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Box 1

Editorial:

## **An international clozapine titration guideline to increase its safety and move forward on the route started by German-speaking psychiatrists in the 1960s**

Running title: clozapine guideline

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**Key words:** Asian continental ancestry group; clozapine/administration and dosage; clozapine/adverse effects; clozapine/blood; clozapine/metabolism; clozapine/therapeutic use; clozapine/toxicity; COVID-19; CYP1A2; drug labeling; European continental ancestry group; infection; inflammation; mortality/drug effects; Native American continental ancestry group; sex; smoking.

Clozapine is the most efficacious antipsychotic for treatment-resistant schizophrenia (TRS) [1] and when patients respond, clozapine should not be discontinued [2], unless continuation poses a risk to the patient. Leucht et al. [3] argued that first-generation antipsychotics [FGAs] were not well studied and should be reconsidered. Clozapine was developed in the FGA era and although its efficacy is well-understood, its pharmacokinetics and safety are understudied [4]. A recent international guideline proposed that clozapine metabolism can be measured by the dose needed to reach the minimum therapeutic range of the plasma concentration of 350 ng/ml. As clozapine metabolism is influenced by: 1) ancestry groups, 2) sex-smoking subgroups, and 3) presence/absence of poor metabolizer (PM) status based on genetic status, personal variables (e.g., obesity) or environmental variables (e.g., oral contraceptives), these 3 levels of variables determine maintenance dose and titration speed [5].

Sixty years after its synthesis, clozapine safety can still be improved beyond the white blood cell (WBC) monitoring. A review of Food and Drug Administration (FDA) data from 1998-2005 found clozapine was associated with 3,277 deaths or serious non-fatal outcomes, making it the third most toxic US drug, following only oxycodone and fentanyl [6]. To this day, the FDA mostly focuses on deaths from clozapine-induced agranulocytosis. A 2019 review of the World Health Organization database [7], which includes reports from drug agencies worldwide, paints a different picture with 550 deaths from 34,931 reports of agranulocytosis providing a relative lethality of 1.6%. These 550 deaths include those prior to the implementation of WBC monitoring. Two other causes of death were more concerning: 1) myocarditis with 539 deaths and relative lethality of 11.7% (539/4586) and 2) pneumonia with 2077 deaths and relative lethality of 29.7% (2077/6983). To prevent myocarditis and aspiration pneumonia during clozapine titration, the international titration guideline uses 1) 6 personalized titrations and 2) weekly C-reactive protein (CRP) measures [5]. Pneumonia occurring during clozapine maintenance may be frequent [8] but clozapine may only contribute 1/3 of the risk while TRS may contribute 2/3 [9]

As the history of clozapine marketing is known [10], this editorial retells the story in the context of how drugs are developed. Since 1996, the FDA has required extensive studies on the safety and

pharmacokinetics of new drugs. These studies were not conducted for clozapine. Clozapine development can be simplified into 8 periods: 1) synthesis and early clinical use by German-speaking psychiatrists, including a group led by Hippus; 2) the poorly-understood clozapine-induced fever; 3) the almost deadly blow of agranulocytosis, 4) the resurrection of clozapine by the US multicenter study, 4) studies on clozapine pharmacokinetics, 5) the emergence of clozapine-induced myocarditis, 6) the pesky issue of Asian dosing, 7) the existence of clozapine PMs, and 8) the realization of the lethality of pneumonia just in time to precede the COVID-19 pandemic.

In 1958, Wander Pharmaceutical Company produced clozapine, which was given to a few clinicians without success; however, some investigators from Germany, Austria and Switzerland found clozapine efficacious. Sandoz took over the drug in 1967 and marketed it as Leponex; it reached West Germany in 1974. Hippus observed that clozapine was efficacious but produced no extrapyramidal symptoms; this contradicted the dogma of the time [10].

In 1972, clozapine-induced fever in the absence of any concomitant infection was mentioned in a German article and German-speaking psychiatrists described: 1) an approximate prevalence of 5%, 2) occurring between the 5<sup>th</sup> and 20<sup>th</sup> days after initiation, and 3) frequently associated with increased erythrocyte sedimentation rate (ESR). Contemporary knowledge reveals that fever is part of the syndrome of clozapine-induced inflammation which develops when the titration is too fast for the metabolism of that specific patient [4,5]. When clozapine was later introduced in the US, a 5% rate of benign hyperthermia was considered normal during clozapine titration and was believed to spontaneously resolve, but in severe cases stopping and restarting would be required [4].

After a promising start, 1974 almost completely derailed clozapine's trajectory. The first study of clinical use in the US was published and US Sandoz initiated the first studies oriented toward FDA approval in the US. Then cases of agranulocytosis were reported in Finland. Published in 1975 in *Lancet*, they included 18 cases with 9 deaths. All US studies were stopped, but a few clinicians kept its

compassionate use for a few patients. German-speaking psychiatrists, including the group led by Hippus, kept clozapine barely alive in Central Europe [10].

In 1982, Sandoz planned to gain FDA approval by focusing on patients with TRS. The randomized study under double-blind conditions, which used chlorpromazine as a control: 1) started in 1984 at 16 US sites, 2) was extremely successful, and 3) was published in 1988. The FDA approved clozapine in September of 1989 requiring WBC monitoring under a complex system that after many years continues to make prescription cumbersome. Clozapine expanded to other Western countries, while China and Russia had continued using it frequently.

The FDA required almost no pharmacokinetic studies in 1989. In 1994, Swedish researchers described: 1) cytochrome P450 1A2 (CYP1A2) as the main metabolic pathway leading to norclozapine and 2) fluvoxamine as an extremely powerful inhibitor while carbamazepine was a powerful inducer [5]. Tobacco smoking is a CYP1A2 inducer while estrogens are inhibitors, so CYP1A2 activity is influenced by sex-smoking subgroups; female non-smokers had the lowest activity and male smokers the highest. Later, oral contraceptives and high use of caffeinated beverages were identified as inhibitors. Valproate has a mixed profile; with sufficient time for induction valproate tends to be an inducer of noreclozapine. Early in a clozapine and/or valproate titration, valproate inhibits clozapine metabolism and increases clozapine levels. Obesity decreases CYP1A2 activity and clozapine metabolism. Any systemic inflammation, including infections, with CRP elevations releases cytokines that can inhibit CYP1A2 and clozapine metabolism [5].

In 1980, Danish researchers published the first case of clozapine-associated myocarditis, where clozapine was started at 300 mg/day (“a rapid titration by a doctor”). The first case of a voluntary overdose (“rapid titration by a patient”) described eosinophilic myocarditis, a sign of drug hypersensitivity. The drug agencies paid attention to a 1999 *Lancet* article describing 23 cases from the Australian drug registry, but ignored the comment by Canadians describing how the Australian rapid titrations were considerably faster than Canadian titrations [4]. Two irreconcilable tales of clozapine-

induced myocarditis emerged. The Dutch and Danish, who use very slow outpatient titration, saw much fewer cases of myocarditis. The Australians continued to titrate patients aggressively and in 2012 reported that even more aggressive titrations and valproate were risk factors for myocarditis. Then they proposed a 3% incidence and “that a similar incidence would be found in other jurisdictions, if a practice of routine monitoring for myocarditis was adopted”. Thus a 3% incidence of clozapine-induced myocarditis became accepted as the expected rate of myocarditis in some hospitals in Canada, the US and Japan. Based on US data and titration practice, Japan’s drug agency approved clozapine, leading to 3% myocarditis and >30% clozapine-induced fever [5].

In Taiwan and Singapore in 1997, studies of Chinese patients treated with half the clozapine dosage had concentrations similar to Caucasians. This was ignored in the West, but Chinese and Indian psychiatrists rarely prescribe more than 300 mg/day of clozapine. US textbooks and the package insert recommend 300-600 mg/day. In 2019, a systematic review of clozapine levels indicates that 223 mg/day was the average dose for reaching the minimum therapeutic concentration of 350 ng/ml in East Asians, and 327 mg/day in Caucasians. Studies using stratification by sex-smoking subgroups demonstrated that all Asians and their descendants, the Native Americans, needed lower clozapine doses. The international clozapine guideline proposes maintenance doses ranging from 175 mg/day (for female non-smokers) to 300 mg/day (for male smokers) for Asians and Native Americans and between 250-400 mg/day for Europeans.<sup>5</sup>

Clozapine PMs need approximately half the dosage when compared to their ancestry group and sex-smoking subgroup. In 2003, a genetic PM was described in France who only needed 81 mg/day of clozapine to reach 350 ng/ml. In 573 Asian patients from 5 samples combined, clozapine PM prevalences included around 2% due to co-prescription of inhibitors, 2% due to inflammation, 1% due to obesity, and 7% without evident cause and with potential genetic explanation [4]. The proposed clozapine maintenance doses for European clozapine PMs are 100 to 200 mg/day [5].

Box 1 presents a summary of the association between clozapine and pneumonia and provides recommendations for COVID-19 infections.

In conclusion, aspects of clozapine safety have been overlooked as it was initially examined in the FGA era. The authors hope that readers consider reviewing the freely available titration guideline [5] and the review article that summarizes the pharmacokinetic details [4]. It is our hope that this will contribute to more safe and effective utilization of clozapine.



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In the last 3 years, GS has served as a consultant for HLS Therapeutics; JMK has been a consultant and/or advisor to or has received honoraria from Alkermes, Allergan, Boehringer Ingelheim, Bristol-Myers Squibb, Dainippon Sumitomo, IntraCellular Therapies, Janssen, Lundbeck, Merck, Minerva, Neurocrine, Otsuka, Pierre Fabre, Reviva, Roche, Saladex, Sunovion, Takeda and Teva. He is a shareholder of LB Pharma, and The Vanguard Research Group; and CUC has been a consultant and/or advisor to or has received honoraria from: AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Axsome, Cardio Diagnostics, Compass, Damitsa, Gedeon Richter, Hikma, IntraCellular Therapies, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Medscape, Merck, Mitsubishi Tanabe Pharma, Mindpax, Mylan, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Relmada, Reviva, Rovi, Seqirus, Servier, SK Life Science, Sumitomo Dainippon, Sunovion, Supernus, Takeda, Teva, and Viatrix. He provided expert testimony for Janssen and Otsuka. He served on Data Safety Monitoring Boards for Lundbeck, Rovi, Supernus, and Teva. He has received grant support from Janssen and Takeda. He received royalties from UpToDate and is also a stock option holder of Cardio Diagnostics, LB Pharma and Mindpax. In the last 3 years, C-JR, CDIC and JdL report no conflicts of interest.

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**Box 1. The association between clozapine and pneumonia**

<b>Pneumonia and CYP1A2 drugs before clozapine</b>
<ul style="list-style-type: none"> <li>• Since the 1970s it has been known that respiratory infections with fever increased theophylline half-life and concentration, so its package insert recommends cutting the dosage in half and monitoring levels.</li> <li>• In the 1990s, it became obvious that this was mediated by the release of cytokines which inhibits CYP1A2, the main metabolic pathway of theophylline.</li> </ul>
<b>Pneumonia is described in clozapine patients</b>
<ul style="list-style-type: none"> <li>• Thus, in 2002, a patient treated by the first author developed clozapine intoxication during a severe upper respiratory infection; the author decreased the clozapine dosage in this patient.</li> <li>• In 2019, he proposed during co-occurring infections and inflammation that clozapine may produce higher morbidity and mortality than was believed.</li> <li>• In a large clozapine cohort of 131 Chinese inpatients, inflammation/infection was present during 2% of days (482/24,789) including 18 different episodes in 16 patients. The episodes were associated with: <ul style="list-style-type: none"> <li>○ no clinically relevant effects in 11% of infection episodes (no leukocytosis or ↑ CRP),</li> <li>○ ↓ clozapine D to 1/2 would be advisable in 61% of the infection episodes, and</li> <li>○ ↓ clozapine D to 1/3 would be advisable in 28% of infection episodes.</li> </ul> </li> </ul>
<b>Pneumonia may be the most important cause of death in clozapine patients</b>
<ul style="list-style-type: none"> <li>• Unfortunately, the WHO pharmacovigilance database demonstrates that the situation is much worse than suspected; pneumonia deaths in clozapine: <ul style="list-style-type: none"> <li>○ are reported 10 times more than in other antipsychotics</li> <li>○ are 4 times more frequent than those of agranulocytosis or myocarditis</li> </ul> </li> <li>• A study in the Danish registry published in 2020 indicates that: <ul style="list-style-type: none"> <li>○ 1/3 of pneumonia risk is due to clozapine</li> <li>○ 2/3 is due to TRS.</li> </ul> </li> </ul>
<b>COVID-19 pneumonia and clozapine</b>
<ul style="list-style-type: none"> <li>• Clozapine intoxications during COVID-19 infections have been described and may contribute to lethality.</li> <li>• Based on data on pneumonia and other severe infections: <ul style="list-style-type: none"> <li>○ Patients should be warned about the risk of COVID-19 infections that include fever and severe symptoms, and they should be told to call their psychiatrists.</li> <li>○ If a COVID-19 infection is present and CRP is ↑, consider halving the clozapine dose to avoid a clozapine intoxication.</li> <li>○ If a patient is hospitalized, we recommend that the internist use clozapine levels to control dosing, since the dosage may not be cut more than ½ to 1/3, or in case of doubt stop clozapine until the infection is over.</li> </ul> </li> <li>• Once CRP is back to normal or if CRP levels are not available, 1 week after cessation of fever, the patient can go back to the prior clozapine maintenance dosage: <ul style="list-style-type: none"> <li>○ If the clozapine maintenance dose has been halved, increase to the prior maintenance dose in 1-2 steps while monitoring for tolerance.</li> <li>○ If the clozapine maintenance dose has been cut to 1/3, increase to the prior maintenance dose in 2-3 steps while monitoring for tolerance.</li> <li>○ If clozapine has been stopped, the approach may be determined by the characteristics of the individual, the prior dose and the stability of the psychosis. Access to clozapine levels facilitates its re-initiation; since if concentrations are detectable, it means some clozapine remains in the body and a faster titration could be used. Some countries have specific rules about clozapine re-initiation.</li> </ul> </li> </ul>

CRP = C-reactive protein, CYP1A2 = cytochrome P450 1A2, D = dose, TRS = treatment-resistant schizophrenia, WHO = World Health Organization