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Professional perception of clozapine use in patients with dual psychosis

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Introduction. Patients with psychotic disorders often have substance use disorders and other addictions. The objective of this study was to know the current treatment situation of these patients focusing on clozapine, which was proposed in most consensus as antipsychotic of first choice in this indication.

Material and methods. A survey with 14 questions on aspects related to the treatment and management of the dual disorders was developed, emphasizing the role of clozapine in this disease.

Results. The survey was answered by 199 experts in mental illnesses (90.5% physicians and 9.5% psychologists). A total of 88.4% of experts were able to prescribe clozapine, but the majority (89.4%) administered the drug to patients with resistant schizophrenia without considering a dual disorder. Only 30.8% considered the use of clozapine in patients with dual psychosis. The underutilization of clozapine in these patients was mainly attributed to controls of the pharmacovigilance plan, including frequent leukocyte count (57.1%), and lack of drug education (35.6%). The main measures proposed to increase its use are fewer blood tests (29.3%), more training (27.8%), and fewer administrative problems (25.1%).

Conclusions. In order to improve the treatment of patients with dual psychosis, it is necessary to simplify the therapy and increase the training of professionals in the use of atypical antipsychotics, especially clozapine, designed to be the drug of choice in the main expert consensus.

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Keywords: Antipsychotics, Dual Psychosis, Professional Perception, Schizophrenia, Alcoholism, Training

Actas Esp Psiquiatr 2020;48(3):99-105

Percepción de los profesionales sobre el uso de la clozapina en pacientes con psicosis dual

Introducción. Los pacientes con trastornos psicóticos presentan con frecuencia trastornos por uso de sustancias y otras adicciones. El objetivo de este estudio fue conocer la situación actual del tratamiento de estos pacientes con el foco puesto en la clozapina, que ha sido propuesta en la mayoría de los consensos como antipsicótico de primera elección en esta indicación.

Material y métodos. Se elaboró una encuesta con 14 preguntas sobre aspectos relacionados con el tratamiento y manejo de la patología dual, haciendo hincapié en el papel de la clozapina en esta enfermedad.

Resultados. La encuesta fue respondida por 199 expertos en enfermedades mentales (90,5% médicos y 9,5% psicólogos). Un 88,4% de los encuestados tenía posibilidad de prescribir la clozapina, pero la mayoría (89,4%) la administraba a pacientes con esquizofrenia resistente sin considerar una patología dual. Solo un 30,8% planteó el uso de la clozapina a pacientes con psicosis dual. La infrautilización de la clozapina en estos pacientes se atribuyó principalmente a los controles del plan de farmacovigilancia, incluido el recuento leucocitario frecuente (57,1%), y a la falta de formación sobre el fármaco (35,6%). Las principales medidas propuestas para incrementar su uso son tener que hacer menos controles hemáticos (29,3%), mayor formación (27,8%) y tener menos problemas administrativos (25,1%).

Conclusiones. Para mejorar el tratamiento de los pacientes con psicosis dual es necesario simplificar la terapia e incrementar la formación de los profesionales sobre el uso de antipsicóticos atípicos, especialmente la clozapina, considerada como el fármaco de elección en los principales consensos de expertos.

Palabras clave: Antipsicóticos, Psicosis Dual, Percepción de los Profesionales, Esquizofrenia, Alcoholismo, Clozapina

INTRODUCTION

Patients with psychotic disorders often have substance use disorders and other addictions. Substance use overshadows the course and prognosis of the disease. In addition, it also makes psychopharmacological treatment and psychotherapeutic approach to mental disorders difficult.

Patients with schizophrenia who use psychoactive substances have different clinical characteristics from non-dual psychotic patients. The age of presentation of psychosis is earlier in addicted patients than in non-addicted patients[1], especially if the substance consumed is cannabis[2]. The coexistence of the schizophrenic phenotype with substance use disorders involves a greater presence of impulsive and aggressive behavior[3] and a higher risk of suicide[4]. At the psychopathological level, more prominent positive symptoms have been found in patients with schizophrenia in relation to substance use[5], with a lesser presence of negative symptoms[6].

In addition to these clinical characteristics, patients with dual psychosis present more relapses and re-hospitalizations, and worse adherence to treatments[7], since they are at greater risk of experiencing side effects, drug interactions, and being polymedicated[8]. At the same time, they have higher rates of social exclusion, lower attendance at health devices, and, in general, a worse prognosis compared to non-dual patients.

Currently there is not enough literature to propose psychopharmacological recommendations in patients with dual psychosis, being frequent the concomitant use of antipsychotics and specific drugs for addiction. Most studies say that antipsychotics produce a clear improvement in psychotic symptomatology and a more controversial effect on substance use disorder[9]. The possibility that atypical antipsychotics do not worsen craving for substance use has been described, suggesting that they may aid in the remission of substance use disorders in schizophrenic patients[10,11]. Of particular note is a study by Scheller-Gilkey *et al.* which stated that atypical antipsychotics are associated with reduced substance use compared to conventional antipsychotics[12].

However, recent controlled clinical trials and meta-analyses have provided new data on the superiority of clozapine over risperidone in subjectively decreasing craving and cue reactivity on cannabis use[13,14]. Both the new and previous findings indicate that clozapine seems to have some advantage in both reducing these symptoms and in substance abuse[10,15,16]. Based on a database of Australian patients with psychosis, one study found that those taking clozapine had a lower risk of consuming alcohol, cannabis, and other drugs than those taking other antipsychotic drugs[17].

Although there are generally few prospective controlled trials, and existing studies have small patient samples[18], they suggest that clozapine should be considered as the treatment of choice in patients with schizophrenia and dual disorders[10,15,16]. However, the requirement for regular monitoring and the risk of serious adverse effects associated with this drug, although very rare[19,20], may explain why it is not used as a first option in routine clinical practice. For this reason the following study was proposed, whose objective is to know the use of clozapine among professionals who treat patients with dual psychosis, and what difficulties these professionals face in its use.

MATERIAL AND METHODS

A cross-sectional study was conducted among medical professionals who routinely treat patients with psychosis and substance use disorders to understand how they use clozapine in clinical practice. The survey consisted of 14 questions about dual disorders and the use of clozapine in these patients, and was distributed among attendants to the first congress of the World Association on Dual Disorders (WADD) and fifth congress of the Spanish Association of Dual Disorders (*Sociedad Española de Patología Dual*, SEPD) held in Madrid between 23 and 26 March 2017. The congress was attended by 2,000 specialists from 72 countries. The surveys were completed by hand and collected during the event. Professionals participated on a voluntary basis and the study was not remunerated.

RESULTS

A total of 199 health professionals completed the survey: 180 were physicians (90.5%) and 19 were psychologists (9.5%). Most of them worked in hospitals (39.9%) or in Mental Health Centers (38.4%). The others were from Acute Psychiatric Units of general hospitals, Addiction Units, and Daycare Centers. Only two of the respondents were doing their

residency period as Medical Interns in Psychiatry at the time of the study. The results of the survey are shown in Table 1.

Most of the respondents were able to prescribe clozapine directly (88.4%), while the rest were able to do so by referring patients to Psychiatric Units (1.5%). Patients already on treatment with clozapine were attended by 70.2% of respondents. However, only 30.8% considered the use of clozapine for dual psychosis, despite the fact that 59.9% of the professionals surveyed knew that clozapine is recommended as the drug of choice for patients diagnosed with schizophrenia and dual disorders.

Only 54.5% of respondents answered that they do not consider using clozapine until 3-5 years after the diagnosis of schizophrenia, and more than 50% only use clozapine after previous administration of 2 or more antipsychotics. A total of 61.8% considered the handling of clozapine more complicated than other treatments, mainly due to the pharmacovigilance plan and blood controls (57.1%), the lack of training in the use of clozapine (35.6%), and problems with inspection visas (7.3%). In fact, just over half of them (59.1%) routinely analyzed plasma levels of clozapine. In addition, more than 20% of the respondents had not received training in the handling, implementation or use of clozapine during their residence period.

The measures chosen by the professionals surveyed to increase the use of clozapine were having to perform fewer blood tests (29.3%), providing more training on the use of the drug (27.8%), having fewer administrative problems (25.1%), and allowing Primary Care physicians to prescribe the drug to psychotic patients with dual disorders (5.8%). A total of 54.8% considered that a Quality Index should be granted to Psychiatric Services with high percentages of patients treated with clozapine, as occurs in other countries.

Table 1 Survey conducted among study participants

Questions and answers	Answers	%
What is your specialty? (n=199)		
Medicine	180	90.5%
Psychology	19	9.5%
What is your place of work? (n=198)		
Hospital	79	39.9%
Mental Health Center	76	38.4%
Acute Unit	19	9.6%
Additions Unit	16	8.1%
Daycare Center	6	3.0%
Internal Physician resident in psychiatry	2	1.0%
Can you prescribe clozapine? (n=198)		
Yes	175	88.4%
No	15	7.6%
Yes, I refer the patient to the Psychiatric Unit	3	1.5%
No, I refer the patient to the Psychiatric Unit	5	2.5%
Do you currently see patients being treated with clozapine? (n=198)		
Yes	139	70.2%
No	59	29.8%
In which patient profiles is the use of clozapine considered? *		
Resistant Schizophrenia	177	89.4%
Patients with pronounced extrapyramidal symptoms	96	48.5%
Psychiatric patients with high levels of aggressiveness	94	47.5%
Psychosis in Parkinson's Disease	83	41.9%
Suicidal thoughts	75	37.9%
Dual disorders	61	30.8%
Did you know that clozapine is the drug of choice for patients with schizophrenia and dual disorders according clinical consensus? (n=192)		
Yes	115	59.9%
No	77	40.1%
From the diagnosis of schizophrenia in a patient, how long does it take to consider the use of clozapine? (n=187)		
1-2 years	68	36.4%
3-5 years	102	54.5%
> 5 years	17	9.1%
When faced with refractory schizophrenia, after how many treatments do you consider clozapine as an option? (n=192)		
1	15	7.8%
2	101	52.6%

DISCUSSION

The survey of the present study has allowed to check the situation regarding the use of clozapine among mental health experts (mainly psychiatrists) for the treatment of patients with dual psychosis. Despite the fact that most of health professionals involved in the treatment of mental illnesses know and have the capacity to prescribe this drug, its low use in dual disorders is attributed to methodological and administrative barriers, pharmacovigilance plans and, above all, to the lack of training. In fact, although a large number of respondents reported receiving information on the use of clozapine during their residence period, there was still a significant percentage of them who did not receive information on its management, implementation, and use. The use of clozapine shown in the present study is consistent with that reported in previous studies about professional pre-

Table 1 Continuation

Questions and answers	Answers	%
When faced with refractory schizophrenia. after how many treatments do you consider clozapine as an option? (n=192)		
3	62	32.3 %
≥ 4	14	7.3%
How do you consider the management of clozapine with respect to other treatments? (n=191)		
Same	53	27.7%
More complicated	118	61.8%
Less complicated	20	10.5%
What do you think the low use of clozapine is due to? (n=191)		
To the pharmacovigilance plan and blood controls	109	57.1%
To the lack of training in the handling of clozapine	68	35.6%
To problems with pharmacy inspection	14	7.3%
Do you analyze the plasma levels of clozapine? (n=193)		
Yes	114	59.1%
No	79	40.9%
During your residency were you trained in the handling. treatment and use of clozapine? (n=192)		
Yes	150	78.1%
No	42	21.9%
What measures would make you use clozapine more? (n=191)		
Having to do fewer blood tests	56	29.3%
Increased formation in the handling of the molecule	53	27.8%
Have fewer administrative barriers	48	25.1%
That Primary Care physicians can prescribe it	11	5.8%
N/A	23	12.0%
Do you think that a Psychiatric Service Quality Index should be awarded when a high percentage of patients treated with clozapine is reached. as is the case in other countries? (n=188)		
Yes	103	54.8%
No	85	45.2%

* Each respondent could choose more than one answer

scription and management in daily clinical practice conducted both in Spain[21] and in other countries[19].

Previous studies conducted in Spain have evaluated the perception of health professionals about the treatment of patients with dual disorders, but until now none of them had focused on the importance of clozapine in these patients[20-24]. In the same way that the respondents in our study highlighted, these studies also reported the lack of training and knowledge about the management and treatment of dual disorders. Respondents described a lack of resources, as well as low patient adherence to treatment. With regard to low adherence to treatment, the experts attributed it to a low patients' knowledge of the disease, the presence of adverse effects, the lack of efficacy of the treatment, and the use of complex dosages. To solve these adherence problems, the respondents proposed using drugs with few side effects and easy to handle, in addition to resorting to psychoeducation, motivational techniques, and individual psychological treatment[20].

Although there are numerous treatment guidelines, either for mental disorders or substance use disorders, just over half of them include at least one recommendation for patients with dual disorders, and few make exclusive reference to dual psychosis[25]. This means that health professionals do not have enough information to identify and monitor the co-existence of substance use disorders and other mental disorders. Some of the main guidelines that make specific reference to this situation are those provided by the Clinical Practice Guidelines for the pharmacological and psychological treatment of adult patients with a severe mental disorder and a substance use disorder, promoted by several Spanish societies of psychiatry and addictions[26], and that of the National Institute for Health and Care Excellence (NICE)[27,28], addressing both the necessary social services and their assessment and management in the health care setting.

Regarding the pharmacological treatment of these patients, and as indicated in the clozapine data sheet, the NICE guidelines state that this drug should be offered to patients with schizophrenia whose illness has not responded adequately to treatment, despite the sequential use of at least two antipsychotics (including atypical antipsychotics)[28,29]. However, the same guidelines make it clear that although this antipsychotic may play an important role in patients with dual psychosis, there is insufficient evidence on its use in them[28].

Despite the controversial evidence and the recommendation of the NICE guidelines, there are numerous papers in clinical practice, and some in controlled trials, that place clozapine as a treatment of choice in patients with dual psychosis[13,17,30], highlighting the difference between clinical guidelines and routine clinical practice. A review of the literature showed that of the atypical antipsychotics described, clozapine was the most effective in reducing the use of alcohol, cocaine, and cannabis in patients with schizophrenia[31].

In another recent systematic review, which mainly included prospective, randomized, multicenter studies, evidence for the use of clozapine in dual- disorders patients was found to be robust[13]. The administration of 200-600 mg/day clozapine for 12 weeks to patients with schizophre-

nia has been shown to decrease nicotine intake compared with lower doses (50-150 mg/day)[32,33]. However, smoking may increase clozapine metabolism by inducing cytochrome CYP1A2. Plasma levels of clozapine may be reduced by up to 50% in patients who smoke and may increase dramatically when they stop smoking abruptly[34]. In short term studies (4 and 12 weeks), patients treated with clozapine showed lower cannabis use than those treated with risperidone[15,35,36]. The effect of clozapine has also been proven in long term studies (2-3 years). It has been observed that the percentage of patients who managed to stay without taking substances was higher with clozapine than with other first-generation antipsychotics, such as haloperidol and fluphenazine[10,37,38].

Despite all the evidence shown regarding the treatment of dual psychosis, many mental health experts still do not administer clozapine to these patients. Although a high percentage of the experts consulted (89.39%) administered this drug to patients with resistant schizophrenia, as indicated in the product's technical data sheet[29], only 30.81% did so in patients with dual psychosis. Likewise, as detailed in the clozapine data sheet, most of these experts administered the antipsychotic after two previous treatments[29]. A large proportion of the respondents in our study claimed that the low use of clozapine in these patients could be due to the greater complication in its use compared to other antipsychotics (>70%), pharmacovigilance plans (57.1%) or lack of training in its use (35.6%). With regard to the management of the drug, the handling of clozapine is more complex than the other second generation antipsychotics, since it requires a personalized dose adjustment and a leukocyte count before starting treatment due to the possibility of agranulocytosis[29]. In contrast, other antipsychotics that are not effective in dual psychosis, such as risperidone, are usually administered at a fixed dose and without the need for such strict blood control[39-41].

The main limitations of this study are the same ones inherent to this type of studies and the possibility that the answers given are very subjective. Another limitation of the study is the number of surveys collected, which, although not a negligible number, represents a very low percentage of the total number of people attending the congress. Given the possible subjectivity of the responses, the results and conclusions must be taken with caution before being extrapolated to normal clinical practice.

CONCLUSIONS

Despite the knowledge of the treatment and the availability of controlled trials on the use of clozapine in patients with dual psychosis, there are still many barriers that make its use difficult in this type of patients. On the one hand there are differences between clinical guidelines and the evidence available in routine clinical practice. The opinions of numerous experts in dual disorders and dual psychosis, can give a more complete vision of the situation of the use of clozapine in these patients. These experts highlight the difficulties they face in treating patients with dual psychosis, including the complexity of managing the drug and the lack of training in its proper use. There is no doubt that simplifying the treatment, reducing administrative barriers, and training professionals in the use of this drug would help increase its prescription and improve the treatment of these patients.

ACKNOWLEDGEMENTS

The authors would like to thank Dr Fernando Sánchez Barbero and Content Ed Net for their help in the preparation of this manuscript.

FUNDING

The authors received funding from ADAMED Spain to cover the costs of preparing the manuscript. ADAMED was not involved in the design of the paper or in the analysis and interpretation of the results.

CONFLICTS OF INTEREST

L.G.L. has received fees for lectures from Janssen-Cilag and Lundbeck. N.S. has received fees for lectures from Janssen-Cilag, Adamed, Lundbeck, Indivior, Shire, and Exeltis. M.T. has received fees for his participation as an advisor for Gilead, Merck Sharp & Dohme, Indivior, Adamed, and Lundbeck. I.B. has received fees for lectures from Lundbeck, Exeltis, and Rovi Laboratories.P.V. has received fees from MSD, Gilead, Abbvie, and Indivior. J.M.R. has received fees for lectures from Lundbeck, Janssen-Cilag, Exeltis, Shire, and Rovi Laboratories. M.C. has received grants, research support and has been an advisor and consultant for the following pharmaceutical companies: Eli Lilly, Janssen-Cilag, Shire, and Laboratorios Rubió. C.R. has received conference fees from Janssen-Cilag, Ferrer-Brainfarma, Pfizer, Indivior, Lundbeck, Otsuka, Servier, GSK, Rovi, Astra, Gilead, MSD, Sanofi, and Exceltis. He has also received financial support for his participation as a consultant from Janssen-Cilag, Lundbeck, Gilead, MSD, Mundipharm, Indivior, Exeltis, and Martindale. He has participated in the PROTEUS project, which has been funded by Reckitt-Benckiser/Indivior. He has received two grants from Gilead.

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