CONSENSUS BY THE COLLECTIVE OF PSYCHIATRISTS FOR THE CLOZAPINE UPDATE

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Treatment-resistant schizophrenia affects one in three patients with schizophrenia, constituting the most severe group of the disease spectrum[1]. It is defined by the lack of satisfactory response after adequate doses and duration of two antipsychotics[2]. Only one drug, clozapine, has shown efficacy during the resistance state[3]. Despite the good therapeutic response, clozapine is not exempt from side effects, some of which are potentially lethal[4]. Monthly haematological monitoring requirements[5], metabolic effects[6] and those related to sedation[7] and sialorrhea, among others, are frequently cited as barriers to starting clozapine[8].

The prescription of clozapine is well below what would be desirable. It is estimated that around 200/100,000 people should receive clozapine[9]. No Western country comes close to that, Finland being the closest with 173 per 100,000 inhabitants. Spain remains at around 44 prescriptions per 100,000, below the European average, with a heterogeneous distribution among the autonomous communities[10].

To understand the barriers to the use of clozapine and propose areas for improvement, 35 experts in the use of clozapine from the different Spanish autonomous communities were divided into four working groups focused on clinical questions of special relevance to update the situation in 2022:

- How can we improve the efficiency of the use of clozapine?
- What does resistance to treatment in schizophrenia mean?
- How can we improve the management of clozapine side effects?
- What are the priorities to innovate in the use of clozapine?
- Finally, all attendees participated in elaborating this consensus of conclusions and proposals presented below.
- How can we improve the efficiency of the use of clozapine?

Clozapine remains the only medication licensed to treat refractory schizophrenia, and there is no doubt about its efficacy. Despite this, its use is still limited in clinical practice and with a very heterogeneous prescription pattern in the national territory[9]. The low use is even more surprising if the economic or efficiency factor is added: the use of clozapine results in significant, direct and indirect economic savings by reducing hospitalizations and derived economic savings. The direct cost of the drug is estimated at one euro cent (€0.1) per patient per day, well below that of any other atypical antipsychotic. Even adding monitoring of plasma levels (around €20-30 per determination), the overall cost is below other drugs for treating schizophrenia or well below drugs in other areas of health (for example, cancer) for resistant pathology.

The barriers that limit the use are possibly undeserved. Still, they remain immovable: 1) the historical consideration of a dangerous drug, even from the lessons in the university, which alienates clinicians and residents (the future of the profession), 2) the fear of high doses, which would be alleviated with the correct use of plasma level monitoring[11], and 3) the stigma with which medications in psychiatry in general and clozapine, in particular, have been labelled. Further academic and clinical promotion of its use is suggested, particularly among residents, and it demystifies the risks. It is also suggested greater involvement of the administration and health authorities in those areas where use is lower.

Off-label use of clozapine was also recognized, including patients diagnosed with bipolar or schizoaffective disorder or cases of personality disorders or psycho-organic disorders where its use is extensive, although not covered by the datasheet. It would be convenient for this clinical practice to be validated by well-controlled and randomized clinical studies or by epidemiological data using databases with sufficient patients.

WHAT DOES RESISTANCE TO TREATMENT IN SCHIZOPHRENIA MEAN?

Clozapine is a drug mainly indicated for patients who do not respond to two antipsychotics. The use for those who do not tolerate other antipsychotics or for psychosis associated with Parkinson's disease is also added.

Following other recent consensuses, experts debated needing a more precise definition of resistance in clinical practice[12]. On the one hand, to rule out pseudo resistance, that is due to poor compliance with the antipsychotic regimen, misdiagnosis or the use of sub-therapeutic doses of antipsychotics[2]. Monitoring antipsychotic plasma levels before clozapine and the pharmacogenetic profile of antipsychotic metabolism was suggested as a necessary and pending revolution in clinical practice in psychiatry. However, its difficult implementation was recognized[11,13].

The concept of resistance should be specified explicitly in the clinical notes, and the use of the specifications extended: resistance to positive, negative, cognitive, affective symptoms or a combination. The use of psychometric and symptom severity scales is very heterogeneous and limited, although it should help to objectively assess response and outline the type of symptomatic response. It is also suggested that the resistance criteria (e.g. TRRIP) include functionality criteria. Perhaps there is no statistically significant decrease in the severity of the symptoms in some cases. Still, there is a change in conflict or readmissions that is significant, and that is not included in the TRRIP.

Clozapine augmentation would benefit from a systematic assessment of symptoms[14]. Beyond the classic combinations with amisulpride or aripiprazole, the limited use of electroconvulsive therapy is highlighted. Greater use of long-acting injectable antipsychotics has been detected as clozapine augmentation, and it would be convenient to validate this clinical practice with scientific studies. Non-pharmacological strategies, such as promoting physical activity, cognitive rehabilitation, neuromodulation or new products such as cannabidiol, are still far from standard clinical practice.

HOW CAN WE IMPROVE THE MANAGEMENT OF CLOZAPINE SIDE EFFECTS?

First is the enormous variability in the recording of clozapine side effects. We are far from unanimous in knowing it is registered regarding side effects and the need to unify the criteria. The difficulty of sharing clinical histories between different centres is also highlighted since the systems are watertight, which hinders patient care. An adequate pharmacovigilance system would allow collecting and sharing the most serious side effects among clinicians.

Developing a unified scale of side effects, which included severity criteria, would be a significant advance for improving treatment, perhaps framed in a unified clozapine follow-up protocol. The systematic use of plasma levels would also prevent the development of side effects, and, once again, there is an insistence on promoting its use[15].

Time was devoted to considering who should lead the management of these secondary symptoms and the fundamental role of nursing. The convenience of expanding knowledge-updating activities to the nursing community and to all those who care for patients undergoing treatment with clozapine is underlined.

WHAT ARE THE PRIORITIES TO INNOVATE IN THE USE OF CLOZAPINE?

There is great variability in the use of clozapine, not only between the different autonomous communities of the Spanish state but also between the different centres. A series of innovation priorities are suggested, ranging from the most feasible to those expected to be the most difficult to implement.

Undoubtedly, the use of plasma levels should be generalized and protocolized[15], which should include not only clozapine but also norclozapine. The assessment should go from being ad-hoc to one more part of the healthcare routine.

Make the indications more flexible or recognize those patients in whom it is prescribed off-label. Randomized clinical trials cannot be carried out for all pathologies, and clinicians often face the dilemma of using drugs such as clozapine off-label in patients with acquired brain damage, intellectual disability or even dementia, bipolar disorder or borderline personality disorder. Perhaps an expert document or a guide by scientific societies would offer greater coverage to clinicians.

The greatest innovations would come from implementing pharmacogenetic programs for cytochromes or determining the blood count or plasmatic levels in-situ[16], although the difficulty of homogenizing these proposals is recognized.

CONCLUSIONS

Clozapine remains the last hope for improving the quality of life in many patients diagnosed with schizophrenia or refractory psychosis. Even so, the use of clozapine remains stagnant, causing unnecessary suffering for patients and wasting financial resources.

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The experts gathered here to stress the need to increase training and academic activity among psychiatrists, especially among residents, to increase the use of clozapine. There is also an insistence on extending the use of monitoring plasma levels in clinical practice. Finally, the implementation or creation of scales for evaluating symptoms and side effects should be prioritized.

CLUB NEMEA members (5th Meeting, Madrid, 22 October 2022)

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