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Drug-related predictors of readmission for schizophrenia among patients admitted to treatment for drug use disorders

Kristine Rømer Thomsen [a,*], Birgitte Thylstrup [a], Michael Mulbjerg Pedersen [a], Mads Uffe Pedersen [a], Erik Simonsen [b,c], Morten Hesse [a]

[a] Centre for Alcohol and Drug Research, Department of Psychology and Behavioural Sciences, Aarhus University, Bartholins Allé 10, 8000 Aarhus C, Denmark
[b] Psychiatric Research Unit, Psychiatry Region Zealand, Toftebakken 9, 4000 Roskilde, Denmark
[c] Institute of Clinical Medicine, Faculty of Medical and Health Sciences, University of Copenhagen, Blegdamsvej 3B, 2200 Copenhagen N, Denmark

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ABSTRACT

Background: Patients with schizophrenia and comorbid drug use disorders (DUD) have a severe course of illness. Despite strong evidence that drug use can exacerbate psychotic symptoms, we have limited knowledge of how specific drugs may increase risk of schizophrenia readmission in this group. This study aimed to assess drug-related predictors of readmission for schizophrenia among a national cohort of patients with a history of schizophrenia admitted to DUD treatment.
Methods: A record-linkage study was used to assess drug-related factors associated with readmission to mental health treatment for schizophrenia, using a consecutive cohort of 634 patients admitted to DUD treatment between 2000 and 2006 in Danish treatment services and tracked until February 2013 or death, controlling for baseline psychiatric treatment variables.
Results: The majority of patients were males (79.8%) and the mean age was 34.7 years. Of all patients, 78.7% were readmitted for schizophrenia during follow-up, and 6.8% died without having been readmitted. We found a robust association between use of amphetamine at baseline and elevated risk of readmission, a less robust association between use of cannabis and elevated risk of readmission, and no association with cocaine, opioids, alcohol, benzodiazepines, and MDMA. Furthermore, one or more psychiatric inpatients visit in the year prior to DUD admission was robustly associated with elevated risk of schizophrenia readmission.
Conclusions: Use of amphetamine and cannabis are risk markers for schizophrenia readmission among patients with a history of schizophrenia and DUD. Psychiatric history is a predictor of schizophrenia readmission in this patient group.

1. Introduction

Patients suffering from schizophrenia often struggle with comorbid substance use disorders (SUD) (Toftdahl et al., 2016). Large epidemiological studies show that SUD are twice as common among individuals with schizophrenia or schizophrenia spectrum disorders (SSD) as in the general population (Arseneault et al., 2004; Wisdom et al., 2011), and that individuals with psychotic disorders have 3–4 times higher risk for smoking tobacco, heavy alcohol and marijuana use, and recreational drug use, compared to the general population (Hartz et al., 2014).

1.1. Comorbid SUD worsen the prognosis of schizophrenia

The course of illness in schizophrenia is highly heterogeneous (Austin et al., 2015). Several lines of evidence show that heavy substance use can exacerbate positive symptoms in individuals diagnosed with schizophrenia and SSD (Arseneault et al., 2004; D'Souza et al., 2009), and leads to more positive symptoms, but fewer negative symptoms, and depressive symptoms, compared to patients with schizophrenia or SSD only (Margolese et al., 2004; Mueser et al., 1998; Potvin et al., 2008). Substance abuse discontinuation has been associated with significant improvements in depression, positive and negative symptoms and global function (Gonzalez-Pinto et al., 2011; Mullin et al., 2012; Weibell et al., 2017). However, there are considerable flaws in study methodology in most studies and there is only a few well-designed long-term follow-up studies in first-episode psychosis (like Gonzalez-Pinto et al., 2011; Hegelstad et al., 2012; Weibell et al., 2017).

Research identifies SUD as among the greatest barriers to functional recovery: compared to patients with schizophrenia or SSD only, patients

* Corresponding author.
E-mail addresses: krt.crf@psy.au.dk (K. Rømer Thomsen), bt.crf@psy.au.dk (B. Thylstrup), mmp.crf@psy.au.dk (M.M. Pedersen), mup.crf@psy.au.dk (M.U. Pedersen), es@regionsjaelland.dk (E. Simonsen), mh.crf@psy.au.dk (M. Hesse).

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with comorbid SUD have poorer medication compliance, increased risk of relapse (Malla et al., 2008; Wade et al., 2006), and more rehospitalization and a high utilization of hospital use in general (Austin et al., 2015; Mueser et al., 1998; Schmidt et al., 2011). In addition, patients suffering from both disorders are more frequently homeless and unemployed, have more physical comorbidities, poorer health and self-care, and lower life expectances (Saha et al., 2007) and increased rates of risky sexual behavior, suicide, criminal behavior, and violence (Buckley, 2006; Crebbin et al., 2008; Mueser et al., 1998).

1.2. Evidence for drug induction and exacerbation of psychotic symptoms

Positive symptoms in schizophrenia are thought to be mediated by enhanced neurotransmission in the mesolimbic dopamine pathway, which may be particularly related to elevated presynaptic dopaminergic function in the striatum (Howes et al., 2012). The activation of the mesolimbic dopamine pathway, which originates in the ventral tegmental area of the midbrain, is believed to mediate aspects of reward and animals will perform an arbitrary operant response to self-administer stimulation of this pathway (Berridge et al., 2009). Substances such as cannabis, amphetamine, alcohol, cocaine, heroin, hallucinogens, and sedatives have all been related to substance-induced psychosis (Alharbi and el-Guebaly, 2016), and common to all substances with addictive liability is their ability to increase synaptic dopamine concentrations in the striatum either directly (e.g. amphetamine and cocaine) or indirectly (e.g. alcohol and cannabis) (Di Chiara and Imperato, 1988).

In particular, studies have investigated causal links between cannabis and schizophrenia and psychosis. Prospective studies following adolescents before onset of schizophrenia estimate that cannabis use is associated with a twofold risk of later schizophrenia or schizophreniform disorder, with indications of a dose-response relationship (Andreasson et al., 1987; Arseneault et al., 2004). Experimental studies indicate that cannabinoids can induce transient schizophrenia-like symptoms in healthy volunteers, and exacerbate psychotic symptoms in individuals with a psychotic disorder (D'Souza et al., 2009; Morrison et al., 2009). One of the main active ingredients in cannabis is tetrahydrocannabinol (THC), which acts as a partial agonist at the CB_1 and CB_2 receptors in the brain (Pertwee, 2008). Acute THC administration indirectly increases synaptic dopamine concentrations through complex interactions including an inhibitory effect on GABA, and is thought to be responsible for the psychoactive effects of cannabis and the increased risk of developing psychotic symptoms and schizophrenia (Bloomfield et al., 2016).

The links between amphetamine and schizophrenia and psychosis have also received substantial attention, and amphetamine seems to be the most potent single drug related to acute psychoses (Vallersnes et al., 2016). Amphetamine increases the availability of dopamine in the striatum by elevating extracellular dopamine (including facilitation of vesicular dopamine release) and prolonging dopamine receptor signaling in the striatum (Calipari and Ferris, 2013). Evidence suggests that amphetamine use can induce transient psychotic symptoms in healthy volunteers, and exacerbate psychosis in individuals suffering from schizophrenia, both of which can be reversed by neuroleptic medications (Alharbi and el-Guebaly, 2016; Curran et al., 2004; Lieberman et al., 1990). A review of experimental studies reflects that a single dose of stimulants can induce a transient psychotic reaction in 50–70% of individuals with schizophrenia and acute psychotic symptoms (Curran et al., 2004).

The link between cocaine use and psychosis has also received attention, and cocaine is among the three most commonly reported drugs in emergency room presentations with psychosis (along with cannabis and amphetamine) (Vallersnes et al., 2016). Evidence indicates that cocaine use can induce transient psychotic symptoms and behavioral symptoms, and possibly also psychosis (Roncero et al., 2014).

1.3. Evidence for drug-related predictors of schizophrenia readmission

In sum, we have clear evidence that: (i) patients suffering from schizophrenia and comorbid SUD have a worse prognosis, including increased risk of relapse and hospitalization, compared to patients without SUD, and; (ii) different types of drugs can induce transient psychotic reactions and exacerbate psychotic symptoms in individuals suffering from schizophrenia. Despite this, we have limited knowledge of the role of specific substances in readmission for schizophrenia among individuals suffering from comorbid SUD.

A prospective study of inpatients in drug treatment found that rates of later psychoses were higher among individuals using amphetamines and cannabis compared to individuals using opiates (Dalmau et al., 1999), and in a more recent study, use of cocaine and cannabis predicted schizophrenia relapse in the univariate analysis, but not in the multivariate analysis (San et al., 2013).

Compared to other substances, risk factors related to cannabis use have received most interest. Evidence indicates that cannabis users have a higher risk of schizophrenia relapse compared to non-users (Manrique-Garcia et al., 2014) and that continued cannabis use after psychosis-onset predicts a higher number of schizophrenia relapses and hospitalizations compared to non-users or former users (Schoeler et al., 2016a). Interestingly, a recent prospective study of patients with first-episode psychosis showed that continued high-frequency use of high-potency cannabis lead to the highest risk of relapse, more relapses, and shorter time before relapse (Schoeler et al., 2016b). Overall, previous studies point to heavy cannabis use as a risk factor for schizophrenia relapse, although the association is not always robust (e.g. San et al., 2013). Furthermore, the majority of studies compare cannabis users with non-users, or compare different patterns of use. Overall, we lack information about the role of different substances from studies examining substance abuse of different types of substances.

The aim of the present study was to assess drug-related predictors of readmission for schizophrenia among a national cohort of patients with a history of schizophrenia admitted to DUD treatment. By looking at patients in DUD treatment we were able to examine possible effects of use of a range of specific drugs including opioids, cannabis, amphetamine, alcohol, benzodiazepines, cocaine, and MDMA.

2. Materials and methods

2.1. Sample and registers

A record-linkage study was used to assess factors associated with readmission to mental health treatment for schizophrenia using a consecutive cohort of 634 patients with a history of schizophrenia (F20) admitted to DUD treatment between 2000 and 2006 and tracked until February 2013 or death. *The Danish Central Psychiatric Research Register* has been keeping records of episodes of psychiatric care since 1970. These records include dates of beginning and end of treatment, diagnoses, type of referral, place of treatment, place of residence, and mode of admission (Mors et al., 2011). *The Registry of Drug Abusers Undergoing Treatment* has been keeping records of admissions to Danish community outpatient DUD services since 1996 and includes records of substances use (The National Board of Social Services and the Ministry of Social Affairs, 2014).

2.2. Dependent variables

The outcome was recurrence of schizophrenia defined as a new treatment episode in hospital-based psychiatric care with a primary diagnosis of schizophrenia, including emergency, outpatient, and inpatient settings. Continuation of treatment for schizophrenia that was already ongoing at the admission to DUD treatment was not included. Hospitalization is a relevant and useful outcome measure in large

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