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

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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 inpatient visits 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.

Keywords: Schizophrenia; Psychosis; Substance use disorder; Dual diagnosis; Amphetamine; Cannabis.

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 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, lower life expectancies (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 CB₁ and CB₂ 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 admitted to DUD treatment with a history of schizophrenia. 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 data-base studies, and is separate from, but closely related to, relapse (Addington et al., 2013).

2.3 Statistical analysis

Time-to-event analyses were carried out using the Fine and Gray method (Fine and Gray, 1999). Time-to-event was calculated as number of days since first admission to DUD treatment to the event. A psychiatric treatment episode was counted if it began after the date of admission to DUD treatment. Patients who died without having received psychiatric care for schizophrenia in the period between admission and death were coded as “competing” observations; patients who did not have any psychiatric care for schizophrenia and did not die before February 2013, were coded as “censored”. Univariate and multivariate time-to-event regression analyses were used to examine associations. Only variables that were statistically significant in the univariate analysis were

subjected to multivariate analysis, with the exception of substance use variables which were included irrespectively. Results were considered significant at $p < 0.05$.

2.4 Ethics

The data for this study are stored on secure servers at Statistics Denmark, and all procedures were approved by the Danish Data Protection Agency. Since the data used for this study were collected and stored for monitoring and quality assurance, no ethics evaluation was needed under Danish law.

3. Results

Participant characteristics are shown in Table 1. Of all 634 patients, 499 (78.7%) were readmitted for schizophrenia during follow-up and 43 (6.8%) died without having been readmitted. The univariate associations are summarized in the right-hand columns of Table 1. Use of amphetamine at baseline was associated with elevated risk of readmission ($p = 0.015$). Furthermore, living outside of an institution ($p = 0.008$), living with children ($p = 0.005$) and time since last psychiatric contact ($p < 0.000$) were associated with lower risk of readmission, while being single ($p = 0.036$), and past year psychiatric emergency room ($p < 0.000$) and inpatient ($p < 0.000$) visits (in the year prior to DUD admission) were associated with elevated risk of readmission for schizophrenia.

Adjusted predictors of readmission are summarized in Table 2. Adjusting for a range of important confounders, use of amphetamine ($p = 0.014$) and cannabis ($p = 0.030$) at baseline was associated with elevated risk of readmission. Furthermore, a history of having one or more past year psychiatric inpatient visits ($p < 0.001$) was associated with elevated risk of readmission. The cumulative adjusted incidence function for amphetamine and cannabis is shown in Figure 1.

4. Discussion

In the present study we tested the relationship between drugs used at first admission to DUD treatment and readmission for schizophrenia. A robust association between use of amphetamine at baseline and elevated risk of readmission for schizophrenia was found in the univariate analysis, and after adjusting for a range of important confounders, this association was further strengthened. After adjusting for confounders, we found an association between use of cannabis at baseline and increased risk of readmission for schizophrenia.

4.1 Amphetamine use increases risk of readmission

The strong positive association between use of amphetamine at baseline and readmission for schizophrenia is in line with previous findings showing that amphetamine exacerbates psychosis in individuals suffering from schizophrenia (Alharbi and el-Guebaly, 2016; Curran et al., 2004). Although acute administration of all substances of abuse increases synaptic dopamine concentrations in the striatum, this is achieved by different mechanisms of action. One hypothesis is that substances such as amphetamine and cocaine, which directly enhance dopamine transmission in nucleus accumbens, are particularly harmful for schizophrenia patients, due to the established link between increased dopamine signaling in striatum and psychosis (Lieberman et al., 1990). However, in the present study we found no association with cocaine. Importantly, amphetamine and cocaine have different mechanisms of action: while both inhibit dopamine reuptake, amphetamine works through a number of additional mechanisms that elevate presynaptic function, including mechanisms facilitating dopamine synthesis and increasing dopamine release (Calipari and Ferris, 2013; Sulzer, 2011). A recent meta-analysis of in-vivo striatal dopaminergic function in schizophrenia patients and controls showed that the primary dopaminergic abnormality in schizophrenia is elevated presynaptic function in the striatum, affecting dopamine synthesis capacity, baseline synaptic dopamine levels and dopamine release (Howes et al., 2012). This offers a potential explanation to why amphetamine is particularly harmful for schizophrenia patients, and may help explain the elevated risk for readmission observed in the present study.

In the present study, substance use was measured in the period 2000-2006 and schizophrenia readmissions were measured during the period from admission to DUD treatment and until 2013. The availability of amphetamine on the Danish market was variable during this period: for example amphetamine constituted 30% of confiscated street drugs in 2004, 23% in 2005, and 33% in 2010, but since 2010, there has been a general decrease (in 2016 amphetamine made up 17% of confiscated street drugs) (Lindholst et al., 2017). At the same time, there has been a marked increase in the availability of cocaine: from 37% of confiscated street drugs in 2010 to 70% in 2016 (Lindholst et al., 2017). The median purity (i.e. the concentration) of amphetamine has decreased slightly from 2003 (9%) to 2013 (5%), and increased to 11% in 2016 (Lindholst et al., 2017). The median purity of cocaine decreased from 2003 (37%) to 2014 (22%), but after 2014 there has been a dramatic increase to 55% in 2016. Future studies are needed to examine whether the increase in availability and purity of cocaine the past few years impacts associations between cocaine use and risk of readmission for schizophrenia.

4.2 Cannabis use increases risk of readmission

In the present study, use of cannabis was associated with elevated risk of readmission in the multivariate, but not the univariate, analysis. Previous studies have shown that use of cannabis increases risk of relapse in patients with schizophrenia (Dalmau et al., 1999), but the association is not always robust (e.g. San et al., 2013), and studies are limited by a lack of inclusion of heavy use of other main substance types. The lack of a robust association in the present study may be linked to methodological limitations, preventing us from differentiating between use of high-potency and low-potency cannabis. It has become increasingly clear that while some cannabinoids increase risk of psychosis (particularly THC), another main cannabinoid in cannabis, cannabidiol (CBD) has the opposite effect on brain and cognition (Curran et al., 2016; Rømer Thomsen et al., 2017). CBD is a negative allosteric modulator of the CB₁ receptor (Laprairie et al., 2015), and accumulating evidence indicates that CBD has a number of medical benefits, including antipsychotic and anxiolytic effects (Bergamaschi et al., 2011; Martin-Santos et al., 2012; Morgan and Curran, 2008), thereby possibly counteracting psychotic symptoms and cognitive impairment associated with cannabis and acute THC administration (Iseger and Bossong, 2015). Findings from functional magnetic resonance imaging (fMRI) studies suggest that these effects are mediated by THC and CBD's opposing effects on the neural circuits affected in schizophrenia, including striatal, hippocampal and prefrontal areas during salience processing (Batalla et al., 2014; Iseger and Bossong, 2015). The importance of looking at subtypes of cannabis is furthermore supported by studies on the role of potency and pattern of cannabis use among patients with first-episode psychosis (Di Forti et al., 2015; Schoeler et al., 2016b). Di Forti et al. (2015) reported that daily use of high-potency, but not low-potency, cannabis was associated with a 5-fold risk of psychotic disorder.

Over the past decades, there has been a general increase in potency of street cannabis, and during the past four years the increase in potency in cannabis resin has been dramatic (Dujourdy and Besacier, 2017). A comprehensive study from France reported an increase in potency of cannabis resin from 10% (mean THC content) in 2009 to 23% in 2016, and in herbal cannabis from 7% in 2009 to 13% in 2016 (Dujourdy and Besacier, 2017). Similar development has taken place in other European countries and in the US (National Academies of Sciences, 2017; Niesink et al., 2015; Zamengo et al., 2015). In Denmark, mean THC levels in cannabis resin rose from 8% in 1992-1993 (Lindholst et al., 2008) to 29% in 2014 (Lindholst et al., 2015), and internal reports from

The Department of Forensic Medicine (Aarhus, Denmark) show a gradual increase up to 2011 followed by a dramatic increase in 2012. In the present study, use of cannabis was measured in the period 2000-2006 and schizophrenia readmission until Feb. 2013, hence covering a period where the Danish market is unlikely to have been dominated by high-potency cannabis. This may help explain the lack of a robust association between cannabis and schizophrenia readmission in the present sample.

4.3 Role of psychiatric and sociodemographic factors

In the univariate analysis, living by independent means, living with children and time since last psychiatric contact were associated with lower risk of readmission, while being single, past year psychiatric emergency room and inpatient visits were associated with elevated risk of readmission. However, after adjusting for confounders, only a history of past year inpatient visit was a risk factor for readmission. This finding is in line with previous studies on the association between previous hospitalizations and risk of schizophrenia recurrence (Addington et al., 2013; San et al., 2013).

4.4 Clinical implications

From a clinical perspective, the elevated risk related to amphetamine use indicates the importance of addressing amphetamine use in patients with a known history of schizophrenia. Although we did not find an equally robust association with cannabis, use of cannabis in this group should call for caution. Other studies point to causal links between cannabis use and exacerbation of positive symptoms (D'Souza et al., 2009; Morrison et al., 2009), and recent studies suggest that this link may be particularly relevant for use of high-potency cannabis (Di Forti et al., 2015; Iseger and Bossong, 2015; Schoeler et al., 2016b). The fact that there has been a dramatic increase in potency of street cannabis (Dujourdy and Besacier, 2017), underscores the need to address use of cannabis in this patient group.

4.5 Generalizability of the findings

The present study is based on patients from a single country, Denmark, and certain characteristics of the Danish health system and the drug market may impact generalizability to other countries or areas of the world. First of all, Denmark has free and easily accessible treatment for DUD, and a single payer system for all healthcare services, including psychiatric care. While this does not mean

that no patients fail to get adequate care in Denmark, a system in which insurance is required may serve patients such as these very differently, and they may not be likely to turn up for care.

Further, the findings may be particularly salient for countries, where amphetamine use is widespread, including parts of Asia and America (United Nations Office on Drugs and Crime, 2014), where patients with schizophrenia are likely to encounter amphetamine-type substances and eventually need care.

4.6 Strengths and limitations

A strength in the present study is the ability to adjust for past psychiatric events and main types of substances. However, some limitations must also be acknowledged. First of all, measures of substance use at baseline are used to predict schizophrenia recurrence. Because we lack information about drug use in the period after DUD treatment, we cannot rule out the possibility that patients may change their patterns of use after discharge from DUD treatment. In addition, we were unable to differentiate between level of potency and frequency of use, which may have contributed to the less robust findings regarding cannabis, considering recent evidence suggesting that frequent use of high-potency cannabis is particularly harmful. Finally, the data bases contain indirect information on severity of the patients at admission (for example, socioeconomic functioning and past psychiatric events), but lack more direct information from psychiatric rating scales and biomarkers of neurological damage. Similarly, we have access to prescription medicine, but very limited information on hospital-based pharmacological treatment. Considering that treatment for schizophrenia is almost exclusively hospital-based, we have very limited information on antipsychotic treatment.

5. Conclusion

Use of amphetamine robustly elevate risk of readmission for schizophrenia in patients with a history of schizophrenia and a current substance use. The association with cannabis use was less robust. Additionally, past year psychiatric inpatient visits at baseline was a significant marker for readmission.

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Table 1. Descriptive statistics and univariate hazard ratios (N = 634).

Variable	Mean	Std. Dev.	Hazard Ratio	P-value
Background variables				
Age	34.67	9.19	1.007 ¹	0.884
Male gender	79.8%		1.238	0.117
Non-Danish ethnicity	9.5%		0.818	0.175
Independent living	50.3%		0.778	0.008
Living with children under 25	3.6%		0.344	0.005
Single	90.4%		1.494	0.036
More than mandatory education	50.3%		1.173	0.223
Active (working or studying)	6.6%		0.842	0.339
Previous offences	79.8%		0.920	0.507
Psychiatric variables				
Time since last psychiatric contact	352.90	537.76	0.698 ¹	0.000
Psychiatric inpatient past year	54.1%		1.835	0.000
Psychiatric emergency services past year	40.4%		1.524	0.000
Substance use variables				
Opioids	50.2%		0.974	0.766
Cannabis	45.3%		1.054	0.553
Amphetamine	21.0%		1.218	0.015
Alcohol	20.7%		0.898	0.421
Benzodiazepines	18.0%		0.965	0.815
Cocaine	15.5%		0.978	0.879

MDMA	3.2%		0.568	0.084
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¹Based on standardized value of the independent variable.

Table 2. Predictors of schizophrenia readmission after DUD treatment (N=634).

Variable ¹	SHR	SE	Z	P-value	CI-	CI+
Sociodemographic variables						
Independent living	0.791	0.108	-1.720	0.085	0.606	1.033
Single	1.156	0.243	0.690	0.491	0.765	1.746
Living with children under 25	0.638	0.233	-1.230	0.218	0.312	1.304
Psychiatric variables						
Time since last psychiatric contact ²	0.948	0.040	-1.260	0.206	0.873	1.030
Psychiatric inpatient past year	1.558	0.173	4.000	0.000	1.254	1.936
Psychiatric emergency services past year	1.160	0.134	1.290	0.197	0.925	1.455
Substance use variables						
Opioids	1.036	0.093	0.390	0.695	0.869	1.235
Cannabis	1.202	0.102	2.170	0.030	1.018	1.420
Amphetamine	1.291	0.134	2.460	0.014	1.053	1.584
Alcohol	0.862	0.144	-0.890	0.371	0.622	1.194
Benzodiazepines	0.840	0.120	-1.220	0.223	0.635	1.111
Cocaine	0.891	0.166	-0.620	0.536	0.618	1.285
MDMA	0.562	0.178	-1.820	0.068	0.303	1.044

¹All associations are adjusted for: living by independent means, being single, living with children, time since last psychiatric contact, past year psychiatric emergency room and psychiatric inpatient visits, and substance use in the year prior to admission.

²Based on log-transformed value of the independent variable to adjust for skew.

Figure 1. The adjusted cumulative incidence function for use of amphetamine and cannabis at baseline.