Letter to the editor

Methadone and buprenorphine treatments in patients with schizophrenia

Dear Editor:

Schizophrenia is associated with high rates of nicotine, cannabis, alcohol, and cocaine use disorders (Volkow, 2009); however, very few studies have assessed the frequency of opioid use disorders (OUD) in patients with schizophrenia. In the NESARC study, respondents with schizophrenia had a lifetime frequency of heroin abuse or dependence of 1.1% (95% CI: 0.1–2.3), and OUD of 3.6%, (95% CI: 0.4–6.8), according to DSM-IV criteria (Martins and Gorelick, 2011). In clinical samples of patients with schizophrenia, the rates of OUD ranged from 0.5% to 13% (Table 1). To our knowledge, there is no study investigating the prevalence of opioid-agonist [treatment] among patients with schizophrenia in the community or in clinical samples.

Therefore, we assessed the proportion of subjects receiving opioid-agonist treatments for OUD (i.e., methadone, buprenorphine, or buprenorphine/naloxone) in a large sample of patients with schizophrenia. A data set was produced from the National Health Data System (Système National des Données de Santé), the French Healthcare Social Security database, which captures 97% of the population. We included all subjects from Hauts-de-France area in Northern France ($N =$ 5,829,677). This initial sample was matched with three databases, using the French social security number (i.e., a unique identifier for each French citizen affiliated with the French Health System). The first database includes all types of antipsychotic medications (i.e: amisulpride, aripiprazole, chlorpromazine, clozapine, cyamemazine, fluphenazine, flupentixol, haloperidol, levomepromazine, loxapine, olanzapine, paliperidone, pimozide, pipotiazine, periciazine, pipamperone, quetiapine, risperidone, sulpiride, tiapride, zuclopenthixol) or opioid-agonist treatments (i.e., methadone, buprenorphine, or buprenorphine/naloxone) delivered to all the patients affiliated to the French Health System in all pharmacies in the area, and dates of delivery. A second database, RIM-P (Recueil d'informations médicalisées en Psychiatrie) database includes the ICD-10 diagnosis data system of public and private hospitals, including both inpatient and outpatient data. This RIM-P database includes schizophrenia spectrum diagnoses, and main socio-demographic characteristics of the patients. Every patient had only one line associated with his/her social security number. A third database included all the patients with ICD-10 diagnosis and receiving a disability pension, which comprises most of the patients with schizophrenia in France. We included all subjects who had been diagnosed with any of the following ICD-10 diagnoses in 2015 and had received antipsychotic treatments at least three times: schizophrenia (F-20), schizotypal disorders (F-21), delusional disorders (F-22), brief psychotic disorders (F-23), substance/medication-induced psychotic disorders (F-24), schizoaffective disorders (F-25), and other schizophrenia spectrum disorders (F-28). The diagnoses of schizophrenia spectrum were made during hospitalizations in Psychiatry or Medicine departments or during the assessment for disability pension.

In this sample of patients positive for schizophrenia-spectrum diagnoses ($n = 29,376$, or 0.5% of the general population in the area), we calculated the frequencies of all subjects receiving opioid-agonist treatments, prescribed by any Medical Doctor (e.g., hospital physicians, general practitioners, psychiatrists, etc.).

We found that among these subjects with ICD-10 diagnoses of schizophrenia-spectrum in 2015, 2.1% ($n = 615$) received opioid-agonist treatments, with 3.2% of the male subjects ($n = 540$) and 0.6% of the female subjects ($n = 75$) receiving opioid-agonist treatments. The mean age of patients with schizophrenia receiving opioid-agonist treatments was 40 years ($SD = 7$). The mean age of subjects without psychotic disorders receiving opioid-agonist treatments was 37.2 years-old, 80.4% were male. The rate of subjects with schizophrenia receiving opioid-agonist treatments (i.e., 2.1%) was higher than the rate of subjects receiving opioid-agonist treatments in the general population in this area (0.4%, $n = 20,523$), χ^2 (df = 1) = 2448.5, $p < 0.0001$.

As 97% of the French population is affiliated with a universal social security system, the strength of the present study was the inclusion of the vast majority of patients with schizophrenia in a highly populated region of France. Since each subject had a single number of identification, no subject could receive an ICD-10 diagnosis of schizophrenia twice. In addition, our study encompassed all patients receiving opioid-agonist treatments in the community, including those receiving these treatments by their General Practitioners.

The present study had some limitations. The patients included in the present study may not have been representative of all patients with schizophrenia in the community. Some subjects with schizophrenia in the community may have been not diagnosed or did not seek treatment. Since some schizophrenia patients who have never been hospitalized or did not receive disability pension may be not included in the study, the rate of schizophrenia patients in the present study may be underestimated; however, the frequency of schizophrenia-spectrum in the general population was 0.5% in the present study, which is consistent with the range of past 12-month prevalence of schizophrenia in Europe (0.06%–0.70%, median: 0.31%) (Simeone et al., 2015). Since the primary objective of the present study was to assess the frequency of antipsychotic medications and other treatments in schizophrenia patients, the database was freezed and the diagnoses of OUD were not available (Trouiller et al., 2017).

The inclusion of substance/medication-induced psychotic disorders (F-24) may increase the prevalence of OUD treatment prevalence in the psychosis group and could be misleading. In a previous study, only 25% of people with substance-induced psychosis diagnoses transformed to a diagnosis of primary psychosis at one year follow-up (Caton et al., 2007), thus 75% did not have schizophrenia. In the present study, the F24 group included only 0.3% of patients with schizophrenia ($n = 38$). Since the data were freezed, we were not able to exclude this group for the analyses. The number of patients with F24 diagnose may be too low to mislead the results.

In the present study 2.1% of schizophrenia patients received opioid-agonist treatments, rate consistent with those found in clinical samples

Table 1
Prevalence of opioid use disorders in clinical samples of patients with schizophrenia.

	Population	N	Mean age Years (SD)	Diagnosis criteria	Lifetime frequency	12 months frequency
Mueser et al., 1990 (U.S.A.)	Schizophrenia/-schizophreniform/-schizoaffective disorder	149	30.3 (8.9)	SCID/DSM-III-R opiate use disorders	4%	Last 6 months: 1%
Rabinowitz et al., 1998 (U.S.A)	First-admission psychotic patients	224	28.7 (9.3)	SCID/DSM-III-R opioid use disorders	2.8% (female); 3.9% (male)	–
Dervaux et al., 2003 (France)	Schizophrenia/schizoaffective disorder	115	35.2 (11.1)	CIDI/DSM-III-R opiate use disorders	6.1%	0.9%
Margolese et al., 2004 (Canada)	Schizophrenia and related psychoses	202	- No SUD: 39.7 (10.5) - SUD: 37.6 (10.0)	SCID/DSM-IV abuse/dependence	–	Heroin: 0.5%: Prescribed opiates: 1%
Wade et al., 2005 (Australia)	First episode psychosis	126	21.5 (3.5)	DSM-IV opioid use disorders	13%	11%
Hides et al., 2006 (Australia)	Recent-onset psychosis	84	24.5 (5.3)	CIDI/DSM-IV heroin use disorders	–	4.9%
Dubertret et al., 2006 (France)	Schizophrenia	205	29.4 (6.9)	DSM-IV opiate use disorders	7.3%	–
Larsen et al., 2006 (Norway)	First episode psychosis	300	27.9 (9.5)		–	Last 6 months: 2%
Petersen et al., 2007 (Denmark)	First episode psychosis	547	- SUD: 26.0 (6.3) - No SUD: 26.8 (6.4)	ICD-10 opioid harm or dependence	0.5%	–
Ongür et al., 2009 (USA)	Schizophrenia/schizoaffective disorder	141	36.9 (12.4)	SCID/DSM-IV opioid use disorder	Schizophrenia: 0% Schizoaffective: 3.2%	–
Lejoyeux et al., 2014 (France)	Schizophrenia	101	40.9 (15.0)	DSM-IV opiate dependence	5%	–
Nesvåg et al., 2015 (Norway)	Schizophrenia	9002	–	ICD-10 opiate use disorders	4.3%	–
Toftdahl et al., 2016 (Denmark)	Schizophrenia	53,035	- SUD: 27.9 (8.2) - No SUD: 27.8 (8.7)	ICD-10 opioid use disorders	5.3%	–
Brunette et al., 2018 (USA)	First episode psychosis	404	23.1 (5.1)	DSM-IV	Opioid abuse: 1.5% Opioid dependence: 3%	–

SUD: substance use disorders.

of patients with schizophrenia, in which the rates of OUD ranged from 0.5% to 13% lifetime and 0.5% to 11% in the last 12 months (Table 1). However, in these studies, the criteria of OUD markedly differed. Since patients receiving opioid-agonist treatments typically present opioid dependence and not opioid abuse, the result of the present study must be compared to those regarding opioid dependence according ICD-10 or DSM-IV criteria in the previous studies.

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18 August 2018