How appropriate is the increased use of methylphenidate?

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CHAPTER 6

General Discussion

Summary of findings per chapter

The overall aim of this thesis was to investigate whether methylphenidate is being appropriately used in the treatment of children and adolescents with attention-deficit/hyperactivity disorder (ADHD) in daily clinical practice. To achieve this aim, I conducted a practice audit among several mental health care and pediatrics clinics, a discontinuation trial, and a survey among general practitioners across the Netherlands. Within these studies, I thus involved child- and adolescent psychiatry, pediatrics settings, and general practitioners' practices, all settings in which methylphenidate is being prescribed to children and adolescents. At the start of this thesis, in *Chapter 1*, I summarized the literature regarding ADHD guideline adherence and the short- and long-term effectiveness of methylphenidate treatment.

In my first empirical chapter (*Chapter 2*), I examined whether the increase in methylphenidate prescriptions between 2008 and 2012 was accompanied by a decrease in ADHD guideline adherence to recommendations for assessing and diagnosing ADHD and initiating methylphenidate or by changes in the proportion of off-label use of methylphenidate. For this study, I conducted an audit of 506 medical files. The findings suggest that the increase in the number of methylphenidate prescriptions, which may be indicative of overtreatment, between 2008 and 2012 cannot be explained by reduced guideline adherence in mental health or pediatrics settings (mean adherence to seven recommendations as documented in the files was 43% in 2008 versus 45% in 2012). I also found no increase in off-label use of methylphenidate (35% in 2008 versus 30% in 2012) that could be indicative of overtreatment or mistreatment. However, there is clearly room for improvement in guideline adherence as the assessment of ADHD severity was almost never conducted (1%) as well as the use of a (semi-) structured parent interview (16%) and providing psycho-education to parents (42%) or teachers (1%) were all rather low.

In *Chapter 3*, using an online survey, I examined general practitioners' opinions about the etiology of ADHD and the growth in ADHD diagnoses and methylphenidate prescriptions as. I also investigated whether general practitioners' policies regarding diagnosing ADHD and methylphenidate treatment were in line with guideline recommendations. Data were collected in the years 2016-2017. The results revealed that the majority (76%) of general practitioners at least sometimes referred children or adolescents to specialized care without feeling this was necessary or felt pressured to prescribe methylphenidate from parents or schools. One third (34%) of the general practitioners admitted they sometimes yielded to parental pressure to prescribe methylphenidate while one in six (17%) indicated they sometimes yielded to similar demands from schools. Most (68%) of the general practitioners regarded the etiology of ADHD as a combination of child related and environmental causes. On average, general practitioners believed that a diagnosis of ADHD was generally given too easily to children and methylphenidate has been prescribed too easily to children in the past 10-15 years. Finally, they poorly adhered to the guidelines for the diagnosis of ADHD (mean adherence to five recommendations concerning the diagnosis of ADHD was 23%). The recommendations for starting methylphenidate (mean adherence to five recommendations was 69%) or monitoring

methylphenidate (mean adherence to eight recommendations was 72%), on the other hand, were better adhered to.

In *Chapter 4*, I investigated the benefits of continued methylphenidate use beyond two years of treatment for children and adolescents on various outcome measures, by conducting a placebo-controlled randomized discontinuation trial. The findings indicate that continued use of methylphenidate is still superior to treatment discontinuation after at least two years of use, as assessed by both investigator- and teacher-rated ADHD symptom ratings. I also found a moderating effect of age, indicating that continued treatment with methylphenidate is especially beneficial for younger children. On the other hand, my results revealed that 60% of the participants who discontinued the pharmacological treatment did not experience any worsening of overall functioning, suggesting some individuals may be withdrawn from methylphenidate without deterioration.

The results of the discontinuation trial on the secondary outcome measures of strengths and difficulties, quality of life, and parenting stress (*Chapter 5)* indicate beneficial effects of long-term methylphenidate use beyond two years for oppositional behaviors in the school environment. I also found beneficial effects regarding hyperactivity and inattention symptoms[1], as rated by parents and teachers, confirming our primary study findings on investigator ratings of ADHD[2]. However, discontinuation of methylphenidate did not appear to impact other problems or aspects of the child's or parental functioning, including children's emotional symptoms, peer relationship problems and prosocial/antisocial behavior as well as child- and parent-rated quality of life and parenting stress.

General discussion

Guideline adherence

Leading international and national guidelines for the diagnosis and treatment of ADHD concur on many recommendations for diagnosing ADHD.[3–8] For example, to establish a diagnosis they recommend to obtain information about the child's functioning from various sources and to use a semi-structured interview or questionnaires, and they indicate the importance of assessing comorbidity. Methylphenidate may be indicated in severe cases of ADHD or after insufficient response to parent training in case of mild to moderate ADHD. In general, my findings indicate that there was much room for improvement regarding guideline adherence in child and adolescent psychiatry and pediatrics settings, at least in the period from 2008 to 2012. In the audit study, I found neither an increase in improper diagnostic procedures, nor a change in the adherence to guideline recommendations concerning the initiation of methylphenidate, nor an increase in off-label use of methylphenidate between 2008 and 2012. However, my findings did reveal that most children in child and adolescent psychiatry and pediatrics settings were diagnosed with ADHD without all necessary diagnostic steps recommended by international and national guidelines being followed.[3–5,7–11] A limitation of the audit study is that I do not know if all diagnostic steps were documented in the files. Similarly, on average, only one quarter of the recommendations regarding the assessment of ADHD were followed by general practitioners. This approach leaves room for critics who presume that children receive an ADHD diagnosis "too easily". It should be noted, however,

that the situation may have changed by now, whether improved or deteriorated. Possible changes may have been caused by the transition of financing of child mental healthcare to municipalities instead of healthcare insurance companies or financial cutbacks in child- and adolescent psychiatry in the Netherlands.

Moreover, the findings from the audit study indicate that one in three children in mental health or pediatrics settings received a methylphenidate prescription off-label (30% in 2008 and 35% in 2012), despite a lack of strong scientific evidence of efficacy and the potential increased risk of adverse events. It is important to note that the term "off-label" does not imply improper, illegal, contraindicated, or investigational use. The frequent off-label prescription of ADHD medication makes one wonder to what extent this medication also works for a broader group of children with other disorders beyond those with ADHD.

I also found that clinicians in child and adolescent psychiatry settings adhered better to guideline recommendations than clinicians in pediatrics settings. This is perhaps due to the typical shorter visits in pediatrics, while assessing ADHD is time-consuming. Another reason could be that clinicians in pediatrics settings receive less specific training in mental health assessments. Since 2015, most pediatrics settings in the Netherlands no longer provide ADHD care. This change is due to the transition of financing of child mental healthcare as mentioned before.

Clinical guidelines provide evidence-based recommendations for safe and optimal care. Therefore, it is important to adhere to guidelines to prevent overdiagnosis and overtreatment. However, the implementation of guideline recommendations into clinical practice is often suboptimal, as has been demonstrated by my own and other studies.[12–16] Sometimes, guidelines are criticized by clinicians, who state that they are unsuitable for their patients. Other barriers regarding guideline usage include low awareness of and familiarity with guidelines as well as negative attitudes towards or disagreement with guidelines.[17] On the one hand, guideline recommendations templates in electronic medical records may remind clinicians continuously of important steps and recommendations that result in better adherence to guidelines.[18,19] On the other hand, guidelines can be improved. For instance, current guidelines include detailed recommendations on how to initiate methylphenidate use, in contrast to the almost complete lack of recommendations regarding the long-term use of methylphenidate.[3–5,7,20,21] Another example is that most guidelines relate ADHD severity to treatment choice, but provide no clear guidance on how to operationalize ADHD severity. Future guidelines should provide such guidance.

Long term benefits

Another aspect regarding the proper use of methylphenidate is that children should use the medication for as long as needed, or, in other words, stop if the medication no longer benefits them. The results of my methylphenidate discontinuation trial indicate that a sizeable number of children may stop the medication without deterioration. One may question why they did not stop earlier if the treatment was no longer beneficial. Although the answer remains unknown, future guidelines could provide more comprehensive recommendations on drug withdrawal. Such advice is rare,

compared with the extensive recommendations for starting medication. It is advisable that guidelines integrate periodic assessments regarding the need to continue treatment into clinical practice. This point is especially important for adolescents, as ADHD symptoms may decrease over time, at least in a subset of children.[22,23]

Furthermore, the effect size of the investigator ratings on the ADHD rating scale (d=-0.23) was approximately one-third (d=-0.71) of the effect size found in studies examining short-term efficacy of methylphenidate.[24] On the one hand, this finding may suggest that the effects of methylphenidate become less pronounced when used over a longer period, which is in line with the long-term MTA data.[25–27] On the other hand, the lower effect size according to the ADHD rating scale compared with those from studies that examined the short-term effectiveness may be explained by the fact that the children in the discontinuation trial used dosages as prescribed in clinical practice. These are often different from optimally titrated dosages in clinical trials, as indicated by the large difference in treatment effect between optimally titrated medication and community care in the MTA study.[28] This illustrates that regular attempts to optimize the dosage of methylphenidate are needed in clinical practice.

Another issue with the discontinuation trial was that many eligible children declined to participate because they argued they "knew it still worked", based on experiences of stopping briefly. Therefore, the children in whom the effects of methylphenidate were less pronounced may have been overrepresented in my sample, which may explain the lower effect size and the proportion who could stop the medication without deterioration. Similarly, my use of gradual down-titration instead of directly discontinuing the medication may have led to an underestimation of the effects of methylphenidate.

The effect size of teacher ratings in my study was more in line with teacher-ratings in trials that studied short-term effectiveness in treatment-naïve children than the effect sizes of the investigator or parent ratings.[24] A reason for the less pronounced effects of methylphenidate, as rated by the parents or investigators, compared with teacher rated effects, could be that the latter typically report a lower placebo response than parents do.[29] Another possible explanation is that parents' desire of improvement of their children's behavior may be more pronounced than that of the teachers. The desire to improve is a known modulator of placebo response.[30] Future research should focus on more elaborate teacher ratings such as behavioral observations in the classroom instead of questionnaires.

I found no effects of discontinuation of methylphenidate on child-rated behavioral or emotional problems (as rated by the Strengths and Difficulties Questionnaire (SDQ), quality-of-life or parenting stress. These findings suggest that children with ADHD can be withdrawn from methylphenidate without a deterioration of behavioral or emotional symptoms or quality of life, or an increase in parenting stress by parents. However, I do not know the extent to which the families experienced these problems at the start of the treatment of the child or adolescent. In addition, perhaps the time it takes to evaluate changes in parenting stress or quality of life is longer than a couple of weeks as used in the discontinuation trial. Suggestions for further research are given later in this chapter.

ADHD and methylphenidate controversies

In the past 15 years, ADHD and methylphenidate have received much attention in the mass media and scientific debates. Among other aspects, the discussions often concern the prevalence of ADHD or the causes of ADHD. Some have claimed there is often overdiagnosis of ADHD, i.e., that children receive the diagnosis too easily.[31–36]Others have argued that ADHD is more often diagnosed because of the increased knowledge about its clinical picture or the risks of no treatment, and that ADHD may previously have been underdiagnosed, particularly in girls.[37] The research attention devoted to ADHD and methylphenidate is considerable, in sharp contrast to the lack of attention paid to other important or concerning issues within child- and adolescent psychiatry: for instance, the off-label use of antipsychotics by children and adolescents.[38,39]

The results of my survey from 2016/2017 of general practitioners revealed that, on average, they believed that diagnoses of ADHD have been given too easily to children in the past 10-15 years. Furthermore, most general practitioners stated they sometimes referred children to specialist care without feeling this was necessary. These findings indicate that most general practitioners think there is overdiagnosis of ADHD in children. However, the Dutch Health Council stated in 2014 there were no indications of an increase (between 2002 and 2012) in the prevalence of ADHD nationally or internationally.[40] Furthermore, the Council indicated there was an increase in requests for help regarding attention or hyperactivity problems in children in both primary and specialized care.[40] Three possible explanations for this increase were offered: (1) an increase in pressure on children to achieve optimal academic results, (2) a decrease in the tolerance of deviant behavior in society, and (3) financial incentives to stimulate diagnoses are present in the educational system and in child mental health care, simply because schools or health care organizations received money per DSM-diagnosis. Based on my audit data, I can provide no direct proof of an increase in ADHD diagnoses, nor conclude that ADHD diagnoses were given too easily. However, various methods are used in clinical practice to establish a diagnosis of ADHD, including the use of questionnaires, clinical interviews, child observations, and global clinical impressions. In my opinion, this variety of approaches may give the impression that clinicians can randomly choose how to make a diagnosis of ADHD. This may lead to diagnoses that are being made too easily, especially since in most cases not all recommended diagnostic steps are followed.

The increase in the number of methylphenidate prescriptions in Europe[41–43] to children also resulted in a debate about possible overtreatment. Following the steep increase in the number of prescriptions at the beginning of this century, the number has declined in recent years.[44] Nevertheless, the Dutch government aims to further reduce the number of methylphenidate prescriptions to children and to 'demedicalize' children with mental health problems.[40] The process of medicalizing involves defining a problem as a medical issue or illness, thereby legitimizing treatment by a medical professional.[40] In the context of deviant behavior, medicalization is often used in a narrower sense, namely, the treatment of deviant behavior with drugs. This narrower conception of medicalization is usually referred to in the social debate which may cause children and adolescents with ADHD and their parents to feel misunderstood in their experience of real problems. The broader component of medicalization is that social and environmental factors are neglected, i.e., factors at

the level of family and school and society, and that too fast an individual (biological) approach is used. Furthermore, it possibly makes medical professionals feel that their professional integrity is not respected. On the one hand, public opinion and the government want to continue to reduce prescriptions. On the other hand, medical professionals may feel pressured by parents or schools to prescribe methylphenidate, as indicated my survey of general practitioners. Both sides of the debate affect general practitioners' professional integrity and independence.

Strengths and limitations

This thesis should be considered in the light of its strengths and limitations. A strength was that all studies were focused on the central aim, i.e., to investigate responsible use of methylphenidate, in a variety of settings. In addition, I also used different methods to answer the research question. Strengths of the practice audit were the large sample and the assessment of adherence to recommendations shared by various international guidelines.[3,4] Another strength was that I investigated guideline adherence during an increase in prescriptions of methylphenidate, which enabled me to examine a possible decline in guideline adherence or an increase in off-label use as possible indicators for overdiagnosis with ADHD or overtreatment with methylphenidate.

A limitation of the audit was that I relied on information from medical records only. Clinicians could have performed specific steps with the parents or child but forgot to document these in the records. Therefore, I could not distinguish between non-adherence and failures to document, which may have led to an underestimation of guideline adherence. Furthermore, it is difficult to estimate the extent to which my results can be generalized to populations from other countries or mental health care facilities. Differences in treatment attitudes, insurance, and accessibility of treatments between countries and organizations may all impact guideline adherence. Additionally, my data are ten years old, so, with respect to guideline adherence, much may have changed in the meantime. Therefore, it is important to repeat this type of study in the future. Finally, I did not investigate whether the number of methylphenidate prescriptions in the clinical settings included in my study increased between 2008 and 2012. Therefore, I cannot conclude or exclude a link between increases in methylphenidate prescriptions and less guideline adherence.

A strength of the discontinuation trial was the double-blind, placebo-controlled, randomized design. Previous long-term studies on outcomes of methylphenidate treatment were purely observational, and therefore provided no evidence regarding the possible absence of ongoing effects of methylphenidate after many years. Other strengths of the trial were its embedding in regular clinical care and the use of rating scales by multiple informants.

One limitation of the trial was that I included only children and adolescents using extended-release methylphenidate of 36 mg/day or 54 mg/day at the time of enrolment. Obviously, these dosages do not reflect the full range of types and dosages of stimulants taken by children and adolescents. However, by allowing children on different formulations to switch to extended release, I am confident I obtained a group that was representative of clinical practice. Second, this study reports on data assessed briefly after the discontinuation of methylphenidate, whereas some measures, such as

quality-of-life, may have a longer latency to take effect or were not fine-grained enough. Finally, I acknowledge the modest sample size of 94. The study was primarily powered to investigate changes in ADHD symptoms; therefore, I cannot rule out the possibility that a larger sample size would still indicate long-term benefits of methylphenidate use on problems or aspects of the child's or parental functioning such as emotional symptoms, peer relationship problems, antisocial behavior and aggression, as well as quality of life or parenting stress.

Future studies

Future studies on guideline adherence should consider more elaborate methods, for instance, a combination of an audit of medical records with surveys and interviews with clinicians, because medical records can be incomplete. Additionally, future investigations should also review the internal guidelines of health care institutions, as these are the guidelines clinicians are likely instructed to follow. A survey among Dutch health care professionals found that, of the professionals who used a guideline, 39.4% used a protocol from their own institution.[45] However, it is unclear whether such protocols include all regular guideline recommendations.

Barriers to adherence likely include negative attitudes towards or disagreement with guidelines as well as low familiarity with and low awareness of guidelines.[46] Research has demonstrated that, to overcome some of these barriers, it may be useful to include guideline recommendations in electronic medical records templates[18,19] as well as to better integrate the importance of guidelines in (continued) education[47,48] and to provide training for clinicians in the use of, for instance, parent and teacher-rating scales.[48] In addition, to my opinion, it is also a task of management to implement guidelines in clinical practice and stimulate their use. Future research should examine whether these recommendations to overcome barriers are considered in clinical practice, and if not, why not.

To my knowledge, my discontinuation study was the first to investigate the effects of stopping methylphenidate use in children and adolescents. In future studies, larger sample sizes are required to investigate the characteristics of children who benefit from continuing treatment and of those who do not. Given the difficulties in including children in my study, cross-over designs could be considered, as this would assure that all participants will discontinue, which reduces the number of participants needed for the study. Also, longer follow-up periods are needed in this type of trials, as children are typically using it for a longer period of time. Future research could also implement discontinuation of methylphenidate into clinical practice, for instance, by making N=1 placebo-controlled discontinuation trials a standard part of clinical practice. A pilot of this approach is currently taking place within Accare. In my study, children participated with doses they used in clinical practice. The question is whether these children were optimally dosed. Studies have shown that although there is a dose-response relationship at the group level, there is also large individual variability in the dose-response relationship.[49,50] In addition, an intensive individual course or evaluation of the full range of the possible therapeutic doses for all individual patients leads to better effectiveness.[49,50] This was already shown in the MTA-study[51] and in the recent meta-analyses by Farhat and colleagues[52]. Future discontinuation trials of methylphenidate should also occur with optimally dosed children to investigate its long-term efficacy.

Conclusions

The overall aim of this thesis was to investigate whether methylphenidate was appropriately used in children and adolescents within different settings, namely child- and adolescent psychiatry, pediatrics and general practitioners' practices. I conclude that methylphenidate is an effective long-term treatment for children and adolescents with ADHD. However, children and adolescents should not be using methylphenidate longer than necessary, as a considerable proportion of children and adolescents may be able to stop their medication without deterioration. My findings indicate that these children and adolescents may currently be longer exposed to potential negative long-term health effects, such as reduced body height, than necessary.[53] In clinical practice, more attention needs to be paid to when and how to discontinue the medication. Many children and their parents indicated they did not want to participate in the discontinuation study because they knew it was still effective. Although my study shows that ongoing benefits are the case for a large group, a discontinuation attempt should still be considered at regular intervals to ensure that children do not use mediation unnecessarily long. In addition, methylphenidate also lends itself well to a short stop because it can be restarted if needed.

Regarding guideline adherence, there is much room for improvement in adherence to guideline recommendations for the diagnosis of ADHD and the appropriate use of methylphenidate in the long term. Particularly in the light of the public debate of overdiagnosis and overtreatment of ADHD, sound methods and guideline adherence are of the uttermost importance. Adherence with guidelines should play a greater role in child and adolescent mental health organizations. Clinicians should be supported by sufficient time, and thus money, to perform proper diagnostics (including severity assessment) or by technical support in, for example, electronic patient records. Where the assessment of ADHD may at first seem expensive and time-consuming, correctly performed assessment could also ensure that children and adolescents and their parents receive the appropriate treatment or that unnecessary treatments are not initiated. In addition, we should look at how to increase support among healthcare professionals and management for adherence to guidelines.

My studies also showed what goes well in clinical practice. For instance, my audit indicated that, in most cases, clinicians did assess comorbidities and involved the teacher in their diagnostic procedures. Furthermore, general practitioners generally performed follow-up visits for methylphenidate use.

Overall, one may conclude that methylphenidate is often used suboptimally. My studies have contributed to new knowledge regarding its appropriate long-term use and indicate that there is much room for improvement of clinical practice in child and adolescents mental health services, pediatrics and also in primary practice.

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