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How appropriate is the increased use of methylphenidate?

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CHAPTER 1

General Introduction

In this thesis, I describe a series of studies related to the appropriate use of methylphenidate in children and adolescents. This first chapter contains a brief overview of Attention-deficit/hyperactivity disorder (ADHD) guidelines, background information on methylphenidate and a summary of findings of its effectiveness for the treatment of ADHD in the short- and long run for children and adolescents. This overview is followed by an outline of the aims and chosen study designs of this thesis.

ADHD, characterized by age-inappropriate attention problems and/or impulsivity and hyperactivity[1], is one of the most commonly diagnosed mental disorders in children and adolescents. Recent estimates suggest that ADHD affects about 3–7% of children and adolescents worldwide.[2,3] A diagnosis can be made when the number of ADHD symptoms exceeds the threshold as specified in the DSM, symptoms are present across more than one setting (i.e., home and school), and result in academic, social, or occupational impairment. Like nearly all forms of psychopathology, a distinction between pathology and normal behavior is made subjectively. The clinical presentation of ADHD is heterogeneous and comorbidity with externalizing, internalizing, and/or other neurodevelopmental disorders such as autism spectrum disorder is common.[4–6]

Typically, treatment of ADHD consists of pharmacological and/or behavioral interventions (e.g., parent training, cognitive behavioral therapy). Clinical guidelines indicate that the psychostimulant methylphenidate is the first-line pharmacological treatment for children with ADHD.[1,7–11] Methylphenidate is often initiated between the ages of 6 and 11[12], with mostly short-acting, immediate-release formulations being prescribed at first and longer-acting, extended-release formulations often being used for longer term treatment. Treatment effects, including reduction of hyperactivity and inattention, occur in the majority of patients.[13–15]. Moreover, methylphenidate is generally well tolerated and adverse events are rare.[16–18]

Controversy

Stimulant treatment of children and adolescents has become increasingly common, with steep increases in prescription rates at the beginning of this century in the Netherlands (prevalence of prescriptions increased from 1.8% in 2008 to 3.9% in 2012 of children and adolescents, a relative increase of 111.9%) as well as other western countries (Denmark + 302.7%, Germany + 62.4%, United Kingdom 56.6%, United States + 10.7%).[19–21] This has led to concerns that children were being overtreated with methylphenidate and overdiagnosed with ADHD. These concerns have also been reflected in the scientific and popular press and mass media sources. For example, some authors have suggested that ADHD was the "diagnosis du jour"[22] or that ADHD may be a desirable diagnosis for some parents.[23] After an episode on parenting hyperactive children, talk show host Dr. Phil McGraw claimed that ADHD is "so overdiagnosed".[24] A documentary of Louis Theroux, "America's medicated kids", claimed to be "a disturbing look into the ever-increasing number of mental disorders now diagnosed in children".[25] But also in the Netherlands television specials with titles such as "the ADHD epidemic" ("De ADHD epidemie")[26], "Peace, Cleanliness, and Ritalin" ("Rust, Reinheid en Ritalin")[27]and more recently an episode of the talkshow Nadia "ADHD, what

to do with it?" ("ADHD, wat moet je er mee?")[28] suggested overdiagnosis of ADHD and overtreatment with methylphenidate.

ADHD care and guidelines

Adherence to clinical guidelines is of critical importance to provide safe and optimal care and prevent overdiagnosis and overtreatment. In the Netherlands, ADHD treatment of children and adolescents typically is carried out by a variety of medical and non-medical professionals at child and adolescent mental health centers, pediatricians at hospitals (until 2015), or general practitioners. In the Netherlands, there are different guidelines for different professions. Professionals at child- and adolescent mental health centers or pediatrics settings should rely on the Dutch Multidisciplinary guideline for the assessment and treatment of ADHD in children and adolescents.[91*] The recommendations of this Dutch guideline mostly correspond with those of leading international guidelines for the assessment and treatment of ADHD (e.g., National Institute for Health and Clinical Excellence [NICE][10], American Academy of Pediatrics [AAP][1], Scottish Intercollegiate Guidelines Network [SIGN][7], European Society for Child and Adolescent Psychiatry [ESCAP][11]). Important similarities in the recommendations regarding diagnostic procedures were the requirement to obtain information about the child's functioning from multiple sources (i.e., parents and teachers), the necessity to use (semi) structured interviews or questionnaire during assessment and the importance to assess comorbidities. Regarding treatment, all European guidelines recommend that methylphenidate should only be the first treatment choice in case of moderate or severe levels of symptoms and impairment associated with ADHD. Parent and/or teacher training should be provided in case of mild symptom severity and impairment. Only if the response to parent training was insufficient and significant impairments remain, prescription of methylphenidate should be considered. The steep increase in the number of methylphenidate prescriptions raised concerns about overdiagnosis of ADHD and overtreatment of children with methylphenidate. However, it is unclear if this increase is accounted for by improper ADHD diagnoses, intentional off-label use, diversion, or increases in use among youth with proper ADHD diagnoses. In other words, little was known to what extent the increase in methylphenidate prescriptions was accompanied by changes in guideline adherence for the assessment and treatment of ADHD in children and adolescents and/or changes in the proportion of off-label use of methylphenidate during.

In the Netherlands, general practitioners have their own guideline,[29] which states that establishing an ADHD diagnosis and providing methylphenidate treatment may be done by general practitioners themselves in moderately impaired children, aged above five years, without comorbidity. However, they can also choose to refer to specialized care. For more complex cases, including severely impaired children and/or those with comorbidity, it is advised to refer to specialized care. General practitioners often have a more general understanding of ADHD and often have unfavorable opinions regarding the validity of the construct of ADHD or towards ADHD in general.[3031] This has contributed to the still ongoing debate in society about possible overdiagnosis of

1 *Near the end of my doctoral research a new guideline has been released in the Netherlands.[58] However, my data is based on the previous guideline.

ADHD and overtreatment with methylphenidate.[32] It is uncertain if the societal debate about possible overdiagnosis of ADHD and overtreatment with methylphenidate has shaped attitudes and opinions of general practitioners regarding diagnosing ADHD and prescription of methylphenidate. It is also unclear how well general practitioners adhere to their clinical guideline.

Methylphenidate

Methylphenidate stimulates the central nervous system. How it reduces symptoms in ADHD is not completely clear. However, it is believed that it increases intrasynaptic concentrations of dopamine and noradrenaline in the frontal cortex as well as subcortical brain regions associated with motivation, reward and cognitive control.[33,34] Methylphenidate blocks the presynaptic membrane dopamine transporter and thereby inhibits the reuptake of dopamine and noradrenaline into the presynaptic neuron.

Methylphenidate is rapidly and almost completely absorbed.[10] Within 1-2 hours after administration maximum plasma concentrations are reached for immediate-release formulations. Immediate release formulations have a duration of action of around 4 hours. Therefore a twice or three times daily dose is needed. Extended-release formulations have been developed to achieve longer duration of action following a single dose. They can be taken once a day, resulting in an initial release of medication like the immediate release formulation followed by a gradual release over 8 to 12 hours. The immediate release formulations have been available since the early 1960's in the Netherlands and have been used for over 50 years for the treatment of ADHD. In the mid-1990s the extended release formulations were introduced. In the Netherlands, apart from methylphenidate also atomoxetine and guanfacine are licensed for the treatment of ADHD in children aged 6 years and older.

Common adverse effects of methylphenidate include decreased appetite, sleep disturbance, headaches, stomach aches, drowsiness, irritability, and tearfulness.[35] Severe adverse events that occur rarely include psychotic symptoms and sensitivity reactions requiring discontinuation of the medication. On the one hand, a recent meta-analysis (data until December 2018) concluded that long-term methylphenidate treatment can result in reduced height and weight but with a rather small clinical impact.[36] On the other hand, the most recent Multimodal Treatment of ADHD study (MTA) follow-up stated consistent treatment with methylphenidate over 16 years is associated with lower adult height, and an increase in weight and body mass index.[37] Furthermore, methylphenidate use may be related to a small but clinically non-significant effect on blood pressure (average increase <5 mmHg)[38] and a slight increase in pulse rate (average <5 bpm).[35] Current evidence on the cardiovascular safety of stimulant use in children, adolescents, and adults with ADHD symptoms indicates a negligible risk of serious cardiovascular events for the short- and medium-term use (< 2 years).[39]

Treatment with methylphenidate

The short-term efficacy of methylphenidate is well-established[14,15,40,41] but became subject of controversy. A Cochrane meta-analysis meant to assess the efficacy and safety of methylphenidate

in children and adolescents with ADHD concluded that, although methylphenidate improves teacher-rated ADHD symptoms, general behavior, and parent-rated quality of life, the quality of the evidence was "very low".[17] This triggered a multitude of critical responses from the scientific community pointing to the quality assessment, which deviated from the typical Cochrane procedure.[42,43] That is, the authors added an additional domain, vested interests, to the list of risks of bias and downgraded the quality of evidence for most part based on that new domain. Furthermore, the authors argued that it may have been possible for people in the trials to know which treatment the children were taking based on the adverse events that occurred more frequently in children on active treatment compared to placebo, which is called "deblinding" by observing typical side effects of the active medication. As a major implication for research the authors recommended comparisons with "nocebo tablets", designed to have similar adverse events as methylphenidate. However, nocebo-tablets have never been a comparator in medicine research so this would imply that most evidence in medicine research is of very low quality.[42] The critical responses indicated that the conclusions of the Cochrane meta-analysis were misplaced and an overly negative interpretation of the evidence.[43] They[42], as well as guidelines[10], suggested that there were more prominent questions that need to be answered, for instance the long-term effectiveness of methylphenidate.

Current evidence for the long-term benefits of methylphenidate is limited to a treatment duration of two years at best.[44–47] Nonetheless, the majority of children (60%) who start stimulant treatment use it for over two years.[8,48] The longest placebo-controlled randomized trial showed a positive effect of methylphenidate on the reduction of hyperactivity symptoms after 28 weeks (based on parent and teacher ratings of an earlier conceptualization of ADHD that emphasized hyperactivity)[49]. In the MTA study[13], four different treatment strategies were compared over a course of 14 months; optimized treatment with methylphenidate, optimized intensive behavioral treatment, optimized combined methylphenidate and behavioral treatment, and routine community care (which often included treatment with psychostimulants). From this randomized phase of the MTA study, we know that children who received methylphenidate (as monotherapy or combined with behavioral treatment) had a larger reduction of ADHD symptoms than children who received only behavioral treatment or routine community care. After the 14-month randomized phase, the MTA study conducted naturalistic and observational follow-up assessments up to 18 years old, including the monitoring of treatments.[50–52] The authors concluded that those still taking stimulant medication after 36 months fared no better in the reduction of symptoms or in social functioning than those who had stopped taking medication. This raised the questions about whether long-term medication treatment is beneficial or needed. Given the naturalistic and observational nature of the follow-ups we do not know if the results are affected by human choices of other factors not related to the treatment strategies. The longest randomized study, which controls for such bias, came from a two year study comparing three treatment modalities (methylphenidate alone, methylphenidate plus multimodal psychosocial treatment, and methylphenidate plus attention control psychosocial treatment). [46,47] The benefits of methylphenidate remained stable over a two-year period. However, children who were treated with methylphenidate were not compared with children who received placebo or children who received no treatment. Therefore, the design did not control for the natural course of ADHD.

Because lots of children and adolescents use methylphenidate for many years, it is of great importance to gain more knowledge about to what extent long-term use is still beneficial. Conducting long-term placebo-controlled trials is not feasible, as this would require withholding active treatments for a long period. Therefore, I chose an alternative design, a double-blind randomized placebo-controlled discontinuation design to investigate whether methylphenidate remains beneficial after 2 years of use regarding ADHD symptoms severity. As secondary objectives, I investigated the proportion of children who would or would not benefit from continued long-term use of methylphenidate as well as changes in comorbid symptoms that often go along with ADHD such as oppositional behaviors, aggression, mood problems, anxiety, and impaired social functioning.[53,54] As patients with ADHD often experience a lower quality of life[55,56] and parents of patients with ADHD frequently experience more parental stress than parents of typically developing children,[57] I also investigated if there where changes in those areas. A final objective was to assess the safety of withdrawing methylphenidate.

Study designs

I conducted a series of studies across the Netherlands in various settings where methylphenidate was prescribed to children and adolescents. For the first study into the possible changes in adherence to guideline recommendations I conducted a practice audit of medical files ($N = 506$) between the years 2008 and 2012 in 9 pediatrics settings and 4 child and adolescents mental health settings. I investigated possible changes in adherence to guideline recommendations concerning the assessment and diagnosis of ADHD, as indicators of possible overdiagnosis, as well as changes in off-label use and adherence to recommendations concerning the initiation of methylphenidate treatment, as indicators of possible overtreatment. As a secondary objective, I compared mental health settings with pediatrics settings regarding differences in guideline adherence and changes in guideline adherence within these settings over the years.

For the second study, into attitudes and current practice regarding ADHD and methylphenidate treatment of general practitioners, a survey was sent to general practitioners all over the Netherlands ($N = 907$).

Finally, I conducted a randomized double-blind placebo-controlled discontinuation trial to investigate the benefits of continued use of methylphenidate beyond two years of treatment. A total of 94 children and adolescents between 8-18 years of age participated in a 7-week discontinuation trial. Half of them continued their use of methylphenidate; the other half discontinued gradually in 3 weeks and subsequently used 4 weeks placebo. I investigated possible changes and differences in ADHD symptoms, overall improvement or worsening in ADHD symptoms, as well as comorbid symptoms such as oppositional behaviors, aggression, emotional problems, and impaired social functioning, quality of life, and parenting stress. We noted all adverse events that were spontaneously reported to the investigator by the child or parents during the discontinuation trial.

Aims and outline of the present thesis

The overall aim of this thesis was to investigate the long-term effectiveness of methylphenidate and the way methylphenidate is prescribed in clinical practice in children and adolescents in relation to clinical guidelines. This thesis starts with the results of a practice audit that examined possible changes in adherence to guideline recommendations for the assessment and treatment of ADHD in children and adolescents between the years 2008 and 2012 **(Chapter 2),** during which the prescriptions of ADHD medication to children and adolescents substantially increased. **Chapter 3** describes a survey to general practitioners to investigate their attitudes towards ADHD and methylphenidate treatment, and their current practice regarding diagnosing ADHD and initiating and monitoring of methylphenidate in comparison to guideline recommendations. **Chapter 4** focuses on the long-term benefits of methylphenidate on ADHD-symptoms (ADHD Rating Scale), investigated by means of a randomized double-blind placebo-controlled discontinuation trial. Secondary outcome measures were the investigator-rated Clinical Global Impressions improvement scale (CGI-I) and the Conners' Teacher Rating Scale–Revised: Short Form (CTRS-R:S). In **Chapter 5,** the outcomes on other secondary outcome measures of the randomized double-blind placebo-controlled discontinuation trial are reported, including oppositional behaviors, aggression, emotional problems, and impaired social functioning as well as quality of life, and parenting stress. In **Chapter 6**, I provide a summary of the findings, a general discussion of my results, and an overall conclusion.

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