

Current issues around the pharmacotherapy of ADHD in children and adults

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Abstract *Background* New drugs and new formulations enter the growing market for ADHD medication. The growing awareness of possible persistence of ADHD impairment beyond childhood and adolescence resulting in increased pharmacotherapy of ADHD in adults, is also a good reason for making an inventory of the what is generally known about pharmacotherapy in ADHD. *Aim* To discuss current issues in the possible pharmacotherapy treatment of ADHD in children, adolescents and adults with respect to the position of pharmacotherapy in ADHD treatment guidelines, the pharmacoepidemiological trends, and current concerns about the drugs used. *Methods* A search of the literature with an emphasis on the position of pharmacotherapy in ADHD treatment guidelines, the pharmacoepidemiological trends, and current concerns about the drugs used in pharmacotherapy. *Results* According to the guidelines, the treatment of ADHD in children consists of psychosocial interventions in combination with pharmacotherapy when needed. Stimulants are the first-choice drugs in the pharmacological

treatment of ADHD in children despite a number of well known and frequently reported side effects like sleep disorders and loss of appetite. With regard to the treatment of adults, stimulant treatment was recommended as the first-choice pharmacotherapy in the single guideline available. Both in children and adults, there appears to be an additional though limited role for the nonadrenergic drug atomoxetine. The increase of ADHD medication use, in children, adolescents and in adults, can not only be interpreted as a sign of overdiagnosis of ADHD. Despite the frequent use of stimulants, there is still a lack of clarity on the effects of long-term use on growth and nutritional status of children. Cardiovascular effects of both stimulants and atomoxetine are rare but can be severe. The literature suggests that atomoxetine may be associated with suicidal ideation in children. *Conclusion* Although pharmacotherapy is increasing common in the treatment of ADHD in both children and adults, there are still a lot of questions about side effects and how best to counter them. This suggests an important role for close monitoring of children and adults treated with stimulants or atomoxetine.

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Impact of findings on practice

- Stimulants are the first-choice drugs in the pharmacological treatment of ADHD in children as well as in adults, despite a number of well known and frequently reported side effects.
- Physicians need to be aware that also rare and possibly severe adverse events might come up as prevalence of use increases.

- Little is known about specific efficacy and safety issues in the use of ADHD medication by adolescents and adults despite the increase of use in these age categories.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common psychiatric disorder among children and adolescents [1]. ADHD is, with a prevalence of 3–7% in school-aged children, considered a major clinical and public health problem because of the association with morbidity and disability in youths and adults [2]. Although, the diagnostic criteria for school-aged children are neutral with respect to gender and age, ADHD is more prevalent among boys than girls with ratios varying from 3:1 to 5:1 in epidemiological studies [3, 4]. Part of this disparity may result from different identification rates, as the disruptive component of the disorder may be less prominent in girls in an educational setting [5]. This type of ADHD where the inattentive component is predominant and the hyperactivity component not present is called attention-deficit disorder (ADD).

ADHD was for long considered a childhood disorder. Nowadays there is growing public and professional awareness that ADHD is also a significant source of impairment for many adults [4, 6, 7]. Although the persistence of ADHD beyond childhood is established, it is difficult to determine the extent of this persistence. Different studies suggest that between one-third and two-thirds of children with ADHD will continue to have disabling symptoms as adults [6–9]. This broad range in persistence is likely to be explained by variation in the diagnostic criteria used, selection criteria, sources of information, changes in source of information, and changes in diagnostic criteria [4, 10, 11]. Depending on clinical measures used and the way diagnostic criteria were applied in different studies, the prevalence of ADHD in adults is estimated 1–4% [12–15]. Diagnostic prevalence of ADHD may be roughly equal for men and women [6].

The goal of this commentary is to present a general overview on several current issues around the pharmacotherapy of ADHD. In this paper, firstly the possible pharmacotherapeutical options in the treatment of ADHD, in children, adolescents, and adults is described. This overview is followed by the epidemiology of ADHD medication use in these different age groups. Then, some concerns caused by the trend in medication use are discussed taking into account the developmental perspectives. Finally, concerns regarding the drugs themselves in different age groups are summarized. This paper makes no distinction between ADHD in general and the subtype ADD, unless specifically needed.

Methods

As there are many developments on various areas concerning ADHD therapy, we have not tried to do a systematic review. For illustrative purposes: the number of publications on pharmacotherapy for ADHD that can be identified by for example PubMed are around 10,000. Even a meta-review on articles that have a review label, would yield almost 3,000 hits. So instead of the standard approach we choose for a commentary of the topics that we, researchers, trained pharmacists and clinician with a special interest in ADHD, identified as issues currently under debate in particular, but by no means limited to, the Netherlands. This resulted in the themes mentioned (pharmatherapeutical options, pharmaco-epidemiological trends and concerns about ADHD medication due to adverse effects), and in particular in the inclusion of all age groups in this paper. Consequently, per theme, information is presented for children, adolescents and adults.

After selecting the themes, literature was collected per item using PubMed. Papers published in languages other than English, Dutch and German were excluded before screening. Completeness of literature was not a primary aim but general coverage was nevertheless controlled for to some extent by comparing the papers we identified and used with those identified in published review papers.

Pharmacotherapy of ADHD

Children and adolescents

Pharmacotherapeutical treatment of children with behavioural problems resulting from psychiatric disorders is a sensitive subject. In guidelines for the treatment of ADHD, however, pharmacotherapy, psychosocial interventions and the combination of the two are mentioned as a valid treatment option [16–21]. Since most ADHD children have comorbid disorders, combination of different treatment modalities is usually indicated [16, 17, 19].

In both European and US guidelines, stimulants (including methylphenidate and dexamphetamine) are mentioned as the first-choice drugs in the pharmacological treatment of ADHD [16–21]. Several short-term clinical trials have demonstrated a significant reduction of ADHD symptoms in children and adolescents compared to placebo [22, 23]. In approximately 70% of the children with ADHD, treatment with stimulants improved symptoms of hyperactivity, impulsivity, and inattention [22]. In addition to improving core symptoms of ADHD, stimulants also improved associated behaviour, including on-task behaviour, academic performance and social functioning on a short term. There is no study yet showing long-term effects on academic performance.

A landmark research project in the study of ADHD treatment is the Multimodal Treatment Study of Children with ADHD (MTA). In this study, long-term effects of medication and behavioural treatment for ADHD children was studied. During the first 14 months, 579 children aged 7–10 years were assigned to one of four different treatments: intensive behavioural therapy, intensive medication management, combination of the two or routine community care. After the end of the 14-month trial phase, children in the medication and combination groups showed significantly greater improvement in ADHD than those in the behavioural or routine community care groups [24]. After these 14 months, the MTA became an observational study in which study subjects were free to choose their own treatment. Analyses of the 24-month assessment shows that children originally assigned to the medication or combination arms of the trial were still doing better than children from the other two groups in terms of ADHD symptoms, but the differences became smaller [25]. After 36 months, the differences between the original groups were no longer apparent among other due to the changes in treatment and medication management intensity since the trial period. Overall, all groups did show symptoms of improvement over baseline [26].

In the Netherlands, methylphenidate is the most frequently used stimulant and the only officially licensed stimulant for this indication in children aged 6–17 years. Dexamphetamine is only available as compounded capsules prepared in the pharmacy. Since 2003, extended release products of methylphenidate are available on the Dutch market providing the possibility of once-daily dosing. Transdermal products with stimulants as the active component are not available in the Netherlands yet, nor are chewing tablets or oral liquids.

The only nonstimulant drug licensed for the treatment of ADHD is atomoxetine. Atomoxetine is a noradrenergic drug, available in the Netherlands since 2005. It is officially licensed for the treatment of ADHD in children and adolescents aged 6–17. One or two daily doses are required to reach optimal benefit. Head-to-head trials that allow for a final comparison of atomoxetine with methylphenidate with regard to effectiveness are not done yet. In a recent 6-week study by Newcom et al. [27], effects of atomoxetine and osmotically released methylphenidate were compared with placebo. In this study, methylphenidate was more effective than atomoxetine. They also showed that about 40% of the children who did not respond on either one of treatments (methylphenidate or atomoxetine) did respond to the other, suggesting different responders types.

Adults

In contrast with the substantial number of guidelines for treatment of ADHD in children, there is to our knowledge

only one published guideline for the treatment of ADHD in adults: the guideline from the British Association for Psychopharmacology [28]. Both pharmacological and psychological interventions are recommended in adults with ADHD. Analogue to what can be read in the guidelines for children, stimulants are recommended as first-line treatment for adults according to this guideline. Also, atomoxetine is mentioned as first-line treatment.

Wilens reviewed the literature on the use of pharmacotherapy in adult ADHD and identified 15 studies on the efficacy of stimulants and 27 studies on nonstimulant pharmacotherapy [29]. Wilens also concluded that stimulants and noradrenergic drugs (atomoxetine) as well as other antidepressants like desipramine had a clinically and statistically significant beneficial effect on ADHD in adults.

In the Netherlands, neither methylphenidate nor dexamphetamine, the two available stimulants, are officially labelled for the treatment of ADHD in adults. Atomoxetine is the only labelled drug for the treatment of adults although only if ADHD treatment has already been initiated before the age of 18 years. This implies that in the Netherlands all pharmacotherapeutic treatment of newly diagnosed adults is off-label.

Increase of stimulant use and subsequent concerns

During the 90s, a rapid increase of stimulant use was noticed in several western countries [30–35]. As these studies looked at stimulants, this section will be limited to stimulants as well.

Children and adolescents

In the US, the prevalence of stimulant use increased from three to seven fold among children under 18 years of age between 1987 and 1996 [35]. Another US study by Castle et al., estimated that the prevalence of ADHD medication among children aged 0–19 increased from 2.8% in 2000 to 4.4% in 2005 [36]. They showed that treatment rates grew more rapidly for girls than for boys. Also in the Netherlands the use of stimulants by children strongly increased. A study in the northern part of the Netherlands among children aged 0–19 years showed that the prevalence of stimulant use increased from 0.15% in 1995 to 0.74% in 1999 and further to 1.2% in 2002 [32, 37]. Another study in the Netherlands showed a comparable increase of the prevalence of stimulant use: from 0.15% in 1995 to 1.0% in 2001 [38]. Here, treatment rates grew more rapidly for boys than for girls.

Adults

In the earlier mentioned study of Castle et al. the prevalence of ADHD medication use was estimated for adults

(≥ 20 years) in addition to children; they concluded that the prevalence in adults doubled from 0.4% to 0.8% in between 2000 and 2005. Treatment rates grew more rapidly for adults than for children and more rapidly for women than for men [36].

Following discussion

The increased use of stimulants was probably due to the increasing number of children, adolescents and adults being diagnosed with ADHD [4] but also to the prolonged duration of stimulant use [32]. This overall increase use of stimulants raised global concerns and led to public and political debates [39–44]. These discussions focussed on issues like the validity of ADHD as a psychiatric disorder, the potential overdiagnosis and overtreatment of ADHD and the risks of treatment with stimulants [33, 42, 45]. It was also questioned whether the use of stimulants by children is addictive and facilitates the abuse of other substances [46, 47].

Overdiagnosis of ADHD?

When people use the term overdiagnosis, they typically refer to children who are diagnosed with ADHD but should not be, i.e. the false positives. It was suggested that ADHD is the diagnosis du jour [48] and that the diagnosis is desirable for some parents [49]. Scituito and Eisenburg evaluated the evidence for and against overdiagnosis of ADHD [50]. They concluded that it does not appear that there is currently sufficient evidence to support the public perception that ADHD is currently systematically being overdiagnosed. In the Netherlands, where the public discussion suggested that ADHD was diagnosed by GPs on a large scale, a national study suggested that the majority of the children receiving stimulant treatment had got an ADHD diagnosis from a child psychiatrist [51].

However, overdiagnosis is only one side of the coin of poor diagnoses. There will also be children who warrant the diagnosis but go unidentified or undiagnosed, i.e. the false negatives. There is scientific evidence that girls have been and may be consistently under identified and underdiagnosed [52, 53]; as they suffer more often from the ADD where the disruptive component is less prominent. Nonetheless, the reduction of any kind of diagnostic failures, whether false positive or false negative, is desirable.

Stimulant abuse and stimulant misuse

The increased use of stimulants led, among others, to the question whether the use of stimulants is addictive and might facilitate the abuse of other substances.

No cases of addictive effects of methylphenidate, when used as prescribed, have been reported so far. Children with ADHD treated with stimulants have been shown to develop less rather than more substance abuse than untreated children [46, 47]. The results of a meta-analysis confirmed these findings [54].

Nevertheless, there is sufficient literature to suggest that stimulants themselves are misused by individuals both with and without ADHD. In a recent literature review [55] reasons for use, misuse and diversion of stimulants include to concentrate, improve alertness, 'get high', or to experiment.

Concerns about using ADHD drugs—adverse events

As the above shows, major concerns about careless prescribing of stimulants are not warranted. However, this does not diminish the concerns about the drugs themselves. Besides the worries about the disease being a psychiatric disorder while living in a social environment, parents and physicians might also worry about adverse events of the drugs and the long-term effects on the development of the children. Because stimulants have been available for a considerable period of time and because they are the most commonly used pharmacotherapy, especially adverse events of this drug class are mostly discussed in the following paragraphs.

Children and adolescents

Adverse events can be very harsh for patients and their parents. This burden is even harder when one realizes that stimulants do not cure the disease but only treat the symptoms, leading to long-term use of the drugs. Luckily, most adverse events of stimulants are relatively mild. In a Dutch survey among parents of stimulant users less than 16 years old, 264 parents (29%) reported their child suffering from inconvenient adverse effects. Most frequently mentioned by these parents were sleep problems (51%) and loss of appetite (42%) [51].

Insomnia is a frequently occurring problem in both treated and untreated children with ADHD which makes sleep problems such a hard to study adverse effect of ADHD medication [56]. In the earlier mentioned Dutch nationwide survey, physicians reported for 22% of children treated with stimulants, sleep disorders as adverse events. Since another 18–25% of all physicians indicated not knowing whether or not the child was suffered from sleep problems this proportion is probably even higher [51]. It is unclear to what extent these sleep disorders are related to ADHD or to the treatment of the disease with stimulants. A systematic review [57] of not drug treated ADHD children

showed that children with ADHD have higher apnea-hypnoea indexes compared to non-ADHD children. The authors found limited evidence from subjective studies suggesting no significant differences in sleep-onset difficulties and bedtime resistance between children with and without ADHD.

Sleep disorders whether secondary to ADHD medication or not, appear increasingly treated with melatonin. In the Dutch survey of 2003, 11% of the parents of stimulant using children under 16 years old reported their child used melatonin [51]. From a cohort of new users (aged 6–17) of ADHD medication between 2003 and 2006, 14% had melatonin dispensed within 1 year after starting ADHD therapy. Use of melatonin was highest among the youngest children (personal communication, data not yet published). Little is known regarding the use and efficacy of melatonin among ADHD children. Van der Heijden et al. found that melatonin advanced the sleep-wake rhythms and endogenous melatonin. Administering melatonin enhanced total time asleep and chronic sleep-onset insomnia in medication-free ADHD children. However, no effect was found on behaviour, cognitive performance, or quality of life [58]. So, children with ADHD might benefit from melatonin but the evidence is not plenty.

Stimulants may affect appetite and growth of children with ADHD; the magnitude of this effect has been controversial for many years. Loss of appetite was reported for 13–60% of ADHD paediatric patients and parents worry about possible growth reduction resulting from this loss of appetite [51, 59]. Two major reviews examined all available data and both concluded that stimulant therapy may be associated with a reduction in expected height gain, at least in the first 1–3 years of treatment [60, 61]. However, the deficits in height and weight do not appear to be a clinical concern for most children treated with stimulants [60]. The slight reduction in height and weight seems to be dose related [62]. If necessary, dose could be lowered [21]. The effect of drug holidays to reduce growth effects of stimulants is ambiguous [63, 64]. With this lack of clarity about the magnitude of the impact of stimulant use on growth, children treated with stimulants need to have their height and weight measured regularly, for example semi-annually. The importance of good nutrition should be pointed out to parents. Therefore, it is worrisome that the results of the Dutch survey revealed that almost one-fifth (19%) of the Dutch children on stimulant therapy did not receive follow-up care concerning treatment with stimulants, implying that no appointment was scheduled or requested by the medical doctor according to the parents [51]. This percentage is worrisome as transfer of prescribing responsibility further increased the risk of not receiving any follow-up care. These findings call for efforts to improve collaboration between primary and secondary care.

Rare but more severe adverse effects of both stimulants and atomoxetine are possible cardiovascular effects. Both drug classes can increase blood pressure, heart rate, and cardiac rhythm, though mostly on a clinically insignificant level [65, 66]. In 2005, Health Canada briefly suspended Adderall XR (mixed amphetamine salts) in reaction to 12 cases of sudden death in children and adolescents. However, a review by the US Food and Drug Administration (FDA) concluded that sudden death rate for children on stimulants did not exceed the base rate in the general population. The FDA concluded that stimulants should be cautiously used in children and adolescents with pre-existing heart disease [67]. Furthermore, atomoxetine has been associated with an increased rate of suicidal ideation among children [68]. After performing a meta-analysis recently, Bangs et al. [69] also concluded that although uncommon, suicidal ideation was significantly more frequent in paediatric ADHD patients treated with atomoxetine compared to those treated with placebo. However, frequencies of suicide-related events in paediatric patients with ADHD did not differ between methylphenidate and atomoxetine treatments. More studies are required to investigate this rare but very serious adverse event.

Because atomoxetine is a relative new treatment option, it is even more important for children and adolescents treated with this drug that they are well-monitored and do receive regular physical check-ups.

Adults

As far as we know, no large scale study on adverse events of ADHD medication among adults was published. However, results from different trials showed a comparable pattern of adverse events. Headache, decreased appetite and insomnia were frequently seen among adults using methylphenidate or amphetamines [70–72].

Conclusion

Overall, pharmacotherapy of ADHD in children is proven to be effective. Especially for stimulants, and methylphenidate in particular, there is an abundance of evidence. In contrast to many other drugs used by relatively large proportions of children, drugs for treating ADHD are licensed and on-label for children. Although ADHD medication is increasingly used by adolescents and adults, not much is published on specific efficacy and safety issues in these age categories. In general, we may conclude that stimulant use increased over the years, and that there is a lack of studies on long-term effects of ADHD drugs in all ages.

Since the use of atomoxetine is new and on a relatively small scale, not much is known yet about adverse events of

this drug. This may bias the atomoxetine-stimulants discussion in favour of the first.

Although stimulants have been used for decades, as prevalence of use increases, physicians need to be aware that also rare and possibly severe adverse events might come up. Also, the increased longevity of ADHD medication use may give rise to new concerns and stresses the importance of monitoring people who use this medication for such a long period.

Last decade there is an increasing awareness that ADHD persists into adulthood for many patients. More research on the symptoms, starting treatment, and adverse events among adult ADHD patients is needed to get more insight in the pros and cons of ADHD medication use in this specific population.

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