

## IMPROVING THE CLOZAPINE PRESCRIBING INFORMATION TO ENHANCE CLOZAPINE SAFETY AND ADDRESS BARRIERS: CLOZAPINE-INDUCED INFLAMMATION, PNEUMONIA, AND REMS

Jonathan G. Leung<sup>1\*</sup> & Ian R. McGrane<sup>2</sup>

<sup>1</sup>Department of Pharmacy, Mayo Clinic, Rochester, MN, USA,  
Leung.Jonathan@mayo.edu

<sup>2</sup>Skaggs School of Pharmacy, College of Health,  
The University of Montana, Missoula, MT, USA

\* correspondence author

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### Dear editor,

The story of clozapine's history includes the withdrawal from European markets due to fatalities associated with severe neutropenia, the halting of FDA approval processes in the United States (US), and 1989 US re-emergence as the only FDA approved medication for treatment resistant schizophrenia (TRS) (de Leon 2022a). Today clozapine is used internationally for approved and off-label indications including TRS, suicidality associated with schizophrenia or schizoaffective disorder, treatment-resistant bipolar disorder, in the setting of tardive dyskinesia when antipsychotic treatment is needed, and psychosis associated with Parkinson's disease. Yet, regardless of the indication, in many countries there are established recommendations or requirements for hematologic monitoring (Nielsen 2016). This monitoring has mitigated the risks of mortality associated severe neutropenia, that mostly occurs within the first 18 weeks of treatment and then decreases over time. Yet, the saga of clozapine does not end here.

Despite clozapine's effectiveness, there is literature that suggests the ongoing struggle to overcome substantial delays of initiation or the avoidance of clozapine all together (Kelly 2018, John 2018). The drivers of clozapine underuse are multifactorial, but in part, relate to monitoring complexities, administrative barriers within regulated monitoring programs, and what has been described as prescriber "clozaphobia" (Kelly 2018, Cetin 2014). The way clozapine came to market in the US may have also contributed to barriers associated with safety (e.g., warnings, interactions).

To receive FDA approval in 1989, clozapine did not require rigorous pharmacokinetic studies, including drug interaction data (de Leon 2022). The warnings and precautions described in detail within the package insert or prescribing information (PI) were also very limited in the original version, and many were subsequently added over the course of 30 years. This not only demonstrates that clozapine was not completely understood, but there should be consideration that mounting "new safety warnings" contributed to growing "fears" surrounding clozapine use. On the opposite spectrum for some prescribers, emerging information on how to safely monitor clozapine and account for interactions may have

been overshadowed by the hypervigilance of hematologic monitoring, which has also changed many times over 30 years in the US.

This letter relates to the recent publication, "*Reflections on a complex history of the concept of clozapine induced inflammation during titration*", (de Leon 2022b) and prior calls for changes to the clozapine PIs worldwide, with context of how the US clozapine PI has undergone a continuous transformation over the last 30 years. While admittedly the following history and discussion are based on US PIs, regulatory changes made by a country can still have farther reaching global impact (Bastiampillai).

### The United States Prescribing Information

The most recent medication PIs worldwide can be found on governments' web pages, including the Drugs@FDA, Health Canada, and the Agency for Medicinal Products and Medical Devices of Croatia. The Parental Drug Association also has a listing of *Global Regulatory Authority Websites* and associated weblinks at <https://www.pda.org/scientific-and-regulatory-affairs/regulatory-resources/global-regulatory-authority-websites>. In the US, it is common for the PI to change from its original state based on post-marketing reports or studies completed after a medication comes to market. This includes both additions and subtractions. While prescribers may not immediately turn to a medication's current PI for their primary source of drug information, changes to a PI can have a significant impact on prescribing patterns and safety practices. In part, this is due to tertiary drug information resources that may frame content around PIs. Information from PIs or tertiary drug information resources may be integrated into an electronic health record that flag warnings during the act of prescribing. Medication PI information is also cited in schizophrenia practice guidelines (Keepers 2020). Additionally, it must be considered that in non-academic settings there can be a lack of access to emerging literature (e.g., paywalls, no library resources). Thus, it is crucial that PIs are up to date with both accurate and relevant information. This is in line with de Leon's reference to Popper's view on scientific advancement (Popper 1963).

In the US, it is recommended that drug manufacturers or the New Drug Application (NDA) holders review the approved PI annually for outdated information. The PI must also be updated when new information becomes available that causes the PI to become inaccurate, false, or misleading. (Center for Drug Evaluation and Research 2022). The NDA holders also submit PI update proposals when new data becomes available that could affect prescribing decisions or the clinical management of patients receiving the drug. All requirements on content and format for PIs in the US are guided by the Code of Federal Regulation (CFR). Ultimately, a medication's PI reflects the "*FDA's findings regarding the safety and effectiveness of the human prescription drug under the labeled conditions of use.*" (Center for Drug Evaluation and Research 2022).

## **Clozapine Prescribing Information Drug and Disease Interactions**

Drug and disease interactions are important contributors to the risk of clozapine-induced adverse events or inflammation during titration. Although reflective of what was known about pharmacokinetic (PK) cytochrome P450 (CYP) interactions in 1989, the original clozapine PI did not contain any, and only theoretical pharmacodynamic interactions were included (Clozaril 1990). One of the first PK interactions mentioned was in 1992 with cimetidine and phenytoin, without reference to CYP450, and this list slowly expanded over the following decade (Physicians' Desk Reference, 1993). CYP2D6 interactions or adjustments for known poor 2D6 metabolizers first appeared by 1994 (Physicians' Desk Reference 1995). However, specific mention of CYP1A2 and CYP3A4 were not introduced to the PI until after the early 2000s (Clozaril 2001). Unfortunately, the 2001 PI until at least 2005, incorrectly described "nicotine" as an inducer of clozapine (Clozaril 2005). This ultimately was corrected to "cigarette smoke" later. While it should be well-known that inhaled polycyclic aromatic hydrocarbons from a burning cigarette is what induces CYP1A2, not nicotine, this likely contributed to some misconceptions of the interaction. A 2019 survey surrounding perceptions and knowledge of clozapine reported that over 75% of respondents incorrectly answered that chewing tobacco impacted clozapine levels (Leung 2019).

The current PI has been modernized to be inclusive of important interactions. This includes dosing adjustment or monitoring recommendations that account for concomitant CYP inducers or inhibitors. However, the recommendations may not be congruent with the literature. Currently the PI lacks the inclusion of factors characterized to reduce clozapine clearance including valproate, obesity, acute inflammatory states, and a patient's ancestry. These all may be reasons to consider slower than usual clozapine titration (de Leon 2022c). Currently the most concrete PI recommendation is to use one-third of the clozapine dose in the setting of strong CYP1A2 inhibitors, with fluvoxamine, ciprofloxacin, and enoxacin specifically mentioned (Clozaril 2021). Clinically, this reduction may not be sufficient. Ciprofloxacin, which was added as an interaction by 2005, generally should be avoided with clozapine. There are prior reports of clozapine levels increasing unpredictably with ciprofloxacin, as high as 500% (Clozaril 2005, Sambhi 2006). Fluvoxamine for the purpose of altering metabolism of clozapine can also be unpredictable and should only be implemented by experts familiar with this management strategy to avoid toxicity. So in general fluvoxamine should not be co-prescribed with clozapine (de Leon 2022c).

In 2013 oral contraception (OC) was introduced in the PI as a CYP1A2 inhibitor but only with recommendations to monitor for adverse reactions and consider a clozapine dose reduction. However, up to 50% reduction may be needed (Schoretsanitis 2020). This may be due to potential inhibition of CYP2C19 as well (Schoretsanitis 2020). If a patient is already on an OC when clozapine is started, titration could occur at a lower starting dose and when able, a clozapine level checked earlier (e.g., once to 150 mg per day). The impact of OC on CYP1A2 substrates has been known, considering the

prescribing information for tizanidine, a medication almost exclusively metabolized via CYP1A2. From the original FDA tizanidine approval review, there was mention that patients taking OC had a 50% lower clearance of tizanidine compared to those not on OCs (Zanaflex 1996). Of note, the tizanidine PI was eventually updated to list concomitant ciprofloxacin and fluvoxamine as a contraindication. This is because ciprofloxacin increases the peak concentration (C<sub>max</sub>) and total exposure (AUC) by 7-fold and 10-fold, respectively. Fluvoxamine increases tizanidine C<sub>max</sub> and AUC by 12-fold and 33-fold, respectively (Zanaflex 2006).

New medications continue to be approved and the clozapine PI should be updated to reflect this. Viloxazine, a strong CYP1A2 inhibitor, is described in its PI as contraindicated with concurrent use of sensitive CYP1A2 substrates or CYP1A2 substances with a narrow therapeutic range (Qelbree 2022). Reasonably this would include clozapine.

Acute infection and inflammation results in the inhibition of multiple CYP pathways specific to clozapine metabolism (e.g., CYP1A2, CYP2C19, CYP3A4) and can cause dramatic elevations in clozapine concentrations (de Leon 2022b, de Leon 2022c). Other causes of acute inflammation (e.g., surgeries) in addition to infection have been associated with decrease CYP function (Lenoir 2021). Overall, information regarding this important interaction related to inflammation should also be included in the PI.

### **An Aggressive, One-size-fits-all Dosing Needs Revision**

Early clozapine PIs described the initial starting dose as 25 mg once or twice daily with subsequent increases of 25 mg to 50 mg per day to a target dose of 300 mg to 450 mg per day by the end of week two. By 1992, the initial dose recommendation was reduced 50% to 12.5 mg once or twice daily (Physicians' Desk Reference, 1992, Physicians' Desk Reference, 1993). The recommendation for subsequent increases by 25 mg to 50 mg per day to a target dose of 300 mg to 450 mg per day by the end of week two has not changed to date (Clozaril 2021). A target of 450 mg by the end of week two is likely too aggressive for many individuals. Though the PI still by 2013, justified higher dosing by continuing to note that the pivotal study leading to clozapine's approval targeted a maximum dose of 500 mg over the first two weeks of exposure (Clozaril 2013a).

More research is needed to better understand the risk of clozapine-induced inflammation in general, not just myocarditis. However, clozapine appears to be pro-inflammatory upon initial exposure (Røge 2012). *An International Adult Guideline for Making Clozapine Titration Safer by Using Six Ancestry-Based Personalized Dosing Titrations, CRP, and Clozapine Level* published in 2022 suggests that there should be a pause in an initial titration or even reduced clozapine dose when signs and symptoms of inflammation (e.g., rise in C-reactive protein [CRP], fever) emerge (de Leon 2022c). This could decrease the pro-inflammatory effects of clozapine, and account for reduced CYP activity in the setting of acute inflammation. Yet more research is needed to confirm this (de Leon 2022a). Continued titration during early clozapine-induced inflammation may precipitate

clozapine toxicity or lead to severe inflammatory adverse drug events. Retrospective data may naturally emerge if there is more widespread adoption of the weekly CRP monitoring following clozapine initiation for the first 4 weeks that is recommended by the recent guideline (de Leon 2022c). In addition, there has been adoption of myocarditis monitoring protocols that incorporate regular CRP monitoring during titrations, along with signs and symptoms of inflammation (Ronaldson 2011, McNutt 2021, Correll 2022).

The *International Adult Titration Guideline* also challenges the status quo of the “typical” 25 mg daily increase of clozapine during titration based on patients at risk for decreased clozapine clearance and inflammatory reactions. This includes factors, de Leon highlights in his *Reflection*, including, drug-drug interactions, smoking status, sex, obesity, and inflammation (e.g., CRP). Importantly, the guideline calls attention to different titration rates based on a patient’s ancestry. Prescribers must critically evaluate and be familiar with these factors to safely titrate clozapine. This may become more familiar of a concept if reinforced by changes to the PI. It should also be clarified that “rapid” is not the use of rapid titration which has been described in the literature, such as up to 100-150 mg of clozapine given on the first day of exposure with 25-100 mg increases per day (Poyraz 2012, Ifteni 2014). Rather, too “rapid” accounting for the individual’s factors of decreased clozapine clearance.

Additionally, the PI could also add that CRP and therapeutic drug monitoring (TDM) can be obtained to guide titration, when available. It should be ensured that any PI recommendations avoid creating new barriers to clozapine use. Of note, the *International Adult Titration Guideline* applies only to inpatient titrations. This is because outpatient titration regimens generally involve dose changes that occur much slower (e.g., on a weekly basis) and may lend to a lower risk of inflammatory reactions with more time to make changes based on TDM.

Finally, we wish to note an interesting comment removed from the clozapine PI’s dosing section by 2013. This comment read, *upon initiation of clozapine therapy, up to a 1-week supply of additional clozapine tablets may be provided to the patient to be held for emergencies (e.g., weather, holidays)*. With the current regulation of the US monitoring program, patients can only get a maximum days’ supply of clozapine that matches their hematologic testing interval (e.g., a one-week supply of clozapine for patients testing weekly). Currently, “extra” supplies are not generally allowed but consideration to add this back could significantly help patients who are becoming accustomed to only receiving a week supply at a time or during transitions of care from the hospital.

### **Accumulating Clozapine Warnings: Sans Pneumonia or Inflammation**

Clozapine has five boxed warnings, which is far greater than other antipsychotics and most other prescription medications. When first approved there were only two boxed warnings specific to clozapine, the risk of severe neutropenia and seizures (Clozaril 1990). By 1992 cardiovascular and respiratory adverse events warning was strengthened to a

boxed warning. This included the risk of severe hypotension with respiratory or cardiac arrest, specifically if two or more days of clozapine had been missed and the previous dose was continued without titration (Physicians’ Desk Reference, 1992). Other cardiotoxicity boxed warnings were added in by 2002 (myocarditis), 2013 (cardiomyopathy), and 2016 (mitral valve incompetence) (Clozaril 2002, Clozaril 2013b, Clozaril 2016). The fifth boxed warning was the 2005 addition of *Increased Mortality in Elderly Patients with Dementia-Related Psychosis*, which now applies to all antipsychotics (Clozaril 2005).

As de Leon notes, pneumonia is the most common cause of clozapine-related death per WHO database results (de Leon 2022a,c, 2020a). There may be a need to draw greater attention to this in the PI. Currently, there are three mentions of pneumonia in the current clozapine PI that address this safety issue either indirectly or without detail (Clozaril 2021). The first is a part of the antipsychotic class boxed warning related to increased mortality when agents are used for dementia related psychosis. In the summary of data, it is included that most deaths were “cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature” (Clozaril 2021). The second mention is under the *Postmarketing Experience* for the “respiratory system” as: *aspiration, pleural effusion, pneumonia, lower respiratory tract infection*. There is no further description or context provided. The third mention is under *Overdosage Experience*, with verbiage of “aspiration pneumonia” reported with overdose. Multiple publications have found an association between antipsychotics and pneumonia either based on national database information or reasons for hospitalization (Kuo 2013, Milano 2020). Unfortunately, there has been little research on prevention of clozapine-associated pneumonia, which may be attributed to the underlying pathophysiology being not well understood. Pneumonia from clozapine may be related to a combination of factors such as sialorrhea, sedation, dysphagia, and anticholinergic properties (Milano 2020).

Since clozapine’s early use, the association with certain inflammatory responses, such as isolated fever, has been known. Fever is mentioned as a highlighted precaution in the original clozapine PI (Clozaril 1990). As more clinical experience and post-marketing reports accumulated it became evident that inflammatory reactions associated with clozapine were very heterogeneous in presentation and vary in severity, including those that may be transient and self-limiting (e.g., transaminitis, eosinophilia) to more fatal adverse drug reactions (ADRs) including serositis, myocarditis and drug rash with eosinophilia and systemic symptoms (de Filippis 2020, Mouaffak 2009). As such, many different inflammatory-type adverse drug reactions have made their way into the clozapine PI. More research is needed to better identify and prevent clozapine-induced inflammation with focus on the underlying pathophysiologic process. Overall, this clozapine-induced inflammation creates a scenario where clozapine indirectly decreases its own metabolism. de Leon describes this as a *hypersensitivity model* where 1) rapid titration results in inflammation, 2) cytokines inhibit CYP1A2 increasing clozapine concentrations, and 3) the titration continues leading to progression of more serious inflammatory illness (e.g., myocarditis).

## Hematologic Monitoring: Can Requirements Continue to Loosen?

Since clozapine approval in the US, the PI has been complete with the specific hematologic monitoring. This has changed multiple times in the US over the past 30 years. In the US, clozapine initially required weekly monitoring of white blood cells (WBC) which was later changed in 1998 to allow for every other week monitoring after an initial 6 months of normal WBC counts (Clozaril 1990, Worrel 2000). This was further liberalized to allow every 4-week hematologic monitoring of both WBC and absolute neutrophil count (ANC) in 2005 (Mechcatie 2005). This compares to monitoring in parts of Europe of weekly for the first 18 weeks before progressing to every 4-week monitoring (Nielsen 2016). Also, the Netherlands Clozapine Collaboration Group has suggested that it may be possible for some patients to have monitoring stopped or completed infrequently after the initial 6 months without hematologic abnormalities (Schulte 2020). While beyond the scope of this letter, some evidence supports the notion that ongoing monthly hematologic monitoring after 1 year in the absence of hematologic abnormalities may be too rigorous (Shulte 2006, Cohen 2013). To address this issue stakeholders, experts in the field, NDA holders, and regulatory bodies where applicable should convene to continue to reduce clozapine barriers associated with hematologic monitoring that is under strict regulation in the US.

Other changes in hematologic monitoring have occurred in the US. This includes how long clozapine treatment gaps can occur before a patient must return to the start of the monitoring protocol (i.e., return to weekly monitoring). Prior to 2005, if a patient was on clozapine for greater than 6 months with no abnormal hematologic events (i.e., having every other week monitoring), and there was a break in treatment of less than 1 year, then the patient could have returned to every other week monitoring. If the gap was greater than 1 year then the patient returned to the start of the monitoring protocol (Physicians' Desk Reference, 2005). This would become more rigid based on a gap in clozapine of either greater than or less than 1 month. For breaks in clozapine of greater than merely 1 month, a patient would need to restart with 6 months of weekly monitoring (Physicians' Desk Reference, 2006). This is still the current requirements in the US as of 2022 (Clozaril 2021). In 2015, the PI eliminated the need for increasing the monitoring frequency after a "substantial drop" in blood counts even when the patient did not have neutropenia. A substantial drop was defined as a "single drop or cumulative drop within 3 weeks of WBC  $\geq$  3000/microL or ANC  $\geq$  1500/microL" which required repeat hematologic testing (Clozaril 2014, 2015). Also, in 2015 the addition of a different set of monitoring parameters and intervention thresholds for those with benign ethnic neutropenia was added (Clozaril 2015).

### Final Thoughts

de Leon, et al., previously called for changes to the clozapine PIs worldwide to reflect that 1) patients of Asian ancestry may require a slower titration and lower target clozapine dose, 2) clozapine is associated with potentially fatal pneumonia, and 3) that the risk of myocarditis (and we would include general inflammation) may be reduced by a slower titration

accounting for patient specific factors (de Leon 2020b). There is a need for studies to evaluate these recommended titrations to further validate its impact on improving safety during titration, such as those done with lamotrigine (Fujii 2020). While there have been many notable changes to the clozapine PI related to dosing, warnings/precautions, and interactions, to date, none of the three suggestions have been specifically made, at least in the US. We support these proposed changes which ultimately may improve awareness of these issues and improve clozapine safety. We also suggest that information related to the interaction between inflammation, decreased CYP450 activity, and clozapine be added to the PI.

Beyond the PI, issues with the current clozapine monitoring program (i.e., the Risk Evaluation and Mitigation Strategy (REMS) program) needs to be resolved with some requirements still suspended by the FDA due to problems in program change implementation in 2021. In at least one reported case, this has caused severe patient harm (ISMP 2022). Confusion and discrepancies have also been created among the community pharmacies who serve as the final gatekeeper to clozapine access (if they even choose to optionally register with the REMS program at all). Over the last 30 years, the hematologic monitoring parameters have however become less rigorous (e.g., reduction of required testing frequency) and helped with clozapine access to those with BEN. Based on evidence and other recommendations, it may be possible to further reduce the hematologic monitoring burden to expand access to this medication associated with decreased mortality and reduced suicidality.

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## CLOZAPINE-INDUCED INFLAMMATION: WHAT PSYCHIATRISTS SHOULD KNOW?

Marina Sagud

School of Medicine, University of Zagreb,  
Department for Psychiatry and Psychological Medicine,  
University Hospital Center Zagreb, Zagreb, Croatia,  
MarinaSagud@mail.com

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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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