METHYLPHENIDATE (RITALIN®) IN THE TREATMENT OF ADHD

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Methylphenidate, sold under the name Ritalin and other tradenames, is frequently used as a first-line medication in the treatment of attention-deficit hyperactivity disorder (ADHD).

Keywords: methylphenidate, Ritalin®, ADHD, attention deficit hyperactivity disorder, medication, psychiatry

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Introduction

Methylphenidate, sold under the tradename Ritalin® and others, is a central nervous system stimulant. It affects neurotransmitter-receptor systems in the brain that contribute to hyperactivity and impulse control. Ritalin is used to treat attention deficit hyperactivity disorder (ADHD), also of the mainly inattentive type, and narcolepsy. It is used for children and adults with ADHD. Since there exists a short acting formulation, it is often used as the starting medication before switching to a longer-acting stimulant, such as Ritalin LA®, Concerta® or Vyvanse®/Tyvense® (lisdexamphetamine), a pro-drug.

Methylphenidate has been shown to alleviate ADHD symptoms and, as such, is currently considered as a first-choice medication. It blocks the dopamine and norepinephrine transporters leading to an increase in extracellular dopamine. The subjective effects can, however, be highly dependent on the pharmacokinetics and the rate of input.

Children

ADHD is one of the most commonly diagnosed and treated childhood psychiatric disorders. Children diagnosed with ADHD find it hard to concentrate. They are often hyperactive (fidgety, unable to sit still for long periods) and impulsive (doing things without stopping to think). ADHD can make it difficult for children to do well at school, because they find it hard to follow instructions and to concentrate. Their behavioural problems can interfere with their ability to get on well with family and friends, and they often get into more trouble than other children. Methylphenidate is the drug most often prescribed to treat children and adolescents with ADHD.

The Preschool ADHD Treatment Study (PATS) was a NIMH-funded, six-center, randomized, controlled trial to determine the efficacy and safety of immediate-release methylphenidate (MPH-IR), given t.i.d. to children ages 3 to 5.5 years with attention-deficit/hyperactivity disorder (ADHD). MPH-IR, delivered in 2.5-, 5-, and 7.5-mg doses t.i.d., produced significant reductions on ADHD symptom scales in preschoolers compared to placebo, although effect sizes (0.4-0.8) were smaller than those cited for school-age children on the same medication. (Greenhill et al., 2006)

In a study by Tannock and colleagues, methylphenidate improved working memory in the nonanxious ADHD group but not in the comorbidly anxious group. By contrast, MPH reduced activity level in both groups. The presence of concurrent learning disabilities did not influence stimulant response. The presence of comorbid anxiety in children with ADHD predicts a less robust response to stimulant treatment and suggests that ADHD with anxiety may constitute a distinct and clinically meaningful subtype of ADHD. (Tannock, Ickowicz, & Schachar, 1995)

Adults

ADHD symptoms start in early childhood and persist into adulthood in about 46% of cases. In some cases, ADHD is not recognized or diagnosed until the person is an adult. Adult ADHD symptoms may not be as clear as ADHD symptoms in children. In adults, hyperactivity may decrease, but struggles with impulsiveness, restlessness and difficulty paying attention may continue. The global prevalence of adult ADHD is estimated to 5.3%, with no difference between Europe and North America (Simon, Rolland, & Karila, 2015). It is often comorbid with substance use disorder, and the prevalence of ADHD among patients with substance use disorder is around 11% as compared to the 4% for those without.

Treatment for adult ADHD is similar to treatment for childhood ADHD. Adult ADHD treatment includes medications, psychological counseling (psychotherapy) and treatment for any mental health conditions that occur along with ADHD.

Efficacy in Adults

Methylphenidate improves ADHD symptoms in adults in a dose-dependent fashion. The efficacy of methylphenidate appears to be reduced in patients with co-morbid substance used disorder, however. Castellis and colleagues searched for randomized, placebo-controlled clinical trials investigating the efficacy of methylphenidate for adults with ADHD and found eighteen studies that met the criteria. Dose, type of formulation and the presence of a substance use disorder appeared to modify the efficacy of methylphenidate. At an average dose of 57.4 mg/day and in a non-continuous-release formulation, methylphenidate had a moderate effect on ADHD symptoms compared with placebo. Efficacy appeared to increase by 0.11–0.12 standard mean deviations for every 10 mg increment of methylphenidate. Continuous-release formulations and co-morbid substance use disorder appeared to reduce the efficacy of methylphenidate, but this was not entirely clear due to co-founding with the substance use disorder covariate. (Castells et al., 2011)

Extended Release Formulations

Several clinical trials have demonstrated statistically significant and clinically relevant effects of methylphenidate extended release in adults with ADHD using self- and investigator-rated ADHD scoring instruments, as well as efficacy measures. In a study by Retz and colleagues, at week 8 a significantly higher decline of the total Wender–Reimherr Adult Attention Deficit Disorder Scale (WRAADDS) score was found in the methylphenidate extended release group as compared to the placebo group. The rates of responders were 50% in the methylphenidate extended release and 18% in the placebo group. Furthermore, similar effects were observed for the ADHD Diagnostic Checklist (ADHD-DC) and the Conners Adult Attention Deficit Disorder Scale (CAARS-S:L) score. 50% of the treatment group and 24.4% of the placebo group were improved “much” or “very much” according to the CGI rating. The treatment was well tolerated, although at week two the mean heart rate was significantly higher in the extended release methylphenidate group as compared to the placebo groupt. (Retz et al., 2012)

Short-Term vs Long-Term

Patients who respond to methylphenidate in the short-term, often respond to long-term treatment with marked improvements in ADHD symptoms and psychosocial functioning. In a study by Wender and colleagues, 116 participants meeting the Utah Criteria entered a randomized double-blind crossover trial

of immediate-release methylphenidate and placebo followed by a longer-term open-label trial. In the double-blind trial more patients improved (50% reduction of symptoms) receiving methylphenidate (74%) than placebo (21%). During the open-label trial, symptom severity decreased 80% from baseline, and the WSAS decreased more than 50% in all subscales. The average GAF improved significantly. (Wender et al., 2011)

Executive Functioning

Biederman and colleagues conducted a 6-week, parallel design, randomized, placebo controlled study in adults with DSM-IV ADHD using the Behaviour Rating Inventory of Executive Function — Adult Version (BRIEF-A) to assess executive functioning deficits. They showed that executive function deficits do not moderate the response to methylphenidate and measures of executive function deficits are not associated with response to methylphenidate. (Biederman et al., 2011)

Adverse Effects

In a Cochrane database study, Epstein and colleagues pooled results from 10 studies, which included 466 participants. The data suggested that adverse effects from immediate-release methylphenidate for adults with ADHD were not of serious clinical significance, although this conclusion may have been limited by the short duration of the published studies. It also suggested that immediate-release methylphenidate was efficacious for treating adults with ADHD with symptoms of hyperactivity, impulsivity, and inattentiveness, and for improving their overall clinical condition. (Epstein, Patsopoulos, & Weiser, 2014)

Co-Morbid Substance Use Disorder

Due to the prevalence of ADHD in substance use disorder and to the benefits of methylphenidate observed in this population, and considering the mild or low side effects observed, the response to methylphenidate treatment should be evaluated individually in adults with comorbid ADHD and substance use disorder (Simon et al., 2015). The choice of the formulation should favour sustained-release methylphenidate over immediate release methylphenidate. Cardiovascular parameters need to be monitored during long-term use, maybe even more importantly than in patients without substance use disorder.

Dopamine and Norepinephrine

While norepinephrine and dopamine are not the only neurotransmitters involved in ADHD, there is considerable evidence that these neurotransmitters play essential roles in attention and thinking. Both contribute to maintaining alertness, increasing focus, and sustaining thought, effort, and motivation. Dopamine is a precursor to norepinephrine synthesis in the brain, and they are structurally very similar, differing only in the presence of a hydroxyl group. Distinctions in their sources of origin and their projections in the brain and differences in the behavioural effect of selective alternations suggest that these neurotransmitters have discrete complementary roles in the brain. Although these neurotransmitters affect related components of attention, they activate distinct receptors, particularly specific receptor subtypes. Methylphenidate inhibits both the dopamine transporter (DAT) and the norepinephrine transporter (NET), which results in an increase in extracellular dopamine and norepinephrine that can readily bind postsynaptic cells.

Dopamine

The dopaminergic system plays a pivotal role in the central nervous system via its five diverse receptors (D1–D5). Dysfunction of dopaminergic system is implicated in ADHD and various other mental health conditions, and there is a high risk of dopamine receptor D5, D2, and D4 polymorphisms in ADHD (Wu, Xiao, Sun, Zou, & Zhu, 2012).

Stimulant medications, such as methylphenidate, enhance brain dopamine signalling. Wang and colleagues assessed methylphenidate-induced dopamine changes with positron emission tomography and a radioactive D2/D3 receptor ligand. Clinical responses were assessed using the Conners' Adult ADHD Rating Scale and revealed a significant reduction in symptoms of inattention and hyperactivity with long-term methylphenidate treatment. Their findings indicate that dopamine enhancement in the ventral striatum, the brain region involved with reward and motivation, was associated with therapeutic response to methylphenidate and that methylphenidate-elicited dopamine increases in prefrontal and temporal cortices may also contribute to the clinical response. (Wang et al., 2013)

Norepinephrine

In vitro, the affinity of methylphenidate for NET is higher than that for DAT. Hannestad and colleagues used positron emission tomography to measure the occupancy of brain norepinephrine transporters by methylphenidate. Their findings were that oral methylphenidate significantly occupies NET at clinically relevant doses. The ED50 was lower than that for DAT. (Hannestad et al., 2010)

Cognitive Functioning

Individuals with ADHD usually have deficits in higher-level cognitive functions necessary for goal-directed behaviours, in so-called "executive functions" (EFs), that are mediated by late developing fronto-striato-parietal and fronto-cerebellar networks (Hobson, Scott, & Rubia, 2011). There is considerable heterogeneity in cognitive impairments, with some patients not showing impairments or only in some cognitive domains.

The most consistent deficits are in so-called "cool" EF such as motor response inhibition, working memory (WM), sustained attention, response variability and cognitive switching as well as in temporal processing (i.e., motor timing, time estimation and temporal foresight), with most consistent deficits in time discrimination and estimation tasks (Zelazo & Carlson, 2012). However, impairment has also been found in so-called "hot" EF functions of motivation control and reward-related decision making, as measured in temporal discounting and gambling tasks, with, however, more inconsistent findings. Evidence for cognitive deficits is more consistent in children than adolescents or adults with ADHD.

In a study by Agay and colleagues, the average digit-span test score was higher in the groups receiving methylphenidate compared to the groups receiving placebo, while diagnosis did not have an effect upon scores. In decision-making tasks, however, methylphenidate did not have an effect upon performance, whereas in one of the tasks the average proportion of risky choices was higher in ADHD adults compared to controls. (Agay, Yechiam, Carmel, & Levkovitz, 2010)

Motivation and Methylphenidate

During an inhibitory control task, children with ADHD exhibit a raised motivational threshold at which task-relevant stimuli become sufficiently salient to deactivate the default mode network. Liddle et al showed that treatment with methylphenidate normalised this threshold, rendering their pattern of task-related default mode network deactivation indistinguishable from that of typically developing children. (Liddle et al., 2011)

Inhibitory Control and Response Time Variability

Improvements in response inhibition and response variability might underlie the reported clinical benefits of methylphenidate. In a study by Nandam and colleagues, methylphenidate led to a reduction in both response time variability and stop-signal reaction time, indicating enhanced response inhibition compared with all other drug conditions. The enhancement of response inhibition by MPH occurred without concomitant changes in overall response speed, arguing against a simple enhancement of processing speed. An acute dose of methylphenidate but not atomoxetine or citalopram was able to improve stop-signal reaction time and reduce response time variability in nonclinical participants. (Nandam et al., 2011)

Neurobiology

The neuropathology of ADHD is not rooted in a single anatomical area, but in multiple parallel and intersecting pathways, which have demonstrated impaired functional connectivity in ADHD brains. Dysfunction in executive function, reward processing, attention networks and default networks play major roles in the neuropathology of this condition. Biological findings vary between individuals, with some showing greater dysfunction at cortical levels and others at subcortical levels, which is in keeping with its clinical heterogeneity. The frontostriatal network is a likely contributor to the pathophysiology of ADHD. This network involves the lateral prefrontal cortex, the dorsal anterior cingulate cortex, and the caudate nucleus and putamen. In ADHD patients, reductions in volume have been observed in total

cerebral volume, the prefrontal cortex, the basal ganglia (striatum), the dorsal anterior cingulate cortex, the corpus callosum and the cerebellum.

Children with attention-deficit/hyperactivity disorder (ADHD) have deficits in performance monitoring, which often improves with methylphenidate. Rubia and colleagues used functional magnetic resonance imaging to investigate the effects of single-dose methylphenidate on activation of error processing brain areas in medication-naive boys with ADHD during a stop task. Methylphenidate, relative to placebo, upregulated activation in dorsomedial and left ventrolateral prefrontal cortices, thalamus, cingulate, and parietal regions and normalized all activation differences between patients and control subjects. During successful inhibition, methylphenidate normalized reduced activation observed in patients under placebo compared with control subjects in parietotemporal and cerebellar regions. (Rubia, Halari, Mohammad, Taylor, & Brammer, 2011) In a study by Stoy, drug-naïve, and treated subjects did not seem to differ significantly in their activations in the ventral striatum and orbitofrontal cortex, while there were indications for decreased insula activation during outcome of loss avoidance in drug-naïve subjects in comparison to both groups, while treated subjects did not differ from controls. Insula activation correlated significantly positive with harm avoidance in the treated group. Basal ganglia reward processing seemed to be unrelated to methylphenidate pre-treatment, but was related to remission. (Stoy et al., 2011)

Emotions

Emotion dysregulation is prevalent in ADHD throughout the lifespan and is a major contributor to impairment. Networks carrying information related to emotions seem to be affected by the mechanisms underlying ADHD. Emotional dysregulation may arise from deficits in orienting towards, recognizing and/or allocating attention to emotional stimuli, which may be caused also by dysfunction within the striato-amygdalo-medial prefrontal cortical network. Working memory impairments of ADHD may allow a momentary emotion to become too strong, flooding the brain with one intense emotion. At other times, the person with ADHD may seem insensitive or unaware of the emotions of others.

Rösler and colleagues conducted a large-scale, multicenter treatment study with adults with ADHD. The medication was statistically superior to placebo in reducing emotional symptoms. Obsessive-compulsive

symptoms and those of problems with self-concept declined until the end of the observation period. The decline was more pronounced in extended release methylphenidate treated individuals. Symptoms of anxiety, depression, anger and hostility, phobia, paranoid ideations and psychoticism were not improved. (Rösler et al., 2010)

Comparison to Atomoxetine

The comparison with atomoxetine is useful, because the latter is not categorized as a stimulant. In a study by Yildiz and colleagues in children with ADHD, methylphenidate led to a significantly greater reduction in teacher T-DSM-IV-S scale scores. Methylphenidate was also observed to be more effective than atomoxetine on several neuropsychological assessments (Stroop-5 time and number of corrections, perseverative errors on WCST). The most frequently reported adverse events in the atomoxetine group were anorexia, nausea, nervousness, weight loss, abdominal pain, and somnolence. In the methylphenidate group, patients most frequently reported anorexia, nervousness, insomnia, headache, nausea, and weight loss. (Yildiz, Sismanlar, Memik, Karakaya, & Agaoglu, 2011) However, in a study by Kratochvil and colleagues with 228 children with ADHD, atomoxetine was associated with therapeutic effects comparable to those of methylphenidate. (Kratochvil et al., 2002) The different result in the second study may be due to the different parameters that were assessed.

Abuse

Methylphenidate may be habit-forming and is a drug that is not infrequently abused. Methylphenidate abuse is defined as any situation in which the drug is being used outside of prescription guidelines. Symptoms of methylphenidate abuse can include increased talkativeness and sociability, a sense of euphoria, suppressed appetite, changes in mood or behaviour, insomnia, paranoia, nausea, headache, agitation, and more.

In a study by Volkow and Swanson, brain imaging and clinical literatures were analysed to identify variables that contribute to the abuse liability as well as to the clinical efficacy of methylphenidate. Four variables were identified (Volkow & Swanson, 2003):

1) Dose

   There is a threshold for methylphenidate-induced dopamine increases to be perceived as reinforcing and to produce therapeutic effects.

2) Pharmacokinetics

   The reinforcing effects of methylphenidate are associated with rapid changes in serum concentrations and presumably fast dopamine increases (as achieved with intravenous injection or insufflation), whereas the therapeutic effects are associated with slowly ascending serum concentrations and presumably smoothly rising dopamine levels (as achieved with oral administration).

3) Individual differences

   Sensitivity to methylphenidate varies across individuals and sets a threshold for blood and brain levels required for reinforcing effects (drug liking) and for therapeutic effects (symptom reduction).

4) Context

   The effects of methylphenidate are modulated by different settings in abuse (rituals of self-administration and powerful conditioning) and in clinical use (external demands of low activity and focused attention). with drug or alcohol abuse.

Neuroenhancement

During the past few years considerable debate has arisen within academic journals with respect to the use of smart drugs or cognitive enhancement pharmaceuticals. However, based on a systematic review and meta-analysis it was shown that expectations regarding the effectiveness of these drugs exceed their actual effects, as has been demonstrated in single- or double-blind randomised controlled trials. For methylphenidate an improvement of memory was found, but no consistent evidence for other enhancing effects was uncovered. (Repantis, Schlattmann, Laisney, & Heuser, 2010) It has also been argued quite convincingly based on the available data that neither drug efficacy, nor the benefit-to-risk balance, nor

indicators of current or growing demand provide sufficient evidence that methylphenidate is a suitable example of a cognitive enhancer with wide appeal. (Outram, 2010)

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