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Prescription stimulant use is associated with earlier onset of psychosis

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ABSTRACT

A childhood history of attention deficit hyperactivity disorder (ADHD) is common in psychotic disorders, yet prescription stimulants may interact adversely with the physiology of these disorders. Specifically, exposure to stimulants leads to long-term increases in dopamine release. We therefore hypothesized that individuals with psychotic disorders previously exposed to prescription stimulants will have an earlier onset of psychosis. Age of onset of psychosis (AOP) was compared in individuals with and without prior exposure to prescription stimulants while controlling for potential confounding factors. In a sample of 205 patients recruited from an inpatient psychiatric unit, 40% (n = 82) reported use of stimulants prior to the onset of psychosis. Most participants were prescribed stimulants during childhood or adolescence for a diagnosis of ADHD. AOP was significantly earlier in those exposed to stimulants (20.5 vs. 24.6 years stimulants vs. no stimulants, $p < 0.001$). After controlling for gender, IQ, educational attainment, lifetime history of a cannabis use disorder or other drugs of abuse, and family history of a first-degree relative with psychosis, the association between stimulant exposure and earlier AOP remained significant. There was a significant gender × stimulant interaction with a greater reduction in AOP for females, whereas the smaller effect of stimulant use on AOP in males did not reach statistical significance. In conclusion, individuals with psychotic disorders exposed to prescription stimulants had an earlier onset of psychosis, and this relationship did not appear to be mediated by IQ or cannabis.

1. Introduction

Recent studies indicate rising rates of the diagnosis of attention deficit hyperactivity disorder (ADHD) and the use of prescribed stimulants for its treatment. In 2012, more than 5 million children and adolescents ages 3–17 years were diagnosed with ADHD, an increase from 4.4 million in 2002 (Chai et al., 2012; Bloom et al., 2013). In the year 2010 alone, 1.9 million pediatric patients were dispensed a prescription for methylphenidate and 1.2 million were dispensed amphetamine or dextroamphetamine (Chai et al., 2012). There has also been a concomitant increase in diversion and misuse of prescription stimulants in adolescents and young adults (Lakhan and Kirchgessner, 2012; Hartung et al., 2013).

Stimulant induced psychosis was first described at length by Connell who reported a case series of individuals who developed psychosis in the context of amphetamine use (Connell, 1958). Since then, numerous studies have described the development of psychosis in individuals abusing amphetamine and methamphetamine (Curran et al., 2004; McKetin et al., 2006). New onset psychosis has also been reported in children/adolescents prescribed amphetamine and methylphenidate for ADHD, although studies of the long-term risk of psychosis in this population are lacking (Cherland and Fitzpatrick, 1999; Ross, 2006).

Prescription stimulants are associated with long-term sensitization of dopaminergic release in the striatum (Vanderschuren et al., 1999; Vezina, 2007). Increased presynaptic dopamine release is a replicated finding associated with psychosis (Laruelle et al., 1999; Howes et al., 2012). Therefore, through the process of sensitization, exposure to stimulants during childhood or adolescence could increase the risk for future psychosis. Consistent with this model, there is evidence that stimulants are associated with an increased risk of developing a psychotic disorder. Psychotic symptoms have been reported to persist in a significant percentage of individuals with methamphetamine-induced psychosis (Tatetsu et al., 1956; Sato, 1992; Sato et al., 1992). Recent studies observed an increased risk of schizophrenia in individuals with methamphetamine and cocaine/amphetamine use disorders (Callaghan

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et al., 2012; Giordano et al., 2015).

One commonly employed method of evaluating psychosis risk is comparing age of onset of psychosis (AOP) in patients with and without an exposure while taking into account potential confounding factors. Multiple studies have shown that cannabis use, substance abuse in general, male gender, family history of psychosis, low level of educational attainment and premorbid IQ are associated with earlier AOP (Gureje, 1991; Suvisaari et al., 1998; Cantwell et al., 1999; Khandaker et al., 2011; Large et al., 2011; Liu et al., 2013). Controlling for educational attainment and IQ is of particular relevance for this study as cognitive impairment may increase the likelihood of being treated for a diagnosis of ADHD or using stimulants to compensate for cognitive deficits. The diagnosis of ADHD itself may also be a confounding factor, as recent prospective studies demonstrate that children with ADHD have an increased risk of developing schizophrenia (Dalsgaard et al., 2014; Maibing et al., 2014). In addition, the severity of ADHD symptoms has been associated with earlier AOP in individuals with schizophrenia with a history of childhood ADHD (Peralta et al., 2011).

The purpose of this study is to test the following hypotheses: 1) A history of premorbid exposure to prescription stimulants is associated with an earlier onset of psychotic disorders. 2) The relationship between prescription stimulant use and earlier AOP will persist after adjusting for gender, cannabis and other substance use disorders, history of first degree relative with psychosis, educational attainment and IQ.

2. Material and methods

2.1. Study sample and clinical assessments

Two hundred and thirty-nine individuals with psychotic disorders (diagnosed with schizophrenia, schizoaffective disorder, psychotic bipolar disorder, psychotic depression or psychosis not-otherwise specified) were recruited from an inpatient psychiatric unit specializing in the treatment of individuals with schizophrenia and bipolar affective disorder as part of a genetic association study used in prior studies (Ongür et al., 2009). The investigation was carried out in accordance with the latest version of the Declaration of Helsinki, and the study design was reviewed by McLean Hospital Institutional Review Board. Informed consent of participants was obtained after the nature of the procedures had been fully explained. The Structured Clinical Interview for DSM-IV (SCID-IV) was used to diagnose psychotic, mood and substance use disorders. The Chronology of Psychotic Symptoms from the SCID-IV Psychosis Module was used to determine AOP. Patient interviews, review of medical records, and information from family members and outside providers were used to determine psychiatric diagnoses and AOP. Please see Ongür et al., for further details (Ongür et al., 2009).

All participants completed a questionnaire which asked about prior use of prescription stimulants, age of onset of stimulant use, type of stimulant(s) used, whether stimulants were prescribed or not, and self-reported diagnosis of ADHD (yes or no). Premorbid IQ was estimated using the North American Adult Reading Test (Crawford et al., 2001). Because IQ was not collected at study initiation and was added at a later time point, IQ was missing in a subset of patients (n = 63).

2.2. Statistical analysis

Demographic characteristics in the stimulant vs. non-stimulant groups were compared using t-tests or χ^2-square tests. Correlation coefficients evaluated the relationship between age of onset of stimulant use and AOP. Non-parametric tests were used when appropriate. All tests of hypotheses were two-sided with a significance level of 0.05. STATA was used for all analyses.

2.3. Primary analysis

Unadjusted AOP was first compared in the two stimulant groups using independent sample t-test. The *a priori* primary analysis was to assess the effect of prior stimulant use on AOP using a multiple regression model controlling for gender, lifetime cannabis use/dependence, other lifetime substance abuse/dependence, presence of first-degree relative with psychosis and educational attainment (years of education completed). We combined presence of lifetime history of opioid, cocaine, sedative/hypnotic, hallucinogen and polysubstance use disorders as diagnosed using SCID-IV into a single dichotomous variable since the number of subjects with individual use disorders (besides cannabis) was small and not sufficiently powered for individual analyses. Because we restricted the primary analysis to variables for which all subjects had complete data, IQ was not included.

2.4. Secondary analyses

As secondary analyses, 1) we first repeated the primary analysis comparing individuals without a history of stimulant use to the subset of individuals prescribed stimulants and to the subset of individuals not prescribed stimulants separately. 2) We next used exploratory multiple regression analyses to look for interactions between stimulant use and each of the potential confounding factors, and repeated the primary analysis with the addition of any significant interaction terms that were identified. Robust standard errors were used for all regression models to correct for departure from the assumption of homoscedasticity of residuals (Hayes and Cai, 2007). 3) We also used a multiple imputation approach that allowed inclusion of subjects with missing IQ data (Van Buuren et al., 1999). This approach is commonly used to allow inclusion of observations with missing independent variable data in multiple regression models (Horton and Kleinman, 2007). One hundred copies of the dataset were created with imputed values for missing IQ. Next, complete-case analyses of these datasets were performed independently. Beta values were averaged to provide a single parameter estimate. Standard errors were calculated accounting for within-imputation and between-imputation variability in the parameter estimates.

3. Results

3.1. Sample characteristics

Out of 239 patients with psychotic disorders, 113 (47.2%) reported a history of use of stimulants. Because we were testing the hypothesis that premorbid use of stimulants is associated with earlier onset of psychosis, we excluded 31 subjects from analysis who reported age of onset of stimulant use after onset of psychosis (mean ± SD: 10.4 ± 9.1 years after AOP). An additional three subjects with stimulant-induced psychosis were eliminated from analysis: one with repeated hospitalizations for methamphetamine-induced psychosis and two subjects with a single isolated episode of stimulant-induced psychosis at study entry. Out of the final sample (n = 205), 82 (40%) reported stimulant use prior to the onset of psychosis. Demographic and baseline characteristics of patients with and without a history of prescription stimulant use are presented in Table 1. There were no significant differences in diagnosis, family history, educational attainment or IQ between the two groups. Individuals exposed to stimulants were significantly more likely to be younger, male, and have a history of a lifetime cannabis use disorder.