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Letter to the Editor

Looking to the future after reintroduction of clozapine

Dear Editor,

Clozapine has superior characteristics among other antipsychotics.[1] Evidence and experience support clozapine as the best treatment in terms of efficacy, effectiveness and well-being, the gold standard for treatment resistant schizophrenia (TRS).[2–4] It has also shown efficacy in differential psychopathological dimensions: negative, cognitive or affective symptoms.[5] It has been demonstrated its results in terms of overall mortality and suicide.[6] Despite its superiority, its use has been limited by the possibility of presenting lethal adverse effects.[7] The risk of associated neutropenia (number of leukocytes less than $3.0 \times 10^3/\mu L$ or absolute neutrophil count less than $1.5 \times 10^3/\mu L$) described reaches between 3.8% and 1% depending on studies.[9]

Rechallenging clozapine after neutropenia is a tough decision and each case should be analyzed individually.[11] We present three clinical cases in which, after presenting neutropenia, clozapine was reintroduced, as well as the evolution of years later, in the first and the second ten and in the third four (Table 1).

Clinical case 1

A 55-year-old patient was diagnosed with paranoid schizophrenia since 1990. He started clozapine in 1998, maintaining psychopathological stability with a sustained dose of 300 mg/24 h. Active consumption of 30 cigarettes per day. In August 2012, neutropenia was detected with numbers of neutrophils: $0.86 \times 10^3/\mu L$, leukocytes: $3.73 \times 10^3/\mu L$, and platelets: $53 \times 10^3/\mu L$. After reducing clozapine and starting aripiprazole (15 mg/d), the neutrophil counts normalized in December. The patient presented signs of psychopathological decompensation. Subsequently, intestinal injury in response to imposing auditory hallucinations was described. This caused the need for urgent surgery in January 2013 with a diagnosis of acute abdomen. Different antipsychotic drugs were tested at appropriate doses and in combination, quetiapine, aripiprazole, olanzapine, haloperidol, risperidone; with little response. It was decided restarting treatment with clozapine at a dose of 50 mg/day associated with lithium carbonate (600 mg). The patient presented progressive psychopathological improvement with no repercussions on haematological figures: plasma lithium levels: 0.54 mEq/l; clozapine plasma levels: 191 ng/mL; neutrophils: $3.77 \times 10^{[3]}/\mu L$, Leukocytes: $5.98 \times 10^{[3]}/\mu L$; Platelets: $149 \times 10^{[3]}/\mu L$. Subsequently, they normalized, remaining in this way during the ten years of follow-up, also presenting psychopathological stability.

Table 1
Summary of the three clinical cases.

	Clinical case 1	Clinical case 2	Clinical case 3
Genre	Male	Male	Female
Age	54 years	20 years	37 years
Diagnosis	Paranoid schizophrenia (F20.0)	Autism spectrum disorder (F84.0)	Paranoid schizophrenia (F20.0)
Disease evolution time	31 years	18 years	10 years
Maximum clozapine dose	300 mg/day	450 mg/day	150 mg/day
Time on clozapine before withdrawal	14 years	1 month	3 years
Blood counts prior to suppression	Leukocytes: $3.73 \times 10^3/\mu L$ Neutrophils: $0.86 \times 10^3/\mu L$ platelets: $53 \times 10^3/\mu L$	$1.5 \times 10^3/\mu L$ neutrophils	Neutrophils of $1.46 \times 10^3/\mu L$
Secondary effect	Neutropenia	Neutropenia	Neutropenia
Response strategy	Reintroduction with lithium carbonate	Reintroduction	Reintroduction
Final resolution	Clozapine maintenance after 10 years of reintroduction	Clozapine maintenance after 10 years of reintroduction	Clozapine maintenance after 4 years of reintroduction

Clinical case 2

A 21-year-old patient with coagulation factor V and VII deficiency and follow-up in Neurology for suspected epilepsy. He has been going to mental health since January 2003, with a diagnosis of autism spectrum disorder. In 2009, the start of clozapine was evaluated after different antipsychotics that had been insufficient for the behavioural control of the patient, starting in December. In January 2010, neutrophils of 1.5×10^3 neutrophils/μL appeared. One month after clozapine withdrawal, neutrophil levels returned to normal. At this time, treatment with clozapine was discontinued, starting with quetiapine, risperidone, olanzapine, aripiprazole, psychostimulants and clonazepam, which was insufficient. Finally, in September 2013, clozapine was reintroduced with close analytical monitoring. In the ten years of evolution in which the patient continues with clozapine, no analytical alterations have been observed.

Clinical case 3

A 38-year-old woman began her mental health follow-up in 2011. She attended urgently due to the presence of commentator-type auditory hallucinations and insomnia. No evidence of previous diseases of interest or consumption of substances of abuse.

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Start of treatment with risperidone; later changes to aripiprazole (30 mg/day). In 2014, she was diagnosed with paranoid schizophrenia. A switch was made to olanzapine (20 mg/day), later to paliperidone (15 mg/day) and ziprasidone (8 mg/day). In January 2016, a clozapine regimen was started, presenting an improvement in the patient's positive and negative symptoms with a 150 mg/day dose. In 2019, a progressive decrease in neutrophils appeared again with minimum levels of $1.46 \times 10^3/\mu L$, requiring a reduction in the dose of clozapine until its withdrawal in August 2019. In October, neutrophil levels were $3.02 \times 10^3/\mu L$, delusional ideation reappearing of reference and control, pseudo-perceptions and negative symptomatology. Clozapine was rechallenge in November 2019. Serial tests have been performed since the reintroduction without a decrease in neutrophil levels.

A review of three clinical cases from our Mental Health management area in which clozapine was reintroduced after discontinuation of treatment due to an episode of neutropenia has been carried out. The importance of these cases lies both in the rechallenge and in the positive evolution that they have had years later. It is recommended to restart clozapine in TRS if it was interrupted due to moderate leukopenia or neutropenia but not with the presence of agranulocytosis.[10] According to the bibliography, the tendency to reintroduce should be different depending on the adverse effect presented. The normalization of haematological values and the study of the cause of neutropenia are essential before reintroduction. It is recommended to monitor haematological values every two weeks for at least 3 months after reintroduction.

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Further reading

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