

# A Rational Use of Clozapine Based on Adverse Drug Reactions, Pharmacokinetics, and Clinical Pharmacopsychology

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## Keywords

Asian continental ancestry group/genetics · Clozapine/adverse effects · Clozapine, blood · Clozapine/metabolism · Clozapine/toxicity · COVID-19 · Drug labeling · Infection · Inflammation · Mortality/drug effects

## Abstract

Using Richardson and Davidson's model and the sciences of pharmacokinetics and clinical pharmacopsychology, this article reviewed the: (1) poor life expectancy associated with treatment-resistant schizophrenia (TRS), which may be improved in patients who adhere to clozapine; (2) findings that clozapine is the best treatment for TRS (according to efficacy, effectiveness and well-being); and (3) potential for clozapine to cause vulnerabilities, including potentially lethal adverse drug reactions such as agranulocytosis, pneumonia, and myocarditis. Rational use requires: (1) modification of the clozapine package insert worldwide to include lower doses

for Asians and to avoid the lethality associated with pneumonia, (2) the use of clozapine levels for personalizing dosing, and (3) the use of slow and personalized titration. This may make clozapine as safe as possible and contribute to increased life expectancy and well-being. In the absence of data on COVID-19 in clozapine patients, clozapine possibly impairs immunological mechanisms and may increase pneumonia risk in infected patients. Psychiatrists should call their clozapine patients and families and explain to them that if the patient develops fever or flu-like symptoms, the psychiatrist should be called and should consider halving the clozapine dose. If the patient is hospitalized with pneumonia, the treating physician needs to assess for symptoms of clozapine intoxication since halving the dose may not be enough for all patients; consider decreasing it to one-third or even stopping it. Once the signs of inflammation and fever have disappeared, the clozapine dose can be slowly increased to the prior dosage level.

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Psychiatric textbooks and article reviews in psychiatric journals ignore the recent scientific advances on the mechanism of adverse drug reactions (ADRs), pharmacokinetics, and clinical pharmacopsychology which are the basis for this article review on the rational use of clozapine for treatment-resistant schizophrenia (TRS).

In an editorial, Fava [1] first used the scheme of Richardson and Doster [2] to propose a rational use of antidepressants. Richardson and Doster [2] proposed that, in evidence-based medical decision-making for individual patients, three dimensions should be considered: (1) baseline risk of poor outcomes from an index disorder that is not treated, (2) responsiveness to the treatment option, and (3) vulnerability to ADRs. This approach is similar to the World Health Organization's (WHO) approach, which characterizes the rational use of medicine as, "Patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community" [3].

This review first introduces the recent advances on ADRs, pharmacokinetics and clinical pharmacopsychology regarding clozapine. After this introduction, the following three sections apply Richardson and Doster's model to TRS, the main clozapine indication. Then the current use of clozapine is reviewed, and a new rational approach is proposed with our current recommendations regarding the COVID-19 infections. The last two sections of this review describe the technological advances that may influence future clozapine use and other clozapine indications.

### ADRs and Clozapine

There are two major classes of ADRs: (1) unpredictable, uncommon and idiosyncratic, and (2) predictable, common and dose-related [4]. The latter are better described as related to serum concentrations [5]. There is recent agreement among the most important medical scientists, such as Vanderbroucke and Psaty [6] or Ioannidis [7], that the status of ADR science is highly deficient. According to them, there are two main reasons for the poor status of ADR knowledge [6, 7]: (1) pharmaceutical companies tend to try to minimize the existence of ADRs, and (2) rare but potentially lethal ADRs, usually idiosyncratic, are usually not detected by the randomized clinical trials (RCTs) required for drug approval, since they are short-term and include only a few thousand patients. These deficiencies have led to several drugs being withdrawn from

the market due to unidentified potentially lethal ADRs [8].

On the other hand, psychiatric textbooks and review articles call ADRs "side effects" and do not explain these two classes of limitations in the field. Similarly, recent review articles [9–11] stressed that clozapine is prone to cause ADRs but do not explain these advances in knowledge of ADRs.

### Pharmacokinetic Introduction to the Rational Use of Clozapine in TRS

A rational clozapine treatment needs first to be based on clozapine pharmacokinetics, which is a major determinant in clozapine dosing. Clozapine depends on the cytochrome P450 1A2 (CYP1A2) for its metabolism and follows pharmacokinetic changes similar to other CYP1A2 drugs. This is not clearly explained in the US package insert. Online supplementary Box S1 (see [www.karger.com/doi/10.1159/000507638](http://www.karger.com/doi/10.1159/000507638) for all online supplementary material) [12–50] provides a critical chronology of the protracted history of the pharmacokinetics of clozapine, and the contributions of two other CYP1A2 drugs, theophylline and caffeine, to its understanding. The inhibitory effects of infections on CYP1A2 were first described in theophylline [15, 18, 19] and 25 years later replicated in clozapine. In 1997, two studies ignored by Western clozapine researchers stated that Chinese have lower clozapine metabolism than Caucasians [24, 25]. Then, 20 years later, a well-controlled study using caffeine demonstrated that East Asians have lower CYP1A2 activity [34]. It is now clear that all Asians have lower clozapine metabolism and need half the clozapine dosage used in the US [45–48].

Measuring serum clozapine levels, called therapeutic drug monitoring (TDM) by pharmacologists, is the cornerstone for the rational use of clozapine personalized dosing since a minimum serum level of 350 ng/mL is needed for clozapine response [51]. Pharmacokinetic science has determined that, in therapeutic dosages, clozapine follows linear kinetics (the relationship between dose and concentration is linear) and provides information on which variables influence clozapine clearance from the body and, therefore, clozapine dosing. The most important clozapine metabolite is norclozapine; clozapine-N-oxide is second. Norclozapine, clozapine-N-oxide, and other hydrosoluble metabolites are then eliminated by the kidney.

Clozapine clearance is measured by the concentration-to-dose (C/D) ratio. Online supplementary Box S2 [5, 44–

46, 48, 52–67] describes the important pharmacokinetic variables for clozapine clearance. Higher clozapine C/D ratios, indicating lower clearance, are associated with females, non-smokers, Asians, genetic poor metabolizers, inhibitors, obesity, inflammation, and possibly with renal impairment and pregnancy. Lower clozapine C/D ratios indicate lack of adherence or higher clearance associated with males, smokers, non-Asians, and inducers.

Two prior TDM review articles [68, 69] are summarized in online supplementary Box S3 [31, 44, 50, 51, 55, 58–61, 63, 65, 68–91] which also describe our extensive experience with thousands of inpatient clozapine TDMs under standard conditions (trough and steady-state levels) in the US [44] and China [45, 65]. Many of these inpatients were followed for months and/or years after changes in important pharmacokinetic variables [31, 44, 50, 58–61, 63, 65, 74, 79, 86–91].

Published review articles [92–94] usually insist on the wide variability of clozapine TDM among individuals and the difficulty of interpreting a single clozapine level, but they fail to pay attention to findings from these two sciences: pharmacokinetics and clinical pharmacopsychology, which help in interpreting variability in clozapine levels. In inpatients, repeated measures allow the calculation of average clozapine clearance in an individual through a mean clozapine C/D ratio, which can be compared using dose-correction factors after changes in important pharmacokinetic variables (e.g., before and after use of an inhibitor).

### **Introduction of Clinical Pharmacopsychology in the Rational Use of Clozapine in TRS**

When dealing with TDM in outpatients, one cannot ignore lack of adherence as a major problem in many clozapine outpatients, frequently leading to hospitalizations [95–99]. This is not surprising to the authors, who are interested in aiding the development of the science of clinical pharmacopsychology [100]. Lack of adherence is a major issue in treatment maintenance in psychiatry [101, 102], and when analyzing outpatient samples, a low clozapine C/D ratio is almost never explained by the patient being a genetic ultrarapid metabolizer and rarely explained by co-prescription of a potent inducer; it is almost always explained by lack of adherence [46, 54, 87]. Unfortunately, experts who write reviews on clozapine TDM do not consider the major relevance of lack of adherence in clozapine outpatients. Clinicians do not appear to be free of this bias and seem to think that

lack of adherence may be a problem for other patients, but their own patients are adherent. TDM results demonstrate that one-third to one-half of the patients considered TRS patients by their psychiatrists are simply not taking their antipsychotics [103, 104]. Unfortunately, no clozapine studies explored the pharmacopsychological variables influencing poor adherence. Based on the pattern of lack of adherence in psychiatric patients, one can hypothesize that each non-adherent clozapine patient may be influenced by one or more factors such as lack of insight about the illness, self-reported attitudes related to their history of medication exposure, or personality style related to feelings of control [105]. Addressing specific pharmacopsychological variables in each non-adherent patient has the potential to improve clozapine adherence.

### **Baseline Risk of Poor Outcomes from TRS without Treatment**

The literature usually describes approximately one-third of schizophrenia patients as treatment-resistant, but the TRS definitions vary from study to study [106]. On the other hand, the literature agrees that: (1) clozapine is the most effective treatment for these patients [107, 108] and (2) among schizophrenia patients, those with treatment-resistant forms have the more obvious abnormalities in brain imaging [109, 110], and are those associated with greater individual and societal burden [111].

To better understand the benefits and risks of clozapine in TRS, one would like to know the effects of TRS on life expectancy and how it is modified by clozapine or other antipsychotics; however, only data on schizophrenia in general is available. In a meta-analysis [112], schizophrenia was associated with a weighted average of 14.5 years of potential life lost. In a recent Swedish cohort with >20,000 patients, the cumulative antipsychotic exposure displays a U-shaped curve for overall mortality with no antipsychotic exposure having the worst outcome [113]. Regarding clozapine, in a meta-analysis of 24 studies with long-term follow-up of treatment, Vermeulen et al. [114] found long-term, crude mortality rate ratios were significantly lower in patients continuously treated with clozapine compared to patients treated with other antipsychotics (mortality rate ratio = 0.56). Online supplementary Box S4 [112–116] describes two additional studies published after the meta-analysis, also showing lower mortality in clozapine patients [115, 116].

## Responsiveness to Clozapine in TRS

Online supplementary Box S5 describes in detail what we know regarding clozapine responsiveness measured by efficacy, effectiveness and well-being.

### *Efficacy: RCTs and Meta-Analysis*

RCTs tend to be of relatively short duration, are biased against including the most severe patients in psychiatry [117] and are, therefore, far from ideal in assessing response in TRS. Later, RCTs are combined in meta-analyses, which Feinstein called “statistical alchemy for the 21st century” [118]. The most complex meta-analysis, the network meta-analysis, compares drugs indirectly, and these comparisons are particularly problematic when there is no similarity in the RCTs [119].

In a TRS meta-analysis, Siskind et al. [120, 121] found clozapine superiority. On the other hand, another research group using network meta-analyses published two articles; one by Samara et al. [122] found no clozapine superiority in TRS, but the other one by Huhn et al. [123] found that clozapine was the best antipsychotic for the acute treatment of multiple-episode schizophrenia in general. Not surprisingly, this TRS network meta-analysis by Samara et al. [122] has been criticized by lack of representativeness of the included RCTs [107, 124, 125].

### *Effectiveness*

If one takes a more comprehensive view of what is important in clinical practice [126], and considers effectiveness based on two systematic reviews of naturalistic cohort studies [127, 128], clozapine was superior to other antipsychotics in decreasing discontinuation and decreasing hospitalization.

### *Clozapine and Well-Being*

The importance of well-being during pharmacotherapy is receiving more and more attention [129] and is particularly relevant in explaining the high adherence of some patients to clozapine, demonstrated by the lower discontinuation rates in cohort studies [127, 128]. Clozapine positive effects on well-being in some patients may be influenced by clozapine effects on extrapyramidal symptoms [130–142], hostility [143, 144] and the “awakening” phenomenon [145–147] (online suppl. Box S5, section 3).

## Vulnerability to ADRs and Prevention

### *Clozapine-Induced Agranulocytosis*

The description of clozapine-induced agranulocytosis in 1975 [14] derailed its widespread use around the world (online suppl. Box S1). The next step was the marketing of clozapine in the US in 1990 [12] with the requirement of weekly white cell blood counts (WBC) and a manufacturer-managed database. Then clozapine was progressively marketed in multiple countries with different levels of WBC monitoring [148]. In the US in 2015 [41], the WBC requirements were modified, returning to a unified WBC database and allowing for lower levels of absolute neutrophil count (ANC) for starting patients with benign ethnic neutropenia, as had previously been done in the UK [149, 150]. Clinicians worldwide need to follow the respective regulations of their countries regarding WBC and ANC monitoring. Currently, agranulocytosis appears to be a well-managed risk. The WHO’s database, VigiBase, has received reports on ADRs since 1968 from 134 drug agencies in countries around the world. Our VigiBase search on July 15, 2019, identified a 2% rate of fatal outcomes (550/34,931) due to agranulocytosis since the onset of clozapine use [49]. Online supplementary Box S6 [49, 151–155] reviews our current knowledge of clozapine-induced agranulocytosis.

### *Pneumonia*

The convergence of two historical findings (online suppl. Box S1) has finally led to the recent realization of the relevance of the association between clozapine and pneumonia and its lethality. The first historical finding was that inflammation releases cytokines that decrease the expression and activity of CYP1A2 with the potential of causing intoxication by CYP1A2 drugs. This was first demonstrated in theophylline [15, 18, 19] and then 25 years later in clozapine [30, 31]. Elevation of c-reactive protein (CRP) is a good marker that cytokines are being released, and that this may increase clozapine levels [156]. The second historical finding is that in 2005, the FDA modified the package insert of all second-generation antipsychotics to include a warning about death by pneumonia in patients with dementia [32]. Despite the fact that clozapine is not indicated for dementia, its package insert was modified, too. The association between clozapine and pneumonia is supported by data from the Taiwan registry [37], other studies previously reviewed [49], and further verified by a mirror-image study in the Danish registry [157].

More concerning is that pneumonia can be highly lethal in clozapine patients and is one of the most impor-

tant causes of mortality in clozapine patients. This has been suggested by observational studies in the US [88, 158], the UK [159, 160], and Denmark [42]. Moreover, a VigiBase search [49] exploring pneumonia lethality in clozapine patients led to very concerning results: (1) 2,077 fatal outcomes (approximately four times higher than those associated with agranulocytosis), and (2) relatively high lethality of 30% (much higher than the 2% of agranulocytosis). Moreover, pneumonia was much more strongly associated with clozapine than the 3 most frequently prescribed second-generation antipsychotics; each of them had around 1/10 of the fatal outcomes of clozapine [161]. The lethality of pneumonia in clozapine patients is explained in that clozapine can contribute to pneumonia, and once pneumonia develops it can cause a clozapine intoxication; therefore, the combination of pneumonia and clozapine intoxication is highly lethal. This complex bidirectional association [162] is described in detail in online supplementary Box S7 [157, 163–169]. Our recommendations for decreasing the risk and lethality of pneumonia in clozapine patients are described in online supplementary Box S8 [65, 162, 170, 171]. The context for the clinical relevance of these recommendations is that pneumonia may be the most significant life-threatening medical event connected with antipsychotic use [172].

### *Myocarditis*

The controversy of clozapine-induced myocarditis is defined by two extreme positions first delineated in 2012 by Cohen et al. [35]. Australian experts think that with adequate monitoring clozapine-induced myocarditis is present in 3% of patients, and those who do not find an incidence of 3% among their patients are ignoring many cases [38]. The position of most clozapine experts in continental Europe is that clozapine-induced myocarditis is very rare. In the Danish registry, Rohde et al. [42] found an incidence of 0.03% and no fatal cases. If we assume that Danish clinicians do not know how to diagnose myocarditis and that they are missing 3% of cases with a mortality rate of 6%, the study by Rohde et al. [42], should have identified 6 deaths associated with clozapine-induced myocarditis instead of no deaths [162].

A recent meta-analysis of clozapine-induced myocarditis provides estimations for these two positions by describing an event rate of 2% in 9 Australian samples and of 0.3% in 15 non-Australian samples [173]. This meta-analysis provided no reason for this roughly 10-fold difference between Australia and other countries.

Online supplementary Box S9 [38, 66, 162, 174–179] describes our model of clozapine-induced myocarditis as a hypersensitivity reaction similar to when rapid titrations of lamotrigine induce Stevens-Johnson syndrome and how to prevent it. Online supplementary Box S10 [16, 21, 26, 27, 33, 36, 45, 46, 48, 50, 54, 58, 69, 87, 180–187] further describes the published data supporting this model in which rapid clozapine titration is key to explaining clozapine-induced myocarditis. Any titration that is too fast for a specific patient can cause clozapine-induced myocarditis or, more correctly, any kind of clozapine-induced inflammation [66]. Our most important recommendation is to always use slow and personalized clozapine titration (online suppl. Table S2) and weekly CRP (online suppl. Box S9).

### *Other Potentially Lethal Clozapine ADRs*

Online supplementary Box S11 [49, 68, 188–207] explains that our VigiBase search [49] provided another four definitive clozapine ADRs associated with fatal outcomes: (1) constipation, (2) arrhythmia, (3) seizures, and (4) syncope.

Clozapine is one of the antipsychotics most strongly associated with weight gain, hyperglycemia, and hyperlipidemia [208, 209]. In a systematic review of cohort studies, clozapine was also associated with higher cardiometabolic-related risk outcomes [128]. As described before, clozapine is associated with longer survival [114]; it appears that its positive effects may outweigh its metabolic risks.

### *Behavioral ADRs*

Behavioral ADRs secondary to psychiatric medications have not received enough attention [131, 132] and one of the best examples is clozapine-induced severe obsessive-compulsive symptoms (OCS). Due to its complexity and lack of good studies, there is no agreement in the literature on its management. In this journal issue, Kim et al. [210] reviewed the limited available literature and provided the very helpful conclusion that adding aripiprazole with/without clozapine dose reduction may be a good alternative to antidepressants for managing clozapine-associated OCS. Future controlled studies will need to clarify whether this conclusion is correct or not.

Clozapine is the second-generation antipsychotic most consistently associated with withdrawal symptoms [211]. Thus, clinicians should warn patients not to stop clozapine suddenly, since it has been associated with several withdrawal syndromes including: (1) cholinergic re-

bound (including nausea, vomiting, diarrhea, headache, agitation, confusion, and diaphoresis) [212], (2) worsening psychosis and/or abnormal movements [213], and (3) even catatonic symptoms in patients who never had catatonia before [91]. When clozapine needs to be stopped suddenly due to serious ADRs, temporary treatment with anticholinergics with slow titration over 2–3 weeks may be a good option for preventing cholinergic rebound [212] and olanzapine may be a reasonable choice [214] for covering withdrawal from psychosis or abnormal movements. Although we do not recommend rapid titration in naïve patients, we have, on rare occasions, used it under very controlled inpatient conditions when previously known patients had severe withdrawal with psychotic exacerbations, or catatonia. These are extremely dangerous situations, and the sedating properties of clozapine can help as long as the patient is closely observed and the prior dosage needed to stabilize the patient and the level of tolerance are known.

A phenomenon even less well described in the literature is that some patients who have shown remarkable improvement in their psychosis and then stopped clozapine on their own never again recovered the dramatic response seen the first time [215, 216]. Clinicians need to explain to any patient with dramatic response to clozapine that this may sometimes be lost by stopping clozapine.

#### *Contraindications*

In patients naïve to clozapine, the most important contraindication is the presence of some kind of myeloproliferative disorder or neutropenia that precludes having a high enough ANC required to start clozapine. Very rarely, patients can develop allergic reactions to clozapine and should not be exposed again. Most of the contraindications that a clinician faces are relative contraindications in which the risk of starting clozapine needs to be carefully balanced by including the patient and the family in the discussion regarding the risks, avoiding DDIs before starting clozapine as much as possible and stabilizing medical problems as much as possible [207]. In many patients, clozapine may be the last option after exhausting all other options with limited benefit.

#### **Current Use**

Most clozapine experts are concerned by the lack of use of clozapine worldwide, in spite of its benefit for TRS. An international study including 17 countries showed

that in most countries clozapine use increased from 2005 to 2014. Nevertheless, great disparities were seen, with greatest use in Finland (189/100,000 persons) and New Zealand (116/100,000), and least in the Japanese cohort (0.6/100,000) and in the privately insured US cohort (14/100,000) [217]. The term “clozaphobia,” phobia of prescribers toward prescribing clozapine, has been proposed [218]. Online supplementary Box S12 describes barriers regarding clozapine use and successes in the Netherlands and New Zealand in increasing clozapine use [219–225].

#### **Proposal for More Rational Use of Clozapine**

A more rational use of clozapine is based on three pillars: (1) modification of the worldwide clozapine package insert reflecting the advances in clozapine pharmacokinetics, (2) the use of clozapine TDM to personalize clozapine dosing, and (3) the use of slow and personalized titration including CRP to avoid myocarditis and other clozapine-induced inflammations.

#### *Changing Worldwide Clozapine Package Inserts*

Clozapine package inserts worldwide should report that [47]: (1) Asians need half the dose prescribed in the US, (2) clinicians should be aware that pneumonia may be highly lethal in clozapine patients, and (3) clozapine-induced myocarditis during dose escalation can be reduced by slow personalized titration.

#### *The Best Way to Personalize Maintenance Dosing Is TDM if It Is Available*

TDM is recommended by the AGNP experts but is not mandatory in any country. In the opinion of the authors, the use of clozapine should become similar to the use of lithium, which requires TDM for dosing. Many countries do not have access to clozapine TDM; therefore, it is not reasonable to make TDM mandatory. However, ideally all countries should provide access to clozapine TDM; it is the best way of personalizing dosing since it reflects the combination of genetic, environmental and personal variables that influence dosing and the specific pharmacokinetics of each drug [5]. Moreover, due to clozapine ADRs and variability in dosing, clozapine TDM is cost-effective [226].

Clozapine TDM is the best way to personalize the best maintenance dose to reach at least 350 ng/ml of serum clozapine concentrations [69]. To rule out lack of response, this clozapine dose should be maintained for

enough time; some have proposed 3 months [106] and others, 8 weeks [227]. Prescribing the lowest dose that delivers therapeutic concentrations and efficacy will decrease the risk of clozapine ADRs and provide the safest baseline in case there are infections or inflammations in the future. Moreover, clozapine TDM helps to determine adherence of clozapine outpatients which may predict re-hospitalization [95–99].

Psychiatrists with no access to clozapine TDM can use online supplementary Table S1, which shows the average clozapine dose recommended based on ethnicity, sex, smoking, and some DDIs. Due to difficulty in predicting clozapine dosage in patients taking fluvoxamine, as it is a potent inhibitor [55, 228], we do not recommend co-prescribing this drug with clozapine without TDM. As valproic acid can be an inhibitor of clozapine metabolism and an inducer of norclozapine metabolism, it is also better to avoid it [57].

#### *Slow and Personalized Titration with CRP Levels*

The Dutch clozapine guideline recommends slow titration with very slow titration for outpatients [223]. This may explain the lack of clozapine-induced myocarditis in the Netherlands. Therefore, there is little need for improving clozapine titration in the Netherlands.

In many other countries, personalized titration based on pharmacokinetic variables may be beneficial. Online supplementary Table S2 provides our recommendations for inpatient titrations and online supplementary Box S9 provides recommendations for preventing clozapine-induced myocarditis. Unfortunately, two unpredictable variables can make a patient behave as a clozapine poor metabolizer: genetics or undetected inflammations. To prevent those situations, our inpatient protocol recommends measuring CRP at the same time as WBC: at baseline and for the first 8 weeks of clozapine titration or until the final clozapine dose is reached. Measuring weekly CRP levels is much easier and less expensive than the intensive heart monitoring recommended by Australian experts [38, 178, 179]. Clozapine should not be started until CRP is normal, so that use of clozapine in patients with unidentified inflammations can be avoided. Subsequently, if the CRP is increased or the patient develops fever, this is a sign that the titration is too rapid for that patient, and the clozapine dose should not be further increased until CRP has normalized; this may prevent the progression of a clozapine-induced inflammation.

## **COVID-19 Infections**

There is no data on COVID-19 in clozapine patients but, based on what we know about clozapine pharmacology, we can hypothesize that clozapine, possibly by impairing immunological mechanisms, may increase the risk of pneumonia in infected patients. More importantly, during this COVID-19 epidemic, psychiatrists should call their clozapine patients and families and explain to them that if the patient develops fever or flu-like symptoms, they should call their psychiatrist, and if they cannot reach their psychiatrist, the patient should cut the clozapine dose in half. If the patient has to be admitted to a hospital due to COVID-19 pneumonia, the treating physician needs to assess for symptoms of clozapine intoxication since halving the dose may not be enough for all patients and consider decreasing it to one-third or even stopping it. Once the signs of inflammation and fever have disappeared, the clozapine dose can be slowly increased to the prior dosage level.

## **Future Use: Technology Advances Coming to Market**

Online supplementary Box S13 [54, 155, 229–241] describes the recent commercialization and/or development of new technologies in pharmacogenetic testing, WBC monitoring, and TDM. The current commercial pharmacogenetic tests should not be used on clozapine patients. Currently, it is not clear whether the point of care devices providing WBC or TDM can facilitate clozapine prescription, or only make it more expensive. It is too early to decide whether some of the TDM technologies in development will provide easy and cheap ways to establish clozapine adherence.

## **Other Clozapine Indications**

This review article focuses on the use of monotherapy clozapine for TRS, which is the main clozapine indication in the US and other countries [148, 242]. We do not know how clozapine changes the life expectancy of patients with other clozapine indications, enumerated in online supplementary Box S14 [29, 139–141, 148, 207, 242–257]. To decide to prescribe clozapine for any of these indications requires the psychiatrist to carefully balance, for each patient, the likelihood of responsiveness and vulnerabilities, remembering that data on responsiveness is limited. If the same clozapine doses for

TRS are used for other indications, the clozapine vulnerabilities and ADRs should be similar. In the experience of the authors, other indications, such as polydipsia or intellectual disability with self-injurious behaviors, may respond to lower clozapine doses and do not require reaching concentrations of 350 ng/ml to gain efficacy [207]. Clozapine dosing and TDM need to be explored by future studies focusing on these other indications. As clozapine may be a last resource for inpatients with extremely severe conditions besides TRS, for which providers have exhausted all other options, each patient with these other conditions should be considered on an individual basis after discussing it with the patient and the family.

Using Richardson and Davidson's model [2] and the sciences of pharmacokinetics and clinical pharmacopsychology, this article reviewed the: (1) poor life expectancy associated with TRS, which may be improved in patients who adhere to clozapine; (2) findings that clozapine is the best treatment for TRS (according to efficacy, effectiveness and well-being); and (3) potential for clozapine to cause vulnerabilities, including potentially lethal ADRs. Our proposal for rational use is based on three pillars: (1) modification of the clozapine package insert worldwide to reflect the advances in clozapine pharmacokinetics, (2) the use of clozapine TDM for personalizing clozapine dosing, and (3) the use of slow and personalized clozapine titrations. This proposal should make clozapine as safe as possible and may contribute to increasing the life expectancy of TRS patients taking clozapine and their well-being. Only time will tell whether this editorial accomplished its goal or further contributed to clozapinophobia.

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## Acknowledgments

The authors thank Lorraine Maw, MA, for editorial assistance. Can-Jun Ruan is supported by a 2019 NARSAD Young Investigator Award from the Brain & Behavior Research Foundation. The authors are grateful to the reviewers and editor who provided important suggestions for improving the article. Moreover, the first author is grateful to the multiple reviewers reviewing his clozapine articles published during 2019 and the first 3 months in 2020; some of their suggestions were also used in this article.

## Disclosure Statement

This article received no support from any funding agency, commercial business, or not-for-profit institution. In the last 3 years, the authors have had no commercial conflicts of interest.

## Funding Sources

None.

## Author Contributions

J.d.L. wrote the first draft. All authors meet criteria for authorship and approved the final manuscript. Since 2015, J.d.L. and C.-J.R. have studied >3,500 clozapine levels in Asians and reviewed the literature on clozapine levels regarding ethnic differences in metabolism and in inflammation in both Chinese and English languages. Since 2017, J.d.L. and G.S. have written articles developing a model for personalizing antipsychotic dosing using levels and focusing on drug-drug interactions. Since April of 2019, J.d.L. and C.D.C. have focused on the pharmacoepidemiology of clozapine adverse drug reactions.



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