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EDITORIAL

Promoting safer clozapine dosing in the Americas

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A recently published international clozapine guideline[1] that proposed dosing variations based on ancestry groups may be helpful for clozapine prescribers in the Americas. There are five major DNA ancestry groups: sub-Saharan Africans, Europeans (including Western Asians), Asians (ranging from Pakistan to Japan), indigenous Americans, and Oceanians.[2] Indigenous Americans (called Native Americans or First Nations) are descended from East Asians.[2] Clozapine is mainly metabolized by cytochrome P450 1A2 (CYP1A2),[3] and for unknown reasons CYP1A2 activity follows three major ancestry-based levels: it is lowest in Asians and Indigenous Americans, intermediate in Europeans, and highest in Africans.[1]

In each of these three ancestry groups, non-smoking females have the lowest ability to metabolize clozapine, while male smokers have the highest. Moreover, some individuals, called CYP1A2 poor metabolizers (PMs), appear to have little CYP1A2 activity. Some cases of CYP1A2 PM status can be explained by CYP1A2 mutations, although they are relatively rare ($< 10\%$) and cannot be identified by currently available commercial pharmacogenetic tests.[4] More frequently, environmental or personal variables decrease CYP1A2 activity and explain CYP1A2 PM status. Clozapine PMs have approximately half the CYP1A2 activity of normal metabolizers and require only half the dose to achieve the same serum levels (Table 1).

CYP1A2 inhibitors can transform normal metabolizers into clozapine PMs. Fluvoxamine is an extremely potent inhibitor of clozapine metabolism and can decrease CYP1A2 activity to 1/5 or 1/10. It should not be prescribed without access to plasma clozapine levels.[3] Moderate inhibitors, oral contraceptives, and high doses of caffeine require halving the clozapine dose (Table 1).

Clozapine, which is lipophilic, is deposited in fat tissue. Increasing from a normal to an obese body mass index ($\geqslant$ 30 mg/kg^2) requires roughly halving the clozapine dose.[3] Any systemic inflammation (whether associated with infection or not) releases cytokines and increases C-reactive protein levels; this is associated with CYP1A2 inhibition and, potentially, clozapine intoxication.[5]

Smoking is a mild CYP1A2 inducer, as is omeprazole, so its effect may not be relevant among those who smoke $\geqslant$ one pack/day (or 20 cigarettes/day), given that heavy smokers are usually maximally induced. In non-smokers, omeprazole co-prescription causes a roughly equivalent induction to that of smoking. Some potent inducers, including rifampicin, carbamazepine, phenobarbital or phenytoin, should not be taken with clozapine when clozapine levels cannot be accessed. For maintenance dosing, valproate should generally be considered a mild inducer, since after several weeks it induces metabolism of the main clozapine metabolite, norclozapine. For titration, valproate should be considered an inhibitor of the parent compound, clozapine.

Readers confused by this brief description of clozapine's pharmacokinetic complexity may consider reading an open-access review of the subject.[2] A plasma concentration of 350 ng/ml is considered the minimum therapeutic concentration. Table 1 represents the dosages required to reach this concentration in inpatients with schizophrenia according to three parameters: 1) DNA ancestry group, 2) sex-smoking subgroup, and 3) clozapine PM status. The plasma concentration should be measured in trough and steady-state conditions. The trough condition refers to the lowest point of plasma concentration during a day. Clozapine is usually taken once or twice a day. Thus, early morning blood collection prior to taking the drug is considered the trough concentration. The steady-state concentration is when equilibrium between absorption and elimination has been reached, which usually requires five half-lives of the drug. Assuming a half-life of 24 hours, most clozapine patients reach a steady state 5 days after consistently taking an increased

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Table 1 Based on current data from pharmacokinetics studies on ancestry, sex-smoking[†] status, and poor metabolizer status, this is a list of approximate clozapine maintenance doses (350 ng/mL) for patients with schizophrenia in the Americas

Approximate daily dose	Asians/Indigenous Americans	Europeans	African Americans (U.S. extrapolation)[‡]
75-100	PM ♀		
100	PM ♂	PM ♀	
150	PM ♂ and ♀🚬	PM ♂	PM ♀
175	♀	PM ♀🚬	
200		PM ♂🚬	PM ♂
225	♂		
250		♀	PM ♀🚬
275	♀🚬	♂	
300	♂🚬		♀/ PM ♂🚬
350			
375		♀🚬	
400		♂🚬	♂
500			♀🚬
600			♂🚬

Patients of mixed ancestry

- No studies have addressed this question. Common sense and erring on the side of safety are recommended.
- For titration, the ancestry associated with the slowest titration is best. Thus, that of Asians/Indigenous Americans is the safest for all patients, independent of ancestry.
- It should be pointed out that most of clozapine's acute side effects occur during maintenance treatment. Sedation, hypersalivation, constipation, and seizures are dose-related or, more accurately, concentration-related. When levels cannot be determined, use side effects to decide clozapine dosage, as long as the dose remains efficacious. The doses in this table are ideal target doses and must be considered in the context of side effects; there is no way to predict who is a genetic PM without determining clozapine levels, although clozapine PMs usually cannot tolerate the ideal target doses for the sex-smoking subgroup in each ancestry group.
- To rule out a lack of response in the absence of side effects and after having reached the therapeutic dose for the patient's ancestry group, it is important to involve the patient's family to determine adherence. If the family verifies daily adherence and levels cannot be accessed, as long as there are no side effects it may be a good idea to consider slowly increasing the dose until the highest possible dose for patients of mixed ancestry. For example, a non-smoking ♀ of mixed European and Indigenous American ancestry will have competing maximum doses: 150 mg/day as an Asian/Indigenous American vs. 250 mg/day as a European. Thus, clozapine should be titrated to the lower dose: 150 mg/day. However, before concluding that the patient has had no response, it may be a good idea, if the patient can tolerate it, to slowly increase the dose to 250 mg/day.

PM = poor metabolizer status, which can be associated with obesity, co-prescription of oral contraceptives, high caffeine intake[§] and, rarely ($\leqslant$ 10%), unknown genetic mutations; U.S. = United States.
🚬 = smoking; lack of this symbol indicates non-smokers.
[†] Heavy smoking can be associated with substantial variability in plasma clozapine concentrations, which might be explained by induction changes; thus this table tends to recommend slightly higher doses for ♂ smokers than the mean concentrations found in the literature.[1] Occasionally ♂ heavy smokers, particularly those on valproate, need higher doses than those found in this table. Testing the plasma clozapine level is the best method for determining therapeutic doses in ♂ heavy smokers.
[‡] Since virtually no data has been published about clozapine plasma concentrations in sub-Saharan Africans, data from African Americans has been substituted.
[§] Caffeine is present in coffee, tea, and other beverages. A detailed list of estimated caffeine content in U.S. beverages is provided here:https://www.caffeineinformer.com/the-caffeine-database. No data have been published on clinically relevant quantities of caffeine. Until prospective studies are available, we recommend caution regarding changes in daily caffeine intake $>$ one cup of coffee (or two cans of caffeinated soda) in non-smokers and $>$three cups of coffee (or six cans of caffeinated soda) in smokers. For example, when a smoker who is taking clozapine increases caffeine intake by three cups of coffee (e.g., from two to five cups per day), clinicians should watch for increased side effects due to m plasma clozapine concentration.

dose. To correctly interpret a trough and steady-state plasma concentration collected in the early morning, one is assuming that the patient has consistently taken the same dose for at least the five previous days and that no dose has yet been taken that morning.

Table 1 provides rough estimates of the typical clozapine dosages required to reach a therapeutic concentration during maintenance treatment based on our current limited knowledge, which could require updating in the future. The best way to personalize dosing is to measure the patient's plasma concentration in trough and steady-state concentrations. Clozapine is a relatively toxic drug with a narrow therapeutic range for schizophrenia (350-600 ng/mL).[3]

The six titrations recommended in the guideline cannot be explained in this brief editorial.[1] One important clinical innovation is the recommendation to measure CRP levels with weekly white blood cell counts at baseline and during the first 4 weeks of titration. Titration that is too rapid for a specific patient's clozapine metabolism can cause clozapine-induced inflammation, which leads to elevated C-reactive protein levels. This can lead to a release of cytokines, which inhibit clozapine metabolism and create a positive feedback loop, which can result in myocarditis and/or aspiration pneumonia.

This editorial proposes a novel clozapine dosing system that is valid worldwide and has not been described in textbooks or package inserts. It is based on 30 years of clinical and research activities. Unfortunately, since clozapine is a generic drug in most countries, it is not supported by large pharmaceutical companies and no funding has been provided for large multicenter studies to prospectively test these titrations. Before dismissing this editorial, readers should consider that 103 co-authors (including clozapine experts and prescribers) from 50 countries/regions support these six personalized titrations[1] and that the

published review[2] which preceded the guideline comprehensively reviewed 257 references in the literature.

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