Scandinavian Journal of Child and Adolescent Psychiatry and Psychology
Vol. 6(1):1-3 (2018) DOI 10.21307/sjcapp-2018-007

Editorial

Occurrence of psychotic symptoms during treatment of ADHD with methylphenidate: Clinical significance and the need for further research

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In this issue of SJCAPP, Ramstad and colleagues review the evidence for psychotic symptoms as an adverse effect of methylphenidate treatment in children and adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD) (1). Their article summarizes relevant results from two Cochrane systematic reviews on methylphenidate treatment for ADHD, which are published elsewhere (2,3). Based on detailed review of existing studies, Ramstad and colleagues report there is not adequate evidence to conclude whether or not methylphenidate is associated with treatment-emergent psychotic symptoms, but available information suggests psychotic symptoms may occur in 1.1 to 2.5 percent of those being treated with methylphenidate, so clinicians should be alert to the possibility that psychotic symptoms may sometimes occur during treatment with methylphenidate.

Ramstad and colleagues include description of randomized as well as non-randomized studies. One key part of the review is description of a meta-analysis including nine placebo-controlled trials. Only 10 of 654 methylphenidate-treated patients and 1 of 508 placebo-treated patients developed psychotic symptoms, so the occurrence of psychotic symptoms seems to be quite rare, at least during short-term treatment with methylphenidate. In the meta-analysis, the overall risk ratio for occurrence of psychotic symptoms during methylphenidate treatment versus placebo is 2.07, with a 95% confidence interval of 0.58-7.35. So, while the risk of psychotic symptoms in patients taking methylphenidate is estimated to be approximately double the risk for those taking placebo, the confidence interval is quite wide, the association is not statistically significant, and no clear conclusion can be drawn. Reported results of trial sequential analysis suggest the meta-analysis is substantially underpowered, so the lack of statistical significance cannot be interpreted as absence of risk for psychotic symptoms during methylphenidate treatment. Ramstad and colleagues also note a number of problems with the existing studies, such as high risk of bias, potential for confounding factors, and issues regarding methods of assessing psychotic symptoms. Although no clear conclusions are possible from existing studies, there is a signal suggesting the need to be alert for possible psychotic symptoms as a side effect of methylphenidate, and the problems with existing studies suggest a need for further study using improved methods and larger sample sizes. One important unanswered question is whether subgroups of individuals with ADHD are more or less susceptible to developing psychotic symptoms as a side effect. In addition to acute treatment-emergent risk for psychotic symptoms, the long-term effect of stimulant use on risk for future psychosis is also unclear.

The review by Ramstad and colleagues has some important clinical implications. As there is some suggestion that methylphenidate may rarely result in psychotic symptoms, it is reasonable and appropriate to reduce or stop stimulant medication if psychotic symptoms arise during treatment with methylphenidate or other stimulant medications. It may sometimes be reasonable to re-challenge the patient with a stimulant in the future if the stimulant previously seemed to have a substantial overall benefit and if the psychotic symptoms were mild or unclear and did not result in dangerous behavior. Extreme caution should be used with any re-challenge in a patient who developed clear psychotic symptoms soon after starting or increasing a stimulant medication, especially if delusional thinking was involved. Depending on the content of the delusions, such thinking may in some cases result in illogical and dangerous behavior. Symptoms such as vague hallucinations with full insight, with absence of

command auditory hallucinations, and no delusional ideas regarding the origin of the hallucinations may not be as problematic, but these milder psychotic-like symptoms are also of concern since it is unclear whether allowing such symptoms to continue might result in worsening of psychotic symptoms over time or other adverse long-term effects. If psychotic symptoms recur with re-challenge, stimulant medication may need to be entirely avoided for that particular patient. If medication treatment for ADHD is indicated but stimulants cannot be tolerated without concerning side effects, non-stimulant ADHD medications can be considered (such as guanfacine, clonidine, or atomoxetine). For those who cannot tolerate or have poor response to multiple ADHD medications, non-pharmacological interventions such as behavioral therapies and appropriate educational accommodations become particularly important.

In future studies of the relationship between stimulant medication and psychosis, a number of additional factors need be considered. Although most children with ADHD will not develop psychotic symptoms or a clear psychotic disorder (whether or not they take stimulants), there is evidence that ADHD itself may increase the risk for psychotic symptoms and even a diagnosis of schizophrenia. Difficulties with attention and related aspects of cognition can occur as precursors to schizophrenia (4). ADHD and other forms of psychopathology occur at increased rates in children of parents who have schizophrenia spectrum disorders (5). Twin and family studies suggest substantial genetic overlap between ADHD and other psychiatric conditions, including schizophrenia (6,7). In one large study, it was determined that among patients with schizophrenia and other forms of psychosis, treatment with stimulant medication was associated with earlier onset of psychosis (8). While this could be due to stimulant medication causing earlier onset of psychotic symptoms, it could also be that the presence of ADHD itself (which leads to stimulant treatment) is more directly associated with earlier onset of psychosis.

One growing area of relevant research is the pharmacogenetic study of medication responses and side effects. A recent review found evidence that variants in several genes are associated with methylphenidate treatment response in children with ADHD (9). Given the rarity of psychotic symptoms as a stimulant side effect, very large sample sizes and detailed, careful assessment of psychotic-like symptoms may be needed to determine whether particular genetic variants increase the risk for psychotic symptoms in patients treated with stimulants for ADHD. One could hypothesize that individuals with genetic risk for schizophrenia or bipolar disorder might be particularly susceptible, so genetic variants that increase risk for these disorders may be particularly important to study.

The following types of future studies may help to clarify the relationship between stimulant medications and development of psychotic symptoms: 1) Large randomized, controlled stimulant medication trials including detailed assessment of psychotic-like symptoms—from mild perceptual disturbances to clear delusional thinking—perhaps also including genetic data for secondary pharmacogenetic analysis, 2) Randomized, controlled stimulant medication trials for ADHD symptoms in children with known personal (based on genetic tests) or family (based on family history) genetic risk for psychosis. Such studies could help determine whether stimulants increase (or perhaps even decrease) the risk for developing psychosis in those who have known genetic risk. These studies could perhaps be of much smaller size since the incidence of psychotic-like symptoms should be higher in those with known genetic risk (whether they are taking medication or placebo). Ideally, such studies should include long-term follow-up considering the average age of psychosis onset in the population. 3) Large population-based studies investigating the risk for developing schizophrenia or psychotic symptoms in ADHD-affected individuals who receive stimulants vs. other ADHD treatments or no medication. There may be high potential for confounding in such studies because individuals with more severe ADHD symptoms may have increased risk for both schizophrenia and treatment of ADHD using medication, but such studies may still provide useful information. Despite inherent limitations, existing insurance claims and national registry databases may be useful for this type of study.

In conclusion, Ramstad and colleagues report a very thorough review of the existing evidence regarding psychotic symptoms as an adverse effect of methylphenidate. Although the amount and quality of existing data does not allow any strong conclusions to be drawn regarding the association of methylphenidate with treatment-emergent psychotic symptoms, clinicians should be alert to the possibility that stimulant medications may in rare cases lead to psychotic symptoms, and further research is needed in order to clarify this possible risk.

Disclosure

Dr. Reiersen has received grant or research support from the National Institutes of Health, the McDonnell Center for Systems Neuroscience, and the McDonnell Center for Cellular and Molecular Neurobiology. She has received travel support from the Child and Adolescent Psychiatric Department, Region Zealand (a hospital in Denmark). Dr. Reiersen does not have any financial relationships with commercial industry.

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