PARAMETERS OF CLOZAPINE TREATMENT IN PATIENTS WITH TREATMENT-RESISTANT SCHIZOPHRENIA

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A project submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

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Declaration

It is hereby declared that

1. The project submitted is my own original work while completing degree at Brac University.
2. The project does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The project does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The project titled "Parameters of Clozapine Treatment in Patients with Treatment-Resistant Schizophrenia" submitted by Nusrat Jahan (18146075) of Spring, 2018 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on November 2022.

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Ethics Statement

This study does not involve any kind of human or animal trials.

Abstract

Treatment-resistant schizophrenia (TRS) is familiar to one in three schizophrenia patient and clozapine is referred as only drug which has the approval for the remedy of TRS. After identifying TRS, clozapine treatment should not be delayed in order to achieve remission. Long delays of prescribing clozapine take place because of the concern over adverse effects, proper monitoring procedure and inexperience at prescribing. For this reason, patients do not achieve favorable outcomes and they are exposed to unnecessary health risks. In this study, clozapine use in TRS, guidelines and strategies to overcome risks and initiate early treatment literature are reviewed. Based on all of these, a review of parameters of clozapine treatment in TRS patients has been summarized in this study with proper evidence.

Keywords: TRS, Clozapine, Neurobiology, Adverse Effects.

Dedication

Dedicated to my parents.

Acknowledgement

At first, I want to say thanks to my respected supervisor Tanisha Momtaz, Lecturer, School of Pharmacy, Brac University. This project could not be completed without the support her. Words are not enough to show my gratitude to this extremely brilliant, kind-hearted and most importantly, a patient soul.

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List of Acronyms

TRS	Treatment-Resistant Schizophrenia
DSP Hypothesis	Dopamine Supersensitivity Hypothesis
DRD2	Dopamine D2 Receptor
NMDA	N-Methyl-D-Aspartate
GABA	Gamma-Aminobutyric Acid
FDA	US Food and Drug Administration
EMA	European Medicines Agency
BPRS	Brief Psychiatric Rating Scale
CGI-S-TRS	Clinical Global Impressions- Severity TRS Scale
PANSS	Positive and Negative Syndrome Scale
SANS	Scale for the Assessment of Negative Symptoms
SAPS	Scale for the Assessment of Positive Symptoms
EOS	Early-Onset Schizophrenia
ANC	Absolute Neutrophil Count
BEN	Benign Ethnic Neutropenia
CYP1A2	Cytochrome P450 1A2
BNP	B-type Natriuretic Peptide
Pro-BNP	Pro-B-Type Natriuretic Peptide
DSFS	Drooling Severity and Frequency Scale
NHRS	Nocturnal Hypersalivation Rating Scale
CRP	C-Reactive Protein
HR	Heart rate

Chapter 1

Introduction

1.1 Background

Schizophrenia is a chronic, severe mental illness that has an impact on a person's relationships with others as well as their thinking, acting, and emotional expression. Despite not being as prevalent as other severe mental illnesses, schizophrenia can be the most persistent and incapacitating. It is combined of widely complicated symptoms which can be classified into 'positive', 'negative' and 'cognitive' categories. In short, positive which does not really mean positive can be identified by unorganized behaviors and imaginary thoughts. For example, repeated psychosis, which means "lack of awareness" and is characterized by hallucinations, delusions, and perplexing behavior. Negative symptoms, in contrast to positive symptoms, mostly include social isolation, emotional numbness, anhedonia (the inability to enjoy pleasure), and reduced initiative and energy. Finally, cognitive symptoms emerge as generalized cognitive deficits (Kahn et al., 2015).

Therapies that target postsynaptic dopamine receptors, in particular, are not always beneficial. Patients suffering from unpleasant symptoms as well as treatment-resistant schizophrenia (TRS). TRS is recognized as an insufficient response to at least two distinct antipsychotics provided with adequate quantities, periods, and tolerability (Buckley, 2020; Howes et al., 2017; Kane et al., 2019). Clozapine has been the only TRS medication that is authorized by regulatory bodies in North America, Europe, and a number of different countries. The drug is a derivative of tricyclic dibenzodiazepine that binds to serotonin, dopamine as well as some muscarinic receptors. Although its poor reactivity for D2 dopamine receptors may account for its absence of extrapyramidal health risks, its glutamate regulating properties might increase higher effectiveness

within TRS. Clozapine is more successful in treating TRS than all other antipsychotic medications, minimizing rehospitalizations and all-cause fatality (Kaar et al., 2020; McQueen et al., 2021; Mizuno et al., 2020; Taipale et al., n.d., 2018; Tiihonen et al., 2009; Wagner et al., 2021).

Some analysis of casual tests observed that clozapine provided significant improvement in symptoms with less treatment than all other second-generation antipsychotic medications, reducing treatment dropouts as well as hospitalization threat. Risk hospitalization rates in patients taking clozapine relatives 0.817 (95% CI 0.725-0.920; P = 0.001) based on research from approximately 50,000 patients (Masuda et al., 2019). However, despite having strong recommendation due to efficacy, clozapine is not used spontaneously. Many patients do not initiate clozapine treatment because of trialing antipsychotic polypharmacy. Clozapine is not widely used because of its adverse effects, the checking process attributed along with the use, and insufficient prescribing knowledge (Bachmann et al., 2017; Correll et al., 2019; Farooq et al., 2019; Howes et al., 2012; Nielsen et al., 2010; Singh et al., 2020; Thien & O'Donoghue, 2019).

Although it is conceivable. to identify or assume TRS at first, doctors typically do not recommend clozapine as the first-line treatment for schizophrenia due to the risk of serious adverse effects that may be associated with it. Furthermore, it is advised that patients taking clozapine have hematological checking, especially during the first six months of treatment when the risk of agranulocytosis is greatest. The potential for adverse cardiovascular, metabolic, gastrointestinal, and neurological effects should also be taken into consideration by clinicians. Some of these effects may be treated by lowering the dose or titrating the dosage while continuing to monitor patients frequently.. (de Berardis et al., 2018) (Nielsen et al., 2016) (Nielsen et al., 2013).

1.2 Aim

Aim of this review is to emphasize early initiation of clozapine treatment with TRS patients. Some parameters should be followed to avoid clinical complication of clozapine such as types of patients, Therapeutic Drug Monitoring (TDM), adverse effects etc. This review also prioritize on showing the effectiveness of clozapine as the only drug for TRS. Keeping aside some clinical complications, proper monitoring and early prescribing of clozapine can reduce risk of Treatment-Resistant Schizophrenia.

Chapter 2

Methodology

This review is based on recently published scientific studies and articles from journals that contain pertinent data. About more than 170 papers have been initially sorted and almost 100 papers have been revised to generate this review study. Research Gate, PubMed, Science Direct, Elsevier etc. are the websites which have been used to gather information for this review, in which the major publications include Nature, Journal of Medicine, Journal of Psychiatry and Neuroscience, The American Journal of Psychiatry, Science, Journal of Psychiatric Research etc. In order to make a satisfactory review on “Parameters of Clozapine Treatment in Patients with Treatment-Resistant Schizophrenia.” Mendeley software is used for adding refference to give credit to the work of the authors.

Chapter 3

Treatment-Resistant Schizophrenia

Treatment-resistant schizophrenia (TRS) refers to the tenacity of symptoms after more than two trials of antipsychotic medications of sufficient dose and timing. Generally, TRS is common in up to 34% of patients with schizophrenia. Along with negative or cognitive persistent symptoms, positive persistent symptoms mostly define the features of TRS. From the very first episode of psychosis, TRS is supposed to be present or it may develop later with the progression of disease. The ultimate results for patients with TRS may be improved if it is identified earlier than being untreated for a long time (Kane et al., 2019) (Dempster et al., 2021).

3.1 Neurobiology of TRS

3.1.1 Dopamine Supersensitivity Hypothesis

Blockade of dopamine D2 receptor (DRD2) is supposed to be the main mechanism of action for antipsychotics. This theory proposes that when blockade of DRD2 occurs continuously, it causes change in dopamine creating some venomous activity which cannot be treated properly after starting antipsychotics. This sequence of events is designed to result in the need to increase antipsychotic drug dosage in order to stabilize clinical signs, as well as quick dropout throughout any revocation or decrease of an antipsychotic drug, or as acceptance improves to continue treatment with heretofore recommended levels of antipsychotics (Kaar et al., 2020) (Demjaha et al., n.d.) (Brugger et al., 2020).

It is suggested that dopaminergic alterations caused by sustained receptor blockage with an antipsychotic treatment entail increases in DRD2 receptor density. Higher dose of antipsychotic drug in order to manage additional leveling up in DRD2 density causes dopamine supersensitivity increase as well as symptom reemergence. It also signifies that TRS is likely to relate to the

duration of antipsychotic treatment; nonetheless, positive symptoms of schizophrenia diminish with age rather than increasing, as the DSP theory suggests (Elkis & Buckley, 2016) (Vita et al., 2019).

3.1.2 Hyperdopaminergic and Normodopaminergic Subtypes Hypothesis

The argument has been contended that not every schizophrenic individual have striatal hyperdopaminergic activity, and that certain individuals with TRS have regular or even hypodopaminergic dopamine restrictions. According to positron emission tomography studies, patients with treatment-responsive schizophrenia have much higher in vivo dopamine synthesis capacity in the striatum than individuals with TRS, who have dopamine synthesis capacity comparable to healthy controls. The ability of the striatum to synthesize dopamine has been shown to be reduced throughout clozapine-responsive TRS patients compared to healthy controls or patients without TRS. A new analysis of the first patients produced proof of that one (i.e., variations manifest from onset of the disease), with rising striatal dopamine synthesis capabilities in first-episode patient populations who responded to antipsychotic medication but undistorted synthesis of dopamine capacity in first-episode patients who were unable to react to the treatment of antipsychotics. This data shows that dopaminergic subtypes of schizophrenia may be resistant to treatment from the start (Vita et al., 2019) (Beck et al., 2019) (Brugger et al., 2020).

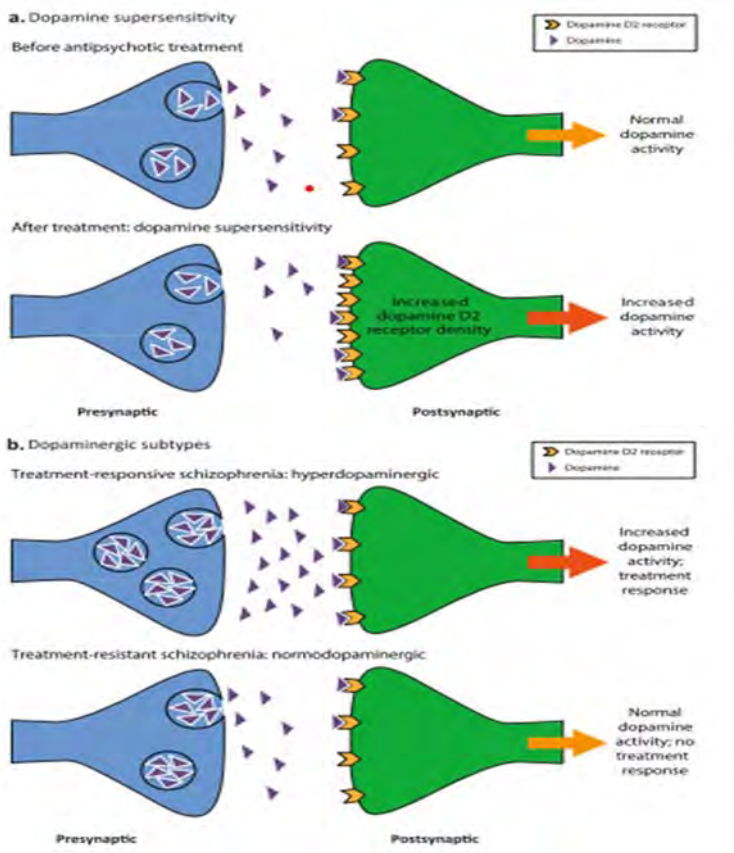

Figure 1: Dopaminergic pathways of TRS; a. Supersensitivity of dopamine, b. Subtypes of dopamine (Adapted from (Potkin et al., 2020)

3.1.3 Hypothesis of Glutamate

Even though disorder of dopamine undoubtedly adds value to schizophrenia clinical signs in several individuals, the inability of antipsychotic dopamine blocking to regulate illness in some patients suggests that some other types of neurotransmitters play a role in the genesis of TRS, as proposed by the subtype theory. The hypothesis of glutamate posits hyperactivity of dopamine which occurs GABA posterior and chemical imbalances of glutamate. It is supposed as widely accepted explanation for such interaction of additional neurotransmission in schizophrenia neurobiology. According to the theory of glutamate, NMDA receptor failure on

GABA interneurons induces glutamate neurons in cortex and hippocampus to the basal ganglia to become uninhibited. This high expression increases reactivity of dopaminergic estimations from the middle of the brain to the forebrain where is the striatum which occurs positive schizophrenia symptoms. (Jauhar et al., 2018) (McQueen et al., 2021; Pillinger et al., 2019).

Chapter 4

Clozapine

4.1 History of Clozapine

Clozapine is an atypical or second-generation antipsychotic drug which had been revealed for the first time by scientists of Wander Laboratories while screening tricyclic compounds for antidepressant activity. Clozapine was regarded "atypical" or "defective" at the time because it had necessary extrapyramidal adverse effects, which restricted initial interest in the molecule. Furthermore, it was found that this atypical antipsychotic (which had no clear extrapyramidal effects) showed great clinical effectiveness across a wide range of symptom domains (Albitar et al., 2020).

As clozapine's use increased throughout European countries, a concerning clinical effect started to restrict its acceptance. According to a Finnish study, 16 individuals developed agranulocytosis, and 8 died from life-threatening illnesses. Because of this revelation, clozapine use has been drastically restricted, and research on the medication has been halted. Despite being virtually removed, limited utilization of clozapine persisted, particularly for individuals who were resistant of other medications and required extremely cautious blood checking (Hynes et al., 2015) (Yuen et al., 2021).

Clozapine's reintroduction in 1989 radically altered the treatment paradigm to people with resistant psychosis. For many patients, it appeared to reduce psychosis and allow them to be managed as outpatients. However, as clozapine became more popular, many other potential side effects of clozapine were discovered, including overweight, myocarditis, seizures and diabetes, which, when combined with the need for frequent blood monitoring, tended to limit the use of this most intriguing drug to a very narrow range of patients. Clozapine is still severely under prescribed by

psychiatrists, with estimates indicating that just 5%-20% of clozapine-eligible patients receive therapy. Many more "atypical" medicines were developed after the launch of clozapine; but none of them matched the benchmark of effectiveness set by clozapine. This has highlighted the need of reconsidering the pharmacology of clozapine and refocusing emphasis on a medicine that may be our greatest option for treating a range of schizophrenia and schizophrenia-related diseases (Khokhar et al., 2018).

4.2 Mechanisms of action of Clozapine

Clozapine broke the mold of first-generation antipsychotics by demonstrating clinical effectiveness without a strong dopamine D2 receptor blockage, lowering the likelihood of extrapyramidal side effects. Clozapine appears to be acting through serotonergic, noradrenergic, and glutamatergic receptors in addition to dopamine receptors, according to imaging and pharmacological investigations, while conventional antipsychotics exhibit strong striatal dopamine receptor binding. Clozapine's actions have significantly enhanced our understanding of the molecular basis of schizophrenia, giving birth to additional atypical medications that operate, for example, on serotonin 5-HT2A and dopamine D2 receptors. It has also been proposed that the activity of clozapine is influenced by its blockage of norepinephrine alpha 2 receptors and potential modulatory effects on an abnormal glutamatergic system (Kaar et al., 2020) (Renzenbrink & Wand, 2021).

4.3 Clozapine treatment for TRS

4.3.1 Initiating Treatment

There are some major factors which affect clozapine levels in the blood including increased accumulation of blood of clozapine, advanced age, female hormones, people from Asia/Native American, overweight, swelling for fast titration of clozapine, excess caffeine consumption, valproate coadministration, downregulation of CYP1A2 , administration of associated CYP1A2 inhibitors etc. On the other hand, clozapine blood levels are decreased by tobacco as well as some CYP1A2 persuaders such as phenobarbital, phenytoin and topiramate at doses above 400 mg/day. Although caffeine and tobacco use are common, patients should be careful not to avoid taking these substances daily since consequences on the digestion of clozapine could be compensated by dose adjustments. Although it is not established but in few studies it was found that the relevant changes were associated with consuming > 3 cups of coffee or > 6 cans of caffeinated beverages in smokers and > 1 cup of coffee or > 2 cans of caffeinated beverages per day in non-smoking patients (Albitar et al., 2020; Clark et al., 2018; Leon et al., 2022; Ruan et al., 2019).

Inflammation decreases enzymatic activity of CYP1A2 and increases blood levels of clozapine and so halving the dose of clozapine is recommended in critically ill patients till the sufferer is afebrile for 3 days. Afterwards, previous clozapine administration can be resumed. Trough plasma levels of clozapine involved into some favorable drug reaction are naturally estimated at 350 ng/mL, although levels above 600 ng/mL carry an increased risk of dose-related adverse events such as seizures. Therefore, therapeutic drug monitoring should aim for the lowest effective level of clozapine. Some patients respond in enhanced level of clozapine and might justify higher doses in combination with the use of prophylactic anticonvulsant therapy (Remington et al., 2013; Siskind et al., 2021).

As the medication is initiated in a hospital, the recommended initial dose is 12.5 mg once or twice daily on day 1, then the regular dose should be increased from 25–50 mg to a minimal dose if tolerated (generally 250–450 mg/day for adults, depending on sex, race, and smoking status). On the first day, 12.5 mg should be given to the elderly, where daily dose increment is 25 mg. A slower titration should be used in outpatient settings or other settings where patients are not constantly monitored (Beck et al., 2014). Most TRS patients will transit from unsuccessful antipsychotic treatment. The unsuccessful antipsychotics must be lessened at the starting of medication. Moreover, the ineffective antipsychotic should be kept persistent for the week 1 when clozapine titration is started, after that reduced by about 25% per week, depending on the severity of the spill and symptoms, stability, burden of side effects. The decreasing rate for ineffective antipsychotics needs the adjustment according to titration rate, adverse effect of unsuccessful antipsychotics and conflicted treatments, patient's tolerability and respond on treatment (Beck et al., 2014).

4.3.2 Monitoring for Side Effects and Measuring Response during Treatment

Clozapine has some side effects such as constipation, lightheadedness, lethargy, neutropenia, sialorrhea, tachycardia, and excess weight are common side effects, as are potentially fatal events such as agranulocytosis, myocarditis, cardiomyopathy, pneumonia, and epilepsy. For this reason, it needs to be monitored following established protocols, especially during the first months of treatment. Throughout the sensitive time, therapeutic drug monitoring (TDM) offers helpful responses to administrate drugs and adherence confirmation. Supervision is also essential for

sensing and managing negative consequences, otherwise, the whole thing will influence on the agreement of treatment (Nielsen et al., 2013; Wagner et al., 2021).

Table 1: Positive and Negative Syndrome Scale-6 (PANSS-6) (Adapted from (Østergaard et al., 2016))

PANSS – 30 Item	Item
P1	False beliefs
P2	Disruption of basic ideas
P3	Imaginary visions
N1	Inability to express emotions
N4	Isolation from society
N6	Absence of motivation

4.3.3 Testing Period of Clozapine

Treatment Response and Resistance in Psychosis (TRRIP) Consensus guidelines indicate that once the therapeutic plasma level is achieved, Patients need to take clozapine under close observation for at least 12 weeks. The duration might take more time and it should be done before evaluating response, otherwise, it would be intolerable for the patients. Individuals with severe adverse effects, aggressive behavior, serious rate of self-harm, testing period of minimum 16 weeks aggressive behavior, serious rate of self-harm, testing period of minimum 16 weeks or more is

required to examine the reaction, otherwise, that will be unacceptable (Howes et al., 2017; Wagner et al., 2020).

4.3.4 Cancellation of Clozapine Treatment

The cancellation of clozapine relies on efficacy, adherence, tolerability, occurrence about life harming clinical signs. If the matter does not rely on necessity, dose of clozapine must be lessened within 6 months depending on response history, tolerability and side effect profile. Whatever the reason for withdrawal, patients must be constantly supervised for the occurrence or exacerbates of mental illness. After that, monitoring of absolute neutrophil counts should be continued for 2 weeks after discontinuation (Blackman et al., 2022).

4.3.5 Therapeutic Drug Monitoring

If sick people tolerate and react appropriately, TDM is not required. This is fruitful at the time of starting clozapine therapy and maitaining, if symptoms are present. Recurrence, occurrence of negative signs are supposed to be drug-related, or sudden change in some factors which affect the blood, for example tobacco consumption. Lower confirmity to treatment is a common reason for not responding which might be identified with TDM. Lower concentrations of blood can take place for the pharmacokinetic effects (Hiemke et al., 2018) (Schoretsanitis et al., 2020).

The dose of clozapine is needed to reach and keep serum concentrations within the level of therapy differs widely from patient to patient. Even in stable patients, there could be significant intra-individual modification in serum concentration. On the other hand, there are several individuals who only respond when the blood clozapine level is above the reference range (350–600 ng/mL) (Stark & Scott, 2012; Turrion et al., 2020). TDM gives result directly in blood levels and does not wait for symptomatic reactions or negative signs because it is a useful tool to support dosage

decisions. In addition, TDM has the potential to increase the confidence of prescriber. Lower/reduced doses is required for individuals who have hepatic or renal disorder (Kane et al., 2019; Kitchen et al., 2021; Schoretsanitis et al., 2020).

Table 2: Therapeutic drug monitoring (TDM)-informed decision-making algorithm for clozapine-treated patients (Adapted from (Schoretsanitis et al., 2020))

Clozapine level	Response	Tolerability	Action
Subtherapeutic (< 350 ng/ml)	Insufficient	Intolerable	Boost the dose gradually to the recommended ranges and, treat any adverse reactions.
	Insufficient	Tolerable	Enhance the dose to recommended range.
	Sufficient	Intolerable	Try reducing the dose.
	Sufficient	Tolerable	Neither modifications are required; proceed with normal adverse effects checking.
Within reference rang (350- 600 ng/ml)	Insufficient	Intolerable	If adverse reactions are tolerated, regard them and gradually boost the dose while remaining within the recommended ranges.
	Insufficient	Tolerable	Gradually boost the dose while remaining within the recommended ranges.
	Sufficient	Intolerable	If therapeutic efficacy does not enhance, reduce the dose, supervise to stay within the recommended ranges.
	Sufficient	Tolerable	Keep an eye on things.
Subtherapeutic (> 600 ng/ml)	Insufficient	Intolerable	Try lowering the dose and tracking. Take into account prophylactic anticonvulsant.
	Insufficient	Tolerable	

	Sufficient	Intolerable	Assess a gradual dose expansion or boosting. Among both, a prophylactic anticonvulsant should be taken into account.
	Sufficient	Tolerable	Reduce the dose gradually and supervise to ensure that it remains within the recommended ranges. Keep an eye on the concentrations. Be mindful for favorable safety and recognize prophylactic anticonvulsant medication.

Chapter 5

Categorization of Patients

5.1 Children

It is stated by both the EMA (European Medicines Agency) and the FDA (U.S Food and Drug Administration) efficacy and security of using clozapine is not established for the children. Conversely, Clozapine treatment is recommended by the UK National Institute for Health and Care Excellence (NICE) and Canada for patients with early-onset schizophrenia (EOS) who meet TRS criteria. From an analysis it was found that efficacy, tolerance level of clozapine was as similar as adults. On that review, most patients treated for EOS were reported facing sedation and sialorrhea (Krause et al., 2018; Siskind et al., 2020) (Abidi et al., 2017).

5.2 Older Adults

Anticholinergic adverse effects in individuals with tachycardia and orthostatic hypotension with impaired heart function, and bowel system problem among elderly, as few older adults had been engaged in the reviews which notified the range of FDA. Care must be taken regarding the action. EMA strongly recommends starting treatment with a low dose and titrating slowly. Another analysis about using clozapine of elderly identified a reduction of careful trials and reviewed ta standard efficacy based on some other research. Comorbidities and concomitant treatments should be carefully considered, taking into account the potential benefits and risks of individual patients (Renzenbrink & Wand, 2021) (Nielsen et al., 2016)

5.3 Pregnancy

Treatment with clozapine has not been prohibited for pregnant women according to FDA or EMA. However, the relatively small number of studies warrants caution and additional oversight. The

World Federation of Societies of Biological Psychiatry does not recommend treatment with clozapine to pregnant women due to adverse event profile like epilepsy, metabolic problem etc. (Renzenbrink & Wand, 2021) (Hasan et al., 2012).

An analysis of the results of continuing clozapine according to few proofs, decided continuation of clozapine during pregnancy requires close monitoring. This decision must take into consideration the significant negative signs to the untreated schizophrenia mother and fetus/child. Use of clozapine during breastfeeding is generally contraindicated as clozapine can be found in breast milk (Fortinguerra et al., 2009; Hasan et al., 2012; Mcallister-Williams et al., 2017; Payne, 2019; Thanigaivel et al., 2021).

Chapter 6

Adverse Effect Checking

6.1 Agranulocytosis

Agranulocytosis refers to deadly reduction in absolute neutrophil count to levels below 500/mm3 which raises inflammation vulnerability. It happens rapidly in the first month of medication with clozapine and affects about 1% of patients receiving treatment. The signs are unpredictable which does not depend on doses (Mijovic & MacCabe, 2020) (Flanagan & Dunk, 2008; Myles et al., 2018).

It is suggested from the studies that it has occurrence of so many genes, including the solute carrier organic anion transporter 1B3/1B7 and members of the human leukocyte antigen complex. Benign ethnic neutropenia (BEN) may be present on the people of African, Middle Eastern, or West Indian descent where the absolute neutrophil counts 1000–1800/mm3. The lower baseline neutrophil levels need a separate checking (Legge & Walters, 2019) (Oloyede et al., 2021). Blood counts have been shown to prevent mortality and are needed for all treated patients. The FDA mandates weekly monitoring for the first 6 months of treatment. If the absolute neutrophil count remains ≥1500/μL (≥1000/μL for BEN), monitoring can be reduced to biweekly for the next 6 months, then monthly. EMA requires weekly monitoring of absolute neutrophil counts for the first 18 weeks of treatment and then monthly throughout treatment (Nielsen et al., 2016).

6.2 Myocarditis

There is the possibility of rare myocarditis in the treatment of clozapine. Myocarditis is a serious condition which involves infection in the myocardium which usually occurs in the first period (month) of medication. In a study where 258,961 people took clozapine, it was found that the rate of myocarditis is 0.7% (95% CI 0.3–1.6) and the cardiomyopathy rate is 0.6% (95% CI 0.2–2.3).

Additionally, some studies of short- and long - term myocarditis which are related to retrospectively identified myocarditis or sensitive laboratory tests such as the cases which are defined as flu-like symptoms plus ≥ 1 symptom/sign of cardiac dysfunction plus ≥ 1 indicative diagnostic abnormality and no evidence of a viral cause etc. implies that the occurrence can be higher. (Bellissima et al., 2021; Manu et al., 2017; Sandarsh et al., 2021; Siskind et al., 2020).

6.3 Gastrointestinal Hypomotility

Use of clozapine can occur gastrointestinal hypomotility, which can lead to constipation, which raises the risk of paralytic ileus and pseudo-obstruction, gastroparesis or dysphagia, aspiration pneumonia, and death. An analysais of 32 studies (n = 2,013 patients) exposed that the cumulative incidence of clozapine-related constipation was 31.2%. On the other hand, a complete study of articles until 2010 demonstrated a rate of death of 15.0-27.5% for life-threatening gastrointestinal hypomotility, while 43.7% for patients developing paralytic ileus. During the first 4 months of treatment, the patients have the highest risk and it stays during the treatment. The risk gradually rises while aging and clozapine dose and it is higher in patients who are receiving concomitant treatment with anticholinergic medications, other medications with anticholinergic properties, or opioids (Cohen, 2017; Every-Palmer et al., 2019; Shirazi et al., 2016).

6.4 Pneumonia

The risk of pneumonia is higher with clozapine than with other second-generation antipsychotics, and clozapine-associated pneumonia has a higher mortality rate than the well-known cardiovascular and hematologic side effects. Associated effects, such as miscarriage, sedation, and dysphagia/diminished gastrointestinal motility, might involve to increased negative signs of

aspiration and development of pneumonia. Additionally, blood levels of clozapine might raise when an inflammation gets detected (Hynes et al., 2015).

Clozapine therapy may need to be reduced or stopped until symptoms resolve. This highlights the importance of using the most effective clozapine dosage to reduce the risk of side effects, while keeping an eye out for signs of respiratory infections. Family members and healthcare workers must be educated about the risks, risk factors, and signs of pneumonia (de Leon et al., 2020)

6.5 Sialorrhea

A common negative effect of clozapine treatment (incidence up to 90%) is bleeding and it also may decrease the tolerability and acceptance. Clozapine-associated bleeding might raise risk of pneumonia in frail patients and it must be checked every time. These are identified in concise adverse effects scales (eg, GASS-C) and can be further monitored using, such as the two-item Drooling Severity and Frequency Severity Scale (DSFS) or the five-point Nocturnal Hypersalivation Rating Scale (NHRS) which may include dose reduction of clozapine, if possible, and anticholinergics. Preparations that limit toxicity must be utilized and care is a must to ignore intentional or accidental consumption of toxic amounts, and they should be avoided in patients who have difficulty following directions for use. In some severe cases, injection of botulinum toxin B into the salivary gland may be considered when other approaches have been failed (Ishikawa et al., 2020) (Steinlechner et al., 2010).

Chapter 7

Conclusion

To conclude, clozapine is only prescribed medicine to treat TRS. Patients who has met the categories for TRS should be treated immediately after getting diagnosed. It will improve the chance of remedy using clozapine. However, adverse effects, careful monitoring and less experience of prescribing clozapine can lead to the chances of failing to get the best result and create a path of higher risk due to mistreatment (Kane et al., 2019). Many more "atypical" medicines were developed after the launch of clozapine; but none of them matched the benchmark of effectiveness set by clozapine. This has highlighted the need of reconsidering the pharmacology of clozapine and refocusing emphasis on a medicine that may be the best option for treating a range of schizophrenia and schizophrenia-related diseases (Khokhar et al., 2018).

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