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# Clozapine as treatment of first choice in first psychotic episodes. What do we know?

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Schizophrenia is currently conceptualized as a neurodevelopmental disorder with progressive clinical, neurophysiological and neurostructural deterioration mostly occurring at early stages of the disease. During the last years, several early intervention programs have tried to modify the natural history of the disease. The choice of antipsychotic treatment adapted to the specific needs of the patient would make it possible to optimize the results of the intervention programs in first psychotic episodes. Clozapine has become a keystone in the treatment of psychosis, with multiple contributions to the treatment of schizophrenia. Clozapine has been proven superior to other antipsychotics in efficacy and effectiveness with comparable cost-effectiveness to that accepted for many medical interventions. On the other hand, recent studies indicate that the incidence and mortality of clozapine-induced agranulocytosis could be lower than previously estimated and that all-cause mortality due to clozapine is less than that associated to other antipsychotic drugs. However, in spite of clinical guideline recommendations, clozapine is used less and later than recommended. There is a lack of studies comparing clozapine with other antipsychotics in first episode psychosis patients. The aim of our paper is to review the current medical evidence about the use of clozapine as a first-line treatment for naive first episode psychosis patients.

**Key words:** Clozapine, Schizophrenia, First episode psychosis

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## Clozapina como tratamiento de primera elección en primeros episodios psicóticos ¿qué sabemos?

La esquizofrenia se conceptualiza, en la actualidad, como una enfermedad del neurodesarrollo con un deterioro clínico, neurofisiológico y neuroestructural, especialmente notorio en las etapas iniciales de la enfermedad. En los últimos años, los programas de intervención precoz buscan tratar de modificar el curso natural de la enfermedad. La elección de un tratamiento antipsicótico ajustado a las necesidades específicas del paciente permitiría optimizar los resultados de los programas de intervención en primeros episodios psicóticos. La clozapina ha sido un fármaco clave en la historia del tratamiento de la psicosis y sus aportaciones en el tratamiento de la esquizofrenia han sido múltiples. Ha demostrado su superioridad sobre otros antipsicóticos en términos de eficacia y efectividad con un coste-efectividad comparable al aceptado para numerosas intervenciones médicas. Por otro lado, estudios recientes indican que la incidencia y mortalidad asociadas a la agranulocitosis por clozapina serían inferiores a las estimadas en estudios previos y la mortalidad global por clozapina inferior a la asociada a otros antipsicóticos. A pesar de las recomendaciones de las guías clínicas, la clozapina se emplea con mucha menor frecuencia y más tardíamente de lo recomendado y los ensayos clínicos comparando la eficacia y efectividad de la clozapina frente a otros antipsicóticos en primeros episodios psicóticos son prácticamente inexistentes. En el presente artículo de revisión selectiva pretendemos revisar la evidencia clínica existente acerca del empleo de clozapina en primeros episodios psicóticos que nunca han recibido tratamiento farmacológico.

**Palabras clave:** Clozapina, Esquizofrenia, Primeros episodios psicóticos

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In the present review article, we have aimed to summarize the existing scientific evidence on the need for early intervention in patients with a first psychotic episode in order to improve the disease prognosis, review the contributions of clozapine versus other antipsychotics in the treatment of schizophrenia and review the studies published

up to date on the use of clozapine as treatment of first choice in first episodes of schizophrenia.

## EARLY INTERVENTION IN FIRST PSYCHOTIC EPISODES

The concept of schizophrenia has significantly evolved in recent years. It is currently understood as a complex disease of neurodevelopment with progressive clinical, neuropsychological, neurophysiological, and neurostructural deterioration, supporting the concept of early psychosis as a dynamic and modifiable disease.<sup>1-4</sup> This deterioration seems to be especially important in the first years of evolution of the disease.<sup>5</sup> On the other hand, the course of schizophrenia has enormous individual variations. For some authors, this would only indicate the clinical heterogeneity of the patients included under this diagnostic category.<sup>6</sup> However, for others it would support the possibility of improving the disease course through interventions that would affect the prognostic factors.<sup>7</sup>

In this sense, there would be unmodifiable prognostic factors (such as age, gender and premorbid adjustment) and modifiable factors (as duration of the untreated psychoses) candidates for interventions aimed at improving the course of schizophrenia.<sup>8,9</sup> In this context, many early prevention programs have arisen in recent years on psychosis based on a psychopharmacological, psychotherapeutic and comprehensive psychosocial approach during the initial stages of the disease.<sup>10</sup>

The association between the duration of untreated psychosis and evolution of schizophrenia is a controversial subject, there being discrepancies in regards to the importance of the early detection and intervention programs in psychosis. In the three main systematic reviews on the subject, Norman et al.<sup>11</sup> found that there was a relationship between the duration of untreated psychosis and the course of schizophrenia only in regards to the positive symptoms. Marshall et al.<sup>12</sup> found that there was also a relationship for the negative, affective and cognitive symptoms and Ho et al.<sup>13</sup> found this relationship was, at least, confusing. A final group of authors defended the existence of an association between duration of untreated psychosis and evolution of schizophrenia, but they attributed it to the premorbid adjustment that would interfere in the search for psychiatric help, acting as a potential confounder.<sup>14</sup> Therefore, there are discrepancies about whether the duration of untreated psychosis would be modifiable through early detection and intervention programs and also about whether their modification would imply an improvement in the prognosis of the schizophrenia.<sup>15</sup>

Early detection and intervention programs in first psychotic episodes include the psychosocial and

psychopharmacological approach. Psychosocial interventions have been clearly demonstrated to be one of the essential pillars in the early approach to psychosis up to the point that a subgroup of patients has been defined in which isolated psychosocial interventions would be the treatment of choice.<sup>16</sup> In regards to this psychopharmacological approach, most contemporary authors coincide that antipsychotic medication is capable of modifying the natural course of schizophrenia, above all if used in the initial stages of the disease.<sup>17-22</sup> However, the mechanism to prevent disease progression continues to be unknown.<sup>23,24</sup> Response to neuroleptic treatment in patients with a first psychotic episode would range from 60% to 87% of the cases.<sup>21,25-29</sup>

Finally, and going deeper into the possibility that it is possible to modify the prognosis of schizophrenia through early intervention, some authors have suggested that improvement of the results would depend largely on the choice of antipsychotic treatment adjusted to the specific needs of the patient, giving special attention to the factors associated to worse prognoses (duration of the untreated psychosis, lack of treatment adherence, relapse, cognitive and negative symptoms, substance abuse and psychosocial incapacity). In this sense, although there are hardly differences in terms of efficacy between the different antipsychotics,<sup>30-33</sup> differences are found in terms of tolerability.<sup>34-36</sup> The following question could be asked: what could clozapine contribute in the treatment of patients with a first psychotic episode and why has its use hardly been contemplated as a treatment of choice in this group of patients?

## CONTRIBUTIONS OF CLOZAPINE IN THE MANAGEMENT OF SCHIZOPHRENIA

In the 1950's, discovery of the first neuroleptics and antidepressants sparked interest in the investigation of the cerebral neurotransmission mechanisms and led to speculation on the relation existing between the chemical structure and clinical effect of the psychopharmaceuticals. Within this context, the Swiss pharmaceutical company, Wander Laboratories, discovered that some tricyclic compounds not only had an antidepressant activity but also a neuroleptic one, identifying clozapine in this new group of drugs in 1959 and marketing it in 1962. Hippus mentioned the skepticism that surrounded the discovery of clozapine on contradicting the "neuroleptic dogma." In spite of the initial reticences, he rapidly and enthusiastically observed that clozapine had a potent antipsychotic effect in spite of the almost total absence of extrapyramidal effects, which was why it was classified as an "atypical" antipsychotic drug.<sup>37-39</sup>

However, in 1975, enthusiasm for the specific profile of clozapine began to disappear due to its association with

severe cases of agranulocytosis.<sup>40-42</sup> This gave rise to an almost complete interruption of research on clozapine and its withdrawal from the market in several countries of the world. However, the existence, worldwide, of an important population of patients resistant to any attempt to switch to another antipsychotic<sup>43,44</sup> together with the confirmation of the usual reversibility of the clozapine induced agranulocytosis,<sup>44,45</sup> led to its reintroduction in the United States in 1990 for the treatment of patients with schizophrenia resistant to other antipsychotic drugs. In Spain, in 1992, the Ministry of Health created a work group to establish a control system of the possible agranulocytosis. This led to its reintroduction in Spain in 1993.<sup>46</sup>

Clozapine has been a key drug in the history of treatment of psychosis. The contributions of clozapine in the treatment of schizophrenia have been multiple. The most important ones are detailed in the following:

- 1) In terms of clinical efficacy: in 1988, Kane et al. published a clinical trial on a sample of patients with resistant schizophrenia that clearly showed the superiority of clozapine (30% of clinical response) in terms of clinical efficacy in resistant schizophrenia versus chlorpromazine (4% of clinical response).<sup>43</sup> Since then, the principal systematic reviews on the subject have supported the superiority of clozapine over typical and atypical antipsychotic drugs in the cases of resistant schizophrenia.<sup>47-55</sup>

The greater clinical efficacy of clozapine versus the other antipsychotic drugs is significant in regards to the positive symptoms (Asenjo Lobos C, 2010) as well as the cognitive ones.<sup>56-59</sup> However, there are questions about whether clozapine in particular and antipsychotics in general are capable of improving negative symptoms in schizophrenic patients.<sup>60-63</sup>

The contributions of clozapine in patients with comorbid schizophrenia with alcohol abuse/dependence or other substances have also been outstanding.<sup>64-67</sup> Finally, clozapine would be capable of reducing suicide attempts and consume suicides<sup>68-72</sup> as well as aggressive behaviors<sup>66,73-74</sup> in patients with schizophrenia. Clozapine could also be superior to other antipsychotics in terms of neuropsychological performance<sup>58,75</sup> as sociolaboral functioning.<sup>76</sup>

- 2) In terms of clinical effectiveness: The clinical effectiveness studies (much closer to reality of the daily practice) have also demonstrated the superiority of clozapine versus first<sup>77</sup> and second generation antipsychotics in terms of therapeutic compliance<sup>78-81</sup> and quality of life.<sup>82</sup> In the CATIE study, the mean time to discontinuation of drug treatment for clozapine was 10.5 months versus 3.3 of quetiapine, 2.8 of risperidone and 2.7 of olanzapine. In this study, it stands out that switching antipsychotics in the case of patients with schizophrenia with partial response to pharmacological

treatment shows no advantages except in the case of clozapine<sup>83,84</sup> as confirmed by the studies made by the World Psychiatric Association.<sup>85</sup> Thus, after the failure of a first atypical antipsychotic drug, 77% of those treated with clozapine respond versus only 23% of those treated with the other atypical antipsychotic drugs.<sup>86</sup> The CUTLASS study manifests a better clinical response - in terms of global psychopathology, improvement in the quality of life and a better degree of satisfaction of the patients with clozapine versus those with other atypical antipsychotic drugs.<sup>87</sup>

- 3) In terms of costs: For Wang PS et al., the use of clozapine as treatment of first choice in first psychotic episodes would lead to an improvement in the quality of life and life expectancy in this group of patients. They consider that the cost-effectiveness of said intervention would be comparable to that accepted for many medical interventions.<sup>88</sup> Duggan A et al. stressed the cost-effectiveness of clozapine, on estimating that its correct and early use could mean a savings of 8.7 million pounds and 53 deaths per year in the United Kingdom.<sup>89</sup> However, Gau SS et al. disagree with the previous authors as they estimate that the cost-effectiveness of clozapine is inferior to that of the rest of the atypical antipsychotic drugs.<sup>90</sup>
- 4) In terms of side effects: Clozapine presents a lower incidence of extrapyramidal symptoms in general and of tardive dyskinesia in particular than most typical and atypical antipsychotic drugs.<sup>91-94</sup> However, the benefits in terms of reduction of the malignant neuroleptic syndrome are less clear.<sup>95</sup> Hyperprolactinemia is also especially uncommon with clozapine.<sup>96-98</sup> However, side effects as sedation, orthostatic hypotension or sialorrhea can become major effects that make it necessary to withdraw the drug.<sup>98,99</sup> Clozapine is, together with olanzapine- the antipsychotic drug having the greatest risk of metabolic syndrome and weight gain in the treatment of patients with a first psychotic episode.<sup>100-102</sup> Other potentially lethal side effects include pulmonary thromboembolism or myocarditis.<sup>103</sup> The clozapine-induced seizures are dose-dependent, their risk being estimated at 0.6% with under 300 mg/day, 1.8% between 300 and 600 mg/day and 14% above 600 mg/day.<sup>46</sup> However, agranulocytosis has been and is, undoubtedly, the most feared side effect with the use of clozapine. The initial estimations on the accumulated incidence of agranulocytosis associated to clozapine use showed values around 1-2%.<sup>42</sup> However, in subsequent studies, it was estimated to be approximately 0.38-0.73%.<sup>104-106</sup> In Spain, the initial analysis of the data of the first years of monitorization provided values of 0.2%.<sup>107</sup> Furthermore, after the first year of treatment, the rate of clozapine-related agranulocytosis has been estimated to be 0.08% versus 0.13% chlorpromazine-related and

0.15% olanzapine-related.<sup>108, 109</sup> This is so much so that a recent study of a Finnish cohort stated that mortality from clozapine is substantially inferior to that associated to other antipsychotic drugs and recommended that the restrictions regarding the use of the drug be re-evaluated.<sup>110</sup>

- 5) In terms of mortality: In a Finnish epidemiological study, it was estimated that clozapine had the lowest rate of global mortality among all the antipsychotics, recommending the review of the restrictions regarding the use of the drug.<sup>110</sup> The agranulocytosis-associated mortality due to clozapine would be, in the initial estimates, approximately 3–4% of the cases of agranulocytosis but later estimates have placed this between 0.01 and 0.016%.<sup>111–113</sup> The reduction in the global mortality in clozapine users would be closely related to the reduction of the risk of suicide.<sup>69, 70, 72</sup> In fact, prevention of suicide associated to the use of clozapine has been stressed by the *International Suicide Prevention Trial*<sup>70–71</sup> and it is estimated that the reduction in suicide risk in schizophrenics could be multiplied by 3.<sup>72</sup> As of now, there have been few studies in this sense, given the restrictions in force for the use of clozapine with the consequent methodological difficulties they entail. However, what knowledge do we have about this?

## EXPERIENCES ON THE USE OF CLOZAPINE IN FIRST PSYCHOTIC EPISODES

The concept of the use of clozapine in first psychotic episodes has appeared since its marketing.<sup>114</sup> However, clinical trials comparing efficacy and effectiveness of clozapine versus other antipsychotics in this group of patients are practically nonexistent. In spite of the recommendations of the clinical guidelines<sup>115–119</sup> that recommend the use of clozapine after two pharmacological trials with adequate doses and times, clozapine is used much less frequently and much later than recommended in the current clinical practice. Thus, it has been estimated that in the United Kingdom there are 63,000 patients with resistant schizophrenia but only 13,400 take clozapine, estimating that clozapine is only used in 14–50% of the recommended cases.<sup>120, 121</sup> The mean duration of the disease prior to administration of clozapine is a mean of 9.7 to 15.1 years.<sup>122, 123</sup> Prior to the introduction of clozapine, the patients were treated with up to 13 drugs or different pharmaceutical combinations.<sup>123</sup>

In the following, we review the studies published up to date on the use of clozapine in first psychotic episodes:

- 1) Studies that use clozapine in "resistant" first psychotic episodes:  
In an observational study,<sup>124</sup> a 12-week trial of treatment with clozapine in 10 patients who previously had been resistant to 3 antipsychotics was offered. No patients

had complete remission after treatment with clozapine but the response rate was approximately 30%, a value similar to that obtained by Kane et al.<sup>43</sup> in a clinical trial with resistant schizophrenia patients, using the same therapeutic response criteria. The small sample size and study design, however, limited the study conclusions.

In another observational study, Agid O et al.<sup>86</sup> offered patients with a first psychotic episode the possibility of treatment with clozapine in the first year of treatment of the disease. The patients were included in the therapeutic algorithm in which treatment was offered to them with a second-generation antipsychotic (risperidone, quetiapine or olanzapine) for 12 weeks. If after 12 weeks, they had not achieved therapeutic response, a trial was initiated with the second antipsychotic from among the three mentioned. If after two trials, there was no response, the possibility was offered of being assigned a treatment, either with clozapine or with the third antipsychotic as yet untested. Of the 123 patients who initiated the therapeutic algorithm, 93 (75.6%) responded to the first antipsychotic and only 7 (23%) responded to the second one. Only 13 of the 23 refractory patients agreed to enter into this study. The patients who took clozapine showed equal results initially, but better long-term results than those who took risperidone, olanzapine or quetiapine on different psychopathological scales (BPRS, BPRS- positive, BPRS-negative and CGI). However, this study had many losses to follow-up, small sample size and lack of randomization, which limits the generalizability of the results.

- 2) Studies that use clozapine in "untreated" first psychotic episodes:  
In the only randomized clinical trial up to date with clozapine in first psychotic episodes without previous pharmacological treatment, Lieberman JA et al.<sup>125</sup> compared the efficacy of clozapine and chlorpromazine (plus benztropine). The patients were maintained under treatment with the drug assigned, with double-blind conditions, for two years (or until the clinical conditions led to a switch in therapeutic regimes), completing a total follow-up period of 9 years in an open unmasked study. Of the 2708 patients screened, 160 (80 in each group) were enrolled in the trial. In all, 15% of the patients assigned to clozapine and 22.5% of those assigned to chlorpromazine did not complete. The study remission rate was 81% in the clozapine group and 79% in the chlorpromazine one. However, remission was achieved in a lower period of time in the clozapine group (50% of the patients with clozapine had remitted in 8 weeks versus 12 weeks in the patients with chlorpromazine). The rate of remission was almost twice in the clozapine group than in the chlorpromazine and once remission was achieved, the patients assigned to

clozapine remained in remission almost twice the time as those assigned to chlorpromazine. The likelihood of remaining in remission was reduced by 15% for each additional year of psychosis without treatment. At 12 weeks, the patients treated with clozapine experienced greater reductions on difference psychopathological scales (BPRS, SANS, CGI, GAF) than those treated with chlorpromazine. However, these differences were not maintained at 52 weeks. However, the authors attributed this last datum to the loss of a greater number of severe patients in the chlorpromazine group (likely relation to the lack of clinical efficacy). In regards to the side effects, patients under treatment with chlorpromazine and benztropine experienced more extrapyramidal effects than those treated with clozapine both at 12 and at 52 weeks.

In 2011, Lieberman et al.<sup>126</sup> published the results of this same clinical trial at 9 years of follow-up. Of the 160 participants, 124 were followed-up for 9 years (79%) in the clozapine group and 61 (76%) in that of chlorpromazine. Of the 36 who did not complete the 9 years of follow-up, 19 (clozapine 9 and chlorpromazine 10) were lost to follow-up during the first year. At 9 years, 29 patients (18%) continued taking the originally assigned medication: 21 (26%) in the clozapine group and 8 (10%) in that of chlorpromazine ( $p=0.01$ ). Mean time accumulated until interruption of original pharmacological treatment was 39 months for clozapine and 23 for chlorpromazine ( $p=0.01$ ). At 9 years, the percentage of time in remission (78%) or relapse (14%) was similar in both treatment groups. The measurements in the different psychopathological scales (BPRS, SANS, CGI, GAF) did not show statistically significant differences in the different follow-up periods. However, there were differences in favor of clozapine in the continuation and permanence in the treatment assigned, which seems to be more related to the tolerability to the drug. Among the patients of the chlorpromazine group, 24 (30%) needed to take clozapine at some point in the study. The opposite occurred in 3 (3.8%) patients ( $p<0.01$ ). Two patients of each group (2.5%) developed agranulocytosis that was solved when the corresponding treatment was withdrawn. One patient from the clozapine group (4.8%) and 2 from that of chlorpromazine (25%) developed tardive dyskinesia ( $p=0.18$ ). There were no statistically significant differences in other side effects. In regards to the study limitations, during the 9 years, the patients of both groups of treatment were in remission during the total follow-up time, an abnormally high value in the era of new antipsychotic treatments probably related to the high rate of adherence to antipsychotic treatment. This could be due to the close follow-up of this sample of patients by the study personnel, it being difficult to measure the additional benefit of said psychosocial measures.

In a longitudinal study,<sup>127</sup> treatment with clozapine was

offered to 34 patients with a naive-treated first psychotic episode. A total of 56% of the patients met the remission criteria during the treatment with clozapine with a mean time up to remission of 11 weeks and a rate of accumulated response at 13 weeks of 66.4%. No patient responded after week 13. However, 42 and 53% of the responders abandoned the treatment with clozapine before 6 and 12 weeks, respectively. The elevated proportion of losses in the follow-up, the limited sample size and absence of a control group hinder the generalizability of the results.

## DISCUSSION

Clozapine is the "gold standard" between the antipsychotics for the treatment of schizophrenia. Clozapine would contribute advantages over other typical and atypical antipsychotics under clinical, neuropsychological and sociolaboral functioning level and in terms of efficacy, effectiveness and efficiency. In terms of clinical efficacy, it could contribute to the improvement of the positive, negative, effective and cognitive symptoms in addition to making it possible to reduce addictive, auto- and heteroaggressive behaviors in schizophrenic patients. Regarding clinical effectiveness, its superiority has been demonstrated in terms of therapeutic adherence, quality-of-life and degree of satisfaction of the patients with the treatment. Furthermore, all of this has a comparable cost-effectiveness to that accepted for many medical interventions.

However, concern about the appearance of its most feared side effect (agranulocytosis) made it necessary to withdraw it from the market and to carry out strict hematological controls for its use after its re-introduction. This fact has consigned the use of the drug to cases of more severe schizophrenia and with proven resistances to other antipsychotics. This is so much so that the epidemiological studies have confirmed that its use occurs even much later than that recommended by the clinical guidelines. In this sense, although not exempt from side effects, recent epidemiological studies firmly recommend reevaluating the restrictions for the use of the drug, placing the morbidity and mortality associated to the use of clozapine among the more favorable ones of those found in all of the antipsychotics.

Parallely, during recent years, special stress has been placed on the need to stop the clinical, neuropsychological, neurophysiological, and neurostructural deterioration in schizophrenic patients. Psychopharmacological, psychotherapeutic and early psychosocial intervention in this group of patients during the first years of evolution of the disease could improve the course of the schizophrenia. In this sense, doubts arose quickly about up to what point

the elective treatment with clozapine versus other neuroleptics in first psychotic episodes could provide substantial advantages. In fact, for several years, different authors have been proposing the need to use clozapine from the debut of the disease in order to improve its course.

However, at present, few studies have been carried out regarding this given the methodological difficulties to carry out clinical trials with clozapine in first psychotic episodes. The results of the study of Woerner et al.<sup>127</sup> should be carefully interpreted given its methodological limitations (high proportion of losses to follow-up, limited sample size and absence of control group). The Lieberman et al. study<sup>125, 126</sup> has undoubtedly been the principal clinical trial on the use of clozapine in this group of patients carried out up to date. The authors concluded that clozapine would be superior to chlorpromazine in reference to continuation and permanence with the assigned treatment (which seems to be related to the tolerability to the drug) but not in the rest of the clinical parameters evaluated. Although the rigorous methodology of this trial gives great internal validity to its results, the therapeutic adherence rate of the patients of the trial is abnormally high for this type of population. Thus, for example, 95.9% of the patients with first psychotic episode agreed to be included in a clinical trial. This casts doubt on the replicability of the study in our setting, again showing the discrepancy existing on occasions between clinical efficacy and effectiveness studies in regards to the applicability of the results.

For all of these reasons, we consider that new experimental studies are needed in our setting that would shed light on the potential prognostic advantages that the use of clozapine could have in schizophrenic patients in incipient stages. We propose the performance of a clinical trial in patients with a first psychotic episode (of schizophreniform characteristics) in which the efficacy of clozapine and risperidone are compared for a series of clinical, neuropsychological and neurophysiological variables with a 2 year follow-up period.

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