



12-16-2018

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Psychostimulants and Psychosis

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An Independent Study

Submitted to the Graduate Faculty

of the

University of North Dakota

in partial fulfillment of the requirements

for the degree of

Master of Science

Grand Forks, North Dakota

December 2018

PERMISSION

Title: Psychostimulants and Psychosis

Department: Nursing

Degree: Master of Science

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Abstract

This study reviews the case of an adolescent male experiencing mood and psychotic symptoms with concurrent illicit Adderall use. Risk factors for developing adverse effects from psychostimulants are reviewed in the literature. Risks of developing mania and psychosis following administration of therapeutic doses of psychostimulants were found to be less than 1%. The likelihood of developing psychosis is far greater when high doses of stimulants are being used as illustrated in the case study. Research demonstrated that the majority of these symptoms subside or disappear completely when stimulant use ceases. Benefits of therapeutic doses of psychostimulants in the treatment of attention deficit and hyperactivity disorders (ADHD) are discussed. Complications can result when individuals are experiencing symptoms of ADHD as well as thought and mood disorders. Clinicians need to ensure schizophrenia and bipolar disorders are treated first as the initiation of psychostimulants can exacerbate manic and psychotic symptoms in this population. This was demonstrated throughout the literature review. Psychostimulants should be used cautiously in children and adolescents with a family history of bipolar and schizophrenia. Literature indicates that psychostimulants can hasten mood and psychotic symptoms in adolescents that already have a genetic predisposition to these mental health conditions.

Background

As America is in the midst of an opiate epidemic, the stimulant crisis appears to be lurking in the shadows. According to the National Institute of Health and Care Excellence, prescriptions for Ritalin and medications similar to it, have doubled in the past decade (2015). The CDC reported that overdose deaths that occurred as a result of psychostimulant abuse rose 30% from the year 2016 to 2017 (www.cdc.gov).

Although psychostimulants remain the first line pharmacotherapy for the treatment of ADHD, they are not without risks. Prescriptions for this classification of medications should be written judiciously. Abuse potential is high and although rare, adverse effects such as psychosis and mania, can occur. This paper will further explore the correlation between the use of psychostimulants and the development of psychotic symptoms.

Case Report

It was a warm, September day when a 17 year-old male patient, A.S., presented to the mental health clinic for his appointment. He walked in wearing a heavy winter coat with a disheveled appearance. His chief complaint was severe anxiety and ongoing depression. A.S. had begun taking Seroquel 50mg nightly within the past 6 months. This was prescribed by his previous provider, and he denied a history of other medication trials. A.S. reported no history of inpatient psychiatric hospitalizations but admitted to feeling depressed for many years. He denied current thoughts or previous attempts of suicide. Socially, the patient was in his final year of high school, but he opted to take online classes because he stated, “I can’t stand being around people.” He lived with his mother and father, but reported he didn’t interact with them much as he spent most of his time in the garage. A.S. reported working full-time in food service. When questioned about being around people, he clarified, “I don’t mind being around people when money is involved.” In the session, A.S. was observed to be hypervigilant with darting eye contact. He described unusual sleep and appetite patterns such as being up for days and then sleeping for days. At times, he would restrict his food intake by going 3-4 days without eating, and then followed this with binging episodes. A.S. was positive for both auditory and visual hallucinations; he reported a time where he saw people in his front yard. “My parents got concerned for me,” he explained. A.S. has heard chatter or noise in the past as well. “But then I

look around the house, and no one else is there,” he explained. He also expressed some bizarre and paranoid thought content throughout the course of the interview. The patient reported never eating the food from his work because “those burgers are not made of beef”. “What do you think they do with all the refugees that come to Minnesota from other countries?” insinuating the food at the restaurant came from human remains. A.S. engaged in high-risk behaviors such as stealing and selling and buying illicit substances. Again, he reiterated the fact that he doesn’t like being around people, but “these guys are my dealers,” he explained. A.S. has bought Adderall off the street for “the past couple years”. He reported taking 30mg in the morning, and an additional 20mg at dinner time on the nights he works late and closes the restaurant. A.S. stated the Adderall helps him feel less depressed and keeps him alert. He denied any history of ADHD. The patient reported he has one brother, who is in treatment for methamphetamine addiction. Other than this, he denied any other family history of mental illness or substance abuse.

This patient showed evidence of both a mood and thought disorder. It was difficult to ascertain if these symptoms were a direct result of the Adderall, or if the Adderall had simply precipitated his psychotic and manic symptoms. A.S. displayed poor insight and judgment, and it appeared unlikely that he will stop using illicit substances. Due to this, it is difficult to get a baseline of what A.S. would be like when he’s not abusing substances. A working diagnosis of substance-induced mood disorder was established. Schizoaffective disorder, major depressive disorder with psychotic features, and schizotypal personality disorder are differential diagnoses to consider. Laboratory tests which included a CBC, CMP, TSH, and Vit D levels were ordered in addition to a urine drug screen. Education was provided on the dangers of Adderall use, and the fact that it was likely contributing to the high levels of anxiety he’s experiencing. Seroquel was increased to 100mg nightly in an effort to reduce anxiety, depression, hallucinations, and

regulate mood and sleep patterns. A.S. was expected to return back to the clinic in 4 weeks for follow-up. Our short-term goals included continuing to build rapport with the patient and allowing a trusting relationship to grow. Although he was unwilling to stop illicit Adderall use at the time of the appointment, this will need to be assessed at each prospective visit. It's unlikely a remission in either his psychotic or manic symptoms will occur if this change does not take place.

Literature Review

The above case report prompted a thorough research investigation between the use of psychostimulants and the onset of psychosis. The databases PubMed, PsycInfo, and CINAHL were utilized. The search terms “psychostimulants” AND “psychosis” were entered. Filters included full-text articles and those published within the past 10 years. PubMed yielded 110 results whereas PsycInfo and CINAHL yielded 131 and 13 research articles respectively. Titles and abstracts were reviewed. Eventually, 12 articles were selected that were found to be the most relevant for the chosen topic.

Prior to sharing research that discusses adverse effects from psychostimulant use, it is remarkable to report there has been an extensive amount of research performed on the benefits of psychostimulants. A 2017 research article discusses the sensitization hypothesis. Animal studies indicate that treatment with amphetamines result in a sensitizing effect. Translating this to humans, the concern is that stimulants could then make the rewarding effects of other drugs more prominent. However, the author found the opposite to be true. Individuals with ADHD, being treated with psychostimulants, were 35% less likely to abuse substances compared to those not being treated with stimulants. Children with ADHD, who received early detection and stimulant

treatment, were less likely to engage in impulsive, risk-taking behaviors. Risks for developing co-occurring substance use disorders as adults also decreased (Asherson, 2017).

Despite the varied benefits of psychostimulants in not only the treatment of ADHD, but also narcolepsy and obesity, risk factors need to be taken into account. To begin, it is important to discuss the action psychostimulants have on the brain. Stimulant medications work by blocking dopamine reuptake transporters leading to an increased concentration of dopamine in the synapse (Ashton, Gallagher, & Moore, 2006).

With increased concentrations of dopamine available to bind to cell receptors, the possibility of developing psychosis or mania presents itself. Psychosis from psychostimulant usage was first described by Connell in 1958. He followed a series of patients that abused amphetamines over a several year period (Martinez-Aquayo, Arancibia, Meza-Concha, Bustamante, Perez-Bracchiglione, & Madrid, 2017). In 2007, the Federal Drug Administration (FDA) issued a warning that psychostimulants being used in the treatment of ADHD can cause hallucinations and delusions (Karatekin, White, & Bingham, 2010). Angelucci, Ricci, Spalleta, Caltagirone, and Mathe (2009) hypothesized the reason for the psychotic symptoms involved the class of proteins known as neurotrophins. Neurotrophins act on dopaminergic neurons that are affected by psychostimulants. Psychostimulants can interfere with these proteins, and the neurotrophins become altered. Since altered neurotrophins are believed to contribute to the development of psychiatric disorders, the authors hypothesize that psychostimulants can cause psychosis through this same mechanism (Angelucci et al., 2009).

The following research studies will emphasize the importance of dosing stimulants at therapeutic levels in an effort to minimize psychotic symptoms. Cheng et al. (2014) performed an animal study using both high and low doses of methylphenidate. In humans, low doses of

methylphenidate can have cognitive-enhancing effects such as improvement in memory and attention. To the contrary, high doses can have psychosis-inducing effects and can produce agitation, restlessness, and hallucinations. Cheng and colleagues studied behavioral patterns in rats. Rodents dosed with low-dose methylphenidate showed an improvement in memory recognition tasks whereas rodents dosed with high amounts exhibited hyperlocomotion and an inability to complete tasks. The researchers hypothesize the high doses of methylphenidate reduce glutamate signals and contribute to hyperactivity. Whereas the low doses are thought to enhance cognition through intensifying the signals of N-methyl-D-aspartate receptors (Cheng et al., 2014).

Vorspan, Warot, Consoli, Cohen, and Mazet (2005) present a case that demonstrates the dangers of high dosing of methylphenidate on a human subject. The researchers examine a 17 year-old male that was placed on modafinil 400mg daily for narcolepsy. Due to poor sleep patterns, a year later, he transitioned to methylphenidate 40mg daily. Following initiation of this, he developed manic symptoms such as irritability, flights of ideas, and hypersexual behaviors. When the patient was taken off stimulants all together, he became withdrawn and anhedonic. Modafinil was re-introduced and a full manic episode ensued which resulted in hospitalization. The patient experienced visual and auditory hallucinations, insomnia, tachypsychia, and logorrhea (Vorspan et al., 2005). Ashton, Gallagher, and Moore discuss common withdrawal effects from discontinuing stimulant use. Depression and anhedonia, similar to what this adolescent patient experienced, are common. Antidepressant medications can serve as an aide to alleviate such symptoms (Ashton, Gallagher, & Moore, 2006).

Martinez-Aguayo and colleagues examine yet another case where improper dosing of methylphenidate led to psychotic symptoms for a 9 year-old boy. This patient had a diagnosis of

ADHD and was ordered to begin methylphenidate 5mg twice daily for one week with a target dose of reaching 10mg twice daily. However, he inadvertently started at 10mg twice daily.

While at school, the psychologist noted he displayed paranoia and was confused and hypervigilant. He reported seeing and hearing goblins and dolls. A couple hours later, he described himself as being scared, and couldn't tell whether these perceptions were real or imagined. His symptoms resolved the following day as the medication wore off.

Methylphenidate was stopped and re-started two weeks later at a fraction of the dose he was previously on. After 6 months, no further psychotic symptoms resurfaced. This therapeutic strategy of suspending the drug and then gradually re-introducing it was effective for this young patient; the researchers recommend this approach (Martinez-Aguayo et al., 2017).

The above scenarios prompted further investigation into the probability of psychotic and manic symptoms developing from the use of psychostimulants. Mosholder, Gelperin, Hammad, Phelan, and Johann-Liang (2009) analyzed data from 49 different randomized, controlled trials in pediatric patients. Medications included in the study consisted of stimulants from the amphetamine and methylphenidate classes as well as Strattera and Provigil. A total of 11 adverse events of mania or psychosis occurred during the 743 person-years study. Common patterns of hallucinations observed in children involved visual or tactile sensations of insects, snakes, and worms. Follow-up reports were reviewed as well. Findings revealed that the vast majority of psychotic and manic symptoms ceased shortly after the stimulant medication was discontinued. The authors report that hallucinosis will occur in approximately 0.25% of pediatric patients treated with stimulants (Mosholder et al., 2009). This statistic is congruent with the Martinez-Aguayo et al. study that reports 1 in 400 patients treated with psychostimulants will develop psychosis. Most often, these symptoms will surface as treatment

is initiated. However, in rare occurrences, psychotic and manic symptoms can emerge several months into the medication therapy (Martinez-Aguayo et al., 2017).

Effectively treating ADHD with psychostimulants can become more complicated when co-occurring psychiatric disorders are present. Martinez-Aguayo and colleagues estimate that patients with ADHD are 4.3 times more likely to develop schizophrenia than the general population. They further explain that genetic factors associated with stimulant-induced psychosis overlap with those seen in schizophrenia. Approximately, 8% of patients experiencing hallucinations secondary to the use of methylphenidate were later diagnosed with bipolar or schizophrenic disorders. The appearance of schizophrenia can be facilitated by stimulant medications in those individuals with a family history of mental illness (Martinez-Aguayo et al., 2017). Prescribers are often reluctant to treat ADHD in patients that are also experiencing psychosis fearing stimulants will further exacerbate their symptoms. However, following stabilization with antipsychotics, researchers address the importance of treating ADHD symptoms in a 2015 journal article. Levy, Traicu, Iyer, Ashok, and Joobar (2015) find that individuals with untreated ADHD are more prone to drug abuse. Drug abuse in turn would further aggravate psychotic symptoms and result in de-stabilization (Levy et al., 2015).

Goldsmith, Singh, and Chang (2011) discuss another common psychiatric co-morbidity of ADHD, bipolar disorder. Their findings indicate that nearly 85% of youth with bipolar disorder also meet diagnostic criteria for ADHD. Much like psychotic disorders, mood disorders should be given treatment priority in relation to ADHD. However, the authors explain that psychostimulants can be added to the treatment plan once mood stabilization has occurred. Their study found that 90% of patients receiving a mood stabilizer to treat bipolar and a stimulant to treat ADHD remained euthymic. Whereas between 2.5 and 10% individuals diagnosed with

both disorders, destabilized following the addition of a psychostimulant. Mania, hypomania, and suicidality were the most common adverse effects to occur (Goldsmith, Singh, & Chang, 2011).

With the alarming rates of individuals experiencing ADHD and other co-morbid psychiatric conditions, researchers have studied what impact, if any, psychostimulants have had on this. Research findings were inconsistent. Karatekin, White, and Bingham (2010) conducted a study on 42 participants with psychosis. The results revealed that individuals exposed to psychostimulants during their childhood had a younger age of onset of psychotic symptoms than those not treated with stimulants. The mean age was 11.2 years in the stimulant exposure group in contrast to 13.7 years in the comparison group. Questions arise from these findings. Were these differences caused by harmful effects of psychostimulants, or was it simply a variation of symptom severity between the two groups studied? Other information revealed in this study was the significant percentage of individuals with adolescent-onset psychosis that had been prescribed psychostimulants, 59%. Other studies reported this correlation to be as high as 77% (Karatekin, White, & Bingham, 2010).

Goldsmith, Singh, and Chang (2011) research implications for stimulant use and bipolar. Similar to findings from Karatekin and colleagues, a study of adults with bipolar exposed to stimulants in childhood reported an earlier onset of manic symptoms. The average age of onset was 11.3 years compared to 15.6 years of those individuals not treated with stimulants. DelBello and colleagues theorized that adolescents exposed to stimulants resulted in increased dopaminergic activity in the brain and may have primed the pathophysiology of mania. However, these results are in contrast to the authors' findings. Goldsmith, Singh, and Chang found that stimulants either did no harm or improved symptoms of mania in patients with bipolar (2011). They found no evidence that stimulants accelerate illness and precipitate mania. The

researchers conclude by saying risks for developing mania and psychosis secondary to stimulants are small. Emphasis is placed on using stimulants to treat ADHD in children, so normal neuronal development and psychosocial functioning can occur. This, in theory, would lead to healthier brain development and therefore decrease propensity towards bipolar disorder (Goldsmith, Singh, & Chang, 2011).

The above literature reviewed indicates that the risks of developing mania and psychosis following therapeutic doses of stimulants are quite low. And if adverse psychiatric symptoms did develop, there was likely an underlying cause. However, research done by Baker and Dawe (2005) on individuals abusing high dosages of amphetamines presents a far grimmer picture. The authors find that repeated amphetamine-induced psychotic episodes lead to the concept of reverse tolerance. This process causes users to have additional psychotic episodes even if lower doses of amphetamines are used in the future. Of methamphetamine abusers admitted to the hospital in this study, approximately half had been diagnosed with a psychotic illness. This was after amphetamine use had commenced. It's often difficult to distinguish between drug-induced psychosis or pre-existing psychosis precipitated by amphetamine use. While the majority of psychotic symptoms brought on by amphetamine binges will resolve within days of drug cessation, this doesn't happen all of the time. To add further intricacies, some individuals will have drug-induced psychotic symptoms that persist throughout the course of their hospitalization and last over a month. One final complication noted by the researchers is the fact that many patients will relapse following discharge from the hospital (Baker & Dawe, 2005). For the reasons stated above, a clear diagnostic picture is difficult to obtain. This leads back to the case study presented at the beginning of the paper. It is probable the young adolescent patient described has a primary mental health condition, but this is challenging to decipher with his

ongoing amphetamine abuse. The amphetamines are likely exacerbating what was already a pre-existing vulnerability.

Current research focuses on reducing the abuse potential and psychotic symptoms occurring with psychostimulant usage. An article by Darakhshan (2013) concentrates on 5-hydroxytryptamine (5-HT). The 5-HT receptor is known to be involved in psychotic symptoms associated with schizophrenia and also plays a role in the rewarding effects of drug abuse. Since 5-HT-1A receptors are elevated in the brains of patients with schizophrenia, the author focuses on this same receptor in regards to psychostimulant use. Amphetamine sensitization is discussed throughout the article and is thought to underlie the reason addicts experience severe cravings. It was suggested that serotonin, not dopamine, was involved in causing and maintaining this sensitization to stimulants. Long-term use of amphetamines is believed to produce changes in 5-HT-1A receptors. Their functions then become disrupted. However, co-administration of 5-HT-1A agonists with stimulants can prevent this change from occurring (Darakhshan, 2013). Although additional work remains, preclinical research looks promising.

Implications

Health care providers need to be mindful of the resulting psychosis and mania that can occur after prescribing a psychostimulant. These symptoms can be minimized by starting patients on low doses of stimulant medications and titrating up slowly. Special precautions should be used in prescribing stimulants to patients that have a genetic predisposition to schizophrenia or bipolar. Although, no research was found to indicate that stimulants contribute to the development of such conditions, current literature suggests symptoms of schizophrenia and bipolar occur at younger ages when patients were exposed to stimulant medications during childhood. Lastly, psychostimulants have many benefits for individuals with ADHD, and this

research was not intended to deter their use. However, providers must continue to utilize sound judgment and weigh the benefits versus risks ratios prior to prescribing this class of medications. Extended release formulations can be used to minimize abuse potential. Additional research needs to be performed on psychosis related to psychostimulant use to promote further understanding. Long-term effects associated with stimulant use is a topic that also warrants supplemental research.

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