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Letter to the FDA Proposing Major Changes in the US Clozapine Package Insert Supported by Clozapine Experts Worldwide. Part I

A Review of the Pharmacokinetic Literature and Proposed Changes

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Abstract:

Purpose/Background: Clozapine was approved in the United States (US) using 1989 regulations and knowledge. After 30 years, many sections of the US package insert (PI) are outdated.

Methods: We comprehensively reviewed the literature to propose PI updates. We present the information in 2 articles. In Part I, we focus on basic pharmacology based on 407 relevant articles. Part II focuses on clinical aspects and pharmacovigilance.

Findings/Results: Based on more recent expectations of Food and Drug Administration regulations, we reviewed clozapine basic pharmacology including the following: 1) clearance, 2) pharmacokinetics and pharmacodynamics, and 3) monitoring tools. We identified 9 major problems in the basic pharmacological sections of the PI including the following: 1) in vivo studies indicate that clozapine is dependent on CYP1A2 for its metabolism, 2) the minor role of CYP2D6 in clozapine metabolism requires removing the PI recommendation to lower clozapine doses in CYP2D6 poor metabolizers, 3) in nontoxic concentrations CYP3A4 has a minor role in clozapine metabolism and potent CYP3A4 inhibitors lack clinically relevant effects, 4) several drug-drug interactions need to be updated based on recent literature, 5) systemic inflammation may decrease clozapine metabolism and increase the risk of clozapine intoxication, 6) obesity may decrease clozapine metabolism, 7) patients of Asian and Indigenous American ancestry need lower clozapine doses, 8) personalized titration and c-reactive protein monitoring should be considered until prospective studies are available, and 9) the half-life section needs to be modified to acknowledge that single dosing at night is frequent in the US.

Implications/Conclusions: An improvement in the US clozapine PI may lead to improvement in PIs worldwide.

Key Words: clozapine/blood, clozapine/metabolism, clozapine/pharmacokinetics, drug interactions, drug labeling

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Clozapine was approved in the United States (US) in 1989. Thus, the package insert was developed when the Food and Drug Administration (FDA) followed regulations that are now outdated and before major pharmacokinetic advances occurred. We have undertaken a comprehensive 2-part review of the clozapine literature to support updates for the US clozapine package insert. Part I focuses on clozapine pharmacology and highlights the major conceptual developments in pharmacokinetics that the FDA has sponsored since 1989. After a drug is marketed, the FDA uses pharmacovigilance to update package inserts regarding previously unknown adverse drug reactions (ADRs). Part II of this article focuses on clozapine pharmacovigilance. Thus, the aims of this

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review are to propose updates of both the basic pharmacology (Part I) and clinical pharmacology (Part II) areas of the package insert in order to use clozapine more safely.

This Introduction addresses the unique role of clozapine in psychiatry by explaining its 1) complicated history, 2) role in treatment-resistant schizophrenia (TRS), and 3) underuse and delayed use in the US.

CLOZAPINE'S COMPLICATED HISTORY

Supplementary Table S1, http://links.lww.com/JCP/A947,[1–35] provides a detailed history of the US clozapine package insert using a 3-column format: the left focuses on pharmaceutical companies, the right on drug agencies, particularly the FDA, and the center on important contributions by independent investigators.

Clozapine was first marketed in German-speaking countries in the early 1970s and later in Scandinavian countries. In 1973, clozapine's marketer (Sandoz which later became Novartis) hired Honigfeld to initiate the US studies.[2] In 1974, Simpson and Varga[4] reported on the first US clozapine trial. In the next year, a pharmacovigilance report from the Finnish drug agency described hematological complications including 16 cases of agranulocytosis with 8 deaths.[5] All US studies were stopped and only a few centers provided compassionate access to the drug and completed a few studies.[2,36] Clozapine continued to be used in some European countries and Sandoz proposed weekly white blood cell (WBC) monitoring for 18 weeks, by which time 90% of the Finnish cases had occurred.[6] In 1982, US Sandoz reconsidered clozapine's development and the FDA asked Sandoz to demonstrate that clozapine was superior to chlorpromazine in a randomized clinical trial (RCT) for TRS.[9] The concept of TRS was created by this RCT,[10] which led to clozapine's approval by the FDA for TRS in 1989 and its marketing in 1990. The FDA required a complex hematological monitoring system with weekly WBC counts and a database registration.[2]

Clozapine has had some negative press since its introduction in European countries[2,37–39] to the present time, highlighting 2 opposing views in the literature: 1) a drug with potential for saving lives; ADRs it produces are manageable with appropriate monitoring,[40,41] versus 2) a toxic drug that scares potential prescribers.[42] There are many barriers to clozapine use.[43,44] An additional element required to understand problems related to the difficulty of improving the pharmacokinetics sections of the US clozapine package insert has been the loss of interest in therapeutic drug monitoring (TDM) in psychiatry after the introduction of the second-generation antipsychotics and antidepressants.[45] On the other hand, since 2004, a group of German experts[46–48] has been updating guidelines for TDM in psychiatry and promoting clozapine TDM. In 2020, US experts cooperated with the German experts in an article endorsing clozapine TDM.[49]

Supplementary Box S1, http://links.lww.com/JCP/A947,[50–74] shows that the cytochrome P450 1A2 (CYP1A2) is the primary metabolic pathway leading to norclozapine, which accounts for approximately one-third of the clozapine concentration in serum/plasma. Clozapine-N-oxide is the second metabolite with only about 1/10 of the clozapine concentration.[63] Supplementary Box S1, http://links.lww.com/JCP/A947, also reviews pharmacodynamic properties of the parent compound.[50–62] The exact mechanism of the antipsychotic effects of clozapine is not well understood,[50] although it is usually associated with low and transient D_2 receptor antagonism.[51] Supplementary Box S1, http://links.lww.com/JCP/A947, reports that norclozapine may contribute to ADRs. Norclozapine was tested as an antipsychotic but never marketed, which is not surprising because it is not a D_2 antagonist.[63–70] Supplementary Box S1, http://links.lww.com/JCP/A947, also reviews the lack of relevant effects of clozapine-N-oxide, which may not contribute to antipsychotic efficacy nor most ADRs[63,67,71] except possibly for myocarditis, according to recent studies.[72–74]

TRS AND CLOZAPINE AS A LIFE-SAVING DRUG

The literature describes TRS as accounting for approximately one-third of schizophrenia cases, but although definitions of TRS vary among studies,[75] there is agreement that clozapine has a unique role in TRS. A recent group of experts reported that 40% of TRS patients have a consistent response to clozapine.[76] Supplementary Box S2, http://links.lww.com/JCP/A947, summarizes the literature that supports the benefits of clozapine use in TRS including the following: 1) meta-analyses of RCTs and systematic reviews of naturalistic studies,[77–83] 2) a decrease in suicide,[84–99] and 3) the best treatment persistence/adherence rate among oral antipsychotics.[100–116]

Supplementary Box S3, http://links.lww.com/JCP/A947, summarizes the literature that supports clozapine as a potentially life-saving drug in TRS according to meta-analyses of fatal outcomes[117,118] and cohort studies in national registries from the Scandinavian countries[88–93] and Taiwan.[94] These findings are favorable despite the unfavorable effects of TRS, for which clozapine is primarily prescribed. TRS is associated with the worst outcomes, biasing the effects of clozapine when compared to other antipsychotics in all naturalistic studies.[119–121]

PROBLEMS RELATED TO CLOZAPINE USE IN THE US: UNDERUSE AND DELAYED USE

Supplementary Box S4, http://links.lww.com/JCP/A947, summarizes the literature that documents the underuse of clozapine in

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BOX 1. Major problems in the pharmacokinetic sections of the US CLO package insert

1. In vivo studies indicate that CLO is dependent on CYP1A2 for its metabolism
- Described by Swedish studies since 1994[13,14] (see Supplementary Box 8, http://links.lww.com/JCP/A947).
- After 30 years, it is time to clarify that in the package insert.

2. CYP2D6 has a minor role in CLO metabolism
Recommendation for lower CLO D in CYP2D6 PMs needs to be deleted
- No other CLO package insert or pharmacogenetic organization recommends lower CLO Ds for CYP2D6 PMs.[379] After 30 years it is time to delete it.
- Potent CYP2D6 inhibitors, such as fluoxetine or paroxetine (likely to phenoconvert the patient to CYP2D6 PM status), have minor effects on CLO C and not clinically relevant in most patients.[159]

3. CYP3A4 has a minor role in CLO metabolism (see Supplementary Box S13, http://links.lww.com/JCP/A947)
- All in vivo studies of these potent CYP3A4 inhibitors have found no relevant effects:
  - Itraconazole[180]
  - Grapefruit juice and ketoconazole[181]
  - Erythromycin.[182]

4. Pharmacokinetic DDIs (see Supplementary Box S8, http://links.lww.com/JCP/A947)
- The section on pharmacokinetic DDIs needs to reflect the studies published after the 1990s, not the arbitrary current description that CYP2D6 and CYP3A4 are important in CLO metabolism.

5. Systemic inflammation can ↑ CLO Cs causing CLO intoxications (see Supplementary Box S17, http://links.lww.com/JCP/A947)
- This has been known about theophylline since the 1970s and is reflected in its package insert.
- Clozapine intoxication during infections, including pneumonia, may contribute to fatal outcomes (see Part II: until 01/15/23, 674 US fatal outcomes in pneumonia versus 218 for agranulocytosis).

6. Obesity may decrease CLO metabolism (see Supplementary Box S16, http://links.lww.com/JCP/A947)
- Some obese patients may behave as CLO PMs.

7. Patients of Asian ancestry need lower CLO doses (see Supplementary Box S12, http://links.lww.com/JCP/A947)
- It is not known why the CLO marketer decided to ignore the studies published in 1997 indicating that patients of Asian ancestry need lower CLO Ds than those recommended by the US package insert. This led to the overdosing of patients of Asian ancestry all over the world.[224]
- The original inhabitants of the Americas, called indigenous Americans, are descendants of Asians[222] and probably need similar lower CLO Ds.[33]
- The FDA definition of Asian phenotype (patients whose ancestry is from the region extending from Pakistan to Japan)[221] is relevant for CLO. Those with ancestry from Western Asia and/or the Middle East may need CLO Ds similar to those of European ancestry.

8. Titration needs to consider DNA ancestry and make use of CRP monitoring
- The international guideline proposed CRP monitoring and personized titration,[34] which are easy and noninvasive options that may ↓ risk of CLO-induced inflammation until a way to fund prospective studies of personalized titration is identified (see Part II).
- Retrospective studies in Australia,[388] Japan,[228,308,389] and Korea[227] indicated that slower personalized titration may be beneficial.
- A systematic review supports the use of CRP monitoring during titration.[390]

9. Half-life (see Supplementary Boxes S20 and S21, http://links.lww.com/JCP/A947)
- The statement on half-life needs to be changed to reflect more recent studies and that single daily dosing is recommended by US experts.[340–343]
- CLO is not completely eliminated in 2 days; it is not known why the FDA recommends initiating "12.5 mg once daily or twice daily" after 2 days or more of discontinuation. Future TDM studies are needed to determine appropriate dosing after short periods of discontinued medication.

C, concentration; CLO, clozapine; CYP1A2, cytochrome P450 1A2; CYP2D6, cytochrome P450 2D6; CYP3A4, cytochrome P450 3A4; CRP, c-reactive protein; D, dose; FDA, Food and Drug Administration; PM, poor metabolizer; TDM, therapeutic drug monitoring; US, United States.

the US, plus associated implications.[122–132] Supplementary Box S5, http://links.lww.com/JCP/A947, describes the small amount of data specifically from the delayed initiation of clozapine in the US, but there is general agreement that early clozapine initiation is important, as delayed initiation is associated with poorer treatment response.[133–151]

METHODS

Parts I and II make up a comprehensive review including more than 500 different articles targeting FDA officials who need to understand why the clozapine package insert is so outdated and where it needs to be updated. In Part I, the results are organized according to what the FDA would expect of studies on clozapine pharmacology that will be approved in 2024. Thus, these 407 references in Part I are organized according to what the FDA now considers standard pharmacological knowledge and are not based on what psychiatrists normally see in clozapine reviews. Supplementary Box S6, http://links.lww.com/JCP/A947, provides a summary of the article search.[62,152–165]

The advances in knowledge are organized in the following 3 subsections focused on: 1) the concept of clearance and its application to clozapine, 2) how advances in the knowledge of the pharmacokinetics and pharmacodynamics of clozapine should influence clinical practice, and 3) advancements in the methods of monitoring clinical use. The text presents a brief version while the details are explained in the Supplementary Material, http://links.lww.com/JCP/A947, using a very comprehensive set of references to support textual changes in many specific paragraphs of the outdated US clozapine package insert.

RESULTS

An update on Clozapine Clearance

Supplementary Box S7, http://links.lww.com/JCP/A947,[15,166–175] explains that 1) clozapine was approved before 1996 when the

FDA realized that ignoring drug metabolism and drug-drug interactions (DDIs) can lead to lethal outcomes and 2) the metabolism of new drugs studied for FDA approval needs to be understood in the context of renal excretion and hepatobiliary excretion. Older clozapine studies mainly focused on its metabolic transformation. This section provides updates on recent conceptual advances regarding the following: 1) metabolic transformation, 2) renal clearance, and 3) hepatobiliary excretion.

Updates on Clozapine Metabolic Transformation

Supplementary Box S8, http://links.lww.com/JCP/A947, shows that there are 3 known major metabolic pathways for clozapine.[13,14,63,72,74,159,176–190] From most to least important, they are N-demethylation to norclozapine, oxidation to clozapine-N-oxide, and conjugation mainly by glucuronidation.[63] In vivo and DDI studies indicate that clozapine behaves as a drug that is dependent on CYP1A2 metabolism. In toxic concentrations, it is possible that CYP3A4 may become more important than CYP1A2[183–188] and this may be relevant for clozapine-induced myocarditis associated with rapid titration.[72,74]

Updates on Clozapine Renal Clearance

Supplementary Box S9, http://links.lww.com/JCP/A947, reviews the important role of the kidneys in clozapine clearance.[35,63,191–196] After clozapine is metabolized, approximately two-thirds of the metabolites are eliminated in urine. Therefore, aged patients may need to have the dose reduced at least by one-third due to their reduced renal clearance, according to a 2024 study.[35]

Updates on Hepatobiliary Excretion and Glucuronidation

Supplementary Box S10, http://links.lww.com/JCP/A947,[190,195,197–200] reviews the glucuronidation of clozapine and its metabolites and how this process facilitates elimination of approximately one-third of clozapine metabolites in the stool.

Update on Clozapine Pharmacokinetics and Pharmacodynamics in Clinical Practice

This section provides updates for clinicians on many issues that are not adequately incorporated into the US clozapine package insert, such as the following: 1) effects of sex and smoking, 2) DNA ancestry, 3) pharmacokinetic DDIs, 4) pharmacodynamic DDIs, 5) obesity, 6) inflammation, 7) poor metabolizer (PM) status, 8) ultrarapid metabolizer (UM) status, and 9) half-life.

Sex and Smoking Effects

Supplementary Box S11, http://links.lww.com/JCP/A947, documents the greater clozapine clearance of males versus females and smokers versus nonsmokers.[28,34,153,201–216]

Clozapine Metabolism and DNA Ancestry

Average metabolizer patients are those who are non-PMs or not under induction other than smoking. Average patients of Asian ancestry had lower CYP1A2 activity in a well-controlled study using caffeine TDM as a probe for CYP1A2 activity[26] (Supplementary Box S12, section 1, http://links.lww.com/JCP/A947). Currently, it is unknown whether differences in CYP1A2 activity between Asians and Europeans may be related to differences at the CYP1A2 gene or other gene/s controlling CYP1A2 function.[34]

Supplementary Box S12, http://links.lww.com/JCP/A947, reviews the clozapine studies demonstrating that average metabolizer patients of Asian ancestry or their descendants, the indigenous Americans, have lower clozapine clearance and need lower clozapine doses.[10,16,17,26,28,33,34,217–228] It is not currently clear why Novartis did not study clozapine dosing in Asians from 1997 to 2003 when Novartis stopped US marketing.[22] The lack of promotion of lower clozapine doses for Asians probably has had deleterious consequences worldwide.[224]

Supplementary Table S2, http://links.lww.com/JCP/A947, provides the currently available information from studies[33,34,218,220,229] that the international guideline[34] used to guide initial target clozapine dosing based on ancestry: lowest for patients of Asian or indigenous American ancestry, intermediate for those of European ancestry and highest for those of African ancestry.[229] Average patients with Asian or indigenous American ancestry should initially be treated with approximately half the dose currently recommended by the US clozapine package insert. Until better information is available, the international guideline[34] recommends using the doses for patients of European ancestry for patients of Middle Eastern and Western Asian ancestry, as well. In a single-dose study, Menkes et al[230] recommended the same doses for patients of European and Maori ancestry (a subgroup among those of Oceanian ancestry). Recently an increase in fatal outcomes associated with clozapine-induced myocarditis has been described in Maori patients in New Zealand.[231]

These average dose recommendations for clozapine based on ancestry groups need to be updated as new data are published. An important caveat in these dose recommendations per ancestry group is that in each ancestry group there are PMs needing lower clozapine doses and those taking inducers other than smoking that may need higher clozapine doses. It follows that TDM is the best way to optimize clozapine at the individual level.

Supplementary Table S3, http://links.lww.com/JCP/A947,[35,232,233] provides the only other source besides the international guideline for guiding clozapine dosing according to ancestry: the studies from the TDM database of the United Kingdom (UK). Unfortunately, the first study[232] did not consider ancestry and recommended extremely high clozapine doses, probably due to ignoring nonadherence and basic pharmacokinetic issues. Two recent pharmacokinetic models using the same data but adjusting for ancestry provided very different recommendations for clozapine dosing.[35,233]

Update on Clozapine Pharmacokinetic DDIs

A series of DDI studies of clozapine[234–243] led to several reviews of pharmacokinetic and/or pharmacodynamic DDIs including clozapine.[155,157–162] Three recent systematic reviews have focused on clozapine DDIs with lithium,[163] antidepressants,[164] and antiseizure medications.[165]

Other clozapine articles provide DDI information on amiodarone,[244] caffeine,[153] Chinese herbal dangguilonghui tablets,[245] flupentixol,[246] isoniazid,[247] levomepromazine,[248] modafinil,[249] minocycline,[250] omeprazole,[251] oral contraceptives,[204,205] nifedipine,[252,253] pantoprazole,[254] perphenazine,[31,255] propranolol,[256] St John's wort,[257] and viloxazine.[132] On the other hand, cases described as possible inhibitory DDIs with ampicillin,[258] erythromycin,[259,260] or disulfiram[261] appeared to be explained by concomitant infections. An article[262] with 2 cases described decreases in clozapine levels after adding cariprazine, which is not known as an inducer; these cases might be explained by decreased clozapine adherence in nonsupervised outpatients.

All articles on clozapine DDIs are summarized and classified by effect size[263] in Supplementary Box S13, http://links.lww.com/JCP/A947, which may need to be updated as new information is published. Valproic acid has a special subsection because the literature has provided conflicting results indicating its potential for being an inhibitor, particularly during titration, and an inducer

during maintenance.[199,264–280] Valproic acid also has complex effects on olanzapine, a drug with metabolism similar to clozapine and also mainly metabolized by CYP1A2 and glucuronidation. In the only prospective study in the literature for clozapine or olanzapine, valproic acid appeared to have the potential to be both an inhibitor and an inducer of olanzapine varying with time, drug concentrations and individuals.[240] Supplementary Box S13, http://links.lww.com/JCP/A947, has an additional subsection on heavy coffee intake in nonsmokers,[218,281–283] cruciferous vegetables,[284] and gemfibrozil.[23,194,285–287]

Update on Clozapine Pharmacodynamic DDIs

Pharmacodynamic DDIs take place directly at the site of action of a drug or indirectly by interfering with another physiological mechanism. Such DDIs are not easy to study because they do not cause TDM changes. Pharmacodynamic DDIs are classified by pharmacologists as the following: 1) additive (ie, equal to the sum of the effects of the individual drugs), 2) synergistic (ie, the combined effects are greater than expected from the sum of individual effects), or 3) antagonistic (ie, the combined effects are less than additive). From the clinical perspective, they can be classified as having the following: 1) beneficial effects (increased efficacy and/or safety) or 2) harmful effects (decreased efficacy and/or safety).[161] Prior articles[156–158,161–165] were used to develop a comprehensive list of harmful pharmacodynamic DDIs for clozapine. Supplementary Box S14, http://links.lww.com/JCP/A947,[63,288,289] describes central pharmacodynamic DDIs. Currently, it is not well known how well norclozapine crosses the blood-brain barrier.[63] Supplementary Box S15, http://links.lww.com/JCP/A947, describes pharmacodynamic DDIs acting only in periphery and likely to involve both clozapine and norclozapine.[290–292]

Obesity May be Associated with Decreased Clozapine Clearance

Supplementary Box S16, http://links.lww.com/JCP/A947,[27,232,293–306] reports that obesity may decrease CYP1A2 activity and clozapine clearance and considers possible mechanisms. Clozapine PM status due to phenoconversion associated with obesity has been described in patients of Asian[218] and European ancestries.[111] The clinical relevance of obesity to decreased clozapine clearance is further supported by obesity being 1) associated with increased severity of toxicity and incidence of poor clinical outcomes in patients with acute clozapine poisoning[307] and 2) a risk factor for clozapine-induced fever[308] and myocarditis[309,310] during rapid titrations.

Inflammation can Reduce Clozapine Clearance

Supplementary Box S17, http://links.lww.com/JCP/A947, indicates that systemic infections and other inflammations leading to C-reactive protein (CRP) elevations can decrease CYP1A2 activity and increase clozapine concentrations in plasma/serum.[7,11,12,21,24,31,311–321]

Update on Clozapine PMs

Supplementary Box S18, http://links.lww.com/JCP/A947, reviews the limited information available on clozapine PMs.[224,321–326] The genetic clozapine PMs are possibly associated with rare CYP1A2 alleles not tested by US commercial tests.[326] Nongenetic clozapine PMs can be associated with obesity, inhibitor co-prescription or inflammation.[326]

Update on Clozapine UMs

Bender and Eap[327] published the first clozapine UM case. Supplementary Box S19, http://links.lww.com/JCP/A947, reviews information supporting the provisional concept of clozapine UM status during weak induction.[218,263,273,279,287,327–333] Many of these articles did not acknowledge that it is normal to be a clozapine UM when taking strong (rifampicin) or moderate inducers (carbamazepine, phenobarbital, or phenytoin) of clozapine metabolism. Nevertheless, it is very important to rule out nonadherence before making this diagnosis.[279]

Most of the cited articles proposed that clozapine UM status may be explained by currently unidentified high-activity CYP1A2 alleles.[326] CYP1A2 induction is regulated by the nuclear and aryl hydrocarbon receptors.[211] Genetic variants of these receptors may influence CYP1A2 metabolism.[333–335] Based on this concept, Schoretsanitis et al[279] proposed that clozapine UMs during weak induction are the following: 1) rare, 2) probably explained by genetic variants of the nuclear and aryl hydrocarbon receptors, and 3) require very high daily doses of clozapine to reach the minimum therapeutic concentration of 350 ng/mL during weak induction from smoking and/or valproate co-prescription. Caffeine is also mainly metabolized by CYP1A2 and similar subjects sensitive to induction through smoking and/or omeprazole have been described among patients with schizophrenia consuming high quantities of caffeine associated with heavy smoking and/or omeprazole treatment.[336]

Update on Clozapine Half-Life

Supplementary Box S20, http://links.lww.com/JCP/A947,[34,186,279,337] shows that the data provided in the package insert on clozapine half-life does not account for clozapine deposits in fat tissue. Moreover, half-life varies from clozapine PMs to UMs, as clozapine's half-life is determined by the clearance of clozapine in the individual. As an approximation, clozapine PMs probably have clozapine half-lives around 48 hours, whereas clozapine UMs during weak induction or when taking strong or moderate metabolic inducers may have half-lives of about 8 hours. Average clozapine metabolizers may have a half-life for clozapine of about 24 hours, which explains why many clinicians use single dosing with good results.[338] As a matter of fact, the Dutch guideline[339] and most US experts.[340–343] recommend single doses at evening/night, which is compatible with a half-life of approximately 24 hours[337] in patients with average clozapine metabolism.

Supplementary Box S21, http://links.lww.com/JCP/A947,[63,65,344–347] describes the limited published information suggesting that norclozapine probably has a 32% longer half-life than clozapine.

An important effect of clozapine's half-life in clinical practice is that clozapine is the second-generation antipsychotic most consistently associated with withdrawal symptoms. Supplementary Box S22, http://links.lww.com/JCP/A947, summarizes the literature on clozapine discontinuation and withdrawal symptoms.[4,36,60,348–354]

An Update on Monitoring Tools

This section provides updates on 1) TDM, 2) pharmacogenetic testing, and 3) CRP monitoring.

TDM in Clinical Practice

The US clozapine package insert does not specifically mention clozapine TDM. Supplementary Box S23, http://links.lww.com/JCP/A947, reviews the clozapine TDM literature including the following: 1) recommendations from the UK drug agency,[355] 2) recommendations from a US schizophrenia guideline,[356] 3) the clozapine therapeutic range in plasma/serum (350–600 ng/mL),[34,46–49,159,357–362] and 4) the relationship with ADRs.[68,69,363–370]

Supplementary Box S24, http://links.lww.com/JCP/A947, summarizes the practical aspects of clozapine TDM[70] for clinicians

including the definitions of the following: 1) minimum therapeutic dose,[279,371] 2) nonadherence,[111] 3) steady-state condition,[372] 4) trough condition,[48,373,374] 5) linear kinetics,[279,375] and 6) convenience of short turnaround.[376]

Pharmacogenetic Tests are Not Ready for Clinical Practice

Supplementary Box S25, http://links.lww.com/JCP/A947,[159,176,326,377–384] reports that there are no current clinical indications for pharmacogenetic testing in clozapine patients and that the recommendation from the US clozapine packages insert for lower clozapine doses in CYP2D6 PMs should be eliminated.

CRP

CRP is a nonspecific marker that can be elevated by clozapine-induced inflammation and/or concomitant infection.[321] There is need for further research of other more specific markers of clozapine-induced inflammation associated with rapid clozapine titrations, including interleukin-6 peak levels.[385]

The Australian protocol first proposed the use of CRP and troponin to diagnose clozapine-induced myocarditis,[386] though CRP can rise up to 5 days before troponin.[387] CRP also probably rises before clozapine-induced fever develops.[388,389] This is why the international clozapine guideline proposes weekly monitoring of CRP during the titration at the same time as WBC monitoring.[34] A recent systematic review supported monitoring CRP levels during the first 4–8 weeks of clozapine treatment.[390]

DISCUSSION

Box 1 summarizes the major problems with the pharmacological sections of the US clozapine PIs with emphasis on pharmacokinetics. These 9 problems include the following: 1) in vivo studies indicate that clozapine is dependent on CYP1A2 for its metabolism,[13,14] 2) CYP2D6 has a minor role in the metabolism of clozapine and the recommendation for lower clozapine doses in CYP2D6 PMs should be deleted,[159,379] 3) in nontoxic concentrations CYP3A4 has a minor role in the metabolism of clozapine and adding potent CYP3A4 inhibitors has had no clinically relevant effects on clozapine concentrations,[180–182] 4) the section on DDIs needs to be updated extensively to reflect currently available studies, 5) systemic inflammation may decrease clozapine metabolism and increase the risk for clozapine intoxications, 6) obesity may decrease clozapine metabolism, 7) patients of Asian and indigenous American ancestry need lower clozapine doses,[33,221,222,224] 8) personalized titration and CRP monitoring should be considered[34,227,228,308,388–390] until prospective studies are available, and 9) the half-life section needs to be modified to reflect that single dosing at night is frequently used and recommended by most US clozapine experts.[340–343] These changes will require collaboration among regulatory bodies, industry representatives and experts.

Need for Future Studies

There is great need of future studies on clozapine pharmacokinetics; for brevity, only 3 important topics regarding dosing in 3 groups of patients are discussed, those with mixed ancestry, CYP1A2 rare mutations and late pregnancy.

Clozapine Dosing in Patients with Mixed Ancestry

Currently there is very limited data on clozapine metabolism in patients with mixed ancestry but it is better to err on the side of safety.[391] For titration in cases of mixed ancestry, it is better to use the guidelines for the ancestry that is associated with the slowest titration. To that end, the titration for Asians/indigenous Americans is the safest titration for all patients independent of their ancestry. For dose maintenance in cases of mixed ancestry, in the absence of TDM, the prescriber should monitor side effects to decide upon the clozapine dosage as long as it also is an efficacious dose. For example, for a nonsmoking female of mixed European and indigenous American ancestry, the prescriber could consider 150 mg/day for Asian/indigenous American ancestry or 250 mg/day for European ancestry. The clozapine should be titrated to the lower dose of the 2 ancestries: 150 mg/day. If there is no response but adherence is verified by supervision of the clozapine intake, before defining a lack of response, it may be a good idea, if tolerated, to slowly try to reach 250 mg/day, the dose for the same subgroup within Europeans. Some patients with indigenous American ancestry and a high percentage of DNA from European ancestors may metabolize clozapine similarly to patients of European descent.[392]

The Role of CYP1A2 Rare Mutations on Clozapine Dosing

The literature described a rare mutation CYP1A2*6 that may impair clozapine metabolism in approximately 1% of clozapine-treated patients of European ancestry,[323] but had never been studied before. A recent Finnish study genotyped 2569 clozapine-treated patients and found 11 with a single copy of this mutation (CYP1A2 1A/*6), providing a frequency <1% (0.43% 2569).[393] The article stated that 5 (46% of 11) developed pneumonia during a 25-year follow-up. More studies are needed of the clinical relevance of this rare mutation found in patients of European ancestry and in the rare mutations that may impair clozapine metabolism in Asians (CYP1A2*8, CYP1A2*11, CYP1A2*15 and CYP1A2*16[324,325]).

Clozapine Dosing During Pregnancy

Studies using markers of CYP1A2 activity, such as caffeine, indicate that CYP1A2 activity decreases remarkably during the second and third trimester of pregnancy due to the increase of estrogens, which are CYP1A2 inhibitors.[394] Aoki et al[395] have published the first longitudinal clozapine TDM study of a clozapine-treated patient during pregnancy. The patient had increases in the third trimester and after delivery the neonate had high clozapine and norclozapine serum concentrations. An emergency cesarean section was needed after decreased variability in the fetal heart rate was observed. Longitudinal TDM studies during pregnancy are required as decreases in clozapine dosing guided by clozapine TDM may be required during the second and third trimesters of pregnancy. Clozapine has a high a penetration ratio into breast milk,[396] so prospective TDM studies in lactating mothers and their babies are needed.

CONCLUSIONS

Part I of this review article focuses on the changes needed in the pharmacokinetic section of the package insert to improve clozapine safety. Part II[397] focuses on the major changes needed in the boxed warnings (previously called black box warnings). A revised US clozapine package insert should increase safety for patients taking clozapine, both inside as well as outside the US. Regulatory drug agencies often later adopt or build upon the FDA's decisions.[398] Moreover, the FDA led the resurrection of clozapine use worldwide by requiring an RCT in TRS.[9] Therefore, the proposed changes in the US clozapine package insert to enhance patient safety as proposed in this article may lead to subsequent changes in clozapine package inserts around the world.

The revisions proposed are important because the safety of clozapine needs improvement globally. Pharmacovigilance is

centralized in the international database, VigiBase.[399] According to the report to this database, clozapine pharmacovigilance is severely underdeveloped in countries including the following: 1) Continental Western Europe,[400] 2) Eastern Europe,[401] and 3) Latin America.[402] China[403] and Russia[404] had relatively high clozapine use. China submitted only a small number of reports on clozapine ADRs to VigiBase and Russia submitted none.[401] Clozapine pharmacovigilance is practically nonexistent in other countries including those of the Middle East,[405] Sub-Saharan Africa,[406] and most Asian countries.[406,407] This is Part I of an article by 40 authors proposing changes in the sections on basic pharmacology of the US package insert and these proposed changes are also supported by 123 other clozapine experts outside of the US who are from 44 countries/regions (Supplementary Table S4, http://links.lww.com/JCP/A947).

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