherlands when starting stimulant treatment.
First, we interviewed physicians about their N-of-1 protocols. Physicians mentioned assessing individuals’ response and dose-finding to be their main purposes for using N-of-1 trials. None of the physicians’ protocols was the same with regard to trial length, dosing schedule and evaluation of the trial. Second, we estimated the use of N-of-1 trials with stimulants in a large pharmacy record database. The annual percentage of children starting stimulant treatment with an N-of-1 trial, fluctuated between 0.6% (3/462) and 3.3% (10/301) from 2000-2004. We could not detect a statistical significant difference between the continuation of stimulant treatment after start with and without an N-of-1 trial. We concluded that N-of-1 trials with stimulants are infrequently and not optimally used in the Netherlands.

Chapter 6 and 7 were dedicated to research on co-medication using a large pharmacy record database. The use of psychotropic co-medication among stimulant-treated children in the Netherlands from 1998 to 2002 is examined in chapter 6. The prevalence of stimulant use among children had increased from 0.6% in 1998 to 1.2% in 2002. The incidence appeared to have stabilized since 2000 around 0.27%. We found that among stimulant-treated children, the use of psychotropic co-medication had increased from 12% in 1998 to almost 15% in 2002. The most frequently used co-medications were antipsychotics, with 8% in 2002. The use of antidepressants and melatonin had increased slightly, though significantly, from both less than 0.2% in 1998 to 1.8% respectively 1.5% in 2002.

Comparing the use of co-medication with figures from other countries was complicated due to differences in timing of the study period. Comparison was further aggravated by the variety of terms used for co-medication, and the lack of information on how co-medication was exactly operationalized. Therefore, in chapter 7 we examined the impact of different definitions for co-medication on the reported proportion of patients having co-medication using pharmacy data. We demonstrated that different co-medication patterns, varying in time window and criteria for overlap, yielded clinical as well as statistical significant different estimates. Uniformity in terminology of co-medication is crucial for a clear communication between clinicians and researchers. We therefore proposed to distinguish the following patterns when studying co-medication: ‘co-prescribing’, ‘concomitant medication’ and ‘possibly concurrent medication’. The research question should determine the co-medication pattern of interest. The medication and disease under study and possible safety aspects are important to determine the time window.

Chapter 8 touched upon the economical aspects of stimulant treatment. ADHD places a substantial economic burden on patients, families and society and it has been suggested that the full costs associated with the treatment of ADHD may be reduced by (more expensive) once-daily dosing regimens. In chapter 8 we investigated the cost-effectiveness of treatment with long-acting methylphenidate-OROS for children with ADHD for whom
treatment with immediate-release (IR) methylphenidate is suboptimal. The incremental cost-effectiveness ratio (ICER) of methylphenidate-OROS treatment compared to IR-methylphenidate was estimated at 2,004 euros per quality adjusted life year. The ICER was sensitive to changes in resource use and the probability of stopping stimulant treatment. From our study methylphenidate-OROS appeared a cost-effective treatment option for this subgroup of children with ADHD.

Discussion

In the following part of this chapter I will discuss the four research questions raised in the introduction, reflect on recent developments in the field of ADHD treatment and give recommendations for future research.

1) Is concern about stimulant use among children justified for the Dutch situation?
Based on the presented data we can not conclude whether stimulants are under or overprescribed for children in the Netherlands. With an estimated prevalence of ADHD of 3-5% [1] and assuming that a conservative half of the children with ADHD could benefit from treatment with stimulants, a prevalence of 1.5 – 3.0% of stimulant use could be expected. We found a lower prevalence of 1.2% in 2002 among 0-19-year-olds (chapter 6). In a study from the USA the authors suggested that many children with ADHD are still undiagnosed and untreated, whereas on the other hand children treated with stimulants do not meet the full diagnostic criteria for ADHD [2]. This suggestion might probably also be valid for the Dutch situation. The prevalence of stimulant use in the Netherlands is not as high as in the USA with 2.9% in 2002 [3]. In Europe, however, the Netherlands is one of the countries with the highest stimulant consumption rate together with the United Kingdom, Belgium, Germany, Iceland and Switzerland [4].

We found that for the vast majority of stimulant-treated children in the Netherlands, stimulant treatment was initiated by specialists, in particular child psychiatrists. According to the parents of stimulant-treated children, they received the first prescription for stimulant medication from the physician after on average four visits [5]. Although we had no information on how the child was assessed and we could not pass judgment on the appropriateness of the diagnosis, according to the parents and physicians almost all children received stimulant medication for ADHD, the indication for which these drugs are approved. Taking all these results into consideration, we think that major concern about injudicious
initiation of stimulant treatment appears unnecessary for the Dutch situation. However, follow-up care for stimulant-treated children appeared to be noticeably inadequate.

Follow-up
Because ADHD affects children over many years and long-term treatment is often indicated, carefully monitoring of the child’s development is very important, as is recommended in most ADHD guidelines [6-9]. The importance of regular monitoring is also supported by findings of the Multimodal Treatment Study of Children with ADHD (MTA) that showed the medication management condition to be superior to ‘treatment as usual’ (community care group), even though two-third of the children in this latter group also received stimulant medication [10]. This reveals the importance of the procedures in the medication management protocol in its entirety, including monthly supportive contacts and treatment adjustments.

Considering the MTA-findings, follow-up care for stimulant-treated children in the Netherlands appeared far from optimal, because for one out of five stimulant-treated children no follow-up visit was scheduled. We found that transfer and sharing of prescribing responsibility increased the risk of not being monitored. In two third of the stimulant-treated children GPs were involved in prescribing of repeat prescriptions, and therefore it is important to clarify their role in follow up care. It is our view that GPs might take over prescribing responsibility after the initiation phase and perform physical monitoring, but only after additional training and in close liaison with the treating specialist. However, the specialist should remain responsible for monitoring the course of ADHD in these children. This is in concordance with the recommendations in the recently published Dutch multidisciplinary ADHD guideline [9]. Apparently careful monitoring is not yet a matter of course, and therefore it is important to develop a clear and comprehensive monitoring system for stimulant-treated children, in which it is only possible to continue stimulant prescribing with periodic monitoring visits.

During follow-up, rating scales for evaluating the effectiveness of treatment were infrequently used and the thoroughness of the physical monitoring depended on the type of physician visited (chapter 3). There should be more uniformity in the physical examinations undertaken during follow-up, and this ought to be independent of the type of physician visited. With respect to physical examinations the Dutch guideline is clear and recommends to measure body weight and length annually and to measure the child’s blood pressure and heart rate before the start of treatment and once the treatment has stabilized [9]. Periodic electrocardiographic (ECG) monitoring is not indicated according to this guideline, which is in agreement with the recommendations of the American Heart Association [11].
Dosing

Another worrisome aspect of stimulant treatment is inadequate dosing. In the Netherlands the mean prescribed daily dose for methylphenidate was approximately 25 mg (chapter 6). Comparing this with the MTA study, this is 13 mg lower than the mean dose in the medication management condition, and 6 mg lower than the mean dose in the medication management condition when combined with behavioral therapy [10]. In addition, in the MTA study children received their medication on a three-times-daily regimen, while in the Netherlands more than half of the children took their stimulant medication in two or less doses per day [5]. For clinical practice these MTA findings imply that careful dose- titration at the start of treatment, three-times-daily administration and regular medication monitoring visits may provide substantial benefits for treatment outcome. The new Dutch ADHD guidelines already incorporated these MTA findings [9]. The guideline also acknowledges the additional value of the N-of-1 method for dose-finding, but points out that for practical reasons the N-of-1 method may not always be feasible. Yet whatever approach for dose-finding is chosen, the critical element is to do it in a systematic way [12].

2) Is stimulant medication part of a multimodal treatment program?

For three-quarter of the children in our questionnaire study, stimulant treatment was or had been combined with a form of non-pharmacological treatment for the child or parents. Non-pharmacological treatment was defined broadly, including e.g. intensive training, parent training and home training, physiotherapy and diet. Children with ADHD and co-morbid psychiatric disorders received considerable more treatment modalities than children with an ADHD diagnosis only, in particular children with co-morbid PDD and ODD/CD. Thus, in the Netherlands the majority of the stimulant-treated children and their families received multimodal treatment. It should be noted that no judgment could be made about the appropriateness of therapies and no distinction was made between continuous and temporary therapies.

Although all guidelines for the treatment of ADHD recommend a multimodal treatment program, the additional value of combined treatment over medication alone is controversial [13]. To date, there are only a few sound studies that compared the effect of combination treatment with either medication or behavioral therapy alone, and these studies gave conflicting results [10,14,15]. The conclusions from the large MTA trial that for core ADHD symptoms no advantage was found of combination therapy to medication management alone are still under debate [10]. A clear advantage of combination treatment was found after alternative outcome analyses of the MTA-trial data on the individual level [16] and
using composite outcome measures [17]. Until more studies on the effectiveness of combination treatment and medication alone become available, a multimodal approach tailored to the child and family has the best likelihood to manage the symptoms of ADHD and that of its co-morbid disorders. Addition of behavioral interventions may be of help when medication has worn off or cannot be taken. The overall treatment will need to be of high-quality and sustained over a long period, resulting in the highest possible quality of life and developmental level for the child.

3) What is the use of psychotropic co-medication among stimulant users?
In this thesis we considered psychotropic co-medication as the use of other psychotropic agents (i.e. antidepressants, antipsychotics, anticonvulsants, lithium, clonidine, hypnotics, anxiolytics and melatonin) besides the use of stimulants. The use of psychotropic co-medication among stimulant-treated children has increased in the Netherlands over the years (chapter 6), but the increase was not as large as reported from the USA [18-20]. Although the vast majority of the Dutch stimulant users received stimulants as monotherapy, nearly one out of five children received psychotropic drugs besides stimulant medication in 2003.

By combining stimulants with other psychotropic drugs clinicians aim to enhance response in partial responders to monotherapy [21], treat co-morbid disorders or adverse effects [22] or potentiate the efficacy of response to antidepressants [23]. However, combining medication may also bring about potential problems, such as drug interactions, adverse reactions and difficulties in assessing the contribution of each drug to the overall effect [24,25]. With respect to stimulant medication there is still a lack of data supporting the effectiveness and safety of the addition of other psychotropic drugs [22].

In contrast to stimulants most other psychotropic medications are not thoroughly studied for the treatment of childhood psychiatric disorders and most of the time not even approved for the use in children. The safety of psychotropic drugs among children have received a lot of attention recently. The ‘off-label’ use of the atypical antipsychotics is substantial and has increased in recent years [20,26], and their risks for weight gain and metabolic disorders was lively discussed in the lay media [27,28]. In our survey, parents reported that nearly one out of thirteen children used an antipsychotic besides their stimulant treatment (chapter 3), a figure that later was affirmed by a study using pharmacy data (chapter 6). The use of antipsychotics was mainly restricted to children with ADHD and co-morbid psychiatric disorders, especially pervasive developmental disorder (chapter 4). We assume that antipsychotics were not used to treat core ADHD symptoms but more to treat
Chapter 9

symptoms of the co-morbid disorder (e.g. aggressive behavior), although we have no data to support this. Also antidepressants, especially SSRIs, have received a lot of negative attention worldwide due to the increased risk of suicidal thinking and behavior in children and adolescents with major depression and other psychiatric disorders [29,30]. Although the use of SSRIs among stimulant-treated children in the Netherlands has increased to 1.8% in 2002 (chapter 6), the use is not as high as the 4.3% reported from the USA [20]. It would be interesting to see whether the negative publicity and the recommendations against the use of SSRIs among children has influenced the course of SSRI use as monotherapy but also as co-medication among stimulant users.

We were surprised that parents reported one out of nine children used melatonin for co-medication. Melatonin is not approved as a drug in the Netherlands and research shows conflicting results about the effectiveness of melatonin for sleep disorders [31,32]. Remarkable were also the regional differences in melatonin prescribing, ranging from 5-26% per ZIP-region (data not shown in thesis). Although no alarming side effects have been reported yet, more systematic research and long-term research has to be done to be conclusive on the effectiveness and safety of melatonin in children.

When the use of other psychotropic drugs together with stimulants is considered, before addition of a second psychotropic drug, first the stimulant dose should be optimally titrated and the effect of stimulants should be carefully examined. Safer et al. recommend to use the N-of-1 method for complex combinations of psychotropic medications to produce a systematic and more objective assessment of the contributions of each drug to the overall effect and possible side effects [22]. However, for most psychotropic medications an N-of-1 trial will be inappropriate, because of their delayed onset and termination of action, causing carry-over effects.

4) Are pharmacy data useful in child psychiatry research?
In all studies described in this thesis the community pharmacy was in some way involved; 1) as a data source for drug utilization studies or 2) as the starting point for the recruitment of users of prescription drugs (or their parents).

Drug utilization studies
Previous studies have demonstrated that pharmacy data from Dutch community pharmacies can be a reliable source of information regarding the use of prescription drugs [33,34]. All prescriptions from general practitioners (GPs) and specialists are dispensed in community pharmacies and due to a high patient-pharmacy allegiance in the Netherlands and
sophisticated and standardized pharmacy software, medication records for each patient are virtually complete [35]. Unfortunately, this completeness might be jeopardized, now that new competitors such as internet pharmacy and outpatient clinic pharmacies have entered the pharmacy retail market.

A limitation of pharmacy data is the absence of clinical information such as the diagnosis, the indication for prescribing medication, the medical history and other features of the patient. For more in-depth clinical research on medication use other data sources should be addressed in addition. To study the current practices of stimulant treatment in the Netherlands, we therefore obtained more specific data on diagnosis and stimulant treatment from parents of stimulant-treated children and their prescribing physician. Another limitation of pharmacy data is the absence of medication used during hospital stay, supplied by dispensing GPs and the incomplete information on over-the counter (OTC) medication, possibly leading to an underestimation of medication use. This is illustrated by the different percentages of melatonin use among stimulant-treated children: 1.5% in 2002 according to pharmacy data (chapter 6) compared to about 7% according to survey among parents of stimulant-treated children in the same regions (chapter 3, regional data not presented).

Recruitment
We used community pharmacies as a starting point to detect stimulant-treated children in their computer system and to function as intermediaries between us researchers and the parents. By using this pharmacy-based recruiting method, stimulant-treated children were selected from the general pediatric population, irrespective of the prescribing physician and without influencing current practice. Recruitment of parents via for example a child psychiatry or pediatric clinic would have led to substantial selection bias. However, Knoester et al. showed pharmacy-based recruitment is also not without selection bias [36]. They demonstrated that their pharmacy-based recruitment procedure lead to selection bias because community pharmacists unintentionally applied selection criteria before approaching their patients for research. Although we provided a very strict recruitment protocol to the participating pharmacists, we can not completely rule out that our pharmacists also added their own selection criteria before sending out the questionnaires. Knoester et al. found that consent was less often obtained among patients with a higher burden of disease, among people living in highly urbanized regions, and among patients using drugs that could be considered as markers for off-label use of the drug of interest. Unfortunately, we had no information on the non-responding parents and their children, hindering a non-response analysis on this level. Information about these non-responders would have refined the interpretation of our results. However, although not completely
without selection bias, we think that for child psychiatry research, pharmacy data and pharmacy based recruitment procedures can a valuable, additional tool for studying drug-related issues.

**Developments and recommendations for future research**
Since the start of the research presented in this thesis four years ago, a lot of developments have taken place with respect to the treatment of ADHD.

**ADHD guideline**
In October 2005, the new Dutch guideline for diagnostics and treatment of ADHD in children and adolescents [9] replaced the old guideline from 1999 published by the Dutch Psychiatric Association [37]. In contrast to the latter, the new guideline was developed by a multidisciplinary group representing the various relevant professional associations and patient organizations. This integrated approach is important because different health care providers and professionals should be involved in detecting, diagnosing and treatment of ADHD. In some regions in the Netherlands the use of a multidisciplinary ADHD team has already proven to be successful [38]. It would be interesting to see whether this approach is adopted by other regions as well. Every effort should be made to effectively implement the new ADHD guideline, in order to guarantee that children and their parents in different regions of the country can expect the same standard of care.

**New formulations and drugs**
Over the past years, new drugs and formulations for the treatment of ADHD have been developed. In the Netherlands two new compounds have been approved for the treatment of ADHD since the end of 2002: methylphenidate-OROS (Concerta®) and atomoxetine (Strattera®). Methylphenidate-OROS is a long-acting, once-daily formulation with methylphenidate. In clinical trials methylphenidate-OROS has been shown to be as effective as three-times-daily immediate release methylphenidate with a similar safety pattern [39]. An advantage of this once-daily formulation is the possibility to simplify the dosing schedule and eliminating the need for in-school administration. In addition, in contrast to immediate release methylphenidate, the methylphenidate-OROS tablet is difficult to crush and its methylphenidate content can not easily be extracted, making it a formulation with a lower abuse potential [40].

Atomoxetine is the first non-stimulant approved for the treatment of ADHD in children and is also dosed once per day. The precise mechanism by which atomoxetine produces its
therapeutic effects in ADHD is unknown, but it is thought to be related to selective inhibition of the pre-synaptic norepinephrine transporter. The efficacy of atomoxetine in children with ADHD has been demonstrated in several clinical trials [41-43], but direct comparison studies with methylphenidate are still lacking. Clinical trials demonstrated that atomoxetine is generally thought to be safe and well-tolerated. However, in September 2005, health care professionals were alerted that children and adolescents taking atomoxetine prescribed for ADHD should be closely monitored for changes in behavior after a meta-analysis showed a small but statistically significant increase (0.4% vs. 0%) in suicidal thinking in children taking atomoxetine compared to placebo [44].

In the Netherlands, methylphenidate-OROS and atomoxetine are not available for all ADHD patients as for both once-daily formulations co-payments up to 97 euros per month are required [45]. In the Dutch Price Reference System (GVS) both drugs are clustered with immediate-release (IR) methylphenidate on GVS-list 1a. This entails a controlled reimbursement limit at the price of IR-methylphenidate, which is 16 to 30% of the price of methylphenidate OROS and atomoxetine. According to the advisory council of the Health Care Insurance Board, there is no evidence that methylphenidate-OROS and atomoxetine are different from IR-methylphenidate with respect to efficacy and safety, and therefore both drugs were not assigned to the GVS-list 1b, entailing liberal price setting. The current reimbursement status of methylphenidate-OROS and atomoxetine, received a lot of criticism from patients’ associations, parents, physicians and teachers [46-49]. We found that in 2005 in the north-eastern part of the Netherlands, 18% of stimulants users younger than 20 years received a prescription for methylphenidate-OROS [InterAction database, data not shown]. This illustrates that a considerable number of parents prefer once-daily methylphenidate-OROS over IR-methylphenidate, despite the extra costs. Since the introduction of the new health care insurance system in the Netherlands in January 2006, it has become possible for patients to pay for an additional non-compulsory insurance, that includes reimbursement of full costs for all prescription drugs.

In the cost-effectiveness analysis presented in chapter 8 in this thesis, methylphenidate-OROS showed to be a cost-effective treatment for ADHD children for whom treatment with IR-methylphenidate is suboptimal. In this analysis no account was taken of direct medical costs associated with e.g. in-school administration of IR-methylphenidate or indirect costs of suboptimal treatment such as parental work-loss because data were lacking. To refine cost-effectiveness analyses on ADHD treatment, future research should endeavor to quantify these direct non-medical and indirect costs associated with ADHD treatment.
Safety
Although stimulant medications have been used for over 60 years and are one of the most extensively studied medications in children and adolescents, still long-term effects and safety of stimulant treatment have not been well established [50]. Recently in the USA, the discussion about the safety of stimulant use flared up after an advisory committee of the Food and Drug Administration unexpectedly recommended to display a ‘black box’ warning label on stimulants, clearly indicating the cardiovascular risks of stimulant drugs [51,52]. This recommendation was not based on new evidence about the cardiovascular risk of stimulants, but was mainly driven by worries that stimulants are being overused in the USA and about the sharp increases in the number of especially stimulant-treated adults. According to the American Heart Association the changes in blood pressure and pulse under the influence of stimulants are clinically insignificant [11] and at the end of March 2006, an FDA’s pediatric advisory committee recommended against the ‘black box’ warning but did recommend adding more clear information to the label [53]. Probably, the discussion about the safety of stimulants will continue, but for now stimulants, with all their risks and benefits, remain the gold standard against which all other ADHD medications are compared.

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