Psychiatry Research Communications 2 (2022) 100056

Contents lists available at ScienceDirect

Psychiatry Research Communications

journal homepage: www.sciencedirect.com/journal/Psychiatry-Research-Communications

Impact of clozapine as the mainstay therapeutical approach to schizophrenia and substance use disorder: A retrospective inpatient analysis

Joana Teixeira [a,b,*], Sara Alexandre [c], Carolina Cunha [d], Filipe Raposo [d], José Pedro Costa [d]

[a] Alcohol and New Dependences' Treatment Unit, Lisbon's Psychiatric Hospital Center, Lisbon, Portugal
[b] Faculty of Medicine, University of Lisbon, Lisbon, Portugal
[c] Pharmacy Department, Lisbon's Psychiatric Hospital Center, Lisbon, Portugal
[d] Nova Medical School, Faculdade de Ciências Médicas, Lisbon, Portugal

ARTICLE INFO

Keywords:
Clozapine
Treatment
Relapses
Schizophrenia
Dual diagnosis
Substance use disorder

ABSTRACT

A retrospective study was conducted to analyze prescription pattern of clozapine in dual diagnosis inpatients' and to find out if there was any association between clozapine prescription and acute relapses either from psychiatric symptoms or from substance use disorder. All patients admitted at Lisbon's Psychiatric Hospital Center during a 4 months' period for psychiatric inpatient treatment with a dual diagnosis at discharge were selected and their clinical files were screened. From 536 patients, 17,5% had a dual diagnosis at discharge. Most frequent psychiatric diagnosis associated with substance use disorder was schizophrenia (50%), followed by major depression disorder (17%) and bipolar disorder (10,6%). Most frequent substance of abuse was alcohol, followed by cannabinoids, nicotine, cocaine, and opiates. At least one antipsychotic drug was prescribed to 85,1% patients, and clozapine was prescribed to 22,3%. There was a statistically significant association between clozapine prescription and prevention of acute relapses of psychiatric symptoms in dual diagnosis patients. Although there was no significant association between prescription of clozapine versus other antipsychotic drugs in the prevention of relapses of substance use, there was a larger than expected number of patients in clozapine that didn't have a relapse of substance use.

1. Background

Dual diagnosis (DD) refers to the simultaneous diagnosis of a psychiatric disorder and a substance use disorder (SUD)(World Health Organization, 1994).

The lifetime prevalence rate of a dual diagnosis in patients with schizophrenia is about 50% (Arranz et al., 2018; Pettinati et al., 2013; Carr à et al., 2012). In patients diagnosed with Major Depressive Disorder, this percentage is similar (about 47%), 40% being for alcohol use disorder and around 17% for any drug use disorder (Pettinati et al., 2013; Carr à et al., 2015; Hasin et al., 2005). As for Bipolar Disorder, it is also around 47%, increasing to 60% in patients with Bipolar Disorder type I (Pettinati et al., 2013; Carr à et al., 2015).

It is well documented that patients with dual diagnosis have a more persistent and severe course for both disorders (Torrens et al., 2015; Volkow et al., 2020; Chilton et al., 2018). This leads to a decreased adherence to treatment (Lacro et al., 2002), and consequently to a higher rate of rehospitalization and treatment failure, higher inpatient care duration, a more chaotic and frequent use of the emergency department (Curran et al., 2003), as well as a higher rate of suicide (Szerman et al., 2012).

In addition, deterioration in social functioning contributes to reduce the patients social support network, considered a protective factor in many psychiatric disorders. Patients with DD present more frequently with impulsive and risky behaviors, linked to a higher prevalence of infections such as HIV or Hepatitis C, precarious socioeconomic situation (financial, occupational and housing) when compared to patients with a psychiatric disorder who do not have a dual diagnosis (Greenberg and Rosenheck, 2013; Buckley, 2006).

Specifically in patients with bipolar disorder, the presence of a concurrent substance use disorder increases the number of clinical decompensations, their complexity in presentation and severity, highlighted by a higher number in self-harm and suicide attempts (Hunt et al., 2016).

All these consequences contribute greatly to increase the burden of disease on the patient and healthcare system, highlighting the

* Corresponding author.Alcohol and New Dependences' Treatment Unit, Lisbon's Psychiatric Hospital Center, Avenida do Brasil 53, 1749-002, Lisbon, Portugal.
E-mail address: joanateixeira@chpl.min-saude.pt (J. Teixeira).

https://doi.org/10.1016/j.psycom.2022.100056
Received 24 February 2022; Received in revised form 30 April 2022; Accepted 5 June 2022

importance of an accurate diagnosis, so that the treatment addresses DD in a unified and comprehensive manner (Buckley, 2006).

Substances most often used by patients with a main diagnosis of Schizophrenia are nicotine (80–90%), alcohol (20–60%), cannabis (12–42%) and cocaine (15–50%) (Arranz et al., 2018). The concomitant misuse of substances has an impact on clinical characteristics – for example, an earlier presentation of a first psychotic episode; also, increased tendency for impulsive and aggressive behavior, and increase suicidal risk (Grau-L ó pez et al., 2020). There is also reduced treatment compliance, and a worsening cognitive performance (Arranz et al., 2018; Lybrand and Caroff, 2009). In addition, misused substances may interact pharmacologically with medications, promoting the occurrence of side effects (for example, making them more prone to parkinsonian symptoms) (Murthy and Chand, 2012). As so, this group of patients has more relapses and re-hospitalizations (Grau-L ó pez et al., 2020; Lybrand and Caroff, 2009).

Although there is a general lack of high-quality evidence studies (namely randomized controlled trials) regarding the most adequate pharmacological treatment in schizophrenia patients with dual diagnosis, some recent systematic reviews have allowed to draw some conclusions on the topic. For instance, first generation antipsychotic drugs do not have a beneficial effect in improving SUD, and in fact may even lead to an increased substance misuse (Arranz et al., 2018; Lybrand and Caroff, 2009). Considering atypical antipsychotic medications, clozapine is the one most often associated with improved outcomes in schizophrenia patients with DD. Several studies have shown that in patients treated with clozapine, the likely rate of decrease in substance use might attain 70–80% (Murthy and Chand, 2012). Clozapine's rapid dissociation of the D_2 receptors and the blockade of 5-HT_{2A} and noradrenergic receptors are actions which are possibly associated with a reduction in substance craving (Arranz et al., 2018; Murthy and Chand, 2012). As an example, the use of clozapine has been shown to decrease nicotine intake (Grau-L ó pez et al., 2020; Lybrand and Caroff, 2009; McEvoy et al., 1995). Also, patients treated with clozapine had lower cannabis use than those treated with risperidone, and it has been shown that clozapine is associated with higher maintenance of alcoholic abstinence, compared to other antipsychotics (Grau-L ó pez et al., 2020; Lybrand and Caroff, 2009).

Despite the existing evidence, and the scientific consensus that clozapine should be offered as first line treatment in schizophrenia with dual diagnosis, this is still not a clinical practice routine (Alsuhaibani et al., 2021). A recent study demonstrated that while almost 90% of clinicians administered this drug in resistant schizophrenia, only about 30% would use it in DD patients. The main barrier identified was the need of surveillance for side effects (mainly hematotoxicity) (Grau-L ó pez et al., 2020).

In this retrospective analysis, we evaluated whether hospitalized patients with a DD (namely schizophrenia and a substance use disorder) had better outcomes regarding relapses of the acute psychotic symptoms and relapses of substance use when treated with clozapine.

2. Methods

A retrospective study was conducted to analyze prescription pattern of clozapine in dual diagnosis inpatients and to find out whether there was any association between clozapine prescription and acute relapses either from the psychotic symptoms or the SUD.

Data pertaining all patients admitted at Lisbon's Psychiatric Hospital Center for 4 months (from 1st June to 30th September 2021) for psychiatric inpatient treatment were collected, and those with a dual diagnosis at discharge were selected. Clinical files from dual diagnosis patients were screened to assess their sociodemographic characteristics, psychiatric diagnosis, substance of abuse, and antipsychotic medication prescribed at discharge.

Statistical analysis was done with SPSS software v.28. Descriptive statistics and Chi-square or Fisher tests were used to analyze if there was any association between clozapine prescription and relapses, either of acute psychotic symptoms or of substance use.

3. Results

3.1. Descriptive statistics of the sample

Lisbon's Psychiatric Hospital Center is the main hospital for acute psychiatric inpatient admissions in the Lisbon area, treating both acute inpatients and chronic psychiatric resident patients. A total of 536 patients were admitted at Lisbon's Psychiatric Hospital Center from 1st June to 30th September 2021 for psychiatric inpatient treatment. Of those, 94 (17,5%) had a dual diagnosis at discharge.

Most patients in our sample were male (71,3%) and the mean age was 43,5 years (age range from 19 to 75 years-old).

From the total of 536 inpatient admitted, there were 314 acute inpatient admissions and 222 chronic psychiatric resident patients at Lisbon's Psychiatric Hospital Center. In our sample, 67 participants (71,3%) were acute inpatients, whilst 27 (28,7%) were chronic psychiatric resident patients.

The most frequent psychiatric diagnosis associated with substance use disorder in our inpatient sample was schizophrenia (n = 47; 50% of the patients). Major depressive disorder was the main diagnosis in 16 patients (17%) and bipolar disorder in 10 patients (10,6%). A personality disorder diagnosis was present in 21 patients (22,3%) (Table 1).

The most frequent substance of abuse was alcohol (n = 62; 66%), followed by cannabinoids (n = 57; 60,6%), nicotine (n = 48; 51,1%), cocaine (n = 28; 29,8%) and opiates (n = 22; 23,4%). A total of 11 patients had a misuse of benzodiazepines (11,7%) and 7 misused amphetamines (7,4%) (Table 2).

3.2. Prescription of clozapine vs other antipsychotic drugs

In our sample, 80 patients (85,1%) had at least 1 antipsychotic drug prescribed; 29 patients had at least 2 antipsychotic drugs (30,9%), and 4 patients (4,3%) were taking at least 3 antipsychotic drugs (3 oral formulation antipsychotics ± 1 injectable) (Fig. 1).

Clozapine was prescribed in our sample to 21 patients (22,3%). Other antipsychotics were prescribed in 62 patients (66%) and only 11 patients (11,7%) had no antipsychotic drugs as part of their therapeutical scheme.

On a closer analysis of the patients with diagnosis of schizophrenia (n = 47), we found that all of them (100%) had at least 1 antipsychotic prescribed, 21 (44,7%) had at least 2 antipsychotics prescribed and 4 of them (8,5%) had at least 3 antipsychotics prescribed.

Clozapine was prescribed to 20 patients (42,6%) with a main diagnosis of schizophrenia while 27 patients (57,4%) had other antipsychotic drug prescription.

3.3. Prescription of long-acting antipsychotics

In our sample, 45 patients (47,9%) had a long-acting injectable antipsychotic prescribed. Of these, 15 patients had an association of a long-acting antipsychotic with clozapine (corresponding to 33,3% of total patients doing a long-acting antipsychotic).

When it came to patients with a schizophrenia diagnosis, 33 patients (70,2%) had a long-acting antipsychotic prescribed. Of these, 14 patients

Table 1
psychiatric diagnosis in sample study.

Psychiatric Disorder	Frequency (N)	Percentage (%)
Schizophrenia	47	50.0
Bipolar Disorder	10	10.6
Personality disorder	21	22.3
Major Depressive Disorder	16	17.0
TOTAL	94	100

Table 2
Substance of abuse in sample study.

Substance	Yes Frequency (N)	Percentage (%)	No Frequency (N)	Percentage (%)
Alcohol	62	66.0	32	34.0
Cannabinoids	57	60.6	37	39.4
Benzodiazepines	11	11.7	83	88.3
Amphetamines	7	7.4	87	92.6
Cocaine	28	29.8	66	70.2
Opiates	22	23.4	72	76.6
Nicotine	48	51.1	46	48.9

(42,4%) had an association of a long-acting antipsychotic with clozapine (Fig. 2).

3.4. *Clozapine vs other antipsychotics in relapse prevention*

When we consider patients to whom an antipsychotic drug was prescribed, we found no statistically significant association between the prescription of clozapine vs other antipsychotic drugs and the prevention of relapses on substance use (Fisher exact test p value = 0,107). However, although non-significant, there was a larger-than-expected number of patients in clozapine that didn't have a relapse of substance use (Fig. 3)

As expected, there was a statistically significant relationship between the prescription of clozapine and absence of relapses of acute psychotic symptoms (Fisher exact test p-value = 0,048).

In patients with diagnosis of schizophrenia, we did not find an association between clozapine prescription and other antipsychotic's prescription in preventing relapse of substance use (Fisher exact test p-value = 0,282) (Table 3)

Despite the statistically significant association between clozapine and a lesser likelihood of having an acute psychotic decompensation, this statistically significance is lost when we consider only the patients with diagnosis of schizophrenia (Fisher exact test p-value = 0,159). However, we find again a higher than expected number of patients on clozapine that don't have an acute psychotic decompensation (Table 4).

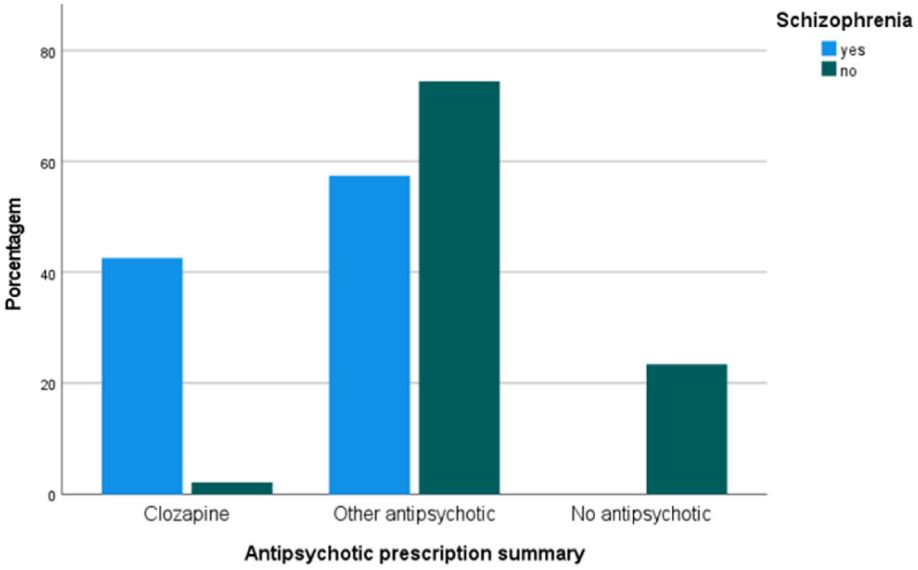

Fig. 1. Antipsychotic drug prescription in patients with diagnosis of schizophrenia.

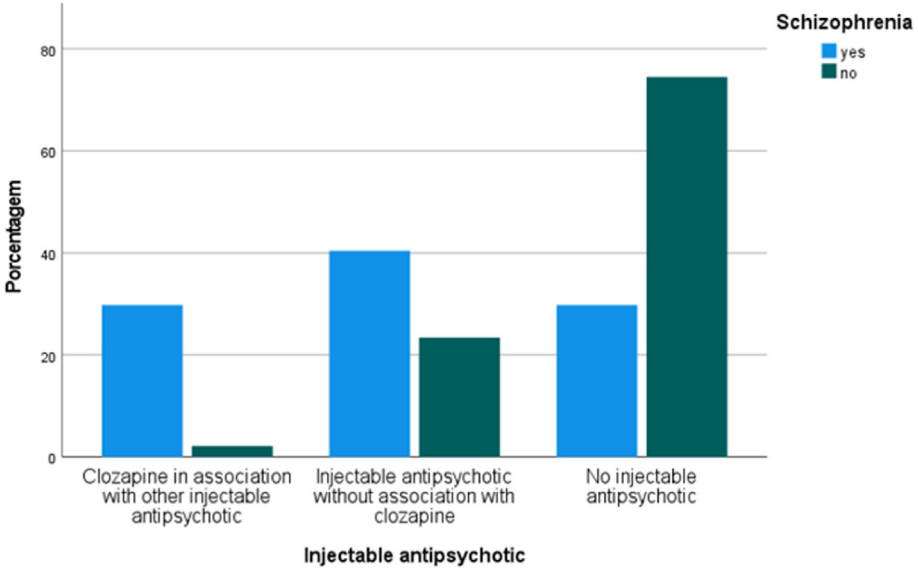

Fig. 2. Long-acting antipsychotic drug prescription in patients with diagnosis of schizophrenia.

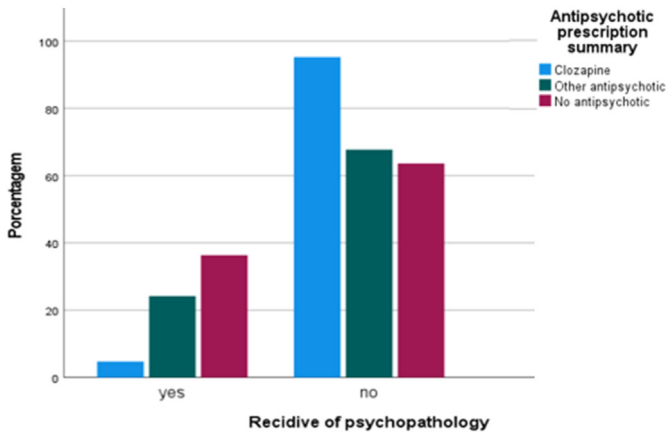

Fig. 3. Relapse of acute psychotic symptoms by antipsychotic drug prescribed.

Table 3
Antipsychotic drug prescription and relapse of drug use.

			Relapse of drug use			
			Yes	No	No value	Total
Antipsychotic drugs	Clozapine	Number	1	20	0	21
		Expected number	3,3	16,4	1,3	21,0
	Other antipsychotic	Number	12	45	5	62
		Expected number	9,7	48,6	3,7	62,0
Total		Number	13	65	5	83
		Expected number	13,0	65,0	5,0	83,0

Table 4
Antipsychotic drug prescription and relapse of acute psychiatric symptoms.

			Relapse of acute psychotic decompensation			
			Yes	No	No value	Total
Antipsychotic drugs	Clozapine	Number	1	20	0	21
		Expected number	4,0	15,7	1,3	21,0
	Other antipsychotic	Number	15	42	5	62
		Expected number	12,0	46,3	3,7	62,0
Total		Number	16	62	5	83
		Expected number	16,0	62,0	5,0	83,0

4. Conclusions

The present study has allowed to improve knowledge about psychiatrist's prescription of antipsychotic drugs, namely of clozapine, for treatment of dual diagnosis inpatients. And also to analyze if there was any association between clozapine prescription and acute relapses, either from psychotic symptoms or substance use in dual diagnosis patients.

Dual diagnosis patients in our sample were mainly male and acute inpatients. The most frequent psychiatric diagnosis present in association with addictive disorder was schizophrenia and the most frequent substance of abuse was alcohol followed by cannabinoids. Although the higher and well-known association between diagnosis of schizophrenia and cannabinoid use, Lisbon's Psychiatric Hospital Center has a specialized alcohol disorder treatment unit which can justify this high frequency of alcohol as being the most frequent drug of abuse in sample patients.

Of remark is the high rate of antipsychotic drugs prescribed in our sample, with most of dual diagnosis patients having at least 1 antipsychotic drug prescribed. Also, half of patients in our sample had a long-acting antipsychotic prescribed and clozapine represented about a quarter of all antipsychotic drug prescriptions in sample patients.

If we look only to patients with diagnosis of schizophrenia, and as expected, all patients had at least 1 antipsychotic drug prescribed while half had at least 2 antipsychotic drugs prescribed. Clozapine was two times more frequently prescribed than in the whole sample of dual diagnosis patients. These results are in line with expert consensus recommendations that indicate clozapine as the drug of choice in treatment of patients with schizophrenia and a diagnosis of substance use disorder associated (Alsuhaibani et al., 2021). Nevertheless, a recent study on psychiatrist's opinion on clozapine prescription for dual disorder patients in Spain (Grau-L ó pez et al., 2020), pointed out that only 30,8% of psychiatrists considered to prescribe clozapine in patients with dual psychosis. The side effects of clozapine and the need of frequent blood account monitorization were the main reasons appointed for the low predisposition to clozapine prescription between Spanish psychiatrists. Similar reasons may probably apply to Portuguese psychiatrists as the number of clozapine prescriptions found in dual diagnosis patients in our sample was still low.

Also relevant is the highly frequent association found in our sample of prescription of a long-acting antipsychotic drug and clozapine in patients with diagnosis of schizophrenia which represents the high severity of patients' disorder in our sample.

Although there was no statistically significant association between prescription of clozapine versus other antipsychotic drugs in the prevention of relapses of substance use, there was a larger than expected number of dual diagnosis patients under clozapine treatment that didn't have a relapse of substance use when compared to patients with other antipsychotic drugs prescribed. This evidence is very relevant and points out the need to do further studies with bigger sample sizes.

A statistically significant association was found between clozapine prescription and prevention of acute psychotic relapses in dual diagnosis patients. This result was already expected as scientific evidence indicate clozapine higher efficacy in treatment of patients with schizophrenia and a diagnosis of substance use disorder associated (Grau-L ó pez et al., 2020).

There are some limitations to our study that should be considered. First, relapses of psychotic symptoms and/or of substance abuse were screened for a short period of time (3 months' follow-up). Then, as all retrospective studies, there may be some information that may not be registered in the clinical file. And at last, relapses were assessed by finding that information registry in patients' clinical file from psychiatric appointment after discharge and by searching for a new inpatient admission to hospital. However, less severe substance use or psychopathological decompensation may not have been severe enough to be told by patients to their psychiatrist or to be assessed by psychiatrists in follow-up appointments.

In conclusion, besides the already known higher efficacy of clozapine for treatment of schizophrenia over other antipsychotic drugs, clozapine seems to be also highly efficacious in preventing substance use relapses in dual diagnosis patients. Nevertheless, due to the severe side effects of clozapine, its prescription should be properly considered to each individual patient.

Author statement

Joana Teixeira: Conceptualization; Methodology; Writing - review and editing.

Sara Alexandre: Investigation; Formal analysis; Writing - review and editing.

Carolina Cunha: Investigation; Formal analysis; Writing - original draft.

Filipe Raposo: Investigation; Formal analysis; Writing - original draft.

José Pedro: Investigation; Formal analysis; Writing - original draft.

Declaration of competing interest

None of the authors have conflict of interest to declare.

References

Alsuhaibani, R., Smith, D.C., Lowrie, R., Aljhani, S., Paudyal, V., 2021. Scope, quality and inclusivity of international clinical guidelines on mental health and substance abuse in relation to dual diagnosis, social and community outcomes: a systematic review. BMC Psychiatr. 21, 209.

Arranz, B., Garriga, M., García-Rizo, C., San, L., 2018 Feb. Clozapine use in patients with schizophrenia and a comorbid substance use disorder: a systematic review. Eur. Neuropsychopharmacol 28 (2), 227–242.

Buckley, P.F., 2006. Prevalence and consequences of the dual diagnosis of substance abuse and severe mental illness. J. Clin. Psychiatr. 67 (Suppl. 7), 5–9. PMID: 16961418.).

Carrà, Giuseppe, Johnson, Sonia, Bebbington, Paul, Angermeyer, Matthias, Heider, Dirk, Brugha, Traolach, Azorin, Jean, Toumi, Mondher, 2012. The lifetime and past-year prevalence of dual diagnosis in people with schizophrenia across Europe: findings from the European Schizophrenia Cohort (EuroSC). Eur. Arch. Psychiatr. Clin. Neurosci. 262, 607–616. https://doi.org/10.1007/s00406-012-0305-z.

Carrà, Giuseppe, Bartoli, Francesco, Clerici, Massimo, el-Guebaly, Nady, 2015. Psychopathology of Dual Diagnosis: New Trumpets and Old Uncertainties, vol. 21, pp. 390–399.

Chilton, J., Crone, D., Tyson, P.J., 2018. Clinical outcomes from a 10-week follow-up psychoeducational program for dual diagnosis. J. Dual Diagn. 1–9. https://doi.org/10.1080/15504263.2018.143142.

Curran, G.M., Sullivan, G., Williams, K., et al., 2003. Emergency department use of persons with comorbid psychiatric and substance abuse disorders. Ann. Emerg. Med. 41, 659–667.

Grau-López, L., Szerman, N., Torrens, M., Basurte, I., Veja, P., Martínez-Raga, J., et al., 2020 May. Professional perception of clozapine use in patients with dual psychosis. Actas Esp. Psiquiatr. 48 (3), 99–105.

Greenberg, G.A., Rosenheck, R.A., 2013. Psychiatric Corr. Past Incarceration Nat. Morbid. Stud. Criminal. Behave Mental. Health 24 (1), 18–35. https://doi.org/10.1002/cbm.187.

Hasin, D.S., Goodwin, R.D., Stinson, F.S., Grant, B.F., 2005. Epidemiology of major depressive disorder: results from the national epidemiologic survey on alcoholism and related conditions. Arch. Gen. Psychiatr. 62, 1097–1106.

Hunt, G.E., Malhi, G.S., Cleary, M., Lai, H.M.X., Sitharthan, T., 2016. Prevalence Comorbid Bipolar Substance Disorder. Clinic. Setting: Systematic. Rev. Meta Anal. J. Affective Dis. 206, 331–349. https://doi.org/10.1016/j.jad.2016.07.011.

Lacro, J.P., Dunn, L.B., Dolder, C.R., Leckband, S.G., Jeste, D.V., 2002. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. J. Clin. Psychiatr. 63, 892–909.

Lybrand, J., Caroff, S., 2009 Dec. Management of schizophrenia with substance use disorders. Psychiatr. Clin. 32 (4), 821–833.

McEvoy, J., Freudenreich, O., McGee, M., VanderZwaag, C., Levin, E., Rose, J., 1995 Apr. Clozapine decreases smoking in patients with chronic schizophrenia. Biol. Psychiatr. 37 (8), 550–552.

Murthy, P., Chand, P., 2012 May. Treatment of dual diagnosis disorders. Curr. Opin. Psychiatr. 25 (3), 194–200.

Pettinati, H.M., O'Brien, C.P., Dundon, W.D., 2013. Current status of co-occurring mood and substance use disorders: a new therapeutic target. Am. J. Psychiatr. 170 (1), 23–30.

Szerman, N., Lopez-Castroman, J., Arias, F., Morant, C., Babín, F., et al., 2012. Dual diagnosis and suicide risk in a Spanish outpatient sample. Subst. Use Misuse 47 (4), 383–389.

Torrens, M., Mestre-Pintó, J.J., Domingo-Salvany, A., 2015. Comorbidity of Substance Use and Mental Disorders in Europe, Insights. European Monitoring Centre for Drug and Drug Addiction (EMCDDA); Publications Office of the European Union: Luxemburg.

Volkow, N.D., Torrens, M., Poznyak, V., Sáenz, E., Busse, A., Kashino, W., Krupchanka, D., Kestel, D., Campello, G., Gerra, G., 2020. Managing dual disorders: a statement by the informal scientific network, UN commission on narcotic drugs. World Psychiatr. 19, 396–397.

World Health Organization, 1994. Lexicon of Alcohol and Drug Terms. World Health Organization, Geneva, Switzerland.