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The treatment of attention deficit hyperactivity disorder has no proven long-term benefits but possible adverse effects

| Opinion

Klaus W. Lange
Institute of Psychology, University of Regensburg, 93040 Regensburg, Germany
Correspondence: klaus.lange@ur.de

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Abstract: Attention deficit hyperactivity disorder (ADHD) is a frequently diagnosed and treated behavioral disorder in children and adolescents and may persist into adulthood. The core symptoms of ADHD frequently cause significant impairment in academic, social and behavioral functioning over many years in children, adolescents and adults. Currently used treatments, such as pharmacotherapy and behavior therapy, can yield significant short-term benefits for many individuals with ADHD. Even though the positive therapeutic effects of medications such as methylphenidate have consistently been demonstrated in children and adults, the extent of their efficacy remains a matter of debate in view of possible bias of research studies and low quality of outcome measures. The therapeutic goals in ADHD should extend beyond the currently described treatment response and should account for the chronicity and long-term impact of the disorder, involving long-term objectives for the treatment of ADHD. The findings of drug trials assessing efficacy and safety over short time periods should be interpreted with caution and cannot be extrapolated to long-term outcomes. It is unclear whether or not the currently used treatments mitigate the negative impact of non-treatment on the quality of life of individuals with ADHD over an extended time period. Long-term randomized controlled trials (RCTs), which are the gold standard for measuring treatment effects, are largely absent and constitute a logistical and ethical challenge. In particular, there are no RCTs supporting the hypothesis that methylphenidate has a long-term "neuroprotective" impact. Long-term administration may result in a diminution of beneficial effects of the drugs used in ADHD, since the brains of individuals with ADHD become more tolerant to the neurotransmitter changes induced by medication. Scant research has adequately evaluated the long-term safety of drugs for ADHD, and systematic monitoring is needed. Possible risks of long-term medication in certain patient subgroups, such as elderly adults, have not been sufficiently investigated. Adverse consequences of ADHD medications may include serious cardiovascular events. While an increased risk of cardiovascular adverse effects is likely to be small in children and adolescents treated with ADHD medications, the risk following long-term administration and in elderly patients may be higher. The long-term safety of ADHD medications remains an open question. Poorly determined long-term beneficial effects of medication need to be carefully weighed against possible over-prescription and a range of potential adverse effects. A method for identifying patients who may obtain more benefits than harms from ADHD medication should be investigated. The close connection of the pharmaceutical industry to the clinical evaluation of ADHD medications is a matter of serious concern, since drug trials funded by industry may result in biased findings and selective reporting of results. Many alternative treatments are rendered questionable by the lack of any methodologically sound evaluation. In future, it may be worth initiating large-scale, well-designed studies investigating the effects of other treatment approaches, such as physical exercise, on ADHD. In summary, treatment of ADHD has no proven beneficial impact on long-term outcomes but may be associated with various adverse effects.
Key words: ADHD; treatment; methylphenidate; long-term efficacy; outcome; adverse effects.

1. Introduction

Medications for attention deficit hyperactivity disorder (ADHD), such as methylphenidate, have repeatedly been shown to have therapeutic short-term efficacy [1-3]. However, the magnitude of the reported treatment effects has been called into question, due largely to the fact that the majority of medication trials were funded by the very companies that produce the drugs tested, suggesting vested interests of the researchers involved, publication bias in favor of positive study results and under-reporting of less favorable findings. Studies on the development and course of ADHD have reported in subjects with ADHD manifold behavioral, social, academic, and occupational long-term difficulties, which, it is claimed, are diminished by treatment, particularly following medication. The present opinion piece will address the question of whether these claims of long-term benefits of ADHD treatment are evidence-based and hold up to closer scrutiny. A critical overview will focus primarily on both possible beneficial and adverse long-term effects of methylphenidate, since this substance is globally the most common pharmacological treatment for ADHD and has been in use since the 1960s. Many aspects and methodological problems discussed here regarding the evaluation of long-term administration of methylphenidate also apply to other medications and may be relevant to non-pharmacological interventions used in the treatment of ADHD.

2. Goals of ADHD treatment

ADHD is one of the most common psychiatric diagnoses in childhood and adolescence, with as many as 10% of youths in the United States carrying this diagnosis [4-6]. ADHD is classified in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as a childhood-onset neurodevelopmental disorder, defined by the presence of developmentally inappropriate and detrimental levels of inattention, hyperactivity, and impulsivity [7]. It has been shown that the symptoms of ADHD can also be found in adult individuals [8], and in two thirds of childhood cases with ADHD, the disorder appears to be a chronic condition that may persist throughout adolescence and adulthood [9]. Various comorbidities are associated with ADHD, including oppositional defiant disorder, conduct disorder, anxiety disorders, and depression. While major impairments in children and adolescents with ADHD involve social and educational problems, serious impairments in adults with ADHD extend to occupational problems, substance abuse, and traffic accidents [10].

Research today adopts a lifespan perspective of the outcomes of ADHD. In this context, it is important to understand the impact of ADHD and its treatment on long-term functioning of individuals affected by this disorder. The core symptoms of ADHD frequently cause significant impairment in behavioral, academic and social functioning, which has an adverse impact on individuals' quality of life. These symptoms frequently persist into adulthood, potentially compromising an individual's functioning over many years. Therefore, it is important to investigate the impact of ADHD on long-term functioning and the potential of treatment to diminish adverse long-term effects.

Most guidelines for the management of ADHD recommend multimodal treatment using two primary treatment methods, i.e. medications and behavior management techniques. The short-term efficacy of pharmacotherapy (with drugs such as amphetamines, methylphenidate, atomoxetine) and cognitive behavioral therapy has consistently been shown (e.g. [11]). When discussing possible positive influences of treatment on a condition, we need to distinguish between clinical efficacy, effectiveness and outcomes. While efficacy is concerned with the best possible results of a particular intervention under perfect conditions, the most likely results of this intervention under real life conditions, taking into account compliance, dropouts, withdrawals, etc., is described as clinical effectiveness. Clinical outcomes are broadly agreed, measurable changes in health or quality of life that result from an intervention.

In many countries, rigorous clinical trials in human beings are legally required to establish claims regarding drug efficacy. Clinical trials of medications for the U.S. Food and Drug Administration (FDA) have used ADHD symptom reduction as the primary outcome measure for treatment response (e.g. [12-14]). The long-term goals of pharmacological therapy for ADHD, beyond symptomatic improvement and short-term response, need to be defined. The therapeutic goals should address optimal treatment outcomes that extend beyond modest reductions of ADHD symptoms and should include syndromatic, symptomatic, and functional remission [15]. Based on a review of the published literature, the following definitions for ADHD therapeutic goals have been proposed: (1) syndromal remission ("no longer meeting diagnostic criteria for ADHD"), (2) symptomatic remission ("symptom scores within the normal range with some remaining functional impairment"), and (3)

functional remission (or recovery, "both symptom scores and functioning within the normal ranges") [15]. However, criteria for symptomatic and functional remission need to be validated and standardized. In addition, valid and reliable tools to assess such outcomes in clinical trial settings remain to be established.

Despite ample evidence that treatments such as medication and behavior therapy yield substantial short-term benefits for many individuals with ADHD, the role of treatment with respect to longer-term outcomes is less well-established. A systematic review attempted to assess the impact of ADHD and its treatment on long-term outcomes in various domains such as social and occupational functioning, antisocial behavior and substance use, driving, and self-esteem [16]. This review, including 351 studies conducted in North America and Europe, examined diverse outcomes over a period of at least two years. In order to compare the findings across the highly disparate studies included, published statistical comparison of outcome results were summarized as poorer than, similar to, or improved versus comparators, and quantified as percentage comparisons of these categories. Treatments and outcomes varied across studies and it was not possible to determine the quality of the treatments administered. The results were interpreted as support for the premise that the long-term outcomes of ADHD are relatively poor in multiple outcome domains in individuals with ADHD without treatment and that these may be improved by treatment, but not necessarily to the level of healthy controls [16]. This review may provide some general suppositions as to outcomes in ADHD, while firm conclusions cannot be drawn due to substantial shortcomings, including the lack of detailed information on the type, duration, and quality of ADHD treatments or the magnitude of treatment effects. The study concluded that the "question remains as to whether the short-term benefits demonstrated by short-term drug or non-pharmacological treatment studies translate into long-term outcomes" [16].

3. Medication in the treatment of ADHD

Medication for ADHD is prescribed to approximately 6% of school-aged children in the United States [6]. Psychostimulants, such as methylphenidate, are the most commonly prescribed drugs for ADHD [17], and have been a first-line medication for ADHD for over 50 years. It is, therefore, important to establish the efficacy, outcome and safety of methylphenidate treatment.

3.1. Short-term effects of ADHD medications

The randomized controlled trial (RCT) is at the top of the hierarchy of evidence in regard to therapeutic questions. Since the first publication of an RCT in the late 1940s, this type of trial has been established as our current best means of evaluating the efficacy of an intervention and as the most effective basis for evidence-based decision making concerning therapeutic interventions [18,19]. Appropriately designed larger RCTs evaluating treatment effects on major clinical outcomes should be conducted rather than small, inconclusive trials assessing surrogate outcomes.

Short-term benefits of stimulants on the symptoms and behavioral problems associated with ADHD have been well established in numerous RCTs. Short-term, randomized, placebo-controlled trials of methylphenidate (as well as d-amphetamine and atomoxetine) have demonstrated marked effects on ADHD symptoms (e.g. [20,21]). The question whether methylphenidate is beneficial or harmful in the treatment of ADHD in children and adolescents was addressed in a comprehensive systematic review [22,23] using the Cochrane Handbook [24] and the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [25,26]. This systematic review focused on the benefits and harmful effects of methylphenidate in parallel and crossover RCTs comparing the active drug with placebo or no intervention [22,23]. None of the previously published reviews of the effects of methylphenidate in children and adolescents with ADHD had been conducted using Cochrane methodology or prepublishing a peer reviewed protocol. Further methodological shortcomings of previously published reviews are listed in Table 1.

Table 1: Problems of reviews of methylphenidate effects in children and adolescents with ADHD (see [23]).

No use of Cochrane and PRISMA guidelines
No prepublication of a peer reviewed protocol
No consideration of methylphenidate dosage
No control for the treatment effect on subtypes of ADHD
No subgroup analyses on comorbidity influencing treatment effects
Combination of outcome data across raters/observers
No separation of outcomes for inattention and hyperactivity or impulsivity
No information regarding adverse events
No systematic assessment of risk of random errors, risk of bias, and trial quality

The Cochrane systematic review of methylphenidate for children and adolescents with ADHD raised several caveats regarding the evidence seeking to underpin the use of the drug for ADHD [22]. The findings of meta-analyses were based on the ratings of ADHD symptoms and general behavior by teachers, parents and observers. The results of the Cochrane systematic review suggest the following: (1) Methylphenidate may improve teacher reported ADHD symptoms, teacher reported general behavioral problems, and parent reported quality of life in children and adolescents diagnosed with ADHD [22]. (2) Within the short follow-up periods of the included trials (median treatment duration of 49 days in 38 parallel group trials, 14 days in 147 crossover trials), methylphenidate was associated with an increased risk of non-serious adverse events, particularly insomnia and decreased appetite, but no evidence of an increased risk of serious adverse events. (3) The vast majority of trials (96.8%) were considered to be at high risk of bias according to the Cochrane guidelines [22]. As a result of such consistent bias and the low quality of outcomes according to GRADE [27], the authors judged the available studies less favorably than previously published systematic reviews and meta-analyses had done, and concluded that the exact therapeutic benefit of methylphenidate is uncertain [22,23]. This conclusion has led to fervent debate, primarily because the authors considered that a high proportion of the available studies involved a risk of bias due to vested interests [28-30].

3.2. Long-term effects of ADHD medications

Evidence-based treatments have been shown to improve functioning in children with ADHD. They fail, however, to normalize long-term outcomes. For example, in the Multimodal Treatment Study of children with ADHD (MTA), the largest RCT for ADHD so far conducted, 14 months of intensive administration of medication, behavior therapy, a combination of both, or community care resulted in substantial improvements in symptoms of ADHD, severity of associated disorders, and multiple aspects of functional impairments [11]. While differences between treatment groups, in regard to symptoms and several domains of impairment, existed at the end of the active treatment period, they were found to have dissipated within two years post-treatment [31]. At long-term follow-up six and eight years after baseline, all groups presented with some of the treatment gains at post-treatment assessment. All groups continued to have substantial impairment compared to their classmates without ADHD [32].

Evidence from controlled trials for longer term benefits of stimulants and atomoxetine is largely absent. Five RCTs and ten open-label extension studies of initial short-term RCTs, with a minimum total follow-up of 24 weeks, were identified in a systematic review [33]. All of these RCTs found that medication was significantly more efficacious than placebo in treating ADHD in adults, and the extension studies suggested that this favorable effect of medication was maintained during the open-label follow-up period [33]. The duration of these trials was limited to a maximum of four years. Further observational studies (naturalistic longitudinal and cross-sectional) provided information about longer term functional outcomes, side effects and complications. These studies also suggested positive correlations between early recognition of the disorder, stimulant treatment during childhood and favorable long-term outcome in adult ADHD patients [33]. Limitations of the currently available long-term studies include the substantial diversity of outcome measures, study designs not allowing for a meta-analytic evaluation, and the focus on ADHD symptoms as a measure of efficacy rather than on the functional implications of drug treatment. In order to comprehensively investigate the long-term effects of ADHD medications, future work needs to incorporate meaningful measures of functional impairment and evaluate the degree to which the patients' behavior has been optimized.

Observational pharmacoepidemiological studies comparing periods when patients are on versus off ADHD medications have suggested potential long-term benefits of treatment on serious co-occurring problems, such as criminal convictions [34], substance abuse [35], transport accidents [36] and suicidal behavior [37].

3.2.1. Social behavior

Peer rejection has been identified as an important factor helping to explain long-term impairments in children with ADHD that persist despite treatment [38]. Childhood peer rejection was uniquely predictive of delinquency, smoking, anxiety, and global impairment in middle adolescence [38]. An important consideration in this context is the distinction between ADHD with comorbid autism and "pure" ADHD. Addressing and evaluating peer rejection in treatment planning may therefore be able to improve long-term outcomes in children with ADHD. A systematic review compared the long-term (at least two years) self-esteem and social function outcomes of individuals with untreated and treated ADHD across childhood, adolescence, and

adulthood [39]. Untreated ADHD was associated with poorer long-term self-esteem and social function outcomes compared to non-ADHD controls. However, the number of studies was small, calling for further long-term studies.

3.2.2. Criminal behavior

In an attempt to assess the role of medication with respect to criminal behavior, it was found that individuals with ADHD were less likely to be convicted of a crime during periods on stimulant or non-stimulant medications than when off medication [34]. Among 25,656 patients with ADHD, pharmacotherapy for the disorder reduced criminality by 32% for men and by 41% for women. No long-term change in criminality was observed after patients discontinued taking ADHD medication [34]. Thus, the reduction in the rate of criminality was associated only with current use of ADHD medications. Possible bias from reverse causation, i.e., patients may have discontinued treatment because of their criminal behavior, rather than the other way around, was avoided by assessing if the order of the change in medication status played a role. It could be shown that the associations found were significant regardless of the order. These findings suggest statistically significant but not dramatic reductions in the overall crime rate in individuals with ADHD on medication. However, taking medication had no long-term effect on reducing criminality.

3.2.3. Substance abuse

The question of whether prescribing stimulants to patients with ADHD increases their risk of future substance abuse has been of long-standing concern (e.g. [40,41]). Long-term follow-up studies found neither positive (i.e. decreasing risk for substance use) nor negative (increasing risk for substance use) effects of clinical treatment with stimulants [42]. Using Swedish national registers, an association between stimulant ADHD medication and substance abuse (as indexed by substance-related death, crime, or hospital visits) was investigated in individuals diagnosed with ADHD (26,249 men and 12,504 women) over four years [35]. ADHD medication was not associated with an increase in the rate of substance abuse. In fact, the rate was 31% lower among those prescribed ADHD medication three years previously. It was also found that the longer the duration of medication, the lower the rate of substance abuse. In summary, this study found no indication of an increased risk of substance abuse among individuals prescribed stimulant ADHD medication [35], which is in accord with a meta-analysis [43].

The Swedish study is population-based and the largest available on the association between stimulant ADHD medication and drug abuse. However, the follow-up was limited to four years, which limits its generalizability over the life course. Substance-related hospitalizations, convictions and deaths from medical and legal records were used to index substance abuse. This has the advantage of not requiring accurate respondent recall and reporting. However, mainly severe cases of substance abuse outcomes were included and may allow no generalization to less severe substance use outcomes.

3.2.4. Serious transport accidents

Difficulties in vehicle driving have been found to be more frequent in individuals with ADHD than in control subjects (for review see [44]). A longitudinal study using data from population-based registers in Sweden showed that ADHD was associated with an increased risk of serious transport accidents as identified by admission to emergency hospital care or death due to transport accident. The rate of serious transport accidents was increased by 42% to 47% in individuals with ADHD compared to those without ADHD [36]. The magnitude of this association was similar to findings of a population-based case-control study in North America [45]. Visual inattentiveness and impulsiveness have been suggested to provide the largest contributions to the risk of transport accidents in patients with ADHD [46]. Medications alleviating ADHD symptoms might therefore be expected to lead to safer driving behavior and a reduced risk of accidents [47]. In male ADHD patients of the Swedish study, ADHD medication was associated with a 58% risk reduction of serious transport accidents, whereas no significant association was found in female patients [36].

3.2.5. Suicidal behavior

A Swedish register-based longitudinal study using a within-patient design followed 37,936 individuals diagnosed with ADHD to determine any association between ADHD drug treatment status and suicide-related events, i.e. suicide attempt and completed suicide [37]. The incidence rate of suicide-related events during ADHD drug treatment periods was compared with that during non-treatment periods. At the population level, drug treatment of ADHD was associated with an increased rate of suicide-related events. It is unclear if

this observation is due to the use of ADHD medication or rather to unmeasured confounding factors, such as baseline severity of ADHD or familial susceptibility to ADHD. The within-patient comparison showed a reverse association between ADHD drug treatment and rate of suicide-related events [37]. Among stimulant users, a reduced within-patient rate of suicide-related events was found during treatment periods. Non-stimulant/mixed users showed no significantly increased within-patient rate of suicide-related events during non-stimulant treatment periods. However, these findings should not lead to the assumption of a potential protective effect of ADHD medication on suicidal behavior. It needs to be borne in mind that a meta-analysis of clinical trials reported a statistically significant association between use of atomoxetine and suicidal ideation, but not suicidal behavior [48]. Findings of observational studies have suggested an increased risk of completed suicide among drug-treated children and adolescents with ADHD [49].

3.2.6. Strengths and weaknesses of population-based register studies

Population-based register data have several strengths compared to clinical studies. For example, the sample size is substantial and representative for the population, therefore avoiding referral bias, selective participation, and other threats to validity and generalizability. In Sweden, ADHD diagnoses are made by specialized psychiatrists and are blind to outcomes [50]. ADHD medication is recorded when a prescription is filled and is, therefore, free from recall bias. However, dispensed prescriptions might inaccurately reflect patients' actual drug intake, since family members or healthcare staff could also collect the drug.

Unlike RCTs, observational studies like the Swedish population-based register studies [34-37] are invariably vulnerable to many threats to validity, such as selection effects, and cannot account for all possible confounding variables involved in the selection of individuals for treatment [51]. Differences in the indications for the drug are the biggest threat: some patients might receive medication because they are different from others, e.g., they may be more severely affected, presenting with more symptoms and comorbid conditions. Selection effects might also have occurred in Sweden, since the registration of outpatient diagnoses was not complete in all parts of the country when the studies were conducted [34]. The Swedish Medical Products Agency recommends pharmacotherapy for ADHD only when other supportive interventions have failed, suggesting that the prescription of ADHD medication is likely to be an indicator of the more severe cases of ADHD [34]. In addition, only treatments by specialist physicians were entered into the National Patient Register.

Caution is needed when attempting to generalize the findings based on the Swedish population data [34-37], since many factors, including prevalence of ADHD diagnosis, rate of medication, concomitant non-pharmacological treatments, and prevalence of illicit drug use or other forms of substance abuse, will vary between countries and cultures.

While the within-individual analyses of the studies from Sweden adjusted for all potential confounders that are constant during follow-up (e.g., genetic predisposition and early environment), the effects of unmeasured confounders and mediators which varied during follow-up (cyclic nature of the disorder, substance use, crime, or engagement with services providing prescriptions) cannot be excluded. RCTs are therefore needed to clarify this issue.

In order to evaluate the net effects of pharmacological ADHD treatment, the benefits with respect to ADHD symptoms and outcomes need to be weighed carefully against the risk of side effects [40,52], potential over-prescription, and development of tolerance, dependence, or addiction [41].

4. Safety and adverse effects of ADHD medication

Common side-effects of ADHD medications include loss of appetite, growth retardation, gastrointestinal symptoms, cardiac problems, insomnia, tics, irritability, mood changes, drowsiness, dizziness, headache, and others [53]. Scant research has been performed on the long-term safety of drugs for ADHD, and it was long unknown to what extent the long-term safety and efficacy of ADHD drugs were evaluated prior to their market authorization. An assessment of premarket safety and efficacy studies for ADHD medications in children identified all such drugs approved by the FDA and extracted data on clinical trials performed by the sponsors and used by the FDA to evaluate the drugs' clinical efficacy and safety [54]. Thirty-two clinical trials were conducted for the approval of 20 ADHD drugs. The median number of participants studied per drug was 75. Eleven drugs (55%) were approved after fewer than 100 participants were studied and 14 (70%) after <300 participants [54]. The median length of time that the drug was tested prior to its approval was four weeks, with five (38%) drugs approved after participants were studied for less than four weeks and 10 (77%) after less

than six months [54]. In summary, the clinical trials conducted for the approval of many ADHD drugs were not designed to assess rare adverse events or long-term safety and efficacy. Therefore, better assurance is needed that proper trials are conducted before or after a new medication is approved. The responsible authorities are required to enforce the completion of post-marketing surveillance studies [54].

In order to assess the long-term safety of drugs for ADHD, an extensive bibliographic search was performed for prospective studies evaluating the incidence of adverse events in children and adolescents treated for ADHD [55]. A total of six prospective studies, all funded by pharmaceutical companies, had monitored drug safety during therapy for at least 12 weeks. The drugs studied were atomoxetine (two studies, 802 patients), osmotic-controlled released oral methylphenidate formulation (two studies, 512 patients), extended release formulation of mixed amphetamine salts (one study, 568 patients) and transdermal methylphenidate (one study, 326 patients) [55]. Heterogeneity was found in the duration of follow-up (ranging between one and four years). The rate of treatment-related adverse events ranged from 58% to 78%, and the rate of discontinuation due to adverse events ranged from 8% to 25% of the children [55]. While decreased appetite, insomnia, headache and abdominal pain were the most common adverse events observed, the studies may have missed rare ones such as suicidal thinking or prolonged and painful erections. To summarize, few studies have evaluated the long-term safety of drugs for ADHD, and systematic monitoring of this is needed.

Under the erroneous assumption that a child is a small adult, most of the psychotropic drugs prescribed to children have been tested only in adults [56]. Furthermore, an increasing number of children of decreasing age are receiving not merely a single psychoactive compound but rather combinations of such drugs, the safety of which has never been investigated [57,58].

4.1. Cardiovascular safety of ADHD medication

ADHD medication may be associated with cardiovascular effects. For example, psychostimulants and atomoxetine are known to slightly accelerate the heart rate and raise blood pressure [59,60]. Conflicting evidence regarding the cardiovascular safety of psychostimulants, including the question of an increased risk of myocardial infarction, sudden cardiac death, or stroke, has emerged over time [61]. Several reports published in 2006 of heart attacks and strokes in children receiving ADHD medications sparked concern and led to a temporary suspension of the marketing of stimulants in Canada [62]. Other findings indicated that frequently prescribed psychostimulants are not associated with an increase in heart attacks, strokes, or sudden deaths [63,64]. However, a methodological problem of these observational studies is under-reporting of side effects.

In the longest prospective follow-up study available, the association between stimulant use and the risk of cardiovascular events was determined in Denmark [65]. Cardiovascular events observed included arrhythmias, hypertension, ischemic heart disease, heart failure, cerebrovascular disease and cardiovascular disease not otherwise specified [65]. These events were rare but twice as likely in stimulant users as in non-users, both in the total national population and in a population-based sample of children and adolescents diagnosed with ADHD [65]. These results suggest an increased risk of cardiovascular disease associated with stimulant treatment in children and adolescents, even after adjusting for a number of potential confounders.

In a case-only study analyzing a population of 114,647 children and adolescents aged 17 or younger with recent commencement of methylphenidate treatment, data on 1,224 adverse cardiac events could be extracted. In this study, methylphenidate use was found to be associated with a statistically significant increase in risk of cardiac arrhythmia shortly after the onset of treatment [66]. The risk was more pronounced in individuals with existing congenital heart disease. No significant risk of myocardial infarction was observed, although the risk increased after the first week of treatment and remained raised for the first two months of continuous treatment [66]. Cases of hypertension, ischemic stroke, and heart failure did not seem to be over-represented in the two months after the start of methylphenidate treatment [66]. The findings of this observational study prompted the authors to suggest that methylphenidate use might trigger the occurrence of arrhythmia in individual patients. In addition, the study underscores the need to closely monitor patients with cardiovascular risk or to consider the option of non-stimulants [67]. While the absolute risk of cardiovascular adverse reactions might be low, the benefits of methylphenidate should be carefully weighed against its potential cardiovascular risks, especially when considering the large-scale, globally increased use of ADHD medication.

A systematic review and meta-analysis has been conducted to evaluate potential cardiovascular effects of

methylphenidate, amphetamines, and atomoxetine in children and adolescents with ADHD [68]. Eighteen clinical trials with data from 5837 participants (80.7% boys) and an average duration of 28.7 weeks (range 4–96 weeks) were included. Small, but statistically significant increases in the difference between pre- and post-treatment measurements of systolic blood pressure were revealed for all three medications [68]. Amphetamine and atomoxetine treatment were also associated with statistically significant pre-post increases of diastolic blood pressure and heart rate. Other cardiovascular effects were reported by 12.6% of participants on medication, and 2% of patients discontinued their medication due to cardiovascular problems [68]. Comparisons between the three medications did not show any significant differences in terms of the above parameters or severity of cardiovascular effects. Since increased blood pressure and heart rate are considered to be risk factors for cardiovascular morbidity and mortality, patients taking ADHD medication should be monitored carefully for heart rate and blood pressure.

In light of an increased use of medications in adults with ADHD, an investigation of cardiovascular adverse reactions is needed for all relevant age groups over extended periods of time. In the published studies assessing cardiovascular effects of pharmacological therapy of ADHD, elderly patients are under-represented and the available results cannot therefore be generalized to this population.

Labeling and treatment guidelines for ADHD medications are required to provide comprehensive information and cautionary notes regarding cardiovascular side effects, especially in individuals with a personal or familial history of cardiovascular disease. It is noteworthy that product labeling for ADHD medications has been shown to provide healthcare professionals and consumers in several countries with inconsistent information regarding the potential causal relationship between stimulant use and specific cardiovascular risks in children and adolescents [69]. Routine electrocardiography and monitoring of blood pressure in individuals taking ADHD drugs should be recommended.

In summary, an increased risk of serious cardiovascular events such as myocardial infarction is likely to be small. However, it needs to be pointed out that the risk following long-term medication and in elderly adults has not been sufficiently investigated and might be higher.

4.2. Methylphenidate and the developing brain

Dopamine dysfunction in the brains of individuals with ADHD could explain why stimulant medications (amphetamine and methylphenidate), which increase dopamine signaling, are therapeutically beneficial. A major concern regarding psychostimulant medications in the treatment of children and adolescents with ADHD is the potential adverse influence on the developing brain, particularly with respect to dopaminergic brain function [70-72]. The findings of two studies in young non-human primates suggest that chronic methylphenidate or amphetamine administration (for 12 or 18 months) initiated in peri-adolescence or adolescence at clinically relevant doses does not significantly alter synaptic dopamine markers in the brain (transporters and D2/D3 receptors) [73,74] or sensitize the brain to drug rewards [73]. However, a major problem of a translational interpretation of these studies is that they were performed in healthy animals and the long lasting effects of chronic stimulant treatment may differ in individuals with ADHD.

Methylphenidate acutely enhances dopamine signaling by blocking the dopamine transporter, which is the main mechanism through which dopamine signals are terminated [75]. Using positron emission tomography, dopamine transporter availability was measured in the brains of 18 never-medicated adult individuals with ADHD prior to and following 12 months of treatment with methylphenidate and in 11 controls who were also scanned twice without stimulant medication [76]. Twelve months of methylphenidate treatment increased striatal dopamine transporter availability by 24% in the caudate, putamen and ventral striatum of individuals with ADHD while there were no changes in control subjects retested after a 12-month period. Upregulation of dopamine transporter availability during long-term treatment with methylphenidate may decrease treatment efficacy and exacerbate symptoms when medication is discontinued [76]. Future studies should investigate the question of whether long-term treatment reduces the efficacy of stimulant medication.

In a qualitative review of 29 brain-scan studies with different methods and goals, it was claimed that the therapeutic administration of stimulants is associated with an attenuation of abnormalities in brain structure, function, and biochemistry in individuals with ADHD [77]. However, several significant limitations of these studies include small sample sizes, differences in the presence of comorbidities, varying durations of medication and wash-out from medications, and, most importantly, the lack of

randomization of medication, i.e., recruitment of participants was according to their medication status [77]. It would therefore be incautious to suggest that stimulant treatment for ADHD leads to a "normalization" of brain functioning, as demonstrated by brain imaging.

The findings of animal studies have suggested striking and deeply concerning effects of clinically relevant doses of methylphenidate on the functioning and plasticity of the juvenile prefrontal cortex (for review see [78]). The translational interpretation of these results could raise the question whether the administration of methylphenidate in children might enhance sustained attention and long-term memory while producing subtle deficits in working memory and behavioral flexibility [78]. The latter effects might have long-term or even life-long consequences. In healthy children and adolescents, the methylphenidate doses previously thought to be therapeutic may in fact impair certain aspects of cognition [78].

5. Conclusion and outlook

Medications for ADHD such as methylphenidate have repeatedly been shown to have therapeutic short-term efficacy and are administered or, as critics suggest, over-prescribed worldwide to an ever-increasing number of individuals diagnosed with ADHD [1-3]. In view of this, a consideration of the quality of evidence underpinning the notion of beneficial long-term outcomes of medication is warranted.

5.1. Long-term efficacy and outcomes of medications for ADHD

Children with ADHD are at substantial risk of adverse outcomes in adolescence and adulthood. A diagnosis of ADHD is associated with poor educational outcomes and premature cessation of education [79] and also predicts serious antisocial behavior, substance misuse in adolescence, and police intervention [80]. A long-term follow-up study has shown that childhood ADHD is associated with adverse social, occupational, and economic outcomes, antisocial personality disorder, risk of substance use disorders, psychiatric hospital admissions, and incarcerations [81]. It, therefore, needs to be established whether medications for ADHD show beneficial effects with respect to the above mentioned adverse outcomes of ADHD.

Despite an abundance of studies reporting positive short-term effects of ADHD medications, there is currently a paucity of available long-term studies. An extrapolation of short-term results to long-term outcomes is not appropriate, and well-designed studies with long follow-up are needed. Long-term RCTs, which represent the highest standard for measuring treatment effects, are largely absent and produce a significant logistical and ethical challenge. A major limitation of observational studies is an unavoidable selection bias due to nonrandom assignment of the intervention. The optimistic view that stimulant therapy of ADHD has long-term beneficial effects and is well tolerated is based on merely a handful of RCTs and open-label extension studies with follow-up periods of as little as 24 weeks [33]. Without the inclusion of these short "long-term" studies, very little data would have been available. There is a clear shortage of sound data deserving the epithet "long-term". If we consider ADHD to be a life-long condition, treatment effects should be investigated over decades rather than months.

Although the description of ADHD in international classification systems [7] seems to reflect a consensus regarding the clinical entity of ADHD, there is still considerable controversy and debate surrounding this issue [5,82]. No distinctive etiology, pathophysiology, biomarker or cognitive profile [83,84] have been identified and a notable overlap of ADHD symptoms and those of comorbid psychiatric disorders exists. Due to the phenotypic and etiopathophysiological heterogeneity of ADHD, potential therapeutic effects of pharmacological and non-pharmacological treatments of ADHD might be confined to patient subgroups as yet unidentified. Furthermore, the findings in clinically referred cases, i.e. narrowly diagnosed or severely affected individuals, may not allow the generalization to non-referred cases in the community.

5.2. Harmful adverse reactions of medications for ADHD

Medications for ADHD appear to be generally well tolerated, with only mild or minor adverse effects. However, their rational use can be guaranteed only through the implementation of evidence-based practices, i.e., by monitoring the safety and efficacy of treatments in the short and long terms with appropriate approaches. Short-term follow-up might not detect potentially serious, long-term adverse reactions. In other words, "an ambitious agenda to assess long-term outcomes in the millions of patients on these medications is warranted" [54].

Although adverse effects are detected within drug trials, they might not be reported appropriately by investigators, in part because reporting is subject to influence by sponsors [85]. It has been suggested that

the pharmaceutical industry conceals unfavorable safety data [86]. Under-reporting of harm can result in a false perception of the benefit-risk ratio of medications. These are compelling reasons why careful, systematic follow-up of individuals with ADHD taking medication is essential. If ADHD is a lifelong condition in some individuals requiring medication over years or even decades, the need to assess possible adverse effects such as cardiovascular risks across the lifespan is clear. The relatively low incidence of such effects in young people is probably not predictive for elderly patients.

When weighing poorly determined long-term benefits of ADHD medication against a range of possible adverse effects, one could argue that the medication should be restricted to as few patients as necessary rather than prescribing it as a treatment of choice. A pressing concern is therefore the clinical characterization of those individuals with ADHD in whom substantial benefits of medication clearly outweigh the risk of adverse effects. In summary, the long-term safety of ADHD medications remains an open question.

5.3. Drug trials and pharmaceutical industry

In the Cochrane review on methylphenidate for ADHD in children and adolescents [22,23], potential conflicts of interest among funders or investigators was the most common single source of bias [22,23]. This highlights the close relationship between the pharmaceutical industry and the clinical evaluation of methylphenidate efficacy.

The impact of the pharmaceutical industry on the practice of medicine can hardly be overstated. Since no distinct etiology, pathophysiology or biomarker has been revealed in ADHD (e.g. [83]), the descriptive diagnostic criteria are based not on scientific evidence but rather on consensus and are therefore accessible to lobbying interest groups. Another central issue causing concern is that the overwhelming majority of studies evaluating the efficacy of ADHD drugs are funded by the very companies that manufacture these medications. For example, the Cochrane review on methylphenidate in children and adolescents [22,23] concluded that about two thirds of the available drug trials were at high risk of bias due to vested interests, e.g., studies funded by or authors working for parties with a possible conflict of interests, such as companies producing or selling methylphenidate. The ferocity of the ensuing debate could have suggested to some that the authors of the Cochrane review had reached an outrageous conclusion in their assessment [28,30,87]. The debate highlights our dependence on clinical findings developed under the influence of industry.

We expect any good product review to be unrelated to the company producing the product. The funding of drug trials and the sponsoring of investigators by industry are therefore often eyed with suspicion by critics. Physicians, whose first obligation is to their patients' wellbeing, and industry, whose primary responsibility is to generate profits for their shareholders, make odd bedfellows when evaluating what is the best available treatment. The suspicion that industry-sponsored research is inferior or tainted was evident as early as the first half of the 20th century, when employees of drug companies were denied membership of the American Society for Pharmacology and Experimental Therapeutics [88].

Possible flaws and shortcomings of drug trials can theoretically be judged after publication of these studies, provided they are, in fact, published. For example, drug trials assessing efficacy and safety over short periods of time are obviously less expensive than long-term investigations, and their findings should thus be viewed with skepticism. More importantly, however, pharmaceutical companies have been reported to only selectively reveal the findings of trials investigating psychoactive drugs [86]. The results of trials showing only little or no effects may remain safely kept in the researchers' drawers and never see the light of day.

Concern has frequently been expressed that drug trials sponsored by the pharmaceutical industry may result in biased findings [89,90]. Investigators with conflicts of interest, financial or otherwise, are more likely to arrive at positive conclusions, possibly as a result of biased study design, industry suppression of negative results, biased interpretation of results by investigators, or preferential funding by industry of projects likely to show positive results [91]. The possibility that industry will sponsor only those research projects that are likely to be positive violates the uncertainty principle which, for both scientific and ethical reasons, states that patients should be enrolled in an RCT only if there is substantial uncertainty as to which of the trial treatments will show the greatest benefit [92-94]. While drug innovation in regard to ADHD has virtually come to a halt in recent years, the pharmaceutical industry has increasingly focused on lobbying, marketing, and public relations. This is an unacceptable situation which may result in over-medication of patients. In addition, three-arm trials, including the experimental drug, an active reference treatment, and a placebo comparator, have

been recommended by the European Medicines Agency and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, specifically for the clinical investigation of ADHD medications [95,96]. This type of head-to-head comparison may not be in the interest of the manufacturer of a new medication since its implementation is more demanding and expensive and it might eventually demonstrate inferior effects and outcomes of the new drug compared to available substances.

Most scientific journals require authors to reveal any relevant conflicts of interest, particularly financial and other business connections. These assurances should not become empty phrases, and readers must make up their own minds as to whether they wish to consider findings and statements of researchers with competing interests when drawing conclusions. Some health care professionals seem to be aware of this potential bias, perceive the methodological quality of studies as negatively influenced by industry sponsorship, and appear less likely to accept and act on findings from industry-funded trials [97]. Responsible and critical doctors and patients can make individual decisions as to whether they believe that findings and claims are rendered untrustworthy by the influences of industry. Many subtle mechanisms have been shown through which sponsorship and conflicts of interest may influence intervention effects on outcomes [98]. Vested interests per se appear to be sufficient to lead to overestimation of benefit and underestimation of harm [98].

It would perhaps be naïve to imagine that medication research could be conducted independently of industry and funded solely by the taxpayer and public research organizations. Therefore, patients, doctors and other health care professionals need to be aware of the tenuous evidence of supposedly large effects following the pharmacological treatment of ADHD.

The Cochrane review on methylphenidate for ADHD in children and adolescents [22,23] has provided us with valuable food for thought on the poor quality of the evidence underpinning the efficacy of methylphenidate. The magnitude of the treatment effects of methylphenidate remains far from clear and the published effect sizes should be viewed with caution. Priorities for future research on ADHD medication should include its effects and outcomes in subgroups and comorbidities of ADHD under real life conditions.

Most of the criticisms discussed here in regard to the problematic influence of the pharmaceutical industry on drug trials, particularly their interest in marketing and sales figures, apply to all suppliers of the ever-expanding number of other ADHD “treatments”, such as patient health guides, computer training programs, coaching, dietary recommendations, food supplements, herbal remedies, exotic exercise regimes, and others. Many of these alternative, unconventional and speculative approaches are rendered questionable by the complete lack of any methodologically sound evaluation, use of standardized evaluation procedures or appropriate assessment of adverse effects (e.g. [99]).

While hundreds of studies have investigated the effects of medication in ADHD [22,23], only a small fraction have been concerned with other treatment approaches such as diet and exercise [100,101]. As yet, the results of trials assessing the effect of polyunsaturated fatty acids and various minerals in ADHD are unconvincing [101-103]. Meaningful studies in this context need to overcome various logistical problems, including the use of RCTs providing dose-response data in large samples with long periods of supplementation and follow-up. The difficulties in conducting an assessment of this kind are obvious. Furthermore, food supplements may have unwanted side effects that elude detection since they may occur many years after administration. Physical exercise has been suggested as a promising alternative or additional treatment option for patients with ADHD [104]. It may be well worth initiating and financing large-scale, well-designed studies investigating the effects of exercise on ADHD, especially since physical exercise will have additional health benefits including positive cardiovascular effects. The challenge will be to secure adequate funding for this kind of approach. Who would benefit financially from additional physical education classes at school?

5.4. The bottom line

Conclusive evidence of long-term benefits of ADHD medications remains elusive. Any claims to the contrary are light on substance and possibly heavy on salesmanship.

Declaration of interests

The author declares no competing interests.

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