




Review

Clozapine and Constipation: A Review of Clinical Considerations and Treatment Options

Amber N. Edinoff ^{1,*} , Emily Sauce ², Carolina O. Ochoa ², Jordan Cross ², Mark Cogburn ¹, Elyse M. Cornett ³, Adam M. Kaye ⁴ , Alex D. Pham ⁵ and Alan D. Kaye ^{3,5} 

¹ Department of Psychiatry and Behavioral Medicine, Louisiana State University Health Shreveport, Shreveport, LA 71103, USA; mark.cogburn@lsuhs.edu

² School of Medicine, Louisiana State University Shreveport, Shreveport, LA 71103, USA; esauce@lsuhsc.edu (E.S.); cochoa@lsuhsc.edu (C.O.O.); jcros2@lsuhsc.edu (J.C.)

³ Department of Anesthesiology, Louisiana State University Shreveport, Shreveport, LA 71103, USA; elyse.bradley@lsuhs.edu (E.M.C.); alan.kaye@lsuhs.edu (A.D.K.)

⁴ Department of Pharmacy Practice, Thomas J. Long School of Pharmacy, University of the Pacific, Stockton, CA 95211, USA; akaye@pacific.edu

⁵ Department of Anesthesiology, Louisiana State University New Orleans, New Orleans, LA 70803, USA; apha5@lsuhsc.edu

* Correspondence: aedino@lsuhsc.edu



Citation: Edinoff, A.N.; Sauce, E.; Ochoa, C.O.; Cross, J.; Cogburn, M.; Cornett, E.M.; Kaye, A.M.; Pham, A.D.; Kaye, A.D. Clozapine and Constipation: A Review of Clinical Considerations and Treatment Options. *Psychiatry Int.* **2021**, *2*, 344–352. <https://doi.org/10.3390/psychiatryint2030026>

Academic Editor: Paolo Girardi

Received: 9 July 2021

Accepted: 2 August 2021

Published: 1 September 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Abstract: Psychosis, a break in reality which is manifested as hallucinations, delusions or the disruption in thought process, is the hallmark of schizophrenia. Despite novel pharmacotherapy advancements of antipsychotic medications that have resulted in some patients having the ability to return to social settings and thereby decreasing psychotic symptoms and reducing hospital admissions, there is still a sub-population of patients who remain symptomatic. Treatment-resistant schizophrenia is defined as failure of treatment with at least two different antipsychotics with the proper length of treatment and titration. Clozapine has been heralded as a drug to resolve the puzzle of treatment-resistant schizophrenia. Clozapine has one side effect that is well known, being the development of agranulocytosis. However, there is another side effect that can limit clozapine's use and can also be life-threatening. Recently, at the end of January 2020, the FDA issued a communications statement which "[strengthened] an existing warning that constipation caused by the schizophrenia medicine clozapine can, uncommonly, progress to serious bowel complications." After identifying ten cases of constipation from between 2006 to 2016 that progressed to hospitalization, surgery, and even death, the FDA focused their attention on this often overlooked, common side effect, especially when considering the strong anticholinergic effects of clozapine. Although patients are screened by their physicians for agranulocytosis by weekly lab monitoring, constipation is also a complication that needs to be identified and treated. Much like opioid-induced constipation, constipation can also be reduced with the use of laxatives and reduction in the co-prescribing of anticholinergic therapies with clozapine.

Keywords: clozapine; treatment-resistant schizophrenia; adverse effects; constipation

1. Introduction

Swiss psychiatrist Eugen Bleuler was one of the first psychiatrists to use the term schizophrenia to describe what was once described as Emil Kraepelin as "dementia praecox". Schizophrenia according to Bleuler would refer to the split of thought, emotion, and behavior [1]. Today, psychosis, defined as a break in reality manifested as hallucinations, delusions or disruption in thought process is the hallmark of schizophrenia.

There are certain risk factors, such as a family history of schizophrenia, pregnancy and birth complications, advanced paternal age, substance abuse of psychoactive or psychotropic drugs during teenage years, and environmental stressors, which increase the risk

of developing schizophrenia [2]. Twin studies have illustrated the heritability and genetic component of this disorder and have been crucial in understanding other contributing factors such as environment [3]. These studies, along with advanced genetic sequencing, have paved the way to understanding this disorder at the molecular level [4].

In the 1950s, the discovery of the first-generation antipsychotic, chlorpromazine, gave promise for successful treatment of schizophrenia. Despite this pharmacotherapy advancement that gave some patients the ability to return to social settings and thereby decrease psychotic symptoms and reduce hospital admissions, there is still a sub-population of patients who remain symptomatic. Treatment-resistant schizophrenia must be distinguished from incomplete recovery and frequent hospitalizations secondary to patient nonadherence, poor social support, or a history of violence [5]. For years, clozapine was thought to be an ideal antipsychotic medication related to its efficacy in treating both positive and negative symptoms, as well as treating treatment-resistant schizophrenia. It has also been demonstrated to decrease suicidal ideation. However, related to severity and incidence of adverse effects, it is now used as a backup in patients who have failed at least two other antipsychotic medications [6]. This review evaluates clozapine, which is considered the first-line therapy for treatment-resistant schizophrenia. Clozapine has a well-known side effect of agranulocytosis. However, there is another side effect that can limit clozapine's use and can also be life-threatening; this complication is clozapine mediated or modulated constipation.

1.1. Treatment-Resistant Schizophrenia

Schizophrenia is a complex disorder that leaves many patients debilitated and unable to function well in society without successful treatment. The majority of patients today respond well to typical or atypical antipsychotics, but approximately one-third of patients are considered treatment-resistant [7]. It is theorized that schizophrenia can be distinguished by subtypes, which might link differences in response to treatment with antipsychotics to certain genetic markers [8].

Treatment-resistant schizophrenia is defined as the persistence of symptoms despite more than two trials of antipsychotic medications of adequate dose and duration with documented adherence [9]. Treatment-resistant schizophrenia cannot be explained by the dopamine hypothesis of schizophrenia [7,10]. The majority of schizophrenia patients respond to pharmacologic blockade of D2 receptors, but a large population continues to remain undertreated and symptomatic to the point of disability [10]. Surprisingly, many of these patients with treatment-resistant schizophrenia will see a response to the atypical antipsychotic clozapine that has relatively low levels of D2 receptor antagonism [11].

This response may indicate that treatment-resistant schizophrenia symptoms are driven by non-dopaminergic abnormalities [7]. A 2014 study using positron emission tomography (PET) scans found that individuals with treatment-resistant schizophrenia had no increased capacity for dopamine synthesis after antipsychotic treatment compared to those with disease responsive to antipsychotic treatment [12]. In a separate proton magnetic resonance spectroscopy study, it was also found that in patients with persistent psychosis, despite antipsychotic treatment, there were elevated glutamate levels in the anterior cingulate cortex compared to those who responded to antipsychotic treatment [12].

1.2. Clozapine

Clozapine was discovered in 1959 as the first atypical antipsychotic [13]. Its use broke the perception that the presence of extrapyramidal symptoms was required for antipsychotic efficacy and it was deemed "atypical" or "defective" [13]. Imaging and pharmacological studies have suggested that, unlike typical antipsychotics, clozapine does not display a high striatal dopamine receptor binding [14]. Rather, it seems to modulate dopamine, serotonergic, noradrenergic, and glutamatergic receptors [15,16].

Further clinical use continued to reveal that clozapine had excellent efficacy for a wide range of psychotic symptoms and it gained popularity; however, what also came to light

was the life-threatening side effect of agranulocytosis [13]. The risk of this side effect drastically decreased the popularity of the drug, but there remained a population of patients in whom the benefit of a drug capable of treating their symptoms when other treatment options were exhausted outweighed the risk of this side effect. In a 1988 multicenter trial based on DSM-III schizophrenics who failed to respond to at least three different neuroleptics and a subsequent six week trial of haloperidol, clozapine efficacy was studied against chlorpromazine [11]. In this double-blind comparison, 30% of clozapine-treated patients responded to treatment versus 4% of chlorpromazine-treated patients [11]. Clozapine was re-introduced in 1989 after a successful FDA application, dramatically changing the management of patients with refractory psychosis [13].

1.3. Mechanism of Action

Clozapine is a tricyclic dibenzodiazepine derivative that works as an antagonist to both dopamine and serotonin receptors [17]. Additionally, clozapine also works antagonistically at adrenergic, cholinergic, and histaminergic receptors [17].

Similar to other second-generation antipsychotics, clozapine exhibits a greater ability to block serotonin 5-HT_{2A} receptors than dopamine D₂ receptors [6]. However, unlike some second-generation medications such as risperidone, clozapine weakly inhibits dopamine binding at D₂ receptors and has a ten times greater affinity for the D₄ receptors [6,18]. These binding properties of clozapine contribute to a lower incidence of extrapyramidal symptoms and a reduction of negative symptoms [18].

Furthermore, clozapine weakly interferes with the D₁, D₃, and D₅ receptors, and has a high affinity for adrenergic, cholinergic, and 5-HT_{2C} serotonergic receptors [17]. Clozapine has also been noted to affect muscarinic receptors (blocking M₁, M₂, M₃, and M₅ receptors, while stimulating M₄ receptors) and histamine receptors [18–20].

It has also been shown in studies to work on the glutamate system. In a study by Evins et al., patients that were given clozapine had increased serum glutamate and aspartate concentrations, with clinical improvement in the negative psychotic symptoms [21]. Glutamate is an excitatory neurotransmitter and glutamate increase is thought to be the reason for the improvement in negative symptoms. Another study postulated that levels of glutamate and brain neurotrophic factors could actually identify clozapine responders, those who have increased levels of these two proteins, from clozapine non-responders [22]. In animal studies, clozapine's mechanism of action on the glutamate receptors was seen in the pre-frontal cortex where it attenuates the increase in extracellular glutamate efflux and blocks the firing of N-methyl-D-aspartate (NMDA) receptors [23].

1.4. Pharmacodynamics/Pharmacokinetics

Clozapine is a highly protein-bound drug that is metabolized to norclozapine (desmethyl-clozapine) and other metabolites by the cytochrome P450 enzymes CYP1A2, CYP3A4, CYP2C19, and also with some effect from the enzymes CYP2C9 and CYP2D6 [6,24]. Each enzyme is more effective at different clozapine concentrations and has its own set of inducers and inhibitors, which makes plasma level monitoring and dose adjustments crucial in maintaining the drug's therapeutic value [24].

Studies investigating the pharmacokinetic parameters of clozapine in patients with schizophrenia also echo this need for monitoring, as clozapine was shown to have a “wide interpatient variability” in the time it takes to reach peak plasma concentrations (1.1 to 3.6 h), elimination half-life (9.1 to 17.4 h), clearance (8.7 to 53.3 L/h), and volume of distribution (1.6 to 7.3 L/kg) [25]. Moreover, clozapine exhibits a dose- and time-dependent effect on lowering the seizure threshold, and when compared to first-generation medications, it has a minimal or transient impact on increasing serum prolactin levels [25,26].

2. Clozapine Side Effects and Black Box Warnings

Antipsychotics are associated with a number of side effects, ranging from mild symptoms such as weight gain and drooling to severe effects such as tardive dyskinesia and

seizures [27]. The side effects of clozapine included common ones such as sedation, hypersalivation, tachycardia, hypo- and hypertension, weight gain, constipation, incontinence, hepatic effects, and neuromuscular effects [27,28]. A notable exception to clozapine's list of adverse effects is extrapyramidal side effects, which are minimal in clozapine unlike other antipsychotic medications [28]. Despite this unique and clinically useful feature of clozapine, it remains highly underutilized and unnecessarily discontinued due to physician uncertainty of management and fear of adverse effects [24,29]. Currently, clozapine has five FDA black box warnings for agranulocytosis, seizures, myocarditis, cardiovascular and respiratory effects, and increased mortality from dementia-related psychosis in the elderly [17]. The most concerning of these is agranulocytosis, although this side effect occurs in about 0.8% to 2% of patients and can be managed through blood monitoring [24]. Similarly, a number of these side effects such as neutropenia, leukocytosis, and tachycardia have been shown to require clinical monitoring, but not necessarily clozapine discontinuation [29]. Nevertheless, clozapine is contraindicated in certain patients such as those with myeloproliferative disorders [17].

Recently, at the end of January 2020, the FDA issued a communications statement which "[strengthened] an existing warning that constipation caused by the schizophrenia medicine clozapine can, uncommonly, progress to serious bowel complications" [26]. After identifying ten cases of constipation from between 2006 to 2016 that progressed to hospitalization, surgery, and even death, the FDA felt that attention was needed on this often overlooked, common side effect, especially when considering the strong anticholinergic effects of clozapine [26,30]. From the reported deaths, the causes include necrotizing colitis, intestinal ischemia, intestinal necrosis, and abdominal distention leading to volvulus [26].

The anticholinergic effects of clozapine can result in gastrointestinal dysfunctions ranging from mild constipation to severe complications such as intestinal obstruction, fecal impaction, and/or paralytic ileus [17]. However, fatal events are rare and constipation can be treated with adequate hydration, avoidance of the coadministration of anticholinergics such as antihistamines, tricyclic antidepressants, antimuscarinics, muscle relaxants, medications for overactive bladder/ incontinence, and use of laxatives or suppositories [17]. Regardless, if a patient presents with distressing gastrointestinal and constipation complaints, consultation with a gastroenterologist is warranted [17,26]. Additionally, other practices such as avoidance of co-prescribing other anticholinergics or constipation-inducing medications (i.e., opioids, iron, calcium, and verapamil), and the use of prophylactic laxatives can help minimize constipation complications [27,28]. Furthermore, critical to prevention and management is patient and caregiver education on the risks, prevention, and treatment of clozapine-induced constipation and its potentially serious complications [16]. Prescribers should be aware and looking out for constipation if patients are also being treated with benztropine or trihexyphenidyl for extrapyramidal symptoms, since these are antimuscarinic agents which can worsen constipation.

2.1. Clinical Studies: Constipation

2.1.1. Prevalence

Several studies have investigated the side effects of clozapine such as agranulocytosis, seizures, myocarditis, and other distressing adverse effects [31]. More recently, studies have been focusing on the troubling side effect of constipation on clozapine patients given that 17% of patients discontinue treatment due to adverse effects [32]. Constipation as a side effect of clozapine has been overlooked for years with the use of the drug despite its known anticholinergic effects. Patients taking clozapine have a prevalence of constipation that is three times higher than those taking other antipsychotic medications [33]. In order to study the prevalence of constipation in clozapine patients, a group of researchers performed a retrospective study. The meta-analysis determined that constipation was a common side effect of clozapine, and showed evidence that the dose of clozapine related to the prevalence of constipation—doses higher than 300 mg/day were more frequently associated with constipation [33]. Furthermore, one study found that there was a low correlation between

antimuscarinic activity and clozapine dose, but a significant correlation came from the clozapine plasma levels [34]. Patients taking clozapine doses of 300 mg/day or higher had higher plasma levels of the drug, thus leading to a higher anticholinergic activity [34].

A study that investigated the prevalence of constipation in patients taking clozapine found a significant trend in the Bristol Stool Form and Constipation Assessment Scale (an increase in severity of constipation) with the use of clozapine. A positive correlation was found between the development of constipation with age, duration of treatment, and duration of illness [35]. The researchers found a higher incidence rate of constipation in clozapine patients, but this could be related to the fact that constipation was being directly investigated compared to previous studies that had been done. Further, patients in this study who received clozapine as a treatment were four times more likely to develop constipation [35]. Not only was the prevalence in the clozapine group higher than the control (a group on a different antipsychotic medication), but they also had a higher severity of constipation. Additionally, the patients with constipation needed pharmacological intervention related to severity.

Additional research in Japan, where the use of clozapine was delayed related to apprehension of agranulocytosis development, showed that patients treated over a 12-week period had a highly significant improvement of their baseline Positive and Negative Syndrome Scale (PANSS) total score [36]. More specifically, patients' PANSS positive, negative, and general subscale scores improved. During this study, one patient developed ileus, and, in addition to two other patients that dropped out, they all recovered in three days after proper treatment. Constipation, along with other adverse effects such as insomnia, nausea/vomiting, and hypersalivation, were observed in 30% of the participants in this trial [36]. This is a significant number of participants, which provides sufficient reasoning to monitor constipation in patients on clozapine as a serious and life-threatening side effect if not caught early. This study shows the efficacy of the use of clozapine in treatment-resistant schizophrenia, and the importance of monitoring side effects, especially constipation.

A cohort study, in Iceland, was done on patients diagnosed with schizophrenia and using clozapine for therapy to determine the prevalence of constipation and development of ileus in these patients. The results of the study found that there was a higher prevalence of constipation in schizophrenic patients on clozapine than what had been previously stated [37]. This discrepancy could be due to the length of study time, detection bias, or differences in diet and lifestyle in other studies that took place. The researchers recommended that the physicians increase their screening of constipation in patients taking clozapine in order to take appropriate action to reduce the risk of developing ileus. Monitoring should also be increased with patients on additional medications that can cause constipation, such as anticholinergics, opioids, and tricyclic antidepressants [37]. With the patients on clozapine plus the additionally previously stated drugs that reduce bowel movement, only half were receiving laxatives, while only 15.6% of those only on clozapine were given laxatives [37]. This data shows that the underuse of laxatives during clozapine treatment can lead to constipation, ileus, or discontinuation of the drug [37]. The researchers were also able to conclude based on their data that the prevalence of ileus is higher than that of agranulocytosis, which is typically monitored when compared to larger studies [37]. This further provides evidence that constipation should be on a physician's radar when treating a patient with clozapine.

2.1.2. Screening

Gastrointestinal hypomotility was further researched in a cross-sectional study with patients taking clozapine. The study found that gastrointestinal hypomotility is a highly significant problem in any patient taking clozapine with no regard to dose, gender, or treatment duration [38]. With that being said, in a previously mentioned study, a positive correlation was found between the development of constipation and age, duration of treatment, and duration of illness [35]. In this study, it was found that patients taking clozapine had a median colonic transit time of 104.5 h compared to the 23 h of the control

group [38]. These results confirm that clozapine has a serious effect on gastrointestinal motility and bowel function. In order to better monitor the development of constipation, research has been done on different types of screenings for constipation. In one such study, a means to objectively identify and question whether or not a patient taking clozapine is affected by constipation was investigated. To develop an accurate and objective screening for constipation, the researchers decided to compare the sensitivity, specificity, and positive and negative predictive values of the patient-reported constipation (PRC) method and screening for Rome criteria—the standard for assessing constipation symptoms. Both the PRC method and Rome criteria screening were conducted by trained nurses. In order to determine the accuracy of each screening method, tests were done using a standardized radiopaque marker and wireless motility capsule to determine if the patient truly suffered from constipation. The results of the study showed that both screening methods had low sensitivity and therefore were not helpful in evaluating constipation symptoms [39]. Despite the low sensitivity of the screenings, patients on clozapine should still be monitored for constipation due to the severity of mortality and morbidity of the clozapine-induced gastrointestinal hypomotility [39].

2.2. Adjunctive and Alternatives

With the severity of side effects that clozapine can cause, especially constipation, there have been few studies on the comparison of effectiveness and risk reduction between clozapine and other drugs, or clozapine with an adjunctive. In one such study, the researchers compared the anticholinergic effects of clozapine and olanzapine. Participants received stable therapeutic doses of each drug in their respective group in order to monitor normal hospital use of these drugs. When directly comparing the anticholinergic properties of the drugs, participants treated with olanzapine scored lower on the adverse effects items such as constipation, palpitations, and micturition disturbances [40]. Additionally, the researchers found a statistical trend for the correlation between clozapine dose and anticholinergic effects, but they did not find any significance with the correlation to the olanzapine dose [40]. Additionally, when compared to other antipsychotic drugs such as haloperidol and antiparkinsonians, clozapine has shown significantly higher activity of antimuscarinic activity, while the others had low [34].

Some patients on clozapine still have remaining symptoms, so further research has been done to investigate additional drugs that could be added to the treatment to further decrease symptoms. Orlistat is a weight control medication that has been used successfully as a laxative for patients with severe constipation. The drug inhibits lipase, which decreases the amount of fat absorbed and helps with the passing of stool. This drug is a desirable treatment for patients with mental illness because the drug does not have any central nervous system side effects. Researchers investigated the use of orlistat as an adjunctive treatment for schizophrenic patients on clozapine; a 16-week double-blind randomized controlled trial with treatment group, orlistat 120 mg, and a control placebo was conducted. The Bristol Stool Chart was used to assess participant's stool. During treatment, 35% of patients in the orlistat group shifted from constipated to non-constipated, while there was no significant change in the placebo group [41]. In the group receiving orlistat, the prevalence of constipation decreased unlike those in the control group [41]. The second hypothesis about weight reduction could not be definitively accepted or rejected due to the possibility of weight reduction being linked to bowel emptying [41]. The results of this study showed that orlistat is a potential adjunctive for those on clozapine to reduce constipation. However, in May of 2010, the FDA issued a warning on post-marketing adverse events regarding the risk of severe liver injury in people taking orlistat [42].

Minocycline has been the drug to show the most viability in testing to reduce additional symptoms in schizophrenic patients [43]. In order to investigate adjunctive minocycline to clozapine, a double-blind, randomized controlled trial was conducted. Throughout the study, the side effects of minocycline were monitored, and it was found that the patients in the minocycline group had similar side effects to the placebo group [43]. This warranted

that the medication was well tolerated by the patients. Headaches and constipation were found to be less frequent in the group that used minocycline in addition to clozapine when compared to the control [43]. Although the researchers did not observe gastrointestinal side effects or weight loss in patients taking minocycline, previous studies have found these side effects with higher doses of minocycline, as well as drug-induced lupus [43]. Therefore, patients taking minocycline should be monitored closely for the development of these side effects and treated as necessary. Previous studies were used to determine the efficacy of minocycline as an adjunct to improve positive and negative cognitive symptoms in patients taking clozapine. This study did not find those results, but this may be due to the power of the study. However, they did find that the use of minocycline as an adjunctive showed significantly improved patients' anxiety/depression, avolition, and working memory [43], which are considered core deficits in schizophrenics. With the benefits of improved deficits, previous studies of improved positive and negative symptoms, and the decrease in headache and constipation, minocycline is another top candidate for adjunct therapy with clozapine.

All of these studies were limited by their sample size and power of their investigation, leading to further research needing to be done. With that being said, the preliminary results of these studies show that constipation is a major side effect of clozapine treatment and should be monitored closely. It is recommended by numerous researchers that monitoring patient constipation and prophylactic treatment with laxatives and high fiber diets should become part of the common treatment procedure to prevent the development of ileus or even death in patients taking the drug [33,38,39,41]. Previous studies have shown that the use of laxatives improves gut mobility time in patients taking clozapine, and is effective in countering the clozapine-induced gastrointestinal hypomobility [39]. This approach would be similar to treatment with opioids for opioid-induced constipation. Additionally, adjunctive drugs can be used with clozapine in order to decrease these adverse effects as well.

3. Conclusions

Schizophrenia is a chronic disease requiring treatment to prevent disability and improve the lives of patients who suffer from this disorder. Antipsychotics are the mainstay of treatment, however, there is still a subsection of patients that may be seen as treatment-resistant. Clozapine has been seen as a good alternative for those who have failed treatment with other antipsychotics. This could be due to the fact that clozapine works on not just the dopamine system like first-generation antipsychotics, and not just the dopamine and serotonin dopamine system like second-generation antipsychotics. Indeed, clozapine also works on the glutamate system which could be the reason why it works better for those who are treatment-resistant; however, it also has anticholinergic properties which makes constipation a complication. Studies have shown that constipation is not a complication to be taken lightly, as it can cause an ileus and intestinal blockage leading to rupture and death. This complication has been shown in studies to be due to gastrointestinal hypomobility. Although patients are screened by their physicians for agranulocytosis by weekly lab monitoring, constipation is also a complication that needs to be considered. Much like opioid-induced constipation, this complication can be reduced with the use of laxatives and reduction in the co-prescribing of anticholinergic therapies with clozapine.

Patients who have schizophrenia depend on the treatment of their psychotic symptoms to live as normal a life as possible. Both agranulocytosis and constipation are limiting side effects. The difference is that one is regularly screened for while the other may not be screened for by clinicians. It is important for clinicians to both recognize and treat/ prevent constipation, as treatment options may be limited for those who have failed treatment with other antipsychotics.

Author Contributions: E.S., J.C., C.O.O., and A.N.E. were responsible for the writing of the manuscript. A.N.E., M.C., A.M.K., A.D.K., E.M.C., and A.D.P. was responsible for editing. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data in this manuscript can be found from articles using pubmed.

Conflicts of Interest: None of the authors of this manuscript have any conflicts of interest to be reported.

References

1. Carpenter, W.T.; Buchanan, R.W. Schizophrenia. *N. Engl. J. Med.* **1994**, *330*, 681–690. [CrossRef]
2. Stilo, S.A.; Murray, R. Non-Genetic Factors in Schizophrenia. *Curr. Psychiatry Rep.* **2019**, *21*, 1–10. [CrossRef]
3. Besteher, B.; Brambilla, P.; Nenadić, I. Twin studies of brain structure and cognition in schizophrenia. *Neurosci. Biobehav. Rev.* **2020**, *109*, 103–113. [CrossRef] [PubMed]
4. Mueser, K.T.; Jeste, D.V. (Eds.) *Clinical Handbook of Schizophrenia*; Guilford Press: New York, NY, USA, 2008; p. 650.
5. Treatment-Resistant Schizophrenia—An Overview | ScienceDirect Topics. Available online: <https://www.sciencedirect.com/topics/medicine-and-dentistry/treatment-resistant-schizophrenia> (accessed on 23 May 2021).
6. Pryor, K.O.; Storer, K.P. Drugs for Neuropsychiatric Disorders. In *Pharmacology and Physiology for Anesthesia*; Elsevier, 2019; pp. 241–269. Available online: <https://linkinghub.elsevier.com/retrieve/pii/B9780323481106000120> (accessed on 22 March 2021).
7. Gillespie, A.L.; Samanait, R.; Mill, J.; Egerton, A.; MacCabe, J.H. Is treatment-resistant schizophrenia categorically distinct from treatment-responsive schizophrenia? A systematic review. *BMC Psychiatry* **2017**, *17*, 1–14. [CrossRef] [PubMed]
8. Farooq, S.; Agid, O.; Foussias, G.; Remington, G. Using Treatment Response to Subtype Schizophrenia: Proposal for a New Paradigm in Classification. *Schizophr. Bull.* **2013**, *39*, 1169–1172. [CrossRef] [PubMed]
9. Potkin, S.G.; Kane, J.M.; Correll, C.U.; Lindenmayer, J.P.; Agid, O.; Marder, S.R.; Olfson, M.; Howes, O.D. The neurobiology of treatment-resistant schizophrenia: Paths to antipsychotic resistance and a roadmap for future research. *NPJ Schizophr.* **2020**, *6*, 1–10. [CrossRef]
10. Snyder, S.H. The dopamine hypothesis of schizophrenia: Focus on the dopamine receptor. *Am. J. Psychiatry* **1976**, *133*, 197–202.
11. 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*, 789–796. [CrossRef] [PubMed]
12. Demjaha, A.; Egerton, A.; Murray, R.; Kapur, S.; Howes, O.; Stone, J.M.; McGuire, P. Antipsychotic Treatment Resistance in Schizophrenia Associated with Elevated Glutamate Levels but Normal Dopamine Function. *Biol. Psychiatry* **2014**, *75*, e11–e13. [CrossRef]
13. Khokhar, J.Y.; Henricks, A.M.; Kirk, E.; Green, A.I. Unique Effects of Clozapine: A Pharmacological Perspective. *Adv. Pharmacol. S. Diego Calif.* **2018**, *82*, 137–162.
14. Mamo, D.; Kapur, S.; Shammi, C.M.; Papatheodorou, G.; Mann, S.; Therrien, F.; Remington, G. A PET study of dopamine D2 and serotonin 5-HT2 receptor occupancy in patients with schizophrenia treated with therapeutic doses of ziprasidone. *Am. J. Psychiatry* **2004**, *161*, 818–825. [CrossRef]
15. Meltzer, H.Y.; Matsubara, S.; Lee, J.C. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin2 pKi values. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 238–246.
16. Sur, C.; Mallorga, P.J.; Wittmann, M.; Jacobson, M.A.; Pascarella, D.; Williams, J.B.; Brandish, P.E.; Pettibone, D.J.; Scolnick, E.M.; Conn, P.J. N-desmethylozapine, an allosteric agonist at muscarinic 1 receptor, potentiates N-methyl-D-aspartate receptor activity. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 13674–13679. [CrossRef]
17. Novartis Pharmaceuticals Corporation. CLOZARIL®(Clozapine) Tablets. CLOZARIL-FDA. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/019758s062lbl.pdf (accessed on 1 March 2021).
18. Stepnicki, P.; Kondej, M.; Kaczor, A.A. Current Concepts and Treatments of Schizophrenia. *Mol. J. Synth. Chem Nat. Prod. Chem.* **2018**, *23*, 2087. [CrossRef]
19. Aringhieri, S.; Carli, M.; Kolachalam, S.; Verdesca, V.; Cini, E.; Rossi, M.; McCormick, P.J.; Corsini, G.U.; Maggio, R.; Scarselli, M. Molecular targets of atypical antipsychotics: From mechanism of action to clinical differences. *Pharmacol. Ther.* **2018**, *192*, 20–41. [CrossRef] [PubMed]
20. Humbert-Claude, M.; Davenas, E.; Gbahou, F.; Vincent, L.; Arrang, J.-M. Involvement of histamine receptors in the atypical antipsychotic profile of clozapine: A reassessment in vitro and in vivo. *Psychopharmacology* **2011**, *220*, 225–241. [CrossRef]
21. Evins, A.E.; Amico, E.T.; Shih, V.; Goff, D.C. Clozapine treatment increases serum glutamate and aspartate compared to conventional neuroleptics. *J. Neural. Transm.* **1997**, *104*, 761–766. [CrossRef]
22. Krivoy, A.; Hochman, E.; Sendt, K.-V.; Hollander, S.; Vilner, Y.; Selakovic, M.; Weizman, A.; Taler, M. Association between serum levels of glutamate and neurotrophic factors and response to clozapine treatment. *Schizophr. Res.* **2018**, *192*, 226–231. [CrossRef]
23. McQueen, G.; Sendt, K.V.; Gillespie, A.; Avila, A.; Lally, J.; Vallianatou, K.; Chang, N.; Ferreira, D.; Borgan, F.; Howes, O.D.; et al. Changes in Brain Glutamate on Switching to Clozapine in Treatment-Resistant Schizophrenia. *Schizophr. Bull.* **2021**, *47*, 662–671. [CrossRef] [PubMed]

24. De Berardis, D.; Rapini, G.; Olivieri, L.; Di Nicola, D.; Tomasetti, C.; Valchera, A.; Fornaro, M.; Di Fabio, F.; Perna, G.; Di Nicola, M.; et al. Safety of antipsychotics for the treatment of schizophrenia: A focus on the adverse effects of clozapine. *Ther. Adv. Drug Saf.* **2018**, *9*, 237–256. [CrossRef]
25. Jann, M.W.; Grimsley, S.R.; Gray, E.C.; Chang, W.-H. Pharmacokinetics and Pharmacodynamics of Clozapine. *Clin. Pharmacokinet.* **1993**, *24*, 161–176. [CrossRef]
26. FDA. FDA Strengthens Warning That Untreated Constipation Caused by Schizophrenia Medicine Clozapine (Clozaril) Can Lead to Serious Bowel Problems. Available online: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-strengthens-warning-untreated-constipation-caused-schizophrenia-medicine-clozapine-clozaril-can> (accessed on 1 March 2020).
27. Lieberman, J.A. Maximizing clozapine therapy: Managing side effects. *J. Clin. Psychiatry* **1998**, *59* (Suppl. 3), 38–43.
28. Miller, D.D. Review and management of clozapine side effects. *J. Clin. Psychiatry* **2000**, *61* (Suppl. 8), 14–17, discussion 18–19.
29. Nielsen, J.; Correll, C.U.; Manu, P.; Kane, J.M. Termination of clozapine treatment due to medical reasons: When is it warranted and how can it be avoided? *J. Clin. Psychiatry* **2013**, *74*, 603–613, quiz 613. [CrossRef]
30. Shirazi, A.; Stubbs, B.; Gomez, L.; Moore, S.; Gaughran, F.; Flanagan, R.J.; MacCabe, J.H.; Lally, J. Prevalence and Predictors of Clozapine-Associated Constipation: A Systematic Review and Meta-Analysis. *Int. J. Mol. Sci.* **2016**, *17*, 863. [CrossRef]
31. Citrome, L.; McEvoy, J.P.; Saklad, S.R. Guide to the Management of Clozapine-Related Tolerability and Safety Concerns. *Clin. Schizophr. Relat. Psychoses* **2016**, *10*, 163–177. [CrossRef] [PubMed]
32. Young, C.R.; Bowers, M.B.; Mazure, C.M. Management of the adverse effects of clozapine. *Schizophr. Bull.* **1998**, *24*, 381–390. [CrossRef]
33. Grover, S.; Sahoo, S.; Hazari, N. Clozapine-Related Constipation: A Retrospective Study. *Indian J. Psychol. Med.* **2019**, *41*, 485–487. [CrossRef]
34. de Leon, J.; Odom-White, A.; Josiassen, R.C.; Diaz, F.J.; Cooper, T.B.; Simpson, G.M. Serum antimuscarinic activity during clozapine treatment. *J. Clin. Psychopharmacol.* **2003**, *23*, 336–341. [CrossRef] [PubMed]
35. Chougule, A.; Praharaj, S.K.; Bhat, S.M.; Sharma, P.S.V.N. Prevalence and Factors Associated with Clozapine-Related Constipation: An Observational Study. *J. Clin. Psychopharmacol.* **2018**, *38*, 42–46. [CrossRef] [PubMed]
36. Kishi, T.; Fujita, K.; Furukawa, O.; Suzuki, T.; Moriwaki, M.; Nitta, M.; Hattori, M.; Tsunoka, T.; Chekuri, R.; Kane, J.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*, 200–207. [CrossRef]
37. Ingimarsson, O.; Maccabe, J.; Sigurdsson, E. Constipation, ileus and medication use during clozapine treatment in patients with schizophrenia in Iceland. *Nord. J. Psychiatry* **2018**, *72*, 1–4. [CrossRef]
38. Every-Palmer, S.; Nowitz, M.; Stanley, J.; Grant, E.; Huthwaite, M.; Dunn, H.; Ellis, P. Clozapine-treated Patients Have Marked Gastrointestinal Hypomotility, the Probable Basis of Life-threatening Gastrointestinal Complications: A Cross Sectional Study. *EBioMedicine* **2016**, *5*, 125–134. [CrossRef]
39. Every-Palmer, S.; Inns, S.J.; Ellis, P.M. Constipation screening in people taking clozapine: A diagnostic accuracy study. *Schizophr. Res.* **2020**, *220*, 179–186. [CrossRef]
40. Chengappa, K.N.R.; Pollock, B.G.; Parepally, H.; Levine, J.; Kirshner, M.A.; Brar, J.S.; Zoretich, R.A. Anticholinergic differences among patients receiving standard clinical doses of olanzapine or clozapine. *J. Clin. Psychopharmacol.* **2000**, *20*, 311–316. [CrossRef]
41. Chukhin, E.; Takala, P.; Hakko, H.; Raidma, M.; Putkonen, H.; Räsänen, P.; Terevnikov, V.; Stenberg, J.-H.; Eronen, M.; Joffe, G. In a randomized placebo-controlled add-on study orlistat significantly reduced clozapine-induced constipation. *Int. Clin. Psychopharmacol.* **2013**, *28*, 67–70. [CrossRef]
42. Research C for DE and FDA Drug Safety Communication: Completed Safety Review of Xenical/Alli (Orlistat) and Severe Liver Injury. FDA. 28 June 2019. Available online: <https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-drug-safety-communication-completed-safety-review-xenicalalli-orlistat-and-severe-liver-injury> (accessed on 21 June 2021).
43. Kelly, D.L.; Sullivan, K.M.; McEvoy, J.P.; McMahon, R.P.; Wehring, H.J.; Liu, F.; Warfel, D.; Vyas, G.; Richardson, C.M.; Fischer, B.A.; et al. Adjunctive Minocycline in Clozapine-Treated Schizophrenia Patients with Persistent Symptoms. *J. Clin. Psychopharmacol.* **2015**, *35*, 374–381. [CrossRef]