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REFLECTIONS ON THE COMPLEX HISTORY OF THE CONCEPT OF CLOZAPINE-INDUCED INFLAMMATION DURING TITRATION

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SUMMARY

Clozapine was synthesized in 1958. The Food and Drug Administration approved it in 1989 when comprehensive pharmacokinetic studies were not required and it was not known that clozapine was metabolized by the cytochrome P450 1A2 (CYP1A2). Currently it is known that clozapine personalized dosing may be influenced by one's DNA ancestry (African, European and/or Asian/Indigenous American), sex/smoking subgroup, and the presence/absence of genetic/non-genetic poor metabolizer (PM) status. The literature does not properly reflect the concept of "clozapine-induced inflammation" during rapid titration. Elaborating upon this concept, this historical review discusses: 1) clozapine-induced fever, 2) the effects of inflammation on clozapine metabolism, 3) clozapine-induced myocarditis, 4) other clozapine-induced inflammations, 4) current support for "clozapine-induced inflammation" as a hypersensitivity reaction, 5) the difficulty in addressing such a concept to a readership with diverse beliefs about it and 6) the limitations of this review in convincing skeptics. Clozapine-induced fever in the absence of any concomitant infection was first described in 1972 and is a mild form of "clozapine-induced inflammation" during rapid titration, which also includes myocarditis and other localized inflammations. They may be part of a hypersensitivity reaction that has 3 phases. In the first phase, the titration is too fast for a specific patient; either the psychiatrist was too aggressive in titrating, and/or the patient is a clozapine PM. This situation leads to a release of cytokines. In the second phase, a positive feedback loop develops; the cytokines inhibit CYP1A2, which further increases plasma clozapine concentrations. In the third phase, if the titration continues, the inflammation becomes complicated by the development of an auto-immune phenomenon leading to localized inflammation. Skeptical readers are challenged to try: 1) 6 titrations proposed for stratified dosing and 2) c-reactive protein (CRP) monitoring for personalized dosing in the absence of genetic testing for clozapine PM status.

Key words: *clozapine/adverse effects - clozapine/metabolism - mortality/drug effects - myocarditis/chemically induced - myocarditis/etiology*

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INTRODUCTION

Evidence-based medicine (EBM) and clozapine

The so-called EBM approach appears to be the dominant philosophy in medicine but it has not been successful in dealing with adverse drug reactions (ADRs) (Vandenbroucke 2004, 2008).

One of the basic assumptions of EBM is that conducting randomized clinical trials (RCTs) preceding a drug's introduction to the market is the best method of obtaining knowledge of that drug. This does not adequately account for a pharmaceutical company's marketing interest in directing drug approval research toward providing an average dose for an ideal average patient. This approach does not fit the experience of most physicians who, as soon they start practicing, observe that some patients need a lower or higher dose to respond. This is reflected in all pharmacogenetic research (Meyer 2004) and has led to the concepts of the poor metabolizer (PM) who tends to have ADRs with average doses, and the ultrarapid metabolizer (UM) who needs high doses for efficacy. These concepts were initially developed for genetic PMs and UMs, but later it was found that personal and environmental variables including drug-drug interactions (DDIs) can have similar effects (e.g., co-prescription of inhibitors can lead to non-genetic PMs and co-prescription of inducers to non-genetic UMs; de Leon 2009). The presence of PMs and UMs complicate those EBM approaches that defend the use of an average dose for all patients (de Leon 2012), which is a major problem in clozapine prescription and requires stratified, personalized dosing (de Leon 2022a).

The EBM approach is particularly problematic when using old drugs introduced after limited study, particularly before RCTs were needed or before pharmacokinetic researchers were required to study the pharmacokinetic variables associated with the existence of PMs and UMs. Clozapine is one such old drug since its marketing has taken place across more than 40 years, starting in the era of the so-called first-generation antipsychotics and extending to the era of the second-generation antipsychotics (SGAs) (de Leon et al. 2022a). Clozapine was not studied in the manner that new antipsychotics are currently studied.

Clozapine history

Clozapine was synthesized in 1958 and was given to several clinicians who found it toxic. It was marketed in German-speaking countries after some small RCTs

through the efforts of a group of clinicians led by Hippius (Crilly 2007, de Leon et al. 2022a). In 1975, after the description of clozapine-induced myocarditis in Finland (Idänpään-Heikk et al. 1975), it was kept alive by these German-speaking psychiatrists (de Leon et al. 2022a). Sandoz took the risk of studying it in the United States (US) for treatment-refractory schizophrenia (TRS) and, fortunately, the comparison RCT against chlorpromazine resulted in major success (Kane et al. 1988). In 1989, clozapine was approved for TRS by the US Food and Drug Administration (FDA) with doses recommended between 300-600 mg/day and up to 900 mg/day. Then clozapine was disseminated to other countries. In 1989, comprehensive pharmacokinetic studies were not required and knowledge of how to complete them was unavailable (de Leon et al. 2022a).

Clozapine pharmacokinetics

In 1994, Swedish researchers from the Karolinska Institute found that clozapine is mainly metabolized by the cytochrome P450 1A2 (CYP1A2) (Bertilsson et al. 1994) and that inducers, such as carbamazepine, or inhibitors, such as fluvoxamine (Jerling et al. 1994), need to be considered in clozapine dosing. Currently, it is evident that co-medications influence clozapine personalized dosing from high to low: 1) potent inducers, such as rifampicin, 2) potent to moderate inducers, such as carbamazepine or phenytoin, 3) mild inducers, such as omeprazole, 4) moderate inhibitors, such as oral contraceptives or high intake of caffeine and 5) potent inhibitors, such as fluvoxamine (de Leon 2022a).

As tobacco smoking is a mild inducer of CYP1A2 and estrogens are moderate CYP1A2 inhibitors, in the absence of other inducers/inhibitors, clozapine personalized dosing goes from high to low: 1) male smokers, 2) female smokers, 3) male non-smokers and 4) female non-smokers (de Leon et al. 2020a).

The original studies of clozapine metabolism were conducted on patients of European DNA ancestry but the people of Asian ancestry (defined as those whose origins range from Pakistan to Japan) have lower CYP1A2 activity and need lower clozapine doses (de Leon et al. 2020b). This label of Asian ancestry is not a geographical label, but follows DNA ancestry history. Therefore, the original habitants of the Americas, or Indigenous Americans, are descendants of East Asians, and behave like Asians for clozapine dosing. Thus, regarding the influence of DNA ancestry and clozapine, dosing may go from high to low in patients with ancestry from: 1) Africa, 2) Europe and 3) Asia and the original American inhabitants, but the data on African ancestry is very limited (de Leon et al. 2022b).

In patients of European ancestry, a genetic clozapine PM was described in 2003 (Allorge et al. 2003) and a UM in 1998 (Bender & Eap 1998). There is general agreement in the literature that a plasma clozapine concentration of 350 ng/ml (Hiemke et al. 2018) is the minimum therapeutic concentration required for therapeutic response and this can be used to calculate the minimum therapeutic dose of clozapine in various patients. The first European PM described had a minimum therapeutic dose of 81 mg/day while the UM needed 2059 mg/day (Ruan & de Leon 2020). Although genetic clozapine PMs and UMs are associated with relatively rare genetic mutations, they are likely to exist in other DNA ancestry groups besides Europeans. With the limited information currently available, genetic PMs are probably <10% across all DNA ancestry groups while genetic UMs are probably <1% (Ruan & de Leon 2020).

CYP1A2 activity varies across: 1) 3 DNA ancestry groups, 2) 4 sex/smoking subgroups, and 3) presence or absence of co-prescribed inducers or inhibitors. Obesity and inflammation can also lead to clozapine PM status when compared with their sex/smoking subgroup. Clozapine binds to fat tissue and that leads to decreased clozapine metabolism (Diaz et al. 2018), while the cytokines released during inflammation inhibit CYP1A2.

The complexity of CYP1A2 activity indicates there is no single best average clozapine dose for all patients despite those who support using the EBM approach (Subramanian et al. 2017). At least 6 major subgroups are required from 3 ancestry groups classified as PMs or non-PMs. To be more precise, in each of these 6 major subgroups, the dose ranges from the highest in male smokers to the lowest in female non-smokers (de Leon et al. 2022b). If this complex picture is true, other CYP1A2 drugs may also be governed by similar heterogeneity in personalized dosing. Olanzapine is mainly metabolized by CYP1A2 and although these details were not studied when olanzapine was marketed, olanzapine personalized dosing may also be influenced by the 3 DNA ancestry groups, 4 sex/smoking subgroups and the presence or absence of genetic or non-genetic PMs (Zang et al. 2021). It is likely that on rare occasions potent inducers or genetic mutations may also explain olanzapine UMs. As olanzapine is less toxic than clozapine, olanzapine personalized dosing may be less relevant than clozapine personalized dosing. Furthermore, there is a difference between clozapine and olanzapine not explained by CYP1A2 activity (de Leon 2022a). Rapid titration of clozapine can lead to what is called in this article clozapine-induced inflammation. Olanzapine does not appear to be prone to that (De las Cuevas et al. 2021).

Clozapine-induced inflammation

Unfortunately, the literature does not properly reflect the concept of "clozapine-induced inflammation" during rapid titration. A PubMed search on May 1, 2022, provided no article with "clozapine-induced inflammation" in the title or the abstract. The only article that may be close to discussing this concept is an article by a Danish group in which the first author was an expert in immunology (Røge et al. 2012). They reviewed the literature in order to describe possible clozapine “pro-inflammatory” activity during early titration. They did not comment on the role of rapid clozapine titration.

In the absence of articles, it is not possible to conduct a systematic review of "clozapine-induced inflammation". This article proposes to review the chronological history of related concepts since several of the concepts used should be included under the concept of "clozapine-induced inflammation." This historical review successively discusses: 1) clozapine-induced fever, 2) the effects of inflammation on clozapine metabolism, 3) clozapine-induced myocarditis, 4) other clozapine-induced inflammations, 4) current information supporting the idea that "clozapine-induced inflammation" is a hypersensitivity reaction, 5) the difficulty in presenting such a concept to a readership with diverse beliefs on the topic and 6) the limitations of this review in convincing a resistant readership.

CLOZAPINE-INDUCED FEVER

Clozapine-induced fever in the absence of any concomitant infection was first described by German researchers in a 1972 article in German (Blum & Mauruschat 1972). The next major step was a 1989 monographic number supported by the pharmaceutical company that marketed clozapine which reviewed experience with clozapine in Central Europe and the US in order to support the US marketing of clozapine. In this monographic number, several German clinicians summarize their clinical experience. Two groups proposed that fever in the absence of another cause developed in approximately 5% of the patients (Gaertner et al. 1989, Naber et al. 1989). More importantly, Helmchen (1989) described it as a transient phenomenon in which fever occurred between the 5th and 20th treatment days and was frequently associated with an increase in the erythrocyte sedimentation rate (ESR). This is the first article associating fever with inflammation.

When clozapine was introduced in the US, the US clozapine experts called this fever "benign hyperthermia." They considered a prevalence of 5% normal during the first 3 weeks of clozapine titration (Safferman et al. 1991). They recommended stopping the clozapine titration when high fever develops (≥101° Fahrenheit or 38.3°C) and ruling out infections. When a second titration is offered, it should be slower (Safferman et al. 1991). In 2001, Tham and Dickson reviewed 93 consecutive clozapine initiations (1991-1999) by retrospective chart review in Canada. They found 20% had clozapine-induced fevers but there was no significant difference in the clozapine discontinuation rate after 1 year. The most important advancement in knowledge was made by Pui-yin Chung et al. (2008). They compiled a retrospective chart of 227 inpatients started on clozapine in Hong Kong with a fever incidence of 14% (31/227). After comparing 31 cases with fever versus 196 controls, the significant multivariate odds ratios (OR) and their 95% confidence intervals (CIs) were 18.9 (5.3 to 66.7) for a rate of titration >50 mg/week, 3.6 (CI 1.5 to 8.9) for valproate and 3.2 (1.2 to 8.3) for the presence of physical illness. A US double-blind RCT using 3 different clozapine doses included a patient who was a clozapine PM due to the co-prescription of oral contraceptives. She could not tolerate the standard titration and developed fever in the absence of infection during weeks 1, 4, 11 and 12. The fever was associated with increases in clozapine levels and further decreases in clozapine metabolism (Schoretsanitis et al. 2020).

INFLAMMATION DECREASES CLOZAPINE METABOLISM

In 1978, Chang et al. reported that acute respiratory viral illness decreases theophylline metabolism. The clinical relevance of this was demonstrated in a medical records review of 2,254 asthmatic children, where Shilalukey et al. (1993) proposed that when a child taking theophylline develops an upper respiratory infection, the theophylline dose should be decreased almost by half. Theophylline was found to be mainly metabolized by CYP1A2 (Gu et al. 1992) and a warning of the risk of intoxication during infections was included in the US package insert. Then, in vitro studies found that the release of cytokines during the infection decreased the activity and synthesis of CYP1A2 (Abdel-Razzak et al. 1993). This would explain the effects of infections on theophylline and presumably any other drugs mainly metabolized by CYP1A2.

Thus, it is not surprising that case reports started to appear of clozapine intoxications during respiratory infections with fever (Raaska et al. 2002, de Leon & Diaz 2003, Haack et al. 2003). Following the recommendation of halving the dose of theophylline during infections with fever to avoid intoxication, the same strategy was recommended in clozapine patients (de Leon 2004). Later on, in a systematic review of the literature through 2016 which added 8 new unpublished cases, Clark et al. (2018) identified 40 cases of elevations of plasma clozapine concentrations during infections. As one would expect based on pathophysiology, the literature described similar cases of clozapine intoxication during systemic inflammation produced by other causes than infections (Egger et al. 2010, Ruan et al. 2018). In an important contribution to the literature, Pfuhlmann et al. (2009) proposed using c-reactive protein (CRP) elevations as markers of the risk that an inflammation may lead to elevations in plasma clozapine concentrations. A recent retrospective review of 131 clozapine inpatients at Beijing Anding Hospital found that infections are clinically relevant for the cohort and for the individuals when assessing clozapine concentrations. Eight episodes of infections/inflammations in 16 patients contaminated 2% (482/24,789) of the days of clozapine treatment. At the patient level the effects varied as follows: 1) no clinically relevant effects on the plasma clozapine concentrations in the 11% of infection episodes which presented with no leukocytosis or CRP elevations, 2) effects indicating that halving the clozapine dose would be advisable in 61% of the infection episodes, and 3) effects indicating that reducing the clozapine dose to one-third would be advisable in

28% of infection episodes. In summary, the determining effect is not the presence or absence of infection, but the systemic severity of the inflammation (Ruan et al. 2020).

CLOZAPINE-INDUCED MYOCARDITIS

First cases

In 1980, Danish authors published in Danish the first case of clozapine-induced myocarditis (Vesterby et al. 1980) which can be described as "rapid titration by doctor" since the patient was started on 300 mg/day. In 2 early cohorts of Scandinavian patients, myocarditis was rare. In 96 Swedish patients one was found dead and the autopsy revealed myocarditis (Lindstrom 1988); among 216 Danish patients, one on clozapine was discontinued due to myocarditis during titration (Juul Povlsen et al. 1985).

In 1992, US authors described the "first rapid titration by a patient". The patient had recently started on clozapine and completed a lethal intentional overdose (2000 mg). The autopsy found an unusual case of eosinophilic myocarditis (Meeker et al. 1980). The same eosinophilic myocarditis was described in Danish by Jensen and Gøtzsche (1994), who first proposed it was an "allergic" myocarditis. This eosinophilic myocarditis is now considered the most typical presentation of clozapine-induced myocarditis (Chopra & de Leon 2006).

Drug agencies

The drug agencies ignored these cases for years. In 1993, the British agency was the first to comment on clozapine as a possible cause of myocarditis (Committee on Safety of Medicines 1993). In 1999, an article by Killian et al. in the journal *Lancet* reviewed 23 cases from the Australian drug registry and placed clozapine-induced myocarditis on the radar of the drug agencies. This article prompted a review by investigators from the WHO database (Coulter et al. 2001) and the FDA (La Grenade et al. 2001) who were somewhat skeptical of the association. It is unfortunate that the drug agencies did not pay attention to a comment on Killian's cases by Canadian authors: Dejeveran et al. (2000) stated that "in all cases, daily clozapine doses were increased rapidly" and that the Australian titrations were much faster than their Canadian titrations. A group of Swedish investigators reviewed the reported cases to the Swedish drug agency and related clozapine-induced myocarditis to hypersensitivity myocarditis and other clozapine-induced eosinophilic syndromes (Hägg et al. 2001). In 2002, the FDA finally added a myocarditis warning to the clozapine package insert (de Leon et al. 2020a).

Controversies surrounding clozapine-induced myocarditis

In 2012, two crucial articles defending two extreme positions on clozapine-induced myocarditis were published by Continental Europeans (Cohen et al. 2012) and Australians (Ronaldson et al. 2012). The European group from the Netherlands brought attention to an incidence rate of 0.7-1.12% in Australia versus 0.07% worldwide (Cohen et al. 2012). This large difference was replicated in a 2020 meta-analysis with an event rate of 2% in 9 Australian samples and of 0.3% in 15 non-Australian samples (Siskind et al. 2020). In the Netherlands, they found almost no cases of clozapine-induced myocarditis in spite of extremely wide use of clozapine in approximately 10% of schizophrenia outpatients (Bogers et al. 2016). It is important, however, to emphasize that the Dutch guideline proposes very slow clozapine titration, particularly for outpatients (Netherlands clozapine collaboration group, 2013).

In a case-control study, Ronaldson et al. (2012) found that clozapine-induced myocarditis in Australia was significantly associated with rapid titration (rapidity was defined on the basis of each additional 250 mg of clozapine administered in the first nine days) with an OR of 1.26 (CI 1.02 to 1.55), while valproate co-administration was associated with an OR of 2.59 (CI 1.51 to 4.42).

Since 2012 these two positions may have become further apart. In their 2015 review of the literature, Ronaldson et al. proposed that the Australian experience is the correct one since the real incidence of myocarditis is around 3% and "that a similar incidence would be found in other jurisdictions, if a practice of routine monitoring for myocarditis was adopted". The Continental Europeans responded with a study from the Danish registry. Rohde et al. (2018) studied all 3,262 outpatient starts of clozapine and found 0.03% developed myocarditis in the first 2 months and, more importantly, that none of the 26 deaths in the first 2 months was explained by myocarditis. If the Danish psychiatrists do not identify clozapine-induced myocarditis as Ronaldson et al. proposed one should expect 97 undiagnosed clozapine-induced myocarditis cases in this cohort with high risk of death due to lack of identification by their Danish psychiatrists (de Leon 2022b).

CLOZAPINE-INDUCED INFLAMMATION AS A HYPERSENSITIVITY REACTION

Rapid titration and clozapine-induced myocarditis

The lamotrigine-induced Stevens-Johnson syndrome, which is a hypersensitivity reaction, was reduced substantially when the company slowed the recommended titration in average patients with further slowing in half in patients taking an inhibitor, valproate (Wang et al. 2015). Thus, in 2015, two articles (de Leon et al. 2015, Freudenreich 2015) independently commenting on the myocarditis review by Ronaldson et al. (2015) used the lamotrigine analogy and proposed that clozapine-induced myocarditis is a hypersensitivity reaction, in this case associated with a rapid titration of clozapine.

Hypersensitivity model

The hypersensitivity model can be simplified into 3 phases (de Leon et al. 2020a). In the first phase, the titration is too fast for a specific patient, as the psychiatrist was too aggressive with it, and/or due to the patient's clozapine PM status; this leads to a release of cytokines. In the second phase, a positive feedback loop develops, the cytokines inhibit CYP1A2, which further increase the plasma clozapine concentrations. In the third phase, if the titration continues, the inflammation becomes complicated by the development of auto-antibodies (or another auto-immune phenomenon) which leads to myocarditis or other inflammations.

Other clozapine-induced inflammations

As a matter of fact, in a literature review, Verdoux et al. (2019) proposed that manifestations of clozapine-induced inflammation due to rapid titration may include a wide variety of presentations including: 1) systemic inflammatory processes: fever, fever with isolated CRP elevation, or lupus, or 2) localized signs of inflammation: myocarditis, serositis, pneumonitis/alveolitis, hepatitis, pancreatitis, nephritis, colitis and dermatological disorders. This classification is somewhat arbitrary since these presentations may lie on a continuum with no clear-cut boundary between them, and several conditions may co-occur. In that sense, a series of reviews by de Filippis (2020, 2021, 2022) indicated a clozapine-related drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome may be another manifestation of clozapine-induced inflammation during a titration that was too rapid. Similarly, a 2020 review on clozapine-induced colitis also commented on the overlap of this presentation with clozapine-induced DRESS and other syndromes associated with eosinophilia (Rask et al. 2020).

The problem of defining rapid titration

If clozapine metabolism is influenced by: 1) one's DNA ancestry (African, European and/or Asian/Indigenous American), 2) one's sex/smoking subgroup, 3) presence or absence of co-prescribed inducers or inhibitors, and 4) presence or absence of obesity or inflammation, it should be evident that it is not easy to define which titration is too rapid for a specific patient. The only way to establish that a titration is too rapid for a specific patient is by seeing elevations in CRP or in plasma clozapine concentrations in relationship to what should be expected based on the clozapine dosage for the patient's ancestry and sex/smoking subgroup (de Leon et al. 2020c, Ertuğrul et al. 2022, Koenig et al. 2022). In 13 myocarditis cases from Turkey and the US, a careful review of the titrations and plasma concentrations showed that all 13 cases appear to be compatible with PM status, in 2 cases due to genetics and in 11 cases due to various combinations of obesity, valproate and/or infection. Additional contributors were the maximum dose reached during titration versus the minimum therapeutic dose for that specific patient and the speed of the titration in the first or second week in relation to the minimum therapeutic dose for that patient (Koenig et al. 2022).

Due to variability in clozapine metabolism, a new guideline proposes 6 clozapine titration schedules may be required (stratified dosing) and, in order to personalize the dosage, measuring basal and weekly CRP during titration provides a safeguard against the unexpected development of clozapine-induced inflammation (de Leon et al. 2022). An update of this guideline (Schoretsanitis & de Leon 2022) recommended using the PM titrations of the corresponding DNA ancestry group for patients taking olanzapine and quetiapine. The World Health Organization (WHO) database on ADRs indicates that co-prescription of olanzapine may increase the severity of clozapine-induced myocarditis (De Las Cuevas et al. 2022). Clozapine-induced inflammation may be associated with saturation of clozapine metabolism and in this circumstance olanzapine may compete for CYP1A2 metabolism, increasing plasma clozapine concentration and further complicating the severity of the inflammation (Schoretsanitis & de Leon 2022). The WHO database indicates that co-prescription of quetiapine may increase the severity and lethality of clozapine-induced myocarditis (De Las Cuevas et al. 2022). An Australian case-control study (Nachmani Major et al. 2020) also found a significant effect of quetiapine, 29% of the 24 patients with myocarditis were taking quetiapine versus 19% of the 121 controls. It is possible that quetiapine may contribute to clozapine-induced myocarditis through a pharmacodynamic mechanism since it may have an independent but minor risk of causing inflammation by itself in an overdose situation (De Las Cuevas et al. 2021).

DIFFICULTY ADDRESSING THIS CONCEPT TO A DIVERSE READERSHIP

There is general agreement among neuroscientists that all human beings are biased (Michael 2017); psychiatrists cannot be expected to be different. The possibility of convincing readers of a complex new concept, such as clozapine-induced inflammation, may be lessened by their preexisting biases on this topic. In the experience of the author, one's background beliefs and clinical exposure to clozapine-induced myocarditis vary widely worldwide among psychiatrists. There are three major sets of beliefs about clozapine-induced myocarditis associated with: 1) the lack of diagnosis; 2) an incidence rate of around 3% of titrations, and 3) a justified low incidence.

Lack of diagnosis of clozapine-induced myocarditis

Chinese and Russian psychiatrists may provide the best example of this type of belief. Clozapine was extremely frequently used in China in the past (Yang et al. 2008). Currently, second-generation antipsychotics

such as olanzapine or risperidone are frequently used, but clozapine continues to be one of the most frequent antipsychotics used (Xu et al. 2020). A review of the literature in English and Chinese indicates that Chinese psychiatrists may have limited awareness of the existence of clozapine-induced myocarditis (De Las Cuevas et al. 2022). The first clinical study included in PubMed on this topic was a forensic study in Shanghai which found 11 myocarditis cases in 24 psychiatric patients who had received autopsies; clozapine was found in the toxicological exams of 2 of the myocarditis cases (Ye et al. 2018).

In Russia, clozapine was prescribed in almost half of the patients with schizophrenia according to a government database but, in many cases, clozapine appeared to be co-prescribed with other antipsychotics (Kostev et al. 2019). Slyundin et al. (2010) reported that clozapine ranked first in drug intoxications in a forensic study conducted in Moscow during the period from 2003 to 2009. A review of the literature in Russian suggests that there are published animal studies modelling clozapine-induced myocarditis but no clinical reports of any case (Kirilochev et al. 2021). In summary, there is no data regarding the incidence of clozapine-induced myocarditis or other forms of clozapine-induced inflammations in China or Russia where clozapine is widely prescribed. As clinicians may not be aware of the relevance of clozapine-induced inflammation during titrations, they do not diagnose clozapine-induced myocarditis.

The incidence rate of clozapine-induced myocarditis is around 3%

When the Australian Ronaldson et al. (2015) proposed that an incidence rate of 3% for clozapine-induced myocarditis is normal, this led authors in several countries to use this reference and justify as normal this incidence rate of 3% in their settings. Rates around 3% have been described in some hospitals in Canada (Higgins et al. 2019), the US (Sandarsh et al. 2021) and New Zealand (Bellissima et al. 2021).

Japan is a special case. In 2009, clozapine was introduced in Japan based on data from US studies and restricted to special inpatient institutions. Following US dosing, the first published clozapine trial used up to 600 mg/day, the maximum approved dose in Japan. The study only included 38 TRS inpatients treated in a 12-week, single-arm clinical trial under real-world conditions using raters masked for the type of antipsychotic (Kishi et al. 2013). The relatively high clozapine dose for the Japanese was associated with a 29% (11/38) incidence of fever. More importantly, the most comprehensive Japanese titration study by Tsukahara et al. (2021) in 152 patients found a 38% (57/152) incidence of fever during the first 4 weeks, a 13% (20/152) incidence of pleuritis, a 5% (7/152) incidence of myocarditis and a 1% (2/152) incidence of interstitial nephritis. Japanese cases of myocarditis have been published (Kikuchi et al. 2013, Otsuka et al. 2019), but those authors were not aware that the titrations officially recommended in Japan are too rapid for Japanese patients who metabolize clozapine at the same rate as other Asians and less efficiently than Europeans (Yada et al. 2021).

Countries with extremely low incidence

Danish and Dutch psychiatrists use very slow outpatient titration and rarely diagnose clozapine-induced myocarditis. Moreover, Danish (Rhode et al. 2018) and Dutch (Cohen et al. 2012) authors have argued that clozapine-induced myocarditis is very rare in their countries while Ronaldson et al. (2015) proposed that countries with such low rates are missing cases due to lack of monitoring. A 2021 search of clozapine-induced myocarditis in the WHO database (De las Cuevas et al. 2022), was reanalyzed to compare these two positions. The Netherlands and Denmark together (around 24 million people) accounted for <1% (29/3274) of the worldwide myocarditis cases and 5.7% of the deaths (9/158), while Australia (<26 million people), accounted for half the myocarditis (50%, 1621/3274) cases and one-third of worldwide mortality (32%, 50/158) (de Leon 2022b). Any objective observer can agree that there is a major difference between these two sets of prevalences.

LIMITATIONS IN CONVINCING RESISTANT READERS

A prior editorial proposing the relevance of DNA ancestry, personalized dosing and clozapine-induced inflammation was rejected by 9 important medical, pharmacological or psychiatric journals until it miraculously found a place in a psychiatric journal (de Leon et al. 2020d). The editorial's rejection and the widespread rejection of all the articles with evidence concerning clozapine-induced myocarditis has led the author to remember a classic concept in the history of science on the influence of generations. A Spanish philosopher, Ortega y Gasset (1961), probably provided the most comprehensive discussion by explaining that a scientific concept not only needs to be true but must be understood, which may require waiting for the next generation. Probably, the most graphic of definition of this concept was provided by the German physicist, Max Planck (1963) in his biography, "A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it."

As the author is a "tired old man" who may not live long enough to survive the opposition of the current journal editors and reviewers, he is going to attempt to discuss the possible biases of skeptical readers of this article by reflecting on: 1) the paradoxes of expertise on this topic, 2) the lack of pharmacokinetic expertise of psychiatrists, 3) the problems of medical science versus clinical judgment, and 4) the importance of prevention rather than diagnosis.

The paradox of expertise in clozapine-induced myocarditis

It is evident that this article proposes that psychiatrists in Denmark and the Netherlands have no expertise in clozapine-induced myocarditis. They have no expertise because they rarely cause this condition with their slow clozapine titrations. Australian psychiatrists have great expertise in myocarditis, but they do not realize that their standard titrations are aggressive and very risky when they are used in patients who are PMs including Asians, obese patients and patients taking valproate who, during titration, may behave as inhibitor. A recent meta-analysis by Australians only identifies valproate as a risk factor (Vickers et al. 2022) and does not quote the low rates of myocarditis in the Danish registry (Rhode et al. 2018).

The lack of psychiatrists' pharmacokinetic knowledge

In 1995, facing an unexpected clozapine intoxication, the author learned that clozapine was metabolized by "something" called CYP1A2 and that explained a DDI (Odom-White & de Leon 1996). In 1996, he began operating a treatment-refractory unit in a state hospital with the 3% of hospital patients who were most seriously ill. These were very complex cases; the patients were taking psychiatric polypharmacy. He had no choice but to become an expert in pharmacokinetics, so he started to study and write about plasma concentrations, DDIs and pharmacogenetics (de Leon 2018, 2020). Twenty-five years later the use of pharmacokinetic thinking led him to develop recommendations for the stratified dosing of antipsychotics, but in the end, plasma concentrations are the only way to personalize dosing in each patient (de Leon 2022a). Measuring concentrations for lithium and tricyclic antidepressants was standard in the 1980s, but after the introduction of second-generation drugs, psychiatrists lost interest in measuring concentrations (de Leon 2018a). Thus, many psychiatrists reviewing for journals have no expertise in plasma concentrations. The author's articles on myocarditis (Ertuğrul et al. 2022, Koenig et al. 2022) describing elevations in plasma clozapine concentrations have been systematically rejected by psychiatrists acting as journal reviewers and who may not able or willing to consider that these concentrations elevations are a true sign of the association of clozapine-induced inflammation and clozapine PM status.

Medical science and clinical judgment

PhDs have a poor opinion of the scientific training of psychiatrists. The author is also extremely skeptical that psychiatrists understand scientific methodology (called the philosophy of science) well; psychiatry is a practical medical discipline needing practitioners, not scientists (de Leon 2013). On the other hand, physicians should value clinical judgment (Fava 2013), which has been used in this article to provide a complex interpretation of more than 50 years of clozapine literature. Psychiatrists tend to get bored by discussions on the philosophy of science, but Table 1 argues that this review of a complex topic and the clinical judgment used is compatible with more recent approaches to science and medicine (Bernard 1927, Popper 1963, Haack 1993, 2003, Haack & Kolenda 1977, The Editors 2005, Fava 2013, de Leon 2018b, Ertuğrul et al. 2022, Koenig et al. 2022).

The problem is not diagnosis but prevention

Several investigators have criticized the clinical concept of clozapine-induced myocarditis by criticizing clinicians who were not following specific diagnostic criteria and overdiagnosing clozapine-induced myocarditis. In a review of an Australian cohort, Winckel and Siskind (2015) proposed that many of the cases were not myocarditis but possible concomitant "5/20 (25%) cases had documented upper respiratory tract infections". Correctly diagnosing myocarditis does not appear to be an important issue in the prevention of mortality if one believes the data from the WHO database that respiratory infections kill four more times clozapine patients in the world than myocarditis (De Leon et al. 2020e). As a matter of fact, pneumonia was the unexpected major cause of mortality during 3,262 clozapine titrations in the Denmark registry where no patient was killed by myocarditis but seven died of pneumonia (Rohde et al. 2018). In a review of a British cohort, Segev et al. (2021) proposed that only 11% (29/228) who had myocarditis diagnosed by clinicians were confirmed as probable for myocarditis but did not discuss the lethality of the confirmed and unconfirmed cases. In the WHO database until 2021, mortality from myocarditis reported by British clinicians was not low: 25 patient deaths were seen in 590 reports (4% lethality).

CONCLUSION

The pharmaceutical company that marketed lamotrigine decreased the risk of a hypersensitivity reaction during titration by recommending in its package insert: 1) very slow titrations and 2) stratified dosing with 3 different titrations based on relevant co-medications (Wang et al. 2015). Clozapine is a generic drug so no company will support new prospective studies. Moreover, clozapine pharmacology is more complex than that of lamotrigine since inflammation provides a positive feed-back decreasing clozapine metabolism. Thus, our current state of knowledge enables us to propose 6 titrations for stratified dosing. Personalized dosing is added by CRP monitoring which is used as a backup to prevent clozapine-induced myocarditis (or another type of clozapine-induced inflammation) in the absence of genetic testing for clozapine PM status (de Leon et al. 2022b).

Table 1. This review in the context of scientific methodology

Scientific advancement: the theory of falsifying a hypothesis by Popper

- Psychiatrists are usually familiar (de Leon 2018b) with the idea proposed by Popper (1963) that science advances by falsifying incorrect hypotheses.
- Popper's model is currently considered a simplistic way of describing the advance of science. More complex methods may be required (Haack & Kolenda 1977).

Science: Haack's analogy of the crossword puzzle

- Haack is a US philosopher who provides a comprehensive and very reasonable way to think of science and its limitations (Haack 2003).
- She has provided a complex analogy of how certainty in science should work by using what she calls the analogy of the crossword puzzle (Haack 1993): "How reasonable one's confidence is that a certain entry in a crossword puzzle is correct depends on: how much support is given to this entry by the clue and any intersecting entries that have already been filled in; how reasonable, independently of the entry in question, one's confidence is that those other already filled-in entries are correct; and how many of the intersecting entries have been filled in."
- The reader would need to decide whether or not this comprehensive review of 50 years of clozapine literature provides a reasonable description of clozapine-induced inflammation during titration, given the analogy of the crossword puzzle.

Clozapine metabolism: evidence on patients with myocarditis

- The literature provides limited information on clozapine metabolism and titration for patients who develop myocarditis. At this time, the author has collected good naturalistic observations only from 13 cases (Ertuğrul et al. 2022, Kethooenig et al. 2022). This is obviously weak evidence from the point of view of mathematical science (de Leon 2018b).
- Psychiatrists have had little interest in collecting clozapine plasma concentrations in patients with myocarditis. Moreover, the author has found 3 articles in which the authors did not describe the concentrations or know how to interpret them, so he asked them for the concentration and republished the samples from New York (Rhee et al. 2019, de Leon et al. 2020c), Turkey (Anıl Yağcıoğlu et al. 2015, Ertuğrul et al. 2022) and Atlanta (Cook et al. 2015, Koenig et al. 2022). Patients were assessed for poor metabolizer (PM) status by comparing their clozapine concentration-to-dose ratio with their controls (averages from the same ancestry group and sex-smoking subgroup).
- This review focuses on pharmacokinetic mechanisms (de Leon 2018b). Mechanistic evidence has been crucial in the advancement of medicine since the 19th century and was defended by Claude Bernard (1927), one of the most sophisticated medical scientists.

Clinical judgment and this review

- "Evidence-based medicine does not appear to provide an adequate scientific background for challenges of clinical practice in psychiatry and needs to be integrated with clinical judgment" (Fava 2013).
- The reader will need to decide whether or not this comprehensive review of 50 years of literature provides a reasonable integration of the literature by using clinical judgment.

The Editors (2005) of the Annals of Internal Medicine on narrative reviews

- "Narrative reviews are particularly useful for topics with a fragmentary evidence base, such as emerging clinical issues, rare diseases, or new technologies."
- The reader will need to decide whether or not this comprehensive review of 50 years of fragmented literature is justified by the lack of available data that can be analyzed in a systematic way.

If the reader believes that science advances by falsifying a hypothesis (Table 1), the author recommends that the reader try to demonstrate that the author's theory is wrong by using the titration guideline in the care of his/her patients. However, by using the international clozapine titration guideline (de Leon et al. 2022b), the author thinks that readers may find out that diagnosing all types of inflammation may be relevant in decreasing clozapine-related lethality in their clozapine patients during the titration.

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References

1. *Abdel-Razzak Z, Loyer P, Fautrel A, Gautier JC, Corcos L, Turlin B, et al: Cytokines down-regulate expression of major cytochrome P-450 enzymes in adult human heaptocytes in primary culture. Mol Pharmacol 1993; 44:707-15*
2. *Allorge D, Chevalier D, Lo-Guidice JM, Cauffiez C, Suard F, Baumann P, et al: Identification of a novel splice-site mutation in the CYP1A2 gene. Br J Clin Pharmacol 2003; 56:341-4*
3. *Anıl Yağcıoğlu AE, Ertuğrul A, Karakaşlı AA, Ağaoğlu E, Ak S, Karahan S et al: A comparative study of detection of myocarditis induced by clozapine: With and without cardiac monitoring. Psychiatry Res 2019; 279:90-7*
4. *Bellissima BL, Vara A, Helsby N, Garavan F & Tingle MD: Incidence and investigation of potential risk-factors for clozapine-associated myocarditis and cardiomyopathy in a New Zealand cohort. Psychiatry Res 2021; 299:113873*
5. *Bender S & Eap CB: Very high cytochrome P4501A2 activity and nonresponse to clozapine. Arch Gen Psychiatry 1998; 55:1048-50*

6. *Bernard C: An Introduction to the Study of Experimental Medicine. Originally published in 1865; first English translation by Henry Copley Greene. New York and London: Macmillan & Co., Ltd; 1927*
7. *Bertilsson L, Carrillo JA, Dahl ML, Llerena A, Alm C, Bondesson U, et al: Clozapine disposition covaries with CYP1A2 activity determined by a caffeine test. Br J Clin Pharmacol 1994; 38:471-3*
8. *Blum A & Mauruschat W: Temperaturanstiege und Bluteiweißveränderungen unter der Therapie mit Neuroleptika-unter besonderer Berücksichtigung des neuartigen Dibenzodiazepin-Derivates Clozapin. Pharmacopsychiatry 1972; 5:155-69*
9. *Bogers JP, Schulte PF, Van Dijk D, Bakker B & Cohen D: Clozapine underutilization in the treatment of schizophrenia: how can clozapine prescription rates be improved? J Clin Psychopharmacol 2016; 36:109-11*
10. *Chang KC, Bell TD, Lauer BA & Chai H: Altered theophylline pharmacokinetics during acute respiratory viral illness. Lancet 1978; 1:1132-3*
11. *Chopra N & de Leon J: Clozapine-induced myocarditis may be associated with rapid titration: A case report verified with autopsy. Int J Psychiatry Med 2016; 51:104-5*
12. *Clark SR, Warren NS, Kim G, Jankowiak D, Schubert KO, Kisely S, et al: Elevated clozapine levels associated with infection: a systematic review. Schizophr Res 2018; 192:50-6*
13. *Cohen D, Bogers JP, van Dijk D, Bakker B & Schulte PF: Beyond white blood cell monitoring: screening in the initial phase of clozapine therapy. J Clin Psychiatry 2012; 73:1307-12*
14. *Committee on Safety of Medicines: Myocarditis with antipsychotics: recent cases with clozapine (Clozaril). Current Problems in Pharmacovigililance 1993; 19:9-10*
15. *Cook SC, Ferguson BA, Cotes RO, Heinrich TW& Schwartz AC: Clozapine-induced myocarditis: prevention and considerations in rechallenge. Psychosomatics 2015; 56:685-90*
16. *Coulter DM, Bate A, Meyboom RH, Lindquist M & Edwards IR: Antipsychotic drugs and heart muscle disorder in international pharmacovigilance: data mining study. BMJ 2001; 322:1207-9*
17. *Crilly J: The history of clozapine and its emergence in the US market: a review and analysis. Hist Psychiatry 2007; 18:39-60*
18. *de Filippis R, Soldevila-Matías P, Guinart D, De Fazio P, Rubio JM, Kane JM, et al: Unravelling cases of clozapine-related drug reaction with eosinophilia and systemic symptoms (DRESS) in patients reported otherwise: A systematic review. J Psychopharmacol 2021; 35:1062-73*
19. *de Filippis R, Soldevila-Matías P, De Fazio P, Guinart D, Fuentes-Durá I, Rubio JM, et al: Clozapine-related drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: a systematic review. Expert Rev Clin Pharmacol 2020; 13:875-83*
20. *de Filippis R, Kane JM, Kuzo N, Spina E, De Sarro G, de Leon J, et al: Screening the European pharmacovigilance database for reports of clozapine-related DRESS syndrome: 47 novel cases. Eur Neuropsychopharmacology 2022; 60:25-37*
21. *De Las Cuevas C, Sanz EJ, Rohde C & de Leon J: Association between myocarditis and antipsychotics other than clozapine: a systematic literature review and a pharmacovigilance study using VigiBase. Expert Rev Clin Pharmacol 2022; 15:65-78*
22. *De Las Cuevas C, Sanz EJ, Ruan CJ & de Leon J: Clozapine-associated myocarditis in the World Health Organization's pharmacovigilance database: Focus on reports from various countries. Rev Psiquiatr Salud Ment (Engl Ed) 2021; 21:S1888-9891(21)00070-7. Epub ahead of print*
23. *de Leon J: Respiratory infections rather than antibiotics may increase clozapine levels: a critical review of the literature. J Clin Psychiatry 2004; 65:1144-5*
24. *de Leon J: The future (or lack of future) of personalized prescription in psychiatry. Pharmacol Res 2009; 59:81-9*
25. *de Leon J: Evidence-based medicine versus personalized medicine: are they enemies? J Clin Psychopharmacol 2012; 32:153-64*
26. *de Leon J: Is psychiatry scientific? A letter to a 21st century psychiatry resident. Psychiatry Investig 2013; 10:205-17*
27. *de Leon J: A critical commentary on the 2017 AGNP Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology. Pharmacopsychiatry 2018a; 51:63-8*
28. *de Leon J: Teaching medical students how to think: narrative, mechanistic and mathematical thinking. Actas Esp Psiquiatr 2018b; 46:133-45*
29. *de Leon J: Personalizing dosing of risperidone, paliperidone and clozapine using therapeutic drug monitoring and pharmacogenetics. Neuropharmacology 2020; 168:107656*
30. *de Leon J: Precision psychiatry: The complexity of personalizing antipsychotic dosing. Eur Neuropsychopharmacol. 2022a; 58:80-5*
31. *de Leon J: The history of clozapine in clinical practice: from its introduction to a guideline proposing personalized titrations. J Psychopharmacol 2022b, 36:657-60*
32. *De Leon J, Sanz EJ, & De Las Cuevas C: Data from the World Health Organization's pharmacovigilance danabase supports the prominent role of pneumonia in mortality associated with clozapine adverse drug reactions. Schizophr Bull 2020e; 46:1-3*
33. *de Leon J, Rajkumar AP, Kaithi AR, Schoretsanitis G, Kane JM, Wang CY, et al: Do Asian patients require only half of the clozapine dose prescribed for Caucasians? a critical overview. Indian J Psychol Med 2020b; 42:4-10*
34. *de Leon J, Rhee DW, Kondracke A, Diuguid-Gerber J: Rapid titration and decreased clozapine clearance may help explain five cases of clozapine-induced myocarditis in a New York hospital. Psychosomatics 2020c; 61:102-3*
35. *de Leon J, Ruan CJ, Schoretsanitis G & De Las Cuevas C: A rational use of clozapine based on adverse drug reactions, pharmacokinetics, and clinical pharmacopsychology. Psychother Psychosom 2020a; 89:200-4*
36. *de Leon J, Ruan CJ, Schoretsanitis G, & Kane JM: Dose and safety concerns of clozapine: worldwide package inserts need revisions. Schizophr Res 2020d; 216:2-4*
37. *de Leon J, Schoretsanitis G, Ruan CJ, De Las Cuevas C, Kane JM & Correll CU: An international clozapine titration guideline to increase its safety and move forward on the route started by German-speaking psychiatrists in the 1960s. Eur Arch Psychiatry Clin Neurosci 2022a; 272:537–40*
38. *de Leon J, Schoretsanitis G, Smith RL, Molden E, Solismaa A, Seppälä N, et al: An international adult guideline for making clozapine titration safer by using six ancestry-based personalized dosing titrations, CRP, and clozapine levels. Pharmacopsychiatry 2022b; 55:73-86*
39. *de Leon J, Tang YL, Baptista T, Chen D & Schulte PFJ: Titrating clozapine amidst recommendations proposing high myocarditis risk and rapid titrations. Acta Psychiatr Scand 2015; 132:242-3*
40. *Devarajan S, Kutcher SP & Dursun SM: Clozapine and sudden death. Lancet 2000; 355: 841.*
41. *Diaz FJ, Josiassen RC & de Leon J: The effect of body weight changes on total plasma clozapine concentrations determined by applying a statistical model to the data from a double-blind trial. J Clin Psychopharmacol 2018; 38:442-6*
42. *Egger C, Muehlbacher M, Grohmann R & Stuppaeck C: Clozapine intoxication in a patient with lamotrigine-induced rash. Pharmacopsychiatry 2010;43:35-6*
43. *Ertuğrul A, Yağcıoğlu EA, Ağaoğlu E, Karakaşlı AA, Ak S, Yazıcı K & de Leon J: Valproate, obesity and other causes of*

clozapine poor metabolism in the context of rapid titration may explain clozapine-induced myocarditis: A re-analysis of a study in a Turkish hospital. Rev Psiquiatr Salud Ment (Engl Ed) 2022. https://doi.org/10.1016/j.rpsm.2021.10.003

44. *Fava GA: Clinical judgment in psychiatry. Requiem or reveille? Nord J Psychiatry 2013; 67:1-10*
45. *Freudenreich O: Clozapine-induced myocarditis: prescribe safely but do prescribe. Acta Psychiatr Scand 2015; 132:240-1*
46. *Gaertner HJ, Fischer E & Hoss J. Side effects of clozapine. Psychopharmacology (Berl) 1989; 99(Suppl):S97-100*
47. *Gu L, Gonzalez FJ, Kalow W & Tang BK: Biotransformation of caffeine, paraxanthine, theobromine and theophylline by cDNA-expressed human CYP1A2 and CYP2E1. Pharmacogenetics 1992; 2:73-7*
48. *Haack MJ, Bak ML, Beurskens R, Maes M, Stolk LM & Delespaul PA: Toxic rise of clozapine plasma concentrations in relation to inflammation. Eur Neuropsychopharmacol 2003; 13:381-5*
49. *Haack S: Defending Science-Within Reason: Between Scientism and Cynicism. Amherst, NY: Prometheus Books, 2003*
50. *Haack S: Evidence and Inquiry. Towards Reconstruction in Epistemology. Oxford, UK: Backwell, 1993*
51. *Haack S & Kolenda K: Two fallibalists in search of truth. Proceedings of the Aristotelian Society 1997; Supplementary 51:63-104*
52. *Hägg S, Spigset O, Bate A & Soderström TG: Myocarditis related to clozapine treatment. J Clin Psychopharmacol 2001; 21:382-8*
53. *Hiemke C, Bergemann N, Clement HW, Conca A, Deckert J, Domschke K, et al: Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. Pharmacopsychiatry 2018; 51:9-62*
54. *Helmchen H: Clinical experience with clozapine in Germany. Psychopharmacology (Berl) 1989; 99 Suppl:S80-3*
55. *Higgins JM, San C, Lagnado G, Chua D & Mihic T: Incidence and management of clozapine-induced myocarditis in a large tertiary hospital. Can J Psychiatry 2019; 64:561-7*
56. *Idänpään-Heikkilä J, Alhava E, Olkinuora M & Palva I: Letter: Clozapine and agranulocytosis. Lancet 1975; 2:611*
57. *Jensen VE & Gøtzsche O: Allergisk myocarditis ved klozapin-behandling [Allergic myocarditis in clozapine treatment]. Ugeskr Laeger 1994; 156:4151-2*
58. *Jerling M, Lindström L, Bondesson U & Bertilsson L: Fluvoxamine inhibition and carbamazepine induction of the metabolism of clozapine: evidence from a therapeutic drug monitoring service. Ther Drug Monit 1994; 16:368-74*
59. *Juul Povlsen U, Noring U, Fog R & Gerlach J. Tolerability and therapeutic effect of clozapine. A retrospective investigation of 216 patients treated with clozapine for up to 12 years. Acta Psychiatr Scand 1985; 71:176-85*
60. *Kane J, Honigfeld G, Singer J, & Meltzer H: Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988; 45:789-96*
61. *Kikuchi Y, Ataka K, Yagisawa K, Omori Y, Shimizu K, Kanbayashi T, et al: Clozapine-induced cardiomyopathy: a first case in Japan. Schizophr Res 2013; 150:586-7*
62. *Kilian JG, Kerr K, Lawrence C, & Celermajer DS: Myocarditis and cardiomyopathy associated with clozapine. Lancet 1999; 354:1841-5*
63. *Kirilochev OO, De Las Cuevas C & de Leon J: Clozapine-induced myocarditis in Russia: animal studies but no clinical studies. Rev Psiquiatr Salud Ment (Engl Ed) 2021 Sep 17:S1888-9891(21)00100-2. doi:10.1016/j.rpsm.2021.09.001. Epub ahead of print*
64. *Kishi T, Fujita K, Furukawa O, Suzuki T, Moriwaki M, Nitta M, et al: Efficacy and tolerability of clozapine in Japanese patients with treatment-resistant schizophrenia: results from a 12-week, flexible dose study using raters masked to antipsychotic choice. Asian J Psychiatry 2013; 6:200-7*
65. *Koenig M, McCollum B, Spivey JK, Coleman JK, Shelton C, Cotes RO, et al: Four cases of myocarditis in US hospitals possibly associated with clozapine poor metabolism and a comparison with prior published cases. Neuropsychopharmacol Hung 2022; 24:29-41*
66. *Kostev K, Osina G & Konrad M: Treatment patterns of patients with schizophrenia based on the data from 44,836 outpatients in Russia. Heart Mind 2019; 3:161-4*
67. *La Grenade L, Graham D & Trontell A: Myocarditis and cardiomyopathy associated with clozapine use in the United States. N Engl J Med 2001; 345:224-5*
68. *Lindström LH: The effect of long-term treatment with clozapine in schizophrenia: a retrospective study in 96 patients treated with clozapine for up to 13 years. Acta Psychiatr Scand 1988; 77:524-9*
69. *Nachmani Major N, Dawson BPharm, Hons JL & Clark SR: Implementation and outcomes of a clozapine-associated myocarditis screening program in a region of South Australia-lessons learned. J Clin Psychopharmacol 2020; 40:250-8*
70. *Meeker JE, Herrmann PW, Som CW & Reynolds PC: Clozapine tissue concentrations following an apparent suicidal overdose of Clozaril. J Anal Toxicol 1992; 16:54-6*
71. *Meyer UA: Pharmacogenetics - five decades of therapeutic lessons from genetic diversity. Nat Rev Genet 2004; 5:669-76*
72. *Michael L: The Undoing Project: A Friendship That Changed Our Minds. New York: W.W. Norton & Company, 2017*
73. *Naber D, Leppig M, Grohmann R & Hippius H: Efficacy and adverse effects of clozapine in the treatment of schizophrenia and tardive dyskinesia - a retrospective study of 387 patients. Psychopharmacology (Berl) 1989; 99(Suppl):S73-6*
74. *Netherlands clozapine collaboration group: Guideline for the Use of Clozapine; 2013. http://www.clozapineplus werkgroep.nl/wp-content/uploads/2013/07/Guideline-for-the-use-of-Clozapine-2013.pdf*
75. *Odom-White A & de Leon J: Clozapine levels and caffeine. J Clin Psychiatry 1996; 57:175-6*
76. *Ortega y Gasset J: The Modern Theme. New York: Harper Torchbooks, 1961*
77. *Otsuka Y, Idemoto K, Hosoda Y, Imamura Y & Aoki T: Clozapine-induced myocarditis: Follow-up for 3.5 years after successful retrial. J Gen Fam Med 2019; 20:114-7*
78. *Pfuhlmann B, Hiemke C, Unterecker S, Burger R, Schmidtke A, Riederer P, et al: Toxic clozapine serum levels during inflammatory reactions. J Clin Psychopharmacol 2009; 29:392-4*
79. *Planck M: Scientific Autobiography and Other Papers. New York: Philosophical Library, 1968*
80. *Popper K: Conjectures and Refutations. New York: Harper Torchbooks, 1963*
81. *Pui-yin Chung J, Shiu-yin Chong C, Chung KF, Lai-wah Dunn E, Wai-nang Tang O & Chan WF: The incidence and characteristics of clozapine- induced fever in a local psychiatric unit in Hong Kong. Can J Psychiatry 2008; 53:857-62*
82. *Raaska K, Raitasuo, V, Arstila M, & Neuvonen PJ: Bacterial pneumonia can increase serum concentration of clozapine. Eur J Clin Pharmacol 2002; 58:321-2*
83. *Rask SM, Luoto KE, Solismaa A, Jokinen E, Jussila A & Kampman O: Clozapine-related diarrhea and colitis: report of 4 cases. J Clin Psychopharmacol 2020; 40:293-6*
84. *Rhee DW, Diuguid-Gerber J & Kondracke A: Five cases of clozapine-associated cardiotoxicity and implications for monitoring. Psychosomatics 2019; 60:524-7*
85. *Rohde C, Polcwiartek C, Kragholm K, Ebdrup BH, Siskind D & Nielsen J: Adverse cardiac events in out-patients initiating*

clozapine treatment: a nationwide register-based study. Acta Psychiatr Scand 2018; 137:47-53

86. *Røge R, Møller BK, Andersen CR, Correll CU & Nielsen J: Immunomodulatory effects of clozapine and their clinical implications: what have we learned so far? Schizophr Res 2012; 140:204-13*
87. *Ronaldson KJ, Fitzgerald PB & McNeil JJ: Clozapine-induced myocarditis, a widely overlooked adverse reaction. Acta Psychiatr Scand 2015; 132:231-40*
88. *Ronaldson KJ, Fitzgerald PB, Taylor AJ, Topliss DJ, Wolfe R & McNeil JJ: Rapid clozapine dose titration and concomitant sodium valproate increase the risk of myocarditis with clozapine: a case-control study. Schizophr Res 2012; 141:173-8*
89. *Ruan CJ & de Leon J: Is there a future for CYP1A2 pharmacogenetics in the optimal dosing of clozapine? Pharmacogenomics 2020; 21:369-73*
90. *Ruan CJ, Zang YN, Cheng YH, Wang CY & de Leon J: Around 3% of 1,300 levels were elevated during infections in a retrospective review of 131 inpatients in a Beijing Hospital with more than 24,000 clozapine days. Psychother Psychosom 2020; 89:255-7*
91. *Ruan CJ, Zhang XL, Guo W, Li WB, Zhuang HY, Li YQ, et al: Two cases of high serum clozapine concentrations occurring during inflammation in Chinese patients. Int J Psychiatry Med 2018; 53:292-305*
92. *Safferman A, Lieberman JA, Kane JM, Szymanski S & Kinon B: Update on the clinical efficacy and side effects of clozapine. Schizophr Bull 1991; 17:247-61*
93. *Sandarsh S, Bishnoi RJ, Shashank RB, Miller BJ, Freudenreich O & McEvoy JP: Monitoring for myocarditis during treatment initiation with clozapine. Acta Psychiatr Scand 2021; 144:194-200*
94. *Schoretsanitis G & de Leon J: Best practices for starting clozapine in patients with schizophrenia: how to switch from the prior antipsychotic(s). J Clin Psychiatry 2022, 83:22ac1450*
95. *Segev A, Iqbal E, McDonagh TA, Casetta C, Oloyede E, Piper S, et al: Clozapine-induced myocarditis: electronic health register analysis of incidence, timing, clinical markers and diagnostic accuracy. Br J Psychiatry 2021; 219:644-51*
96. *Shilalukey K, Robieux I, Spino M, Greenwald M, Shear N & Koren G: Are current pediatric dose recommendations for intravenous theophylline appropriate? J Asthma 1993; 30:109-21*
97. *Siskind D, Sidhu A, Cross J, Chua YT, Myles N, Cohen D, et al: Systematic review and meta-analysis of rates of clozapine-associated myocarditis and cardiomyopathy. Aust N Z J Psychiatry 2020; 54:467-81*
98. *Slyundin DG, Livanov AS, Anuchin VV, Merkin AG, Bobrinskaya IG & Gutova EV: Specific features of psychopathological manifestations in criminal clozapine intoxications. Neurology Neuropsychiatry Psychosomatics 2010; 2:57-63 [Article in Russian]*
99. *Subramanian S, Völlm BA, & Huband N: Clozapine dose for schizophrenia. Cochrane Database Syst Rev 2017; 6:CD009555*
100. *Tang YL, Mao PX, Jiang F, Chen Q, Wang CY, Cai ZJ, et al: Clozapine in China. Pharmacopsychiatry 2008; 41:1-9*
101. *Tham JC & Dickson RA: Clozapine-induced fevers and 1-year clozapine discontinuation rate. J Clin Psychiatry 2002; 63:880-4*
102. *The editors. Reviews: making sense of an often tangled skein of evidence. Ann Intern Med 2005; 142:1019-20*
103. *Tsukahara M, So R, Yada Y, Kodama M & Kishi Y: Clinical utility and safety of slower-than-recommended titration of clozapine for treatment-resistant schizophrenia: a retrospective cohort study. Psychiatr Q 2021; 92:703-13*
104. *Vandenbroucke JP: When are observational studies as credible as randomised trials? Lancet 2004; 363:1728-31*
105. *Vandenbroucke JP: Observational research, randomised trials and two views of medical science. PLoS Med 2008; 5:339-43*
106. *Verdoux H, Quiles C & de Leon J: Clinical determinants of fever in clozapine users and implications for treatment management: A narrative review. Schizophr Res 2019; 211:1-9*
107. *Vesterby A, Pedersen JH, Kaempe B & Thomsen NJ: Pludselig død under behandling med klozapin (Leponex) [Sudden death during treatment with clozapine (Leponex)]. Ugeskr Laeger 1980; 142:170-1*
108. *Vickers M, Ramineni V, Malacova E, Eriksson L, McMahon K, Moudgil V, et al: Risk factors for clozapine-induced myocarditis and cardiomyopathy: A systematic review and meta-analysis. Acta Psychiatr Scand 2022; 145:442-55*
109. *Wang XQ, Lv B, Wang HF, Zhang X, Yu SY, Huang XS, et al.: Lamotrigine-induced severe cutaneous adverse reaction: Update data from 1999-2014. J Clin Neurosci 2015; 22:1005-11*
110. *Winckel K, Siskind D, Hollingworth S & Wheeler A: Clozapine-induced myocarditis: separating the wheat from the chaff. Aust N Z J Psychiatry 2015; 49:188*
111. *Yada Y, Kitagawa K, Sakamoto S, Ozawa A, Nakada A, Kashiwagi H, et al: The relationship between plasma clozapine concentration and clinical outcome: a cross-sectional study. Acta Psychiatr Scand 2021; 143:227-37*
112. *Ye X, Shi C, Shen YW, Zhao ZQ, Jiang Y& Li LL: Forensic analysis of 24 Cases of long-term antipsychotics use-induced sudden unexpected deaths. Fa Yi Xue Za Zhi 2018; 34:644-7*
113. *Xu SW, Dong M, Zhang Q, Yang SY, Chen LY, Sim K, et al: Clozapine prescription pattern in patients with schizophrenia in Asia: The REAP survey (2016). Psychiatry Res 2020; 287:112271*
114. *Zang YN, Dong F, Li AN, Wang CY, Guo GX, Wang Q, et al: The impact of smoking, sex, infection, and comedication administration on oral olanzapine: a population pharmacokinetic model in Chinese psychiatric patients. Eur J Drug Metab Pharmacokinet 2021; 46:353-71*

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