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CLOZAPINE-INDUCED INFLAMMATION: WHAT PSYCHIATRISTS SHOULD KNOW?

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Dear editor,

Clozapine continues to stand out as the most effective drug in the treatment of schizophrenia. It remains the only drug approved for the treatment-resistant schizophrenia, which, unfortunately, affects up to a quarter of people even in the early stages of this disorder (Siskind et al. 2022), and also the only antipsychotic with antisuicidal effects (Forte et al. 2021). At the same time, clozapine has a number of safety considerations, which contribute to its substantial underutilization (Gurrera et al. 2022). Clozapine has a narrow therapeutic index, and a highly variable metabolism. More specifically, clozapine pharmacokinetics is influenced by ancestry, sex, co-treatment, smoking status (DeLeon et al. 2022) and age (Bhattacharya et al. 2021). While smoking might lead to decreased effectiveness of clozapine in smokers, intoxication could occur after smoking cessation (Sagud et al. 2018). However, even knowing genetic and environmental factors, it is difficult to predict plasma clozapine concentration and therapeutic drug monitoring is strongly recommended (Olsson et al. 2015). More than any other drug in psychiatry, it requires individual approach. The present article of Professor de Leon in this *Psychiatria Danubina* issue (de Leon 2022), extends the series of his recent articles (for example, Schoretsanitis et al. 2022, de Leon et al. 2022, de Leon et al. 2022a, de Leon 2022a) which emphasize the need for highly individualized clozapine dosing and titration. This article (de Leon 2022) addresses yet incompletely understood, and somehow neglected concept of clozapine-induced inflammation. While patients are closely monitored for potential agranulocytosis, clozapine-induced inflammation, including myocarditis, which may occur especially during rapid titration, was not given much attention to. The results of such disregard may be devastating, such as the risk for patients dying from pneumonia or myocarditis (de Leon et al. 2022a).

Two periods are delineated (de Leon 2022), which require particular attention regarding clozapine and inflammation: 1)

period of introduction to clozapine, 2) the onset of co-occurring infection. Namely, a bidirectional relationship between clozapine and inflammation was suggested. Clozapine-induced fever, myocarditis and other clozapine-induced inflammations are drug-related reactions, and a three-phase hypersensitivity model, induced by rapid titration, was proposed (de Leon 2022). However, clozapine metabolism is also influenced by inflammation. Proinflammatory cytokines inhibit the activity of CYP1A2 enzymes. Given clozapine's low therapeutic index, infections may result in clozapine intoxication. This may be particularly important during the Covid-19 pandemic. While mild infections seem not to influence clozapine levels, in more severe cases significant cytokine release may inhibit clozapine metabolism, resulting in high clozapine levels. Case reports were published on the clozapine intoxication during COVID-19 infection (Cranshaw et al. 2020, Tio et al. 2021). Anyway, it would be wise to carefully observe patients during any infection, to detect as soon as possible indicators of raising clozapine levels, such as hypersalivation, constipation, sedation or myoclonus (Arrojo-Romero et al. 2022).

Inflammation in relation to clozapine is of great clinical concern. Given that rapid clozapine titration is sometimes used in extreme situations, such as in violent patients (Ifteni et al. 2021), those individuals appear to be at the highest risk for clozapine-induced inflammation and require very careful monitoring for the first signs of this adverse event. In conclusion, the present article (de Leon 2022) would increase

1) the awareness of clozapine-induced myocarditis, and other inflammatory conditions, because psychiatrists lack the expertise in those potentially preventable illnesses, 2) monitoring of potential signs of clozapine toxicity in patients experiencing acute infections, including COVID-19, and 3) help clinicians choose the most appropriate clozapine dose. The „one size fits all“ approach definitely does not apply to clozapine dosing. Therefore, not only slow initial titration, but personalized dosing throughout the course of clozapine treatment, should become the standard of care for our vulnerable patients. It would encourage clinicians to improve their clinical judgment, in order to get the best out of the very effective, but also potentially toxic drug clozapine.

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THE TORTOISE BEATS THE HARE: THE CASE FOR SLOW CLOZAPINE TITRATIONS WITH SERIAL CRP MONITORING

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Dear editor,

Findings from decades of research have secured clozapine's role as the cornerstone of pharmacotherapy for treatment-resistant schizophrenia (Siskind et al. 2016). Yet,

clozapine remains grievously underutilized in many countries around the world (Bachmann et al. 2017), with prescribers identifying concern about adverse effects as one of the main barriers limiting more widespread use (Cotes et al. 2022, Verdoux et al. 2018). Dr. de Leon's article in this edition of *Psychiatria Danubina* gives the community much to ponder on clozapine-induced inflammation and poses questions and concepts which merit further scientific inquiry (de Leon 2022).

The first 6-8 weeks after clozapine initiation are the most critical in a clozapine titration. The titration rate depends on clinical urgency, setting (inpatient or outpatient), other anti-psychotics and concomitant medications, the patient's age/smoking status, ancestral origin, support system and other factors. There is no one-size-fits-all approach for a titration, and the International Titration Guideline is a step forward in taking an individualized approach rooted in principles of ethnopsychopharmacology (de Leon et al. 2021). Infrastructure must be in place to obtain vital signs frequently, obtain and interpret labs, and develop a feedback system for how the patient can reach the prescriber quickly.

The relationship between titration speed and clozapine-induced inflammation remains a key question. Ronaldson et al. (2012) found an increased risk of clozapine-induced myocarditis (CIM) for every additional 250 mg of clozapine administered over 9 days. However, cumulative dose was not found as a risk factor for CIM in a recent meta-analysis that included the Ronaldson study and six others (Vickers et al. 2022). Rapid titration may be associated with inflammation including fever (Verdoux et al. 2019) and hypotension (Poyraz et al. 2016), and may result in the patient getting a higher clozapine dose than necessary. Additionally, if patients develop side effects from a titration that is too rapid, they may be more likely to discontinue it themselves (Velligan et al. 2009), and for patients on clozapine there are often no other suitable alternatives (Schulte et al. 2014). Rapid titrations have been studied but have included a relatively small sample size and have not systematically monitored C-reactive protein (CRP) or clozapine levels (Ifteni et al. 2014, Poyraz et al. 2016). These rapid titrations should be reserved for emergency situations on inpatient units with clear understanding of the possible risks.

We also agree with the idea of weekly serial monitoring of CRP in addition to troponin I/T for the first 6-8 weeks of a clozapine titration (Goldsmith & Cotes 2017), as well as weekly creatinine for the first eight weeks to screen for interstitial nephritis (Elias et al. 1999, Meyer & Stahl 2019). Clozapine levels can be particularly helpful early in the titration to identify ultra-rapid or poor metabolizer status, and to ensure that inflammation and increased CRP are not driving up levels unexpectedly. This is a key point from Dr. de Leon's paper – systemic inflammation may drive elevations in clozapine levels leading to adverse events including the possibility of clozapine toxicity. This is not only a key issue in clozapine titrations, but through the course of clozapine treatment and adjustments should be considered in patients with evidence of inflammatory illness. Indeed, utilization of a novel immunoassay to measure clozapine levels can provide same day results and allow for real-time dose adjustment, rather than waiting several days for the send out test (Buckley et al. 2020).