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The need for alternative treatments for attention-deficit/hyperactivity disorder

| Opinion

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Abstract: In 2019, an application for the addition of methylphenidate for the treatment of attention-deficit/hyperactivity disorder (ADHD) to the World Health Organisation (WHO) Model List of Essential Medicines was rejected by the WHO Expert Committee due to uncertainties concerning the benefit-versus-harm profile of the drug. This decision highlights the many problems related to the use of methylphenidate in individuals with ADHD. Doubts regarding the effectiveness of commonly used ADHD therapies on clinically relevant outcome measures, the unproven long-term efficacy of treatment and concerns surrounding potentially serious adverse effects of medication have led to a search for alternative treatment options. Lifestyle factors, such as quality of diet, physical and sedentary activities, sleep patterns and electronic media use, may be precursors or consequences of ADHD. The identification of these health-related lifestyle risk factors would seem to be important in individuals with ADHD, since interventions in these areas may improve behavioural, cognitive and physical symptoms of the disorder. Current evidence suggests that symptoms of ADHD may be ameliorated by improved lifestyle choices. A greater emphasis, in both research and clinical practice, should therefore be placed on lifestyle factors associated with ADHD.

Keywords: Attention-deficit/hyperactivity disorder; methylphenidate; alternative treatment; lifestyle; diet; nutrients; physical activity; sleep patterns; media use.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common psychiatric diagnoses in childhood and adolescence and is also diagnosed in adults. The disorder is characterised by age-inappropriate levels of inattention, impulsivity and hyperactivity and is associated with long-term academic, social and mental health problems [1,2]. Both pharmacotherapy and behaviour therapy yield short-term symptom reduction in individuals diagnosed with ADHD. Psychostimulants and atomoxetine have been shown to improve attention and to decrease activity levels in children in the short term. However, their apparent failure to address the broader clinical needs of many people with ADHD has brought their effectiveness into question, especially in the longer term [3]. For example, the impact of medication on academic performance and quality of life is low [4,5], and initial symptomatic effects are not usually sustained on long-term follow-up [6,7]. Furthermore, concerns have been raised regarding possible adverse effects of medication, which can be as serious as growth retardation, severe cardiovascular events and possibly an increased risk of basal ganglia and cerebellar diseases [8–10].

2. Problems with medication in the treatment of ADHD

In 2018, an application was made to include methylphenidate for the treatment of ADHD in the World Health Organisation (WHO) Model List of Essential

Medicines [11]. The application provided a systematic review of the use, efficacy, safety, availability and cost-effectiveness of methylphenidate in children, adolescents and adults, compared with other stimulant and non-stimulant medications. However, due to concerns regarding the quality and interpretation of the evidence for benefits and harms of methylphenidate [12], the WHO Expert Committee declined to recommend the addition of the drug for the treatment of ADHD to the Essential Medicine List and Essential Medicine List for Children.

Methylphenidate was the first drug to be approved for the treatment of symptoms of hyperactivity or inattention. It had been available internationally since 1954 and received marketing authorisation in the early 1960s prior to the introduction of more stringent rules for the registration process [13]. This means that no balance of efficacy and side effects has been published. Methylphenidate is now used for the treatment of hyperactivity in both children and adults. The background of its authorisation for use in adults merits special attention. In 2010, an application was made, by means of the EU decentralised procedure, for the registration of one form of methylphenidate (Concerta®) for the treatment of ADHD in adults [14,15] in the European Union. However, because the research findings submitted did not clearly demonstrate the efficacy of methylphenidate, and its safety was not sufficiently guaranteed [13,14,16], the United Kingdom Medicines and Healthcare Products Regulatory Agency rejected this application. These safety concerns were related primarily to cardiovascular and psychiatric side effects, as well as the risk of anxiety, aggression and dependence. A further concern was the potential for abuse by adults simulating the disorder in order to receive the drug. These negative conclusions, regarded as trade secrets, have not been made public by the regulatory authorities [13]. In 2017, another attempt was made to acquire a licence in the European Union for the use of methylphenidate in the treatment of adults with ADHD. Since a licence had been granted in Germany in 2011 [17], the drug was also recognised in the entire European Union through mutual recognition by the European Medicines Agency, despite the fact that no further clinical studies had been performed by the manufacturers to support their repeated applications for a licence [13]. In addition, a Cochrane systematic review and meta-analysis of methylphenidate for adults with ADHD [18] was withdrawn from the Cochrane library due to a number of methodological shortcomings and the very low quality of the trials included [19].

Short-term symptomatic benefits of pharmacotherapy in ADHD have consistently been demonstrated in many studies. However, the recommendation of methylphenidate as first-line treatment for children and adolescents with ADHD has been questioned on the basis of two Cochrane reviews [20,21], which have raised concerns regarding the overall quality of the available methylphenidate trials. The therapeutic goals should address optimal treatment outcomes that extend beyond modest reductions of ADHD symptoms and should include syndromatic, symptomatic, and functional remission [22]. ADHD medications have been demonstrated to produce statistically significant improvement of core symptoms compared to placebo, as assessed using rating scales. However, a statistically significant effect does not necessarily equate to any clinically relevant effect or improvement in symptoms or subjective wellbeing. In fact, the effects of medication on quality of life or academic performance appear to be low in ADHD [4,5].

Very few trials on the benefits and harms of methylphenidate in children, adolescents and adults with ADHD with a duration of more than three months are available. Observational population-based register studies from Sweden comparing periods with patients on versus off ADHD medications have suggested potential long-term beneficial effects of treatment on serious co-occurring problems, such as transport accidents [23], criminal convictions [24], substance abuse [25] and suicidal behaviour [26]. However, observational studies 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 [27]. Differences in the indications for the drug are the greatest threat: some patients may receive medication because they appear different from their peers, e.g., they may be more severely affected, presenting with more symptoms and comorbid conditions. In addition, caution is needed when attempting to generalise the findings of the Swedish population studies [23–26], 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.

An important cause for concern is the funding of the overwhelming majority of studies evaluating the efficacy of ADHD drugs by the very companies that manufacture these medications. The Cochrane review on methylphenidate in children and adolescents [28,29] concluded that approximately two thirds of the available drug trials

were at high risk of bias due to vested interests, e.g. through the employment of authors by companies producing or selling methylphenidate and the funding of studies by these companies. Pharmaceutical companies have been reported to only selectively reveal the findings of trials investigating psychoactive drugs [30], highlighting our dependence on clinical findings developed under the influence of industry. In addition to those surrounding the failure to publish trial results showing little or no effect, concerns have frequently been expressed that drug trials sponsored by the pharmaceutical industry may result in biased findings [31,32]. Many subtle mechanisms have been described through which sponsorship and conflicts of interest may influence intervention effects on outcomes [33]. Vested interests alone appear to carry sufficient weight to effect an overestimation of benefit and underestimation of harm [33]. With respect to ADHD medications, the magnitude of the treatment effects remains far from clear, and the published effect sizes should be viewed with caution. In particular, 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.

In summary, doubts have been voiced regarding the effectiveness of commonly used ADHD therapies on clinically relevant outcome measures and the unproven long-term efficacy of treatment, and concerns regarding potentially serious adverse effects of medication have been raised. The present state of information may indicate that pharmacotherapy for ADHD should be used with great caution or even be discontinued after a few months. These circumstances call for a search for alternative treatment options.

3. Alternative treatments of ADHD

Growing evidence suggests that lifestyle may play a role in the pathophysiology and management of mental disorders [34], including ADHD [35]. A range of lifestyle factors have been proposed as potential precursors or consequences of ADHD. These include the consumption of micronutrients and macronutrients, diets, physical activity and digital media use among others; all these factors may be viewed as potential targets of therapeutic intervention.

3.1. Nutrients and diets

As early as the 1920s, a possible association between food and hyperkinetic behaviour was suggested [36]. Children with ADHD and healthy controls appear to have different dietary patterns [37–39]. Major dietary compounds proposed to be helpful in the treatment of ADHD include micronutrients, such as minerals and vitamins, and polyunsaturated fatty acids (PUFAs). Several studies have demonstrated reduced blood plasma levels of various minerals, such as magnesium, iron and zinc, in children with ADHD at group level, and their supplementation may reduce ADHD symptoms in individuals with respective deficiencies. However, evidence in support of this is lacking [40]. The questions of whether vitamin deficiencies are involved in the pathophysiology of ADHD and whether vitamin supplements exert therapeutic effects also remain open [41]. The role of omega-3 PUFAs in the pathophysiology and treatment of ADHD is controversial [40,42]. Since blood levels of several omega-3 PUFAs have been found to be significantly reduced in children with ADHD compared to controls, numerous clinical studies have examined the effects of the supplementation of omega-3 PUFAs. A systematic review of meta-analyses of double-blind placebo-controlled trials, in which ADHD symptoms were rated by parents and teachers, concluded that the effect sizes for PUFA supplementation were small [43]. The pooling of the negative results of a more recent study with previous findings showed no overall effect of omega-3 PUFAs on ADHD symptoms [44]. Thus, there is little support for the efficacy of omega-3 PUFA supplements in the management of the core symptoms of ADHD. In regard to PUFAs, the mode of administration (fish or supplements), the type of PUFA employed (omega-3 or omega-6 or a combination) and the ratio between different omega-3 PUFAs are likely to be important. Focusing solely on the supplementation of omega-3 PUFAs may not be an adequate treatment approach, since an increase in the ratio between blood levels of omega-6 to omega-3 PUFAs has been suggested to be more significant in children with ADHD than the absolute concentrations of either [45,46].
The findings of studies of micronutrient or omega-3 PUFA supplementation may have been influenced by various factors, including heterogeneity of design type, dosage, trial duration, or assessment of response. Whether or not individuals with low levels of certain micronutrients are more responsive to dietary supplementation is unknown. It is therefore important to identify subgroups of individuals who are most likely to benefit from micronutrient administration, including those with low baseline status. There could also be a micronutrient threshold status, above which dietary supplementation has little effect. Furthermore, given the high prevalence of comorbid conditions accompanying ADHD, it is probable that significant numbers of participants included in the trials of supplementation of micronutrients may have had

co-occurring conditions. Observations in several ADHD studies showed that treatment response varied depending on the participants' comorbidities [47]. Moreover, the questions whether micronutrient administration is effective at any time during the life span and whether a critical time window for positive supplementation effects exists need to be examined. The targeting of diet during pregnancy and infancy may be necessary in the early prevention of ADHD [48,49].

An important consideration when administering macronutrients and micronutrients is the risk of unwanted side effects. For example, the supplementation of omega-3 PUFAs, especially at supra-physiological doses for prolonged periods, could be associated with serious adverse effects. Fish oil supplements commonly contain antioxidants and oxidation products of omega-3 PUFAs, both of which may cause adverse reactions. Omega-3 fatty acids are highly prone to oxidative degradation, and a substantial proportion of omega-3 fish oil preparations have been reported to significantly exceed the international voluntary safety recommendations for total oxidation [50]. Animal studies have found that oxidised lipid products can cause harm, including DNA mutations and cancer [51]. The effects of oxidised oils on human health should therefore be examined carefully. Possible adverse consequences of the long-term use of vitamin E added as an antioxidant to fish oil supplements should also be considered, since large-scale trials of α-tocopherol supplementation have suggested a link to elevated rates of prostate cancer [52].

Recent studies have examined the role of dietary patterns and whole diets in ADHD rather than that of specific micronutrients. Low adherence to a Mediterranean diet was found to be positively associated with an increased likelihood of an ADHD diagnosis in children and adolescents [53]. However, cross-sectional investigations of the effects of micronutrients and diets commonly focus on one or several compounds without regard to other lifestyle factors, such as physical activity or sedentary behaviour. Interrelationships between diet and other lifestyle factors have been reported in ADHD. For example, children with ADHD were observed to be almost twice as likely to engage in fewer healthy behaviours [54]. Primary diagnoses of ADHD were significantly reduced in children with better quality of diet, higher levels of physical activity and less time spent playing video games [55].

The role of food hypersensitivities in ADHD appears to be a promising avenue worthy of further exploration. The hypothesis of a relationship between food hypersensitivity and ADHD is supported by several studies [56–60]. A few-foods diet, which excludes many foods and additives, may offer new treatment options [43]. A restricted elimination diet has been demonstrated to be a valuable tool in examining whether ADHD symptoms are induced by individual foods [59]. Furthermore, using a randomised controlled trial, considerable effects of this diet were observed in an unselected group of children with ADHD [59]. A recent open non-blinded pilot study assessed the effects of an oligoantigenic diet, eliminating individual foods for four weeks, in children with ADHD. This study showed a response rate of around 60%, with statistically significant, positive effects on attention and behaviour at group level, dramatic improvements in some children and a significantly improved quality of life [61].

To sum up the available findings regarding nutrients, diet and ADHD, unhealthy dietary patterns may precede a poor nutritional biochemistry status affecting ADHD behaviours, and the management of nutrition and diet should always be considered as an avenue towards improving ADHD symptoms. While several lines of evidence point to a potential role of micronutrients and diets in ADHD, a number of caveats need to be considered before any therapeutic recommendation can be made [62]. Observational studies demonstrating associations between diet and micronutrient levels in people with ADHD and the presence or severity of symptoms do not allow any conclusions on causal relationships, since the preference for certain foods or dietary patterns may be a consequence of ADHD behaviours. A role of individual nutrients in the treatment of ADHD at group level is not supported by current evidence. However, therapeutic benefits of supplementation may be seen in individuals with specific nutrient deficiencies. Potential severe adverse effects of nutritional supplements need to be taken into consideration, especially when administered at supra-physiological doses over extended periods of time. Generally improved lifestyle choices may provide more substantial benefits to children with ADHD than dietary changes alone. The administration of an oligoantigenic diet with subsequent reintroduction of nutrients may provide a more personalised therapeutic approach to ADHD. This kind of intervention should always be considered in children with ADHD.

3.2. Physical activity

Emerging evidence suggests that physical activity may be a protective factor in ADHD. Increased physical activity and greater weekly energy expenditure in adolescence have been shown to be significantly associated with

reduced ADHD symptom levels in early adulthood [63]. The findings of a meta-analysis of randomised controlled trials suggest that short-term aerobic exercise (over 6–10 weeks) had a moderate to large effect on ADHD core symptoms such as attention, hyperactivity and impulsivity, as well as related symptoms, including anxiety, executive functioning and social disorders, in children and adolescents with ADHD [64]. Preliminary evidence from another review, summarising the evidence for the management of ADHD with long-term aerobic physical activity, suggests that physical activity can be beneficial for ADHD symptoms, executive function and motor abilities [65]. A systematic review of 30 short-term and long-term studies supported the finding of clinical benefits of physical activity on behavioural, cognitive and physical symptoms in individuals with ADHD [66]. Adverse effects of physical exercise were not reported in any study.

In summary, preliminary evidence suggests that physical activity may be a protective factor in ADHD and may have positive effects in children with ADHD. Further prospective, randomised studies using larger samples are needed in order to examine the effectiveness of exercise programmes in ADHD. Present evidence is insufficient to support a recommendation of physical activity as a monotherapy.

3.3. Sleep patterns

Sleep problems are common in ADHD and may exacerbate the expression of daytime symptoms [57]. Cross-sectional studies have shown a prevalence of insomnia in adults with ADHD ranging from 43–80%, which is higher than in the general population (31–56%) [67]. Longitudinal evidence for a link between childhood-onset ADHD and insomnia later in life is mixed [67]. Current overall ADHD symptom severity in adults, especially the severity of hyperactivity, has been shown to be associated with the current presence and history of persistent sleep problems [68]. Clinically significant ADHD symptoms as well as inattention and hyperactivity symptom dimensions in adults were consistently associated with insomnia symptoms and altered sleep duration [69]. Adults with ADHD have been reported to differ significantly in a number of subjective sleep parameters when compared to those without ADHD, while no significant differences were observed for polysomnographic parameters [70]. Future studies should investigate if and to what extent sleep-related complaints are underpinned by objective sleep alterations. A cross-sectional study comprising a large sample of 15,291 preschoolers in China showed that a delayed bedtime was significantly associated with a risk of high levels of ADHD symptoms [71], as were longer sleep latency, no naps and frequent sleep-related problems, while longer sleep duration (> 8.5 h) was associated with a decreased risk of high levels of ADHD symptoms [71]. These findings suggest that sleep schedules, encouraging regular sleep habits, may attenuate ADHD symptoms in preschoolers. In summary, the associations between ADHD symptom severity and insomnia symptoms indicate that sleep disturbances require attention in clinical practice.

3.4. Media use

Over recent decades, children's use of electronic media, including internet, television, social networks and video games, has changed significantly and has increased to several hours per day [51]. The use of fast-paced, arousing and violent entertainment media has a significant impact on the development and daily activities of children, with an increase in the use of visual compared to auditory communication, a displacement of activities believed to stimulate cognitive abilities more than screen entertainment media, and a change from free play in groups to solitary web-based media use. A daily screen time of approximately seven hours was observed in youths attending a psychiatric clinic [72]. The findings of various studies suggest that ADHD in children and adolescents is associated with excessive use of digital media entertainment [73,74]. Children with ADHD may be particularly vulnerable to overuse of such activites, including computer games, which operate in short segments, demand relatively little attention and offer immediate rewards. The results of a meta-analysis indicated a small but significant association of electronic media use with increased symptoms of ADHD [75]. Digital media use could be one factor linking altered sleep to ADHD (see above). While a strong case for a link between ADHD and both internet and off-line video gaming has been made [73], the causal relationship of this correlation needs to be investigated in future studies. A better understanding of the relationship between ADHD and electronic media use, particularly in regard to causality, individual susceptibility and the underlying mechanisms, is needed in order to develop prevention and intervention strategies.

Table 1. Treatment options in ADHD

Problems of medications in ADHD
Short-term improvements in ratings of ADHD core symptoms.
Initial symptomatic effects are not usually sustained on long-term follow-up (>12 weeks).
Decreased efficacy of long-term use due to tolerance?
Low impact on on clinically and ecologically relevant outcome measures (e.g. academic performance, quality of life).
Apparent failure to address the broader clinical needs of many individuals with ADHD.
Concerns regarding long-term safety. Adverse events in adults?
Majority of studies evaluating the efficacy of ADHD drugs funded by pharmaceutical companies (vested interests).
Summary: Evidence of benefits and harms of medication is inconclusive.
Alternative treatments of ADHD
Nutrients and diets
Role of single micro- and macronutrients (minerals, vitamins, PUFAs) in the therapy of ADHD is unclear.
Benefits of single nutrients in ADHD may be confined to individuals with respective deficiencies.
Role of dietary patterns and whole diets in ADHD?
Interrelationship between diet and other lifestyle factors.
Possible relationship between food hypersensitivity and ADHD (few-foods diet, restricted elimination diet, oligoantigenic diet).
Physical activity
Moderate to large effects of short-term aerobic exercise on ADHD core symptoms in children and adolescents with ADHD.
Beneficial effects of long-term aerobic physical activity on ADHD symptoms, executive function and motor abilities.
Association of increased physical activity in adolescence with reduced ADHD symptom levels in early adulthood.
Physical activity may be a protective factor and may have positive effects in children with ADHD.
Present evidence is insufficient to support a recommendation of physical activity as a monotherapy in ADHD.
Sleep patterns
Sleep problems are common in ADHD and may exacerbate the expression of daytime symptoms.
ADHD symptom severity in adults is associated with the current presence and history of persistent sleep problems.
Association of clinically significant ADHD symptoms in adults with insomnia symptoms and altered sleep duration.
Association of delayed bedtime and longer sleep latency in preschoolers with risk of high levels of ADHD symptoms.
Association of longer sleep duration (>8.5 h) in preschoolers with decreased risk of ADHD symptoms.
Media use
Link between ADHD and both internet and off-line video gaming (causal relationship?).
Digital media use could be a factor linking altered sleep to ADHD.
Summary: Current evidence suggests that individuals with ADHD may benefit from improved lifestyle choices.

4. Conclusions

In view of low quality of outcome measures and possible bias of available clinical studies, the extent of the efficacy of methylphenidate and other medications in the treatment of ADHD remains a matter of debate. A recent application for the addition of methylphenidate to the WHO Model List of Essential Medicines for the treatment of ADHD was rejected due to uncertainties as to the benefit-versus-harm profile of the drug. In particular, conclusive evidence of long-term benefits of pharmacotherapy remains elusive, since long-term randomised controlled trials, which represent the highest standard for measuring treatment effects, are largely absent. Extended administration of methylphenidate in ADHD from childhood through adolescence is associated with suppression of adult height with no accompanying reduction in symptom severity. These findings in respect of the long-term management of ADHD call for alternative research and treatment strategies (see Table 1).

Lifestyle factors, such as nutrient intake and diet, physical activity and exercise, as well as sleep patterns and digital media use, may be precursors or consequences of ADHD. Current evidence suggests that individuals with ADHD may benefit from improved lifestyle choices. The role of single micro- and macronutrients, such as minerals, vitamins and PUFAs, in the therapy of ADHD remains unclear and benefits may be confined to individuals with respective deficiencies. The interrelationship between the entire diet and other lifestyle factors may be of greater importance than individual nutrients. Emerging evidence suggests that physical activity may be a protective factor for ADHD and that exercise may be a promising alternative treatment option. The well-established relationship between ADHD and insomnia, and the small associations of electronic media use with ADHD-related behaviours call for further investigations. The identification of health-related lifestyle risk factors, such as quality of diet, physical and sedentary activities, sleep patterns and use

of digital media, appears to be important in individuals with ADHD, since interventions in these areas may improve behavioural, cognitive and physical symptoms of ADHD. In summary, lifestyles associated with ADHD should be afforded greater emphasis in both research and clinical practice (see Table 1). Given that the biological and environmental mechanisms associated with ADHD are multifactorial, heterogeneous and complex, it is unrealistic to expect a one-fits-all solution in regard to nutrients, diets or any other treatment.

Conflict of interest

The author declares no conflict of interest**.**

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