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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

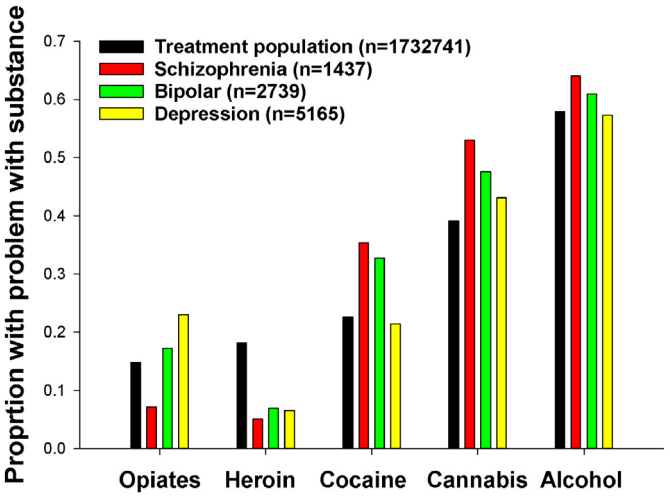

Fig. 1. Proportion of each patient group reported to have a problem with the identified substances in the 2011 TEDS-D dataset.

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dataset with opiate or heroin problems is due to these patients having higher levels of treatment with opioid agonists. However, a chi-square test shows significant differences in the proportion of the four groups receiving opioid agonist treatment ($\chi^2(df = 3) = 328$, $p < 0.001$), with the proportion of schizophrenia patients on opioid agonist treatment (0.6%) being lower than in the overall treatment population (6.1%; $\chi^2(df = 1) = 74.8$, $p < 0.001$).

The TEDS-D datasets also include a variable reporting frequency of use of substance identified as a problem for that individual. This frequency is reported as an ordinal variable ranging from no use over past month to daily use over past month. Kruskal-wallis tests find significant differences between patient groups for frequency of heroin use ($\chi^2(df = 3) = 372$, $p < 0.001$) and opioid use ($\chi^2(df = 3) = 271$, $p < 0.001$; see Fig. 2). For both heroin ($\chi^2(df = 1) = 53.1$, $p < 0.001$) and opioids ($\chi^2(df = 1) = 39.9$, $p < 0.001$), patients with schizophrenia had less frequent use of drug over the prior month compared to the general treatment population. For opioids, schizophrenia patients had less frequent use of opioids compared to patients with depression ($\chi^2(df = 1) = 8.87$, $p = 0.003$) and patients with bipolar disorder ($\chi^2(df = 1) = 9.03$, $p = 0.003$), but these patient groups did not differ in frequency of use of heroin.

3.1.3. Cocaine/crack

There were significant differences in proportions of the four groups identified as having a problem with cocaine ($\chi^2(df = 3) = 298$, $p < 0.0001$). The proportion of schizophrenia patients identified as having a problem with cocaine (35.4%) was significantly higher than the overall proportion of treatment-seeking individuals reported as having a problem with cocaine (22.6%; $\chi^2(df = 1) = 134$, $p < 0.0001$). This was also significantly higher than the proportion of depressed patients (21.4%, $\chi^2(df = 1) = 119$, $p < 0.0001$) reported as having a problem with cocaine, but not significantly higher than the proportion of bipolar patients with a cocaine problem (32.7%, $\chi^2(df = 1) = 2.94$, $p = 0.091$).

3.1.4. Cannabis

There were significant differences in proportions of the four groups identified as having a problem with cannabis ($\chi^2(df = 3) = 238$, $p < 0.0001$). The proportion of schizophrenia patients identified as having a problem with cannabis (53.0%) was significantly higher than the overall proportion of treatment-seeking individuals reported as having a problem with cannabis (39.1%; $\chi^2(df = 1) = 118$, $p < 0.0001$). This was also significantly higher than the proportions of bipolar patients (47.6%, $\chi^2(df = 1) = 10.9$, $p < 0.001$) and depressed patients (43.1%, $\chi^2(df = 1) = 44.4$, $p < 0.0001$) reported as having a problem with cannabis.

3.1.5. Alcohol

There were significant differences in proportions of the four groups identified as having a problem with alcohol ($\chi^2(df = 3) = 33.0$, $p < 0.0001$). The proportion of the schizophrenia group identified as having a problem with alcohol (64.0%) was significantly higher than the overall proportion of treatment-seeking individuals reported as having a problem with alcohol (57.9%; $\chi^2(df = 1) = 21.4$, $p < 0.0001$). This was also significantly higher than the proportion of depressed patients (57.3%, $\chi^2(df = 1) = 20.7$, $p < 0.0001$) reported as having a problem with alcohol, but not significantly higher than the proportion of bipolar patients with an alcohol problem (61%, $\chi^2(df = 1) = 3.47$, $p = 0.065$).

3.2. Influence of social functioning and age on substance abuse in schizophrenia

Although the TEDS-D datasets do not contain measures of psychopathology or objective measures of cognition or social functioning, the datasets do include data on marital status, employment and education levels. Here we examine these variables as proxy measures of functioning among schizophrenia patients to determine if this influences pattern of substance abuse.

Mann-Whitney *U* tests were used to examine if the ordinal measure of education level differed between individuals with schizophrenia reporting or not reporting problems with the selected substances. As reported in Table 1, there were significant trends for schizophrenia patients with cocaine ($Z = -2.96$, $p = 0.003$) or cannabis ($Z = -4.43$, $p < 0.001$) problems to have lower education, while patients with alcohol problems tended to have higher levels of education ($Z = 2.79$, $p = 0.005$). However, there were no significant trends regarding education levels for patients identified as having problems with heroin or opiates.

Chi-square tests were used to examine if the proportion of schizophrenia patients with problems with the selected substances differed by employment status (Table 2). Schizophrenia patients who were unemployed were more likely to have a heroin problem than patients not in the labor force or employed part-time, but not compared to patients employed full time ($\chi^2(df = 3) = 11.6$, $p = 0.009$). Proportions of schizophrenia patients using opioids were not different based on employment status ($\chi^2(df = 3) = 2.40$, $p = 0.40$).

Chi-square tests were used to examine if the proportion of schizophrenia patients with problems with the selected substances differed by marital status (Table 3). Schizophrenia patients who were separated or divorced/widowed were more likely to have an opiate problem than never married patients ($\chi^2(df = 3) = 15.7$, $p = 0.001$), but no significant trends were found for patients with heroin problems ($\chi^2(df = 3) = 1.12$, $p = 0.77$).

4. Discussion

Schizophrenia patients seeking treatment for substance abuse problems at facilities that report diagnostic data to SAMSHA are considerably less likely to have a problem with heroin or other opiates relative to the

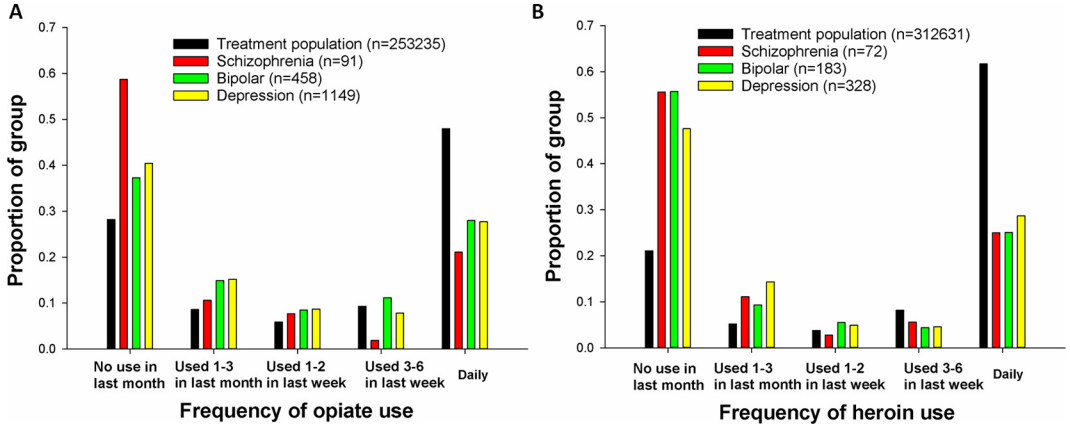

Fig. 2. Frequency of use over preceding month of opiates (A) or heroin (B) by patient group.

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Table 1
Percentage of individuals with schizophrenia within each education level reported to have problem with listed substance.

	Education level					Mann-Whitney U Z statistic	*p*-Value
	<9 years ($n = 111$)	9–11 years ($n = 440$)	12 ($n = 583$)	13–15 ($n = 228$)	>15 ($n = 25$)		
Alcohol	65.8	57.3	69.6	68.0	60.0	2.79	0.005
Cocaine	48.6	37.0	35.0	32.0	16.0	−2.96	0.003
Cannabis	65.8	60.7	47.5	51.3	36.0	−4.43	<0.001
Heroin	8.1	3.6	6.5	3.9	0.0	−0.29	0.78
Opiates	6.3	10.0	6.7	7.9	4.0	−1.25	0.21

general population of people seeking help for substance abuse. A lower proportion of schizophrenia patients had problems with opiates compared to patients with depression or bipolar disorder, as well as the general substance abuse treatment population. In contrast, the proportion of schizophrenia patients seeking help for cannabis, cocaine and alcohol use disorders was comparable to or higher than these comparison groups. These contrasting trends represent a clinical phenomenon with implications for understanding the high comorbidity between schizophrenia and substance use disorders.

One possible hypothesis for the relatively lower rates of heroin/opiate use disorders among schizophrenia patients is that these individuals may lack the social skills involved in acquiring illicit substances (Dixon et al., 1990, 1991). In the TEDS-D dataset, schizophrenia patients who had been married but are separated or divorced were more likely to have an opiate use problem than never married patients, lending some support to the possibility that higher social functioning is associated with use of opiates. However, schizophrenia patients reporting problematic use of heroin or opioid did not have higher levels of education and are not more likely to be employed full-time. Additionally, it is difficult to reconcile the hypothesis that social skills are necessary to acquire illicit substances with the data suggesting that schizophrenia patients are relatively more likely to have problems with cocaine or cannabis. Beyond social skills, financial resources may influence choice of drug among schizophrenia patients. Compared to alcohol, illicit drugs are more expensive, especially when used habitually. Cannabis and cocaine may be more conducive to a binge-type pattern of use, with users able to tolerate periods of abstinence when they are unable to afford the drugs, whereas abstinence from heroin or opiates due to lack of money may be associated with more withdrawal symptoms. However, the TEDS-D data do not suggest that schizophrenia patients who are employed are more likely to have an opiate or heroin problem than unemployed patients.

As the current data do not provide a clear indication that demographic factors related to social functioning explain the relatively lower rate of opioid use in schizophrenia, we return to the self-medication and primary addiction hypotheses for an explanation. Historically, opioid drugs have been used to treat individuals with schizophrenia, especially in the pre-neuroleptic era (Kern et al., 2014). Several small-scale trials have observed improvement of psychotic symptoms following administration of buprenorphine and methadone (Brizer et al., 1985; Schmauss et al., 1987). In this context, the lower rate of opioid use found in this study may further contradict the self-medication hypothesis. Even if opioids do not have true antipsychotic effects but instead provide only anxiolytic and sedating effects, it is difficult to reconcile the current data with the hypothesis that drug choice among individuals with schizophrenia is motivated by the desire to reduce symptoms or distress.

The primary addiction hypothesis predicts a shared neurobiological basis for vulnerability to schizophrenia and to substance abuse disorders, largely based on the unifying model of addiction that considers the mesolimbic dopamine system as the common pathway for drug reward, sensitization, and craving (Chambers et al., 2001). However, there are subtle differences in the neurobiological pathways underlying opiate reward compared to other drugs of abuse (reviewed by Badiani et al., 2011). Notably, increased dopaminergic activity in the ventral striatum has not been found to be related to the 'high' of opioids in humans, in contrast to effects of other drugs (Daglish et al., 2008); nor does dopaminergic activity appear necessary for morphine-induced conditioned place preference in rodents (Hnasko et al., 2005). Thus, the data reported here may still be consistent with the hypothesis that abnormalities in reward circuitry in schizophrenia contribute to an increased risk for substance use disorders (Krystal et al., 2006). However, further attention should be given to the possibility of abnormalities in the cortical opioid system in schizophrenia. Analysis of post-mortem tissue found increased expression of mRNA for the mu-opioid receptor in a prefrontal region of schizophrenia patients compared to controls (Volk et al., 2012). It is also notable that schizophrenia patients have decreased pain sensitivity compared to controls (Stubbs et al., 2015), though it is unclear if this reflects abnormalities within the endogenous opioid system (Urban-Kowalczyk et al., 2015).

Antipsychotic medications should also be considered as a factor contributing to the relatively low proportion of schizophrenia patients with heroin or opiate problems. Preclinical studies show that D2 receptor knock-out mice exhibit deficits in the rewarding effects of morphine (Elmer et al., 2002, 2005), although the rewarding effects of cocaine are largely intact (Caine et al., 2002). Preclinical studies have also found that antipsychotic medications reduce the rewarding effects of morphine (Torigoe et al., 2012) and may attenuate the processes of tolerance and physical dependence on morphine (Tang et al., 2006; Yang et al., 2011). These findings raise the possibility that antipsychotics could "protect" schizophrenia patients from developing opiate problems by limiting the rewarding properties of opiates and inhibiting tolerance; in contrast, since low D2 receptor availability may be a risk factor contributing to use of psychostimulants and alcohol (though perhaps not cannabis or nicotine – see Nutt et al., 2015), antipsychotics may not have a similar effect for all drugs of abuse. For instance, a systemic review of studies examining the use of antipsychotics for alcohol dependence found no evidence for a benefit of antipsychotics, with

Table 2
Percentage of individuals with schizophrenia within each employment status reported to have problem with listed substance.

	Employment status				Chi-square	*p*-Value
	Full-time ($n = 30$)	Part-time ($n = 50$)	Unemployed ($n = 343$)	Not in labor force ($n = 972$)		
Alcohol	50.0	64.0	70.0	63.4	7.77	0.051
Cocaine	10.0	16.0	30.9	39.6	26.85	<0.001
Cannabis	53.3	58.0	58.0	51.5	4.71	0.19
Heroin	6.7	0	8.2	4.1	11.59	0.009
Opiates	13.3	10.0	8.5	7.4	2.40	0.49

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Table 3
Percentage of individuals with schizophrenia within each marital status reported to have problem with listed substance.

	Marital status				Chi-square	*p*-Value
	Never married ($n = 745$)	Currently married ($n = 83$)	Separated ($n = 73$)	Divorced or widowed ($n = 122$)		
Alcohol	61.3	62.7	60.3	68.9	2.65	0.45
Cocaine	31.7	24.1	39.7	37.7	6.15	0.11
Cannabis	58.0	43.4	38.4	34.4	33.61	<0.001
Heroin	4.6	3.6	2.7	5.7	1.12	0.77
Opiates	5.6	7.2	12.3	14.8	15.73	0.001

pooled data suggesting antipsychotics performed worse than placebo for some outcome measures (Kishi et al., 2013). However, this hypothesis cannot be tested in the available TEDS-D dataset, which does not include any data regarding antipsychotic medications.

Some of the limitations of the data examined in this study must be considered. Most importantly, due to the nature of the data the results reported here cannot be interpreted as inferring that schizophrenia patients have a lower risk of opiate use or dependence compared to the general population. Indeed, with 5.1% of the individuals with schizophrenia in this sample reported as having a problem with heroin and 7.2% having a problem with other opioids, this suggests a substantial amount of comorbidity between schizophrenia and opioid use disorders. This is not standard epidemiological survey data, and a dataset based on treatment-seeking individuals could inadvertently miss a large group of schizophrenia patients with opiate use disorders. Potentially this 'missing' group of opiate abusing schizophrenia patients, if it exists, represents a subgroup of individuals who are particularly reluctant to seek treatment for substance use disorders, perhaps due to paranoia, lack of insurance, or inability to access substance abuse services. However, it seems unlikely that schizophrenia patients reluctant or unable to access substance abuse treatment would preferentially abuse opiates or heroin as opposed to alcohol, cannabis or cocaine. The proportion of individuals with schizophrenia with opiate use disorders may also be suppressed if schizophrenia was associated with a higher frequency of lethal overdoses with opiates, which is plausible given the frequent prescription of other sedating medications in this disorder. With this data set it is also difficult to gauge the reliability of reported psychiatric diagnoses. Although contributing facilities were asked to distinguish between substance-induced psychosis versus a primary psychotic disorder, it is possible that some individuals with cocaine or cannabis-induced psychosis may have been inappropriately reported as having schizophrenia, artificially raising the proportion of that group reporting problems with cocaine or cannabis. In many addiction treatment settings, a thorough evaluation for mental health problems may not be emphasized or even feasible if the staff does not include a trained psychiatrist. This may underlie the discrepant findings for the depression and bipolar samples in this analysis, which had elevated or comparable rates of non-heroin opioid use but lower rates of heroin use compared to the entire treatment population; the acute presentation of heroin dependence may limit the potential for a proper mental health assessment to an even greater degree than other opioid use disorders. The current analysis also does not examine trends regarding polysubstance use within the schizophrenia sample; this analysis may provide further information regarding trends of comorbidity between substance use disorders and schizophrenia, but is beyond the scope of the current study.

This report analyzed a large dataset of individuals in substance abuse treatment and found that schizophrenia patients are less likely to be in treatment for heroin or opiate related problems compared to the overall population of individuals seeking treatment for substance abuse. Despite the emergence of a national epidemic of opioid misuse and dependence, schizophrenia patients still appear to preferentially use alcohol, cannabis, and cocaine. If the apparent relative lack of preference for opiates in schizophrenia has a psychopharmacological or neurobiological basis, this would represent a valuable subject for study because of the potential implications for the pathophysiology of schizophrenia, and possibly also for opiate use disorders.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2017.05.004.

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Contributors

Joshua Chiappelli contributed to data analysis and prepared the first draft of the manuscript. Shuo Chen, Ann Hackman, and Elliot Hong contributed to data analysis, writing and editing. All authors contributed to and have approved the final draft of the manuscript.

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Conflict of interest

Dr. Elliot Hong has received or is planning to receive research funding or consulting fees from Mitsubishi, Your Energy Systems LLC, Neuralstem, Taisho Pharmaceutical, Heptares, and Pfizer. All other authors declare no financial interests that could represent a conflict of interest.

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