

REVIEW ARTICLES

PSYCHOTIC SYMPTOMS DURING STIMULANT TREATMENT FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

SINTOMAS PSICÓTICOS DURANTE O TRATAMENTO COM PSICOESTIMULANTES PARA A PERTURBAÇÃO DE HIPERATIVIDADE COM DÉFICE DE ATENÇÃO

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ABSTRACT

Introduction: Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder. Pharmacological treatment, either alone or in combination with psychosocial interventions, is important in the therapeutic strategy. Psychostimulants remain the most effective medication and are generally well tolerated. However, one of its rare but significant side effects is development of psychotic symptoms.

Objectives: To perform a literature review about the risk of psychotic symptoms during ADHD treatment with stimulants and discuss possible pharmacological treatment implications.

Methods: A literature search was conducted on PubMed database using the terms “ADHD”, “central nervous system stimulants”, and “psychosis”. The search was supplemented with data retrieved from published guidelines.

Results and discussion: ADHD diagnosis has been increasing, as well the use of stimulants for its treatment. However, using these drugs is not without controversy. ADHD pharmacological treatment is rarely associated with psychotic symptoms. Reported symptoms include hallucinations and paranoid delusions, and occasionally also euphoria, grandiosity, and other mania and hypomania features. These symptoms are generally short-lived and self-limited within days after stimulant discontinuation. One study comparing amphetamines and methylphenidate suggested that the former was more likely to cause psychosis compared with the latter. Additionally, study authors agreed that stimulant-induced psychosis seems to be associated to susceptibility factors.

Conclusion: Psychostimulants are highly beneficial for ADHD patients. However, small studies and case reports suggest an association with new-onset psychotic symptoms. Physicians should be aware that psychotic symptoms may arise during stimulant ADHD treatment. Further investigation is required to identify patients who are most at risk of experiencing such adverse events.

Keywords: ADHD; amphetamine; methylphenidate; psychostimulants; psychotic symptoms

RESUMO

Introdução: A perturbação de hiperatividade com défice de atenção (PHDA) é uma perturbação do neurodesenvolvimento comum. O tratamento farmacológico, isoladamente ou associado a intervenções psicossociais, constitui um elemento importante na estratégia terapêutica global. Os psicoestimulantes continuam a ser os fármacos mais efetivos sendo geralmente bem tolerados. Contudo, o aparecimento de sintomatologia psicótica é um efeito adverso raro, mas significativo, que lhes está associado.

Objetivos: Efetuar uma revisão de literatura sobre o risco de desenvolvimento de sintomas psicóticos associados à utilização de estimulantes no tratamento da PHDA e discutir possíveis implicações terapêuticas.

Métodos: Foi efetuada uma pesquisa bibliográfica na base de dados PubMed utilizando os termos “PHDA”, “estimulantes do sistema nervoso

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central” e “psicose”, tendo sido posteriormente complementada com informação recolhida de recomendações formais publicadas sobre o tema.

Resultados e Discussão: O diagnóstico de PHDA tem vindo a aumentar, assim como a prescrição de estimulantes para o seu tratamento. No entanto, a utilização destes fármacos não é desprovida de controvérsia, tendo sido pontualmente observados sintomas psicóticos associados à sua utilização. Os sintomas descritos incluem alucinações, delírios paranoides e, ocasionalmente, euforia, grandiosidade ou outras características de mania ou hipomania. Habitualmente, estes sintomas são autolimitados e de curta duração, cessando alguns dias após a suspensão do estimulante. Um estudo que comparou a utilização de anfetaminas e metilfenidato sugere que as primeiras são mais propensas a causar este tipo de sintomas. Os autores do estudo consideraram ainda que a psicose induzida por estimulantes parece estar associada a fatores de suscetibilidade.

Conclusão: Os psicoestimulantes são altamente benéficos para indivíduos com PHDA. Contudo, pequenos estudos e relatos de casos sugerem uma associação a sintomas psicóticos de novo. Os médicos devem estar cientes de que podem surgir sintomas psicóticos associados à utilização de estimulantes no tratamento da PHDA. São necessários mais estudos que permitam identificar quais os doentes com maior risco de desenvolver este tipo de reação adversa.

Palavras-chave: PHDA; anfetamina; metilfenidato; psicoestimulantes; sintomas psicóticos

INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder that begins in childhood and frequently persists into adolescence and adulthood.¹⁻⁵ The diagnosis is based on clinical evaluation of whether the child presents excessive inattention, hyperactivity, and/or impulsivity, associated with high levels of functional impairment and reduced quality of life.^{6,7} The estimated prevalence in children and adolescents ranges between 3% and 8%, with boys more likely to be diagnosed than girls.⁴⁻⁸ ADHD etiology is not completely understood, but seems to be multifactorial involving genetic, environmental, and social factors.⁴⁻⁵ Current ADHD treatments include a range of social, psychological, behavioral, and pharmacological interventions.^{5,9} According to guidelines, psychosocial interventions are initially recommended for younger children and for cases with mild-to-moderate symptoms. For more severe ADHD symptoms, medication, either alone or in combination with psychosocial intervention, is an important element in the therapeutic strategy.^{1-3,5,9,10} Psychostimulants have remained the most effective medication for ADHD over the last decades, particularly methylphenidate and amphetamines, which are generally well tolerated.^{1,2,4,5,9,11} Efficacy and safety of these medications is supported by an extensive literature of controlled studies. Nevertheless, like other psychotropic medications, psychostimulants have a wide range of potential adverse effects. An uncommon but significant undesirable side effect is development of psychotic symptoms.^{1,6,11-17} Because so many people, especially children and adolescents, are prescribed methylphenidate and amphetamines, it is relevant to better understand the risk of psychosis associated with these drugs, as it can be a traumatic event for patients and families.

OBJECTIVES

The aim of this study was to perform a literature review investigating the risk for psychotic symptoms associated with ADHD treatment with stimulants and discuss possible implications on pharmacological treatment.

METHODS

A non-systematic literature review was performed in PubMed database using the terms “ADHD”, “central nervous system stimulants”, and “psychosis” without setting a specific time period. The electronic search was performed during April 2019 and yielded 106 results. Titles and abstracts of retrieved articles were screened and a manual selection of papers was subsequently performed, based on their relevance for the subject in matter. No restriction criteria were established regarding study design. Eligibility criteria for full-text articles of records deemed potentially relevant included studies with patients diagnosed with ADHD according to the International Classification of Diseases (ICD) or the Diagnostic Statistical Manual (DSM) diagnostic criteria and reports of patients with psychotic symptoms during methylphenidate or amphetamine treatment or up to 60 days after withdrawal. Exclusion criteria comprised the use of other medications for ADHD management (e.g. atomoxetine) and articles reporting assessment of substance-abuse psychosis. Further bibliographic references were retrieved from review articles and guidelines. Only English language reports were included. Finally, 33 eligible studies were identified, including observational studies (comparative and non-comparative cohort studies, patient-control studies, one naturalistic observational study, cross-sectional

studies, and a Phase IV open-label study in Europe), patient reports/series, comprehensive and systematic reviews of clinical data from randomized controlled trials, and meta-analyses.

RESULTS AND DISCUSSION

The number of children and adults diagnosed with ADHD is steadily increasing in several parts of the world, including North America and Europe.¹⁸⁻²⁰ Consequently, stimulant prescription has also dramatically increased.^{11,18,19} Methylphenidate and amphetamines have been used for decades with no specified preference of one over the other.^{11,21,22} Additionally, current guidelines are inconsistent in treatment recommendations. Some rank methylphenidate over amphetamine for children, while others recommend psychostimulants as first-line treatment without distinguishing between drugs.^{2,5,23} Amphetamine is available for use as dexamphetamine, mixed-amphetamine salts (levoamphetamine plus dextroamphetamine), or lisdexamphetamine, a dexamphetamine prodrug and the only formulation available in Portugal.^{4,7} Generic and branded methylphenidate are also available, including long-acting and immediate-, extended-, and slow-release formulations. Methylphenidate is the most frequently prescribed drug globally, with recent data showing that amphetamine is more commonly used in the United States and Canada.^{4,11,16,21} Both stimulant types are thought to enhance dopamine and noradrenaline efflux in the central nervous system.^{4,18,21} However, while methylphenidate acts on their reuptake inhibition, amphetamine brings about reuptake blockade and presynaptic release, resulting in higher dopamine availability within the synaptic cleft.^{4,11,18}

ADHD-prescribed stimulants are considered equivalent regarding standard efficacy endpoints, with some patients better responding to and tolerating one drug over the other.^{4,7,10,11,21,25} Typical side effects include decreased appetite, weight reduction, initial insomnia, somnolence, headache, and rebound irritability, which are generally acceptable for being mild and/or temporary.^{4,7,10,26} Yet, safety of these medications remains controversial.²¹ Hallucinations and other psychotic symptoms have been reported as additional uncommon significant adverse effects.^{3,4,11,16,18,25,27,28}

Some side effects may be too uncommon to be detected in randomized controlled trials (RCTs), particularly when rare, delayed, or observed in specific patient subgroups. For this reason, cohort studies, patient-control studies, and even patient reports/series included in this review may be of value. Systematic reviews and meta-analyses were also included in article selection, some of which belonging to The Cochrane Library, a collection of systematic reviews that follows a scientifically rigorous protocol to generate robust evidence.

Stimulant-induced psychosis

Stimulant-induced psychosis has been described since the 1950s in individuals abusing amphetamine and methamphetamine.¹⁹ Psychosis literature review showed that few data exists regarding this phenomenon in ADHD. Most published data concerns clinical case reports, case series, and small clinical trials. In these studies, the term “psychosis” is defined at symptom level and does not imply a full-blown psychotic disorder.^{10,26} The most reported psychosis symptoms are hallucinations and paranoid delusions, and occasionally also euphoria, grandiosity, and other mania and hypomania symptoms are described.^{6,10,15,25-27} All revised studies showed that stimulant-induced psychosis is generally short-lived, can occur at therapeutic levels, and resolves within days after stimulant discontinuation.^{11,15,16,20,26,27} In the vast majority of cases, there was no personal or family history of psychiatric disorder. To the best of our knowledge, affected patients have not used recreational drugs, although some assumed having taken higher-than-prescribed doses.²⁰ No other risk factors were identified potentially accounting for reported psychosis or mania-related events.^{6,18,20,26,28-30} Study authors agree that stimulant-induced psychosis appears to be related to susceptibility factors.^{29,30} Several common genetic biomarkers have been identified between amphetamine-induced psychosis and schizophrenia, which may justify why some patients are more vulnerable to amphetamine-induced psychosis and probably other stimulants.^{30,31} In healthy individuals, some authors consider that a high stimulant dose over a short period of time plays an important role in psychosis development. However, that does not explain why some individuals develop psychotic symptoms at a certain stimulant dose and others do not. In this context, it was hypothesized that the relationship between stimulant-induced psychosis and primary psychosis could be perceived within the framework of a stress vulnerability paradigm. Individuals with lower stress vulnerability require higher stimulant doses to precipitate acute psychosis than highly stress vulnerable individuals. The least susceptible individuals are those who took stimulants but never experienced psychosis. Conversely, the most vulnerable individuals are schizophrenic patients who become psychotic without using any stimulants at all. The stress vulnerability paradigm assumes that the more life stressors an individual has, the lower the psychosis threshold.²⁹⁻³¹

A few years ago, the Food and Drug Administration (FDA) sought to evaluate the frequency of psychotic- or manic-like stimulant reactions in ADHD patients.^{24,25} Based on results from a small preapproval trial, as well as on post-marketing spontaneous reports, FDA required ADHD drug manufacturers to include in US package inserts warnings about psychiatric side effects in patients with no prior history of psychosis.^{6,11,20,21,24-26}

Comparative risk

Until now, very few data has been reported on the comparative risk of psychosis during treatment with methylphenidate and

amphetamines.¹⁶ In a recent cohort study using insurance claim databases, the authors followed 221.486 teens and young adults with ADHD aged 13 to 25 years who were prescribed stimulants for the first time. Half of the study cohort received amphetamines and the other half methylphenidate. Researchers subsequently investigated whether patients had a psychosis diagnosis within four to five months severe enough to warrant antipsychotic medicine. New-onset psychotic symptoms occurred in 343 (approximately 0.15%) teens and young adults. The risk of this rare but serious side effect was twice as high among patients taking amphetamines than among those taking methylphenidate (0.21% vs. 0.1%).^{11,16} Study authors considered that the different biological mechanisms of methylphenidate and amphetamine activity on neurotransmitters could explain findings.¹¹ This data is consistent with a meta-analysis of randomized trials suggesting a more favorable safety profile for methylphenidate than for amphetamine in young patients.³²

Risk of developing schizophrenia

Some evidence suggests that vulnerability to psychostimulant-induced psychosis and schizophrenia may be physiologically and genetically related.^{13,33} However, there is no agreement on the predictive value of psychotic symptoms associated with the use of psychostimulants in children.³³

Several studies indicate that patients with schizophrenia, schizotypal personality traits, and family history of such psychiatric disorders are more prone to psychotic episodes associated with the use of stimulants.^{13,27,30} The “dopamine hypothesis of schizophrenia” attributes psychotic symptoms to hyperactive dopaminergic signal transduction. At the same time, psychostimulants increase dopamine levels in some cerebral regions. Combination of these two factors causes dopamine overflow in the central nervous system, making the patient more likely to suffer from stimulant-induced psychosis.^{13,30,33}

In contrast to schizophrenic psychosis, which follows a chronic course, stimulant-induced acute psychosis seems to have a brief duration and resolve with abstinence.^{13,16,25-27} Still, symptoms persist for more than one month in a minority of patients, suggesting prodromal schizophrenia symptoms that were exacerbated by psychostimulant use or an underlying schizophrenia vulnerability triggered by psychostimulant use.^{13,27,29,30}

To further complicate the picture, FDA reported that 8% of patients with psychosis secondary to psychostimulants were diagnosed with schizophrenia or bipolar disorders after some years.^{13,27,33} Some authors argued that ADHD-like symptoms may be a premorbid psychotic disorder state, particularly among patients with early-onset psychosis.^{3,19,33} Interestingly, it has been reported that childhood history of ADHD is common in patients suffering from chronic psychotic disorders.^{3,19,33} Several possible explanations can be put forward to account for this association, including genetic susceptibility, neurobiological pathophysiology, family history, and social environmental factors.^{3,30,31} A population-based study in a

large sample of 73.049 ADHD-newly diagnosed patients and 73.049 controls from Taiwan’s National Health Insurance database found that ADHD alone is a risk factor for psychotic disorders.³ This study also suggested that patients with ADHD taking psychostimulants had a significantly increased risk of developing psychotic symptoms, but not schizophrenia.^{3,30,31}

CONCLUSION

Psychostimulants are highly beneficial for ADHD patients and a valuable part of their treatment. However, as expected from pharmacological profile, these drugs are associated with new-onset psychotic symptoms, even at therapeutic doses.^{18,27} Episodes tend to occur early in the course of therapy, resolve with drug discontinuation, and present no immediate danger, but may be particularly traumatic and undesirable both for patients and parents.^{18,20,27} In most reported stimulant-induced psychosis cases, no preexisting psychiatric comorbidities or substance abuse history were identified.¹⁸ Thus, physicians should be aware that psychotic symptoms may arise during ADHD stimulant treatment and caregivers should be educated about this side effect.^{20,27}

One study comparing two commonly prescribed stimulants – amphetamines and methylphenidate – suggested that amphetamines are more likely to cause psychosis than methylphenidate.¹¹ However, one non-randomized/controlled single study based on a national insurance claim database is not enough to decide on the best course of action for these patients.

Further investigation is necessary to identify patients who are most at risk of psychotic episodes. Until risk factors are clarified, caution should be exercised when treating ADHD in patients with a history of psychotic episodes or with family history of psychotic disorders.^{6,11,26,28} Since there is no strong evidence that stimulant-induced psychosis is associated with future schizophrenic or bipolar disorders, psychostimulants should remain first-line pharmacological treatments for ADHD, maintaining patients on close supervision.^{26,33} The potential benefits of stimulant therapy on children’s behavior, family life, and school functioning should be weighed against possible risks.¹⁰

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