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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).

The relationship between inflammation and clozapine needs continued study. A significant proportion of patients with schizophrenia already have high levels of inflammation at baseline (Goldsmith et al. 2016). Clozapine may contribute to transient initial increases in markers of inflammation (Miller & Goldsmith 2019) though how much that contributes to adverse events such as fever and myocarditis remain untested and unknown. Moreover, there is evidence from both clinical and preclinical studies that clozapine may decrease immune activation over time (Giridharan et al. 2020, Löffler et al. 2010, Robichon et al. 2020). Dr. de Leon has posed some important questions which merit further study, while raising awareness of key issues related to clozapine titration that every clinician who prescribes clozapine should be mindful of.

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**Conflict of interest:**

Outside of this work, Dr. Cotes has received research funding from Otsuka, Alkermes, and Roche. He is a paid consultant Saladax Biomedical, an unpaid consultant to HLS Therapeutics, and speaker for Clinical Care Options. Dr. Goldsmith has no disclosures to report.

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## COMMENTARY ON REFLECTIONS ON THE COMPLEX HISTORY OF THE CONCEPT OF CLOZAPINE-INDUCED INFLAMMATION DURING TITRATION

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Dear editor,

While Dr. De Leon's manuscript focuses on the ongoing history of clozapine-induced inflammation (CL-II) (de Leon 2022), he masterfully summarized several topics of high clinical and scientific relevance surrounding the use of clozapine (CL), which is positioned as a key agent in