Stimulant treatment in children
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Introduction
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The first description of the effect of stimulants on behavioral problems was published in 1937 by the psychiatrist Charles Bradley [1]. He observed a spectacular improvement in the behavior of children under influence of the amphetamine benzedrine, especially leading to remarkably improved school performance and better self-control in approximately half of the children. His research and that of others established the benefits of stimulants in the treatment of attention-deficit/hyperactivity disorder (ADHD). Ever since, over 200 controlled trials with stimulants have been performed, demonstrating the efficacy of stimulants in improving ADHD and associated symptoms [2,3].

ADHD
ADHD is prevalent among approximately 3-5% of the school-aged children and therefore it is the most common psychiatric disorder among children [4]. In the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), ADHD is characterized by symptoms of inattention and/or hyperactivity/impulsivity being persistent for at least 6 months in a more frequent and severe way than in other children with a comparable developmental level [4]. Some of these symptoms must be present before the age of 7 years and cause impairment in two or more settings, e.g. at home and school. To avoid misdiagnosing it is therefore important to obtain as much information as possible from different sources. ADHD is more prevalent among boys than girls, with ratios varying from 3:1 to 5:1 in epidemiological studies [3]. The etiology of ADHD is still unknown, but evidence points to neurobiological and genetic factors to play a dominant role in the disorder [3,5].

ADHD is often accompanied by other psychiatric disorders. About 50-60% of all children with ADHD meet the criteria for either oppositional defiant disorder (ODD) or conduct disorder (CD) [6], 20-30% have mood disorders and 19-26% have a learning disorder [7]. ADHD is considered a chronic disorder as follow-up studies of clinically referred children with ADHD indicated that symptoms persist into adulthood in 10–65% of the cases [3]. The large variation in the reported level of persistence across studies probably reflects different definitions used for remission from ADHD [8].

Children with ADHD may face developmental and social difficulties, manifesting itself in school problems, academic underperformance and troublesome relationships with family members and peers [9,10], which may give rise to poor self-esteem and demoralization. Therefore, early diagnosis and effective treatment of ADHD is important to halt the downward spiral in the child’s development into adulthood.
Treatment of ADHD

Two treatment modalities have proven to be effective in reducing ADHD symptoms: psychosocial interventions and pharmacotherapy [3,11]. In guidelines for the treatment of ADHD, medication and psychosocial interventions or the combination of both are mentioned as a valid treatment option [12-17]. Since most hyperactive children have many problems, combination of different treatment modalities is usually indicated [12,13,15].

Psychosocial treatment for ADHD consists of behavioral interventions focused on the child, parents and/or the teacher. Behavioral parent training and behavioral interventions in the family and classroom setting have been demonstrated to contribute to improvements in the child’s behavior [11,18,19]. Only limited evidence is available for the benefits of cognitive behavioral interventions, such as social-skills and problem-solving training for children [3,20].

Stimulants are the first-choice drug in the management of ADHD. Several short-term clinical trials have demonstrated a significant reduction of ADHD symptoms compared to placebo [21,22]. In approximately 70% of the children with ADHD, treatment with stimulants improves symptoms of hyperactivity, impulsivity and inattention [21]. In addition to improving core symptoms of ADHD, stimulants also improve associated behavior, including on-task behavior, academic performance and social functioning. However, for long-term academic performance and social skills, stimulants have failed to show consistent benefits [23].

In the Netherlands, methylphenidate and dexamphetamine are the two stimulants available for the treatment of ADHD, of which methylphenidate is most frequently used. Stimulants are sympathicomimetic agents probably causing their effect by facilitating the action of dopamine and norepinephrine by increasing the intrasynaptic levels of dopamine by blocking the dopamine transporter and/or stimulating the release of dopamine. Methylphenidate has a short half-life of 2-4 hours, which necessitates multiple daily dosing. Since 2002 controlled-release, once-daily methylphenidate-OROS has become available in the Netherlands. For some children stimulant preparations with a longer half-life may be beneficial, for example if symptoms worsen at the end of the dosing interval, administering medication at school is problematic or in case of compliance difficulties. Dexamphetamine has a half-life of about 11 hours [24] and is only available as compounded capsules prepared in the pharmacy. Methylphenidate and methylphenidate-OROS, but not dexamphetamine, are officially licensed for the treatment of ADHD. As amphetamine-like substances with potential risk for misuse and addiction, methylphenidate, methylphenidate-OROS and dexamphetamine are covered by the Opium Act.

Side effects due to stimulants occur early in treatment, are generally mild and can be managed by adjusting the medication dose or timing [23,25,26]. Observed side effects are
decreased appetite, sleep problems, stomach ache, headache, anxiety, irritability, and proneness to crying [25,26]. However, among children with ADHD some of these symptoms are also present without stimulant use, suggesting that these side effects are characteristics of the disorder rather than the treatment [25,26]. Stimulants are also associated with suppression or delay of growth [27-29]. Nonetheless, studies have found a little, but not a clinically relevant, decrease in the expected height and for most of the children any decrease in growth early in treatment was compensated for later on [28,29].

The Multimodal Treatment Study of Children with ADHD (MTA) was the first major clinical trial examining the effects of combined behavioral treatment and medication compared to behavioral treatment and medication alone [30]. A sample of 579 children with ADHD was included to compare four treatment conditions; medication management, intensive multimodal behavioral therapy, the combined condition of medication management and multimodal behavioral therapy, and treatment as provided by community care. The latter ‘care as usual’ arm resulted in stimulant medication in two third of the cases. After 12 months all four treatment arms showed a significant reduction of ADHD symptoms. However, medication management, with and without additional behavioral therapy, demonstrated to be superior to behavioral therapy and considerably more effective than community care. No significant differences were found comparing medication management alone and the combination of medication management with behavioral therapy, although alternative outcome analyses did indicate some additional value of behavioral therapy [31,32]. Although the MTA study is considered the landmark study in the field of ADHD treatment, the design and methodology has also received a lot of criticism [33,34], suggesting an underestimation of the effect of behavioral therapy. Also the feasibility of the extensive treatment programs in daily practice has been questioned [35].

Concern
In the nineties a rapid increase of stimulant use was noticed in several western countries [36-41]. In the USA for example, the prevalence of stimulant use increased 3- to 7-fold among children under 18 years of age between 1987 and 1996 [41]. Also in the Netherlands the use of stimulants strongly increased. Among children aged 0-19 years in the northern part of the Netherlands the prevalence of stimulant use increased 5-fold from 0.15% in 1995 to 0.74% in 1999 [38]. The increased use of stimulants was probably due to the increasing number of children, adolescents and adults being diagnosed with ADHD [3] and to the prolonged duration of stimulant use [38]. This explosive increase of stimulant prescriptions raised global concern and became subject to public and political debate [42-44]. The discussion focused on the validity of ADHD as a psychiatric disorder, the potential
overdiagnosis and overtreatment of ADHD, and the risks of treatment with stimulants [39,42,45]. It was also questioned whether the use of stimulants for children with ADHD is addictive and facilitates the abuse of other substances. When using the prescribed dose orally, however, no cases of addictive effects of methylphenidate have been reported so far, and children with ADHD treated with stimulants have been shown to develop less rather than more substance abuse than untreated children [46,47].

Also in the Netherlands the increase of ADHD diagnoses and stimulant use caused public concern [48-52]. The lay media claimed excessive prescribing of stimulant medication by GPs. Also questions were raised about the quality of the care provided and the sole reliance on stimulant medication. This turmoil, however, was based on studies from North America, as no information was available on the Dutch situation. In 1999 the Minister of Health asked the Dutch Health Council for advise on the diagnosis and treatment of ADHD. The Health Council stated in their following report that improvements in diagnosing and treatment of ADHD were required and that research was urgently needed to gather information on the way ADHD and stimulant treatment was dealt with, not only by child psychiatrists, but also by pediatricians, GPs and other health care providers [53].

This thesis describes our research on current practice of stimulant treatment among children in the Netherlands using different data sources and qualitative as well as quantitative methods, aiming to answer the following research questions:

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?

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