

Press release; European College of Neuropsychopharmacology (ECNP) congress, Copenhagen

ADHD medication: how much is too much for a hyperactive child?

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When children with ADHD don't respond well to Methylphenidate (MPH, also known as Ritalin) doctors often increase the dose. Now a new review shows that increasing the dose may not always be the best option, as it may have no effect on some of the functional impairments associated with ADHD. The researchers caution against increasing the doses is based on findings that this effect may only be observed for behavioral factors (such as reduction in attention and/or hyperactivity/impulsivity) and not for the child's ability to control their impulses. This work is presented at the ECNP Conference in Copenhagen.

Attention-Deficit/Hyperactivity Disorder (ADHD), is the most common childhood-onset psychiatric disorder, characterized by symptoms such as inattention, hyperactivity and impulsivity. Worldwide, around 5% of children and adolescents suffer from ADHD*.

ADHD is a complex condition comprising both behavioural and neurocognitive symptoms, but diagnosis requires only that a patient exhibit at least 6 *behavioural* symptoms. You can see a list of these symptoms at: <https://www.nhs.uk/conditions/attention-deficit-hyperactivity-disorder-adhd/symptoms/>. Treatment is normally judged on how well these behavioural symptoms are improved. However, children with ADHD can also be characterized, by looking at functional impairments such as *neurocognitive* functioning, including inhibitory control which is a measure of how they keep their impulsiveness under control.

Methylphenidate (MPH) has been commonly used as a first line medication to treat children with ADHD since the 1990s. It is generally effective and well tolerated, but around 30% of children taking MPH don't respond to standard doses, often leading doctors to consider increasing the dose.

Like all drugs, MPH carries the risk of side effects, which may become more significant at increased dose and with long-term use. These side effects include growth retardation and difficulty in gaining weight: 3 years of MPH use can cause a child to be 2cm shorter and 2.7 kg lighter than normal.

To understand and distil the effects of the drug on children with ADHD, Karen Vertessen (MD & PhD student at the Vrije Universiteit Amsterdam) and colleagues undertook a review of all the scientific literature (a *metanalysis*) relating to dose effects of MPH on inhibitory control (an aspect of impulsiveness) in children and adolescents.

They managed to identify 18 studies, comprising in total 606 subjects with ADHD. They were able to classify the MPH doses reported as low, medium, or high dose. Results showed that a medium dose of MPH had the strongest beneficial effects on inhibitory control. However increasing the dose past the medium dose did not make the drug work more effectively.

Karen Vertessen said, "*Scientifically, this is an interesting result. Generally, high doses of MPH does not help the child or adolescent keep their inhibitions under better control, although an increased dose, in general, does have a greater effect on the core behavioral symptoms of ADHD.*"

Even though inhibitory control is just one aspect of impulsivity, we suggest that medically we need to be cautious about just increasing the dose when a child does not instantly respond to the drugs. Children are more vulnerable than adults in these cases, especially since they will be just beginning to receive treatment, and so many treatment variables will still need to be established. If clinicians decide to start therapy with MPH, they need to keep a close eye on the patient and objectively evaluate every dose, to make sure that the higher dose is actually having an effect. Current ADHD evaluation only uses behavioral outcomes, whereas we suggest adding neurocognitive outcomes to this evaluation, given that these outcomes are important for, among others, academic functioning. In other words, checking for whether or not MPH is dealing with inhibitory control might allow us to see if increasing the dose makes sense. To see to what extent these findings might have a clinical impact we are currently investigating the other most relevant neurocognitive factors related to ADHD”.

Commenting, Dr Kerstin von Plessen (Centre Hospitalier Universitaire Vaudois, Lausanne) said:

“This is an elegant and highly relevant study, which sheds light on an interesting phenomenon which has not received sufficient attention up to now. However the study does not address the question why some children receive this higher dosage. This is probably due to the lower dose having a lesser effect. This means that the findings agree with the clinical reality telling us that children, who do not respond sufficiently to the regular dosages of MPH, require a second more comprehensive diagnostic examination before increasing the medication. In addition, not all children respond to MPH, and so other treatment options should also be explored. The conclusion of the study, that we should add neurocognitive tests to the evaluation, may be a highly useful option to further identify academic capacity and behaviour, but should not be a substitute for the clinical evaluation of impulsivity (inhibitory control) during any change of medication.”

This is an independent comment: Dr von Plessen was not involved in this work.

* Polanczyk G , de Lima MS , Horta BL , et al: The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry 164(6):942–948, 2007. See also USA statistics, Centre for Disease Control, <https://www.cdc.gov/ncbddd/adhd/data.html>

**See <https://www.ncbi.nlm.nih.gov/pubmed/21970086>

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Notes for Editors

European College of Neuropsychopharmacology (ECNP)

The ECNP is an independent scientific association dedicated to the science and treatment of disorders of the brain. It is the largest non-institutional supporter of applied and translational neuroscience research and education in Europe. Website: www.ecnp.eu

The 31st annual ECNP Congress takes place from 7th to 10th September in Copenhagen. It is Europe’s premier scientific meeting for disease-oriented brain research, annually attracting up to 6,000 neuroscientists, psychiatrists, neurologists and psychologists from around the world. Congress website: <https://2019.ecnp.eu/>

ADHD - Disorder;Genetic & molecular approaches - Method;Anxiety - Disorder

Methylphenidate and inhibition in children with ADHD: a meta-analysis on dosage effects

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Background:

Attention-deficit/hyperactivity disorder (ADHD) has been associated with a broad range of neurocognitive deficits, with response inhibition as one of the most frequently reported functions playing a central role in etiological models of ADHD [1]. Methylphenidate (MPH), the preferred pharmacological treatment for ADHD in children and adolescents, is found to ameliorate neurocognitive deficits [2]. Group effects of MPH-dose on behavioral symptom reduction show a linear effect (higher dose, larger reduction) [3] although at an individual level best-dose levels are evenly distributed between low- medium and high doses [4]. For neurocognitive outcomes dose-effects are less studied and both linear and quadratic dose-response curves (with the best outcomes on medium dosages) for response inhibition have been reported [5] This meta-analysis was aimed to elucidate MPH dose effects on neurocognitive functioning in children with ADHD.

Methods:

Electronic databases were searched to identify published placebo controlled trials that compared MPH (fixed) dosages with placebo on response inhibition tasks in children and adolescents (5–18 years) with a formal diagnosis of ADHD (DSM III-R, IV en 5). The fixed dosages were categorized as low, medium and high doses and compared with placebo. With low doses range: 0,10 mg/kg- 0,39 mg/kg, medium doses range: 0,40 mg/kg - 0,69 mg/kg and high dose range: 0,70 mg/kg - 0,99 mg/kg.

Results:

Nineteen studies, including 34 inhibition measures, fulfilled inclusion criteria and were included in our meta-analysis. Methylphenidate was superior to placebo in all analyses: Medium doses had the strongest effects on improving inhibition with low dose: (Cohen's $d = -0,27$, 95% CI: $-0,45 - -0,09$, $p < 0,005$), medium dose: (Cohen's $d = -0,32$, 95% CI: $-0,48 - -0,15$, $p < 0,001$) high dose (Cohen's $d = -0,22$, 95% CI: $-0,47 - 0,03$, $p < 0,082$).

Conclusions:

These data support potentially important dose-dependent effects of MPH on inhibition in children with ADHD. Medium doses of MPH have the largest effects on inhibition, with a decrease of the effect for the high doses. This suggests that titration with an optimal result on ADHD symptoms does not ensure an optimal effect on neurocognitive outcomes. Considering the complex relationship between ADHD symptoms, cognition and academic performance and the role of executive functioning in academic performance these findings can be clinically relevant and consideration should be given to adding cognitive outcomes to the treatment outcomes of pharmacological therapy for ADHD.

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