

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:

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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

treatment resistant schizophrenia. Still, barriers exist which preclude the optimal CL use. These are drug-related barriers, psychiatrist and health system-related barriers, and patient and family-related barriers (Rezaie et al. 2022). Underlying most of these barriers are concern about the numerous CL-induced side effects.

De Leon work also shows us the landscape for clinical practice and research for the next few years. The message follows this path:

- the perilous course of CL history is leaving behind the risk of agranulocytosis, but it is now clear that it is associated with significant inflammation in several organs early on treatment, such as the myocardium, lungs and many others, through mechanisms that are actively investigated.
- clozapine's kinetics is highly complex, particularly regarding ethnicity, sex, obesity, tobacco consumptions, infections and the use of pharmacological agents that may inhibit or enhance its metabolism.
- many clinicians (and countries) use fast CL titration rate and tend to standardize the initial CL dose disregarding or without knowing the above-mentioned influential variables.

I believe that CL clinical use will change forever (for better) after this set of research summarized and often conducted by Dr. de Leon himself.

Clarification of the mechanisms involved in CL-II is in an early stage, but de Leon proposes that it is related to a three-phase hypersensitivity reaction:

- Cytokine release, associated with fast titration and/or high early CL dose and poor metabolizer status, this mainly related to Asian/Indigenous American ancestry. Ethnicity is thus, a new variable that practitioners must consider when choosing CL dose (de Leon et al. 2022).
- Cytokines inhibit CYP1A2, which is the main CL metabolic pathway, hence, further increasing its serum concentration.
- And lastly, if the titration continues, an auto-immune phenomenon develops leading to localized inflammation.

The pathophysiology of such a three-phase hypersensitivity reaction is far from clear, but Dr de Leon heuristically compares it with the lamotrigine-induced hypersensitivity reaction, which was successfully controlled through a slow titration schedule. But other strategies besides drug titration are necessary.

For example, in subjects with bipolar disorders, it is presently unclear the precise relationship between central and peripheral cytokine dynamics (Nascimento & Lafer 2022). In the case of CL-related cytokine dysfunction, a CL-associated central and peripheral overactivation of the sympathetic nervous system might be involved and might set the base for preventive measures in selected patients, such as administration of beta blockers and/or renin-angiotensin system regulators (Baptista et al. 2015). Another example of a potential adjunctive treatment to modulate cytokine dynamics is lithium

salts, which appear to regulate the blood-brain barrier and might prevent excessive cytokine influx into the brain (Nascimento & Lafer 2022).

At least two additional issues are relevant when discussing current CL use. First, coagulation and inflammation activity are under genetic control; this may predispose patients and their families to clinically significant inflammation, with relative independence of drug treatment (Carrizo et al. 2008). This key topic will benefit from advanced molecular biology techniques such as single cell research (Vaziri et al. 2022). And second, there is a growing out-label, low dose CL utilization in mental disorders others than schizophrenia and in neurological patients. The relevance of CL-associated inflammation in these patients waits for further investigation.

As a coda, this manuscript is a distillate of the intensive collaborative work of Dr de Leon with research groups all around the world, for the benefit of patients with severe mental disorders.

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