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Evidence for differential opioid use disorder in schizophrenia in an addiction treatment population

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ABSTRACT

Although people diagnosed with schizophrenia are known to have elevated risks of abuse and dependence for nicotine, alcohol, cocaine, and cannabis, it is less clear if schizophrenia is associated with higher rates of opioid use disorders compared to either the general population or individuals with other major psychiatric disorders. Here we examine a large publicly available database from substance abuse treatment centers to compare how frequently patients with schizophrenia report problems with heroin or other opioid drugs compared to other major drugs of abuse. For comparison, the pattern of substance abuse in schizophrenia is contrasted with individuals with major depression, bipolar disorder, and the entire sample of individuals seeking substance abuse treatment. We find that a significantly lower proportion of patients with schizophrenia are reported to have problems with heroin (5.1%) relative to the entire treatment population (18.2%). The schizophrenia sample also had a significantly lower proportion of individuals with a non-heroin opioid problem (7.2%) compared to the entire treatment population (14.8%), patients with depression (23%), and patients with bipolar disorder (17.3%). In contrast, the schizophrenia sample had significantly higher proportions of individuals with problems with alcohol, cocaine, and cannabis relative to the treatment population. Although these data do not allow conclusions on the relative rate of opioid addiction in schizophrenia compared to the general population, the results suggest a discrepancy in patterns of drug choice that may aid our understanding of schizophrenia and substance use comorbidity.

1. Introduction

Rates of substance abuse disorders are very high in patients with severe mental illnesses, including schizophrenia. Schizophrenia is associated with high rates of abuse and dependence of a wide variety of drugs, including nicotine, cannabis, alcohol, and cocaine (Volkow, 2009). However, some evidence suggests that people with schizophrenia are not as likely to abuse heroin and other opioid-agonist drugs (Schneier and Siris, 1987; Dixon et al., 1991). This pattern of choice of drug among those with schizophrenia is worth further investigation, as there may be implications for understanding the comorbidity of addiction and schizophrenia.

The 'self-medication hypothesis' has been an influential theory in our understanding of the elevated rates of substance use disorders in schizophrenia. However, it has been challenged on the basis of several lines of evidence, including the lack of clear evidence that alcohol, nicotine or illicit drugs provide any measurable symptom relief, the wide range of psychopharmacological effects of the various drugs that patients are vulnerable to abusing, and the lack of evidence that symptom relief achieved with antipsychotics reduces substance abuse (Chambers et al., 2001). Chambers et al. (2001) proposed the 'primary addiction hypothesis' as an alternative, arguing that shared neuropathology between schizophrenia and addiction, most likely involving dopaminergic and glutamatergic regulation of the mesolimbic pathway, leads to a higher risk of both schizophrenia and use of addictive substances. A limitation of the primary addiction hypothesis may be the assumption that neurobiological abnormalities in schizophrenia coincide with increased vulnerability to *all* drugs of abuse; in this regard the possible lack of higher rate, or even a reduced rate, of opioid use disorders in schizophrenia becomes an important topic.

Previous studies on the comorbidity of opioid abuse/addiction and schizophrenia have been somewhat inconsistent. A review of earlier literature on substance abuse in schizophrenia found that people with schizophrenia were less likely to abuse opioids than comparison groups in these studies; however, most of these older studies had low sample sizes (Schneier and Siris, 1987). The large scale Epidemiologic Catchment Area study found elevated comorbidity between opioid abuse and schizophrenia, but the study population was associated with small overall prevalence rates and so the study was underpowered to determine if the findings were statistically significant (Regier et al., 1990). Another large sample study examining a prison population showed that prisoners with schizophrenia were significantly less likely than other prisoners to

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have a history of heroin dependence (Farrell et al., 2002). The Clinical Antipsychotic Trials of Intervention Effectiveness study found overall low rates of opioid abuse or dependence, though with some evidence that patients under-reported use of opiates (Van Dorn et al., 2012).

Here our aim is to test the primary addiction hypothesis by examining large datasets of substance abuse treatment in the United States, with the null hypothesis being that individuals with schizophrenia will report problems with alcohol, cannabis, cocaine, and opiates similarly across substances. Although this dataset does not allow comparisons between patterns of substance use between schizophrenia and the general population, we can compare the patterns of substance use in schizophrenia compared to the general treatment seeking population, with the null hypothesis that patterns of substance use disorders in schizophrenia will be proportionally similar to this group. To determine if any differential patterns of substance use are specific to schizophrenia, and to account for selection biases regarding the rates at which individuals with serious mental illness seek treatment for substance use disorders, we also compare the patterns of substance use disorders in schizophrenia to those of samples of individuals with depressive and bipolar disorders.

2. Methods

We analyzed publicly available data from the Treatment Episode Data Set – Discharges (TEDS-D) series collected by the United States Substance Abuse and Mental Health Services Administration (SAMHSA). These data sets are part of a national census of annual discharges from substance abuse treatment facilities. The core required data submitted by treatment centers to SAMHSA includes the type of substances leading to the treatment episode (up to three substances per case); supplementary data includes psychiatric diagnoses, reported in broad categories. The 2011 TEDS-D dataset is used as this is the most recent dataset available (United States Department of Health and Human Services, 2011). For this analysis, we selected groups based on TEDS-D cohort categories; the group of interest is schizophrenia/other psychotic disorders (simply called schizophrenia from here on). However, the 2011 dataset contains only 1437 individuals identified as having schizophrenia, compared to a total of over 1.7 million cases. Even accounting for the 58.5% of cases for which no DSM axis I diagnosis was reported, this indicates that the identified sample of individuals with schizophrenia represents a gross underestimate of the true number of schizophrenia cases in the sample. Addiction treatment centers may often not emphasize evaluations for primary psychiatric disorders. Because of this likely selection bias, we chose to compare the schizophrenia sample to three other groups: depressive disorders, bipolar disorders, and the 'treatment seeking population'. The 'treatment seeking population' includes all individuals included in the TEDS-D database who were not specifically reported as having a psychotic, depressive, or bipolar diagnosis. Within the dataset were 2739 individuals with bipolar disorder, and 5165 individuals with a depressive disorder, leaving 1,723,400 cases as the treatment population. For each group, we calculated the proportion of individuals reported to have problems with alcohol, cocaine/crack, marijuana, heroin, and non-heroin opioids ('opioids' is used here to refer to both opium-derived and synthetic opioids).

The primary analyses included Chi-square tests to compare the proportions of individuals reported as having problems with the above substances in the 2011 TEDS-D. Because the TEDS-D dataset includes up to three substance problems for each case, the proportions of groups with problems for each substance are not independent. Therefore, separate chi-square tests were performed for each substance. As this amounts to 5 different analyses, each containing 6 comparisons, a Bonferroni correction was applied for 30 analyses, such that the corrected threshold for significance is $p < 0.0017$. To further investigate factors that might be related to pattern of drug abuse among individuals with schizophrenia, exploratory analyses examined the influence of education levels, marital and employment status, medication assisted opioid therapy, and frequency of use of opiates or heroin; these analyses employed chi-square tests for nominal data and Mann-Whitney *U* tests for ordinal measures.

3. Results

3.1.1. Comparison of proportions of patient groups with problems with drugs of interest

The proportions of the overall treatment population and individuals with schizophrenia, depressive disorders, or bipolar disorders with problems with the five target substances are displayed in Fig. 1. Temporal trends displaying these proportions over time between 2006 and 2011 for opiates and heroin are displayed in Supplementary Figs. 1 and 2.

3.1.2. Opioids and heroin

There were significant differences in proportions of patient groups identified as having a problem with non-heroin opiates ($\chi^2(df = 3) = 350$, $p < 0.0001$). The proportion of schizophrenia patients reporting a problem with non-heroin opiates (7.2%) was significantly lower than the overall proportion of treatment-seeking population reporting a problem with opiates (14.8%; $\chi^2(df = 1) = 65.4$, $p < 0.0001$). This was also significantly lower than the proportion of bipolar patients (17.3%, $\chi^2(df = 1) = 80.1$, $p < 0.0001$) and depressed patients (23.0%, $\chi^2(df = 1) = 177$, $p < 0.0001$) reporting a problem with opiates. These group differences appear to be stable between 2006 and 2011 despite the increase in proportion of the general treatment population with an opiate problem over this period (Supplementary Fig. 1).

There were significant differences in proportions of the four groups identified as having a problem with heroin ($\chi^2(df = 3) = 868$, $p < 0.0001$). The proportion of schizophrenia patients reporting a problem with heroin (5.1%) was significantly lower than the proportion of the overall treatment seeking population (18.2%; $\chi^2(df = 1) = 167$, $p < 0.0001$). This proportion was nominally significantly lower than the proportion of bipolar patients (7.0%; $\chi^2(df = 1) = 5.91$, $p = 0.016$) or patients with depression (6.6%; $\chi^2(df = 1) = 4.33$, $p = 0.036$), though these results do not survive Bonferroni correction. The proportions of both the depression and bipolar samples with a heroin problem was significantly lower than that for the entire treatment population ($\chi^2(df = 1) = 470$, $p < 0.001$ and $\chi^2(df = 1) = 232$, $p < 0.001$, respectively). These trends appear to be stable between 2006 and 2007 (Supplementary Fig. 2).

In the TEDS-D datasets, individuals who are prescribed methadone or buprenorphine for opiate or heroin use disorders are not classified as having problems with opiates or heroin. Thus there remains the possibility that the low proportion of schizophrenia patients in the TEDS-D

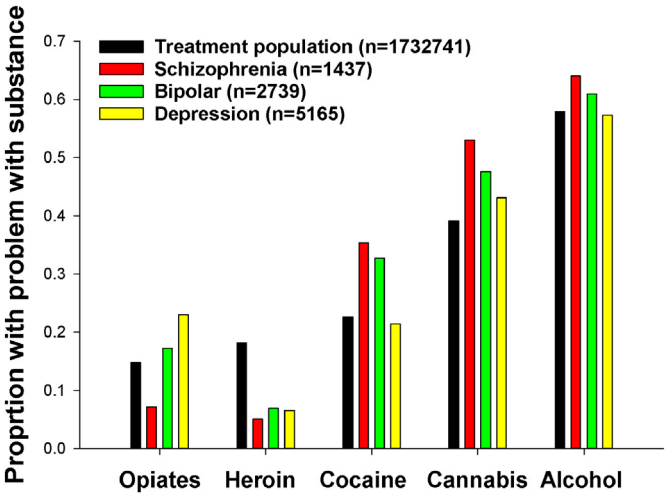

Fig. 1. Proportion of each patient group reported to have a problem with the identified substances in the 2011 TEDS-D dataset.

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