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# SELECTED NEUROLOGIC AND PSYCHIATRIC OUTCOMES IN PATIENTS TREATED WITH CLOZAPIN

**(Review Article)**

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**Abstract**

*Clozapine is a second-generation antipsychotic mostly used for treatment-resistant schizophrenia and acute suicidality. Although clozapine's efficacy is well-documented, it has various side effects which need to be promptly addressed. In this article, we focus on neurological and psychiatric side effects. Among these side effects, seizure is a well-known complication of clozapine therapy. The articles that we reviewed concerning seizures and EEG changes in association with clozapine plasma levels and doses, found significant relations in some but not all cases. In addition to seizures, extrapyramidal side effects are common adverse effects of clozapine which can be an acute or chronic condition. Clozapine is also associated with ocular disturbances such as retinal pigmentation. It has also been shown to cause cataplexy. Moreover, clozapine can cause significant sedation. Effects of clozapine on sleep is still a controversial subject. The studies demonstrate inconsistent results. Cholinergic rebound syndrome is a rare complication of longterm clozapine use, which itself can be the inducer of insomnia. Apart from this, hypersalivation is one of the most frequent side effects with a paradoxical pathophysiology. Finally, clozapine is associated with severe psychiatric side effects, some of which need prompt intervention.*

## EEG Changes and Seizures

### Introduction

A seizure is an important and well-known side effect of clozapine treatment. Patients on this drug can develop seizures at all phases of the course: at low doses during titration and at higher doses during maintenance [1]. We reviewed the articles that assessed plasma levels of clozapine, doses of clozapine, or both and their relation to seizures and electroencephalogram changes.

### EEG abnormalities

EEG changes can be epileptiform (focal, generalized spikes, or sharp waves) or nonepileptiform (focal or generalized slowing). One of the articles that we reviewed analyzed 12 different papers that provided data about EEG changes in 565 patients on clozapine treatment [1] Another source that we utilized was a study on 26 patients from Japan [2]. In both papers, the authors described the EEG abnormalities. Varma et al. found that although a variety of changes were noted, the most common abnormality was nonspecific generalized slowing waves, while Kikuchi et al. found spike and wave complexes to be more common.

### Clozapine dose and EEG relationship

Using the regression model Varma et al. found a significant relationship between the mean dose of clozapine and the percentage of patients with EEG changes. According to the paper, every increase in mean clozapine dose by 100mg resulted in 8% increase in patients with abnormal EEG findings (0.08, 95% confidence interval [CI] 0.01-0.15, p=0.022) [1]. On the other hand, Kikuchi et al. describe EEG changes in 10 out of 26 patients studied (38.5%) with a daily dose of clozapine varying from 125mg to 600mg with a mean of 305mg daily. In this case, a significant relationship was not seen between EEG changes and mean dose of clozapine but found that mean age and mean illness duration in the abnormal EEG group were significantly lower ($p<0.01$) [2].

### Clozapine plasma levels and EEG relationship

According to Varma et al., a significant relationship was found between the two with regression analysis [1]. A 12% increase was noted in the percentage of patients with abnormal EEG with each 100µg/l increase in clozapine plasma level (0.12, 95% CI 0.03-0.21, p=0.023). Kikuchi et al. study did not investigate plasma level relation to EEG changes [1].

### EEG changes and seizure relationship

Some of the studies that Varma et al. used theorized that seizures are not necessarily predicted by EEG changes (exemplifying a case report about a patient with myoclonic seizure with a normal EEG before the event). On the other hand, they conversed in a study that found EEG changes as a sensitive indicator to seizures [1].

### Seizures

Varma et al. used 10 different studies where 113 patients out of 6344 seizures. According to Kikuchi et al., 6 out of 26 had seizures. Varma et al. states that in all studies that they reviewed clozapine-induced seizure risk was higher compared to 1% risk associated with conventional antipsychotics [1]. In one of the papers, premarketing studies were analyzed that reported seizures at a crude rate of 3.5% over the course of a year. Other studies found that seizure risk was increasing cumulatively and reached 10% in 3.8 years of the drug therapy. Post marketing study in the US reported seizures in 1.3% of patients in the first 6 months of drug release. In terms of seizure types, the majority of them were generalized tonic-clonic type, while 4 out of 6 patients had myoclonic seizures as stated by Kikuchi et al [2].

### Clozapine dose and seizure relationship

Varma et al. carried out a regression analysis and did not find a significant relationship between clozapine dose and seizures ($p=0.353$), although, in general, higher clozapine dose is correlated with increased risk of seizures [1]. Most case reports described seizures in patients taking more than 600mg of clozapine daily. However, a post marketing study failed to find dose-related risk for seizures. Kikuchi et al. found that clozapine dose varied from 300mg to 600mg with a mean of 383.3mg/day at the time of a first seizure experienced by the patients [2].

### Clozapine plasma levels and seizure relationship

Varma et al. found a statistically significant relationship between plasma levels of clozapine and seizures. They based this on 3 case reports about 4 patients. According to the study, clozapine plasma levels of more than 1300μg/l were associated with increased risk of seizures [1]. It is worth mentioning that patients with preexisting seizure disorder are at increased risk of seizures with lower concentrations of clozapine in plasma.

### Movement Disorders

Antipsychotic medications are commonly associated with movement disorders while taking the drug, nevertheless studies exist that suggest that some antipsychotics in this scenario Clozapine can be beneficial in treating selected movement disorders. Extrapyramidal side effects are set in two different groups: acute which includes: Parkinsonism, acute akathisia, acute dystonia and chronic: Tardive dystonia, chronic akathisia, Tardive dyskinesia. Tardive dyskinesia has been listed as the most common movement side effect of Clozapine. Tardive dyskinesia (TD) is a disorder that results in involuntary, repetitive body movements, which may include grimacing, sticking out the tongue, or smacking the lips. Additionally, there may be rapid jerking movements or slow writhing movements. If we take a closer look, Clozapine is associated with lower rates of TD compared to other antipsychotics such as Haloperidol. One study done in 1993 by J M Kane, M G Woerner, S Pollack, A Z Safferman, J A Lieberman which was done to detect any causative relationship between Clozapine and TD shown that two out of 28 schizophrenic patients who has never had any history of TD were rated to have mild dyskinesia by Simpson dyskinesia scale, although this study was not able to conclude whether clozapine was primary associative factor in development of TD in these patients it has shown that patients treated with Clozapine have lower rates of developing TD compared to other typical neuroleptics [3]. Moreover, another study done by C A Tamminga, G K Thaker, M Moran, T Kakigi, X M Gao comparing Haloperidol and Clozapine has shown that dyskinesia rebound which occurred equally in both study groups was subsided in Clozapine group but sustained in Haloperidol group [4]. Another interesting topic is switching to Clozapine from other antipsychotic medication which decreases TD, for that we take a closer look to studies showing that Offending antipsychotics administered at the time of TMS onset were second-generation antipsychotics in 88.6% of patients. Tardive movement syndrome symptoms were remitted in 65.7% of patients after switching to clozapine this raises the point that Clozapine seems to be an excellent treatment option for

TMS in the era of second-generation antipsychotics, especially for younger patients with mild tardive dyskinesia. Clinical trials comparing the effect of switching antipsychotics to clozapine with add-on therapy of new drugs targeting TMS are difficult to design in ordinary clinical settings. Therefore, more naturalistic observational studies are warranted to identify predictors of TMS response to clozapine. Akathisia consists of motor restlessness accompanied by subjective feelings of inner tension and discomfort, mainly in the limbs another study which was done to detect the prevalence of akathisia and in patients receiving stable doses of clozapine has shown that 6.8% of study population has shown signs of akathisia. Multiple studies have been done to find out solution of akathisia caused by Clozapine [5-7], of which one interesting study is a case report of a patient who had Clozapine-induced akathisia that was treated by Gabapentin [6]. 39 y.o female who has been diagnosed with paranoid schizophrenia for 4 years, at first 3 years she has been treated with other antipsychotic medications than Clozapine, but drug was introduced at the age of 38. The treatment at the beginning included lower dosage of the drug but got increased to 425 mg/day in the end which caused increased akathisia, which was not that severe before, that is why 600 mg/day Gabapentin enacarbil was introduced to his medication list that subsided akathisia caused by higher doses of Clozapine. Study has not concluded the mechanism by which Gabapentin decreased akathisia but an opinion was made that it might manage dopamine dysregulation by increasing GABA activity in the brain, however, future research should evaluate and verify this mechanism.

Controversial theory was made by study which has shown possible effectiveness of Clozapine treating resting tremor in Parkinson's disease, bringing a table from this study shows significant decrease in resting tremor, but as it was suggested it was a theory that needs further studies are needed to understand its mechanism and effectiveness (**Figure 1**).

Pre- and post-treatment total tremor score in clozapine-treated PD patients with tremor as an indication

| No. | Age | Medication Before Clozapine and Changes After the Addition of Clozapine | Total (Rest and Action) Tremor Score (UPDRS) Preclozapine Treatment[a] | Total tremor Score (UPDRS) Postclozapine Treatment at Last Assessment[a] |
|---|---|---|---|---|
| 1 | 52 | Total L-dopa dose: 2,500 mg/day, sertraline 100 mg/day; no change in medication | 8 | 0 |
| 2 | 62 | Total L-dopa dose: 875 mg/day, quetiapine 75 mg/day (on stable dose with no effect on tremor), stopped just before initiation of clozapine. Rivastigmine 3 mg/day was added and L-dopa was decreased to a total L-dopa dose of 625 mg/day between assessments of tremor score | 15 | 0 |
| 3 | 75 | L-dopa/benserazide and LD/CD: total L-dopa 1,750 mg/day in 11 doses amantadine 200 mg/day; no change in medication | 8 | 8 |
| 4 | 56 | Total L-dopa dose: 1250 mg/day, total pramipexole dose 1.25 mg/day, lorazepam 1 mg at 3 AM; no change in medication | 6 | 4 |
| 5 | 74 | Total l-dopa dose: 1,600 mg/day, total pramipexole dose: 3 mg/day; no change in medication | 4 | 0 |
| 6[b] | 77 | Total L-dopa dose: 800 mg/day, trihexyphenidyl 1.5 mg/day, pramipexole 2 mg/day, entacapone 800 mg/day,clonazepam 0.5 mg/day, and quetiapine 25 mg/day; no change in medication | 6 | 5 |
| 7 | 70 | Total L-dopa dose: 300 mg, pramipexole 1.5 mg/day, and clonazepam 1 mg/day; no change in medication | 24 | 9 |
| 8 (case report) | 75 | Total L-dopa dose: 1,050 mg/day, pramipexole 0.75 mg/day, and levodopa reduced by 450 mg/day | 6 | 1 |

[a]Items 20 and 21 of UPDRS; maximum possible score = 28.
[b]Clozapine was stopped 3 months after initiation because of seizures.

CR, controlled release.

**Figure 1**: Pre- and Post-treatment total tremor score in clozapine-treated PDF patients with tremor as an indication

### Ocular disturbances, cataplexy, and sedation

### Clozapine and ocular side effects

Clozapine is rarely associated with ocular side effects. Even though it is a second generation antipsychotic, it has been found to be associated with the ocular disturbances classically seen with both high and low potency first generation antipsychotics. Clozapine-related ocular side effects can be divided into structural and functional which will be discussed in the following paragraphs [8-12].

Case report from Borovik, Bosch, et al. describes a 55 years old female patient with 16 year history of taking clozapine (800mg/day) for treatment resistant schizophrenia who developed decreased visual

acuity in both eyes (OS 6/60 and OD 6/9). Bilateral deposits in corneal epithelium and stellate cataract were discovered on ocular exam. Fundoscopic exam revealed macular atrophy and retinal pigmentation. Patient's dose was reduced from 800mg/day to 600mg/day but her ocular defects did not improve. This case report lets us draw two important conclusions about clozapine-related structural ocular abnormalities: 1. Corneal deposits and cataract are classically associated with a low-potency first generation antipsychotic, namely chlorpromazine while retinal pigmentation and macular atrophy are associated with another low-potency first generation antipsychotic, thioridazine. Hence, clozapine shares several side effects of typical antipsychotics. 2. Clozapine-related structural eye defects are largely irreversible (**Figure 2**).

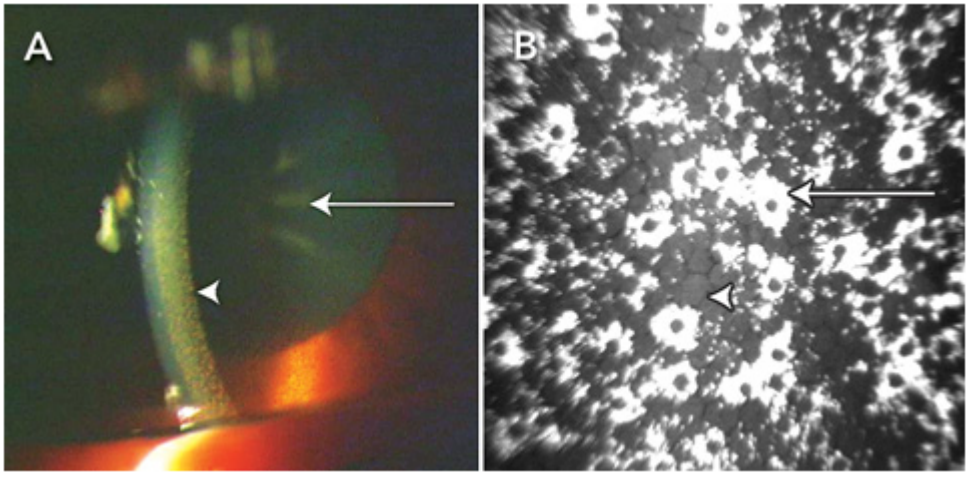


**Figure 2**: Clozapine-induced ocular defects. Right: corneal band deposit. Left: electron microscopy of retina affected by clozapine.

Case report from Nebhinani, Avasthi et. Al describes a 25 years old male patient with 7 years history of treatment resistant schizophrenia who started taking clozapine (300mg/day) after failing therapy with risperidone (6-12 mg/day), chlorpromazine (800mg/day) and quetiapine (800 mg/day). After a year he started experiencing an oculogyric crisis (OGC), i.e. reduced mobility and painful fixation of eyeballs in upward vertical position. Patient used to develop OGC episodes 4-5 times/week regardless of situation, time, diet, stress. After thorough discussion of risks and benefits of reducing the dosage, patient decided to reduce the clozapine dosage from 300mg/day to 150mg/day. After dose adjustment, the frequency of OGC declined from 4-5/week to 4-5/month but at the same time, the patient started experiencing symptoms of his underlying schizophrenia, namely mood swings, suicidal ideas and irritable mood. This case report lets us draw two important conclusions about clozapine-related functional ocular abnormalities: 1. OGC is dose-dependent side effect of clozapine. 2. Reduction in dosage of clozapine causes significant improvement in frequency of OGC episodes but it causes reemergence of schizophrenic symptoms (**Figure 3**).

| Author | Demographics | Diagnosis | Presentation | Treatment and outcome |
|---|---|---|---|---|
| OGC on clozapine therapy | | | | |
| Uzun and Doruk, 2007 | 38 years female<br>19 years female<br>45 years female | Schizophrenia | Experienced multiple episodes of OGC on clozapine (dose unknown). Onset 6 months to 2 years after starting clozapine | Follow-up details were not mentioned |
| Chakraborty and Chatterjee, 2007 | 37 years male | Schizophrenia | Experienced episode of OGC on clozapine (150 mg/day) at 9th day of treatment | Treated successfully with stat IM promethazine (50 mg). Recurrence on discontinuing trihexyphenidyl (4 mg/day) |
| Hoseini Sheikh Moonesi, 2007 | 27 years female | Schizophrenia | Experienced multiple episodes of OGC on clozapine (dose unknown) | Treated successfully with anticholinergic medication (Artane) |
| Salehifar and Hosseini, 2007 | 42 years female | Schizophrenia | Experienced two episodes of OGC on clozapine (150 mg/day) | Treated successfully with biperiden |
| Dave, 1994 | Male | Schizophrenia | Experienced multiple episodes of OGC on clozapine (dose unknown), and earlier also experienced with perphenazine | Treated successfully with anticholinergic agents |
| OGC on clozapine discontinuation | | | | |
| Mendhekar and Duggal, 2006 | 18 years female | Mental retardation | OGC after 2 days of clozapine discontinuation (given 300 mg for 6 weeks) | Treated successfully with reinstatement of clozapine |

OGC – Oculogyric crisis

**Figure 3**: Summary of case reports about clozapine-treated schizophrenia.

**Clozapine-induced cataplexy**

Cataplexy is a neurologic phenomenon characterized by sudden loss of generalized or local muscle tone in the body frequently resulting in a fall. Even though Cataplexy is classically associated with a neuropsychiatric disease called narcolepsy, it was also discovered to be a rare side effect of clozapine. As it is described in the next two case reports, clozapine-induced cataplexy involves mostly hands and knees.

One of the earliest sources of case reports about clozapine-induced cataplexy is the one from Chiles, Cohn et.al, who described 4 patients under their direct therapeutic supervision who developed clozapine induced cataplexy. One of their case reports is about 45 years old female diagnosed with chronic, undifferentiated schizophrenia who started taking clozapine after failing nine different antipsychotic medications. Due to the severe nature of her condition, she was directly started on 550mg/day of clozapine. Her symptoms seemed to be controlled but after 1 year she reported reemergence of auditory hallucinations which prompted physicians to increase her dose from 550mg/day to 600 mg/day. 6 months after the last dose adjustment, patients reported sudden episodes of involuntarily dropping the objects and knee buckling. Dose of clozapine was reduced back to 550 mg/day which caused cessation of these cataplectic episodes.

Another Case report from Desarkar, Goyal et.al describes a 29 years old female with treatment-resistant schizoaffective disorder, manic type who started taking clozapine after 4 years of failing multiple antipsychotics and mood stabilizers. Her dose of clozapine was gradually increased to 150mg/day and although this dose adjustment controlled her psychiatric symptoms, she started experiencing sudden onset knee weakness and dropping of the objects. These episodes were neither triggered by emotional stress (as in narcolepsy) nor followed by loss of consciousness. These episodes of cataplexy used to happen 2-3 times per day. Once the clozapine dose was reduced from 150mg/day to 125 mg/day, the frequency of cataplectic attacks was reduced to 1-2 episodes on alternate days. Despite this improvement, the patient was not able to tolerate cataplexy attacks and she discontinued clozapine which resulted in complete cessation of cataplexy. Even though the exact pathophysiologic mechanism of clozapine induced cataplexy is unknown, Desarkar, Goyal et.al conclude that this rare side effect is supposedly related to clozapine's ability of blocking alpha 1 and 2 receptors which in turn affects presynaptic D2 and D3 receptors.

In light of the above case reports, we can conclude that although it is a rare side effect, clozapine induced cataplexy significantly interferes with patients' activities of daily living and lowers their quality of life.

**Clozapine-induced sedation**

Clozapine is well known for its sedating nature. According to multiple different studies, 10% to 58% of patients were found to feel sedated, drowsy, and fatigued shortly after starting clozapine therapy (Fitzsimons et.al, 2005; Joseph & Lieberman, 2004). Although sedation can potentially occur at any time along the course of treatment, it is most common at the beginning of therapy and it gradually decreases in the first 4-6 weeks.

There is a clear, well-established neurochemical explanation for clozapine-induced sedation. In addition to its effects on dopaminergic and serotonergic pathways in the brain, clozapine has a significant antagonistic effect on Histamine H1 receptor (Kane, Honigfeld, Singer & Melitzer, 1988) and muscarinic M1 receptor. The blockade of these two receptors mediates sedation and drowsiness.

There are several practical ways of minimizing clozapine-induced drowsiness without using other medications: 1. Physicians can titrate the dose slowly to allow the patient enough time for adaptation 2. Physicians can encourage the patient to take clozapine at night (especially if the patient suffers from insomnia) to benefit from its sedating properties. 3. Physicians might decrease the maintenance dose if the patient's condition is considered to be well-controllable after receiving a larger dose.

While we can manipulate the dose and the timing of clozapine to make sedation more tolerable for patients, there are several drugs that can be used in combination with clozapine to counteract its drowsiness. Stimulants such as dextroamphetamine, modafinil, modafinil or antidepressants with stimulant effects such as bupropion decrease sedation and increase wakefulness. However, in light of their side effects, these medications are used only for patients with refractory or severe clozapine-induced sedation.

From the information above, we can conclude that sedation and drowsiness are very prevalent side effects of clozapine and we can minimize them by slowly titrating the dose or using the drugs with stimulant effects to counteract sedative properties.

### Clozapine and sleep

Effects of clozapine on sleep have been a subject of discussion for quite a long time. There are mixed and inconsistent ideas about the effects being positive or negative. Psychiatric disorders, especially schizophrenia and schizoaffective disorder, are strongly associated with impaired sleep continuity. Clozapine, and generally the second generation antipsychotics have been reported to improve sleeping patterns, but some results have been questionable.

Fifteen people (11 women, 4 men), all of them with DSM-IV criteria diagnosed bipolar or schizoaffective disorder participated in the study. Their sleep was monitored at baseline and late after 6 months of clozapine therapy. According to the results of the study, clozapine elongated sleep latency and increased the amount of awakenings, while total sleep period (TSP) and time in bed (TIB) were significantly increased (range: $F=6.2\text{-}17.9$; df=l,12; $p<0.05$). As for individual sleeping stages, stage 2 and slow-wave sleep were both increased, which demonstrates that clozapine is more of a NREM sleep enhancer. Sleeping pattern was clearly better after the drug administration with small but significant improvement, in how refreshed and rested participants felt after awakening ($t=-2.1$; df=26; $p<0.05$) [13]. Primarily the results were positive, but the increased number of awakenings is still a matter of debate.

According to the second study, restless leg syndrome (RLS) during sleeping has been reported as one of the effects of clozapine. Other than anti-serotonergic and dopaminergic activity it has significant antihistamine properties, which is one of the contributing factors of inducing restless leg syndrome. Reports suggest that this is a dose dependent phenomenon. The patient bore 100mg/d clozapine for a long time without ever inducing RLS, but after the increase in a dosage she developed symptoms [14]. Studies stated variable dosages ranging between 50–325 mg/d, proving that the threshold of RLS induction is distinct in different individuals. RLS is a significantly underdiagnosed condition in primary care settings. Therefore, primary care physicians should be warned about this side effect of clozapine.

Sleeping disturbances have been reported as a symptom of clozapine withdrawal. Rebound cholinergic syndrome is usually very rare, but there have been cases of patients developing it after abrupt discontinuation of clozapine. The study describes a case of a 66 years old Spanish male, who was treated with clozapine for bipolar disorder type I. Three days after clozapine termination he developed insomnia, mutism, dysphagia and trismus. He was catatonic, hypertensive and tachycardic [14]. Some of the other symptoms of cholinergic rebound syndrome are agitation, anxiety, sialorrhea, confusion, psychosis, diarrhea, nausea (with or without vomiting) and sweating. Multiple cases of the syndrome are described in the literature, with the patients on high dose treatment for schizophrenia. This case was quite unusual because the patient was taking 50mg/d of clozapine which is considered as a low dose. Another study describes a case of sleep polygraphically documented rebound insomnia after long-term use of clozapine in a 30 years old schizophrenic male [15]. The patient was taking high doses of clozapine for a long period of time and developed withdrawal symptoms one day after the discontinuation, which could be stopped by clozapine administration. In this case withdrawal symptoms were not explained by cholinergic rebound or dopaminergic sensitivity, but indicated participation of GABAergic and antiglutamatergic activities of clozapine.

### Clozapine and hypersalivation

Hypersalivation is a well-known side effect of clozapine affecting 30-80% patients taking this medication. One study reported an even higher rate of 91% [16]. It has a huge toll on the person affected, because of how stigmatizing it can be. It is associated with notable social embarrassment, humiliation, in severe cases aspiration pneumonia and the most importantly higher chance of a patient's poor compliance with the medication. Extreme drooling has also been noted to induce insomnia, because of the uncomfortable state patients are in.

Since clozapine has anticholinergic activity that should reduce secretions, this specific side effect is quite paradoxical. Clozapine-induced hypersalivation (CIH) can be explained by understanding its pathophysiology on a molecular level. Muscarinic receptors both M3 and M4 are expressed in salivary

glands and have opposing actions on one another. When M3 is blocked and M4 activated, they both induce salivation. With all the other previously mentioned properties, clozapine has anticholinergic activity affecting muscarinic receptors (M1, M2, M3, M5) but it stimulates M4 receptors. The combined cholinergic activity of clozapine can be the explanation of CIH paradox.

**Clozapine and Its Psychiatric adverse effects**

There is a significant association of clozapine with obsessive-compulsive symptoms (OCS) [17-22]. Antipsychotic can lead to de novo or aggravation of OCS in patients who receive clozapine for long term but these symptoms may be managed with reduction in dose or by addition of SSRIs. So far there is no exact theory explaining this fact however long-term case observation and its hypothesis assumes that OCS may be the side effect of second-generation antipsychotics and mostly clozapine. The case where a 35 years old man with treatment-resistant schizophrenia was prescribed 200 mg/d clozapine is the best example of everything mentioned above. Three weeks later, his psychosis improved substantially, but obsessions and cleaning compulsions developed. Patient's family history was positive for OCD. After investigation clozapine was thought to be the cause of his symptoms, so the dose was reduced to 300 mg/d over a period of 1 week. Although the OCS decreased, his psychosis worsened. After that the conclusion was made that Clozapine was re-increased back to 400 mg/d however Aripiprazole (15 mg/d) was added, and the OCS gradually diminished, with complete resolution after 5 weeks. (Alasdair et.al.)

Overall there is about 20-30% risk of primary OCS in patients with schizophrenia. This is considerably the high incidence and it deserves explanation, but until now pathological connection of these comorbidities is not clearly understood. However, everyday there are new case reports, case series and systematic evaluations mention the new de-novo obsessive compulsive symptoms or aggravation of primary symptoms after receiving clozapine.

Some patients with pre-existing OCS/OCD had worsening symptoms with clozapine while others remained at the same level or even improved moreover the number of de-novo OCS in patients within 12 months are highly noticed. But as I mentioned already symptoms are reversible with reduction in dose of medication or by addition of SSRIs.

Clozapine remains the drug of choice in patients with resistant schizophrenia however it is also well known for its side effects. One of the life-threatening psychiatric side effects of the drug is delirium. Several studies were done to show the reality of delirium complication of clozapine, in one of them 139 patients were rolled in from which 72 were women and 67 men. Their ages were 40 +/- 12 years, with clozapine given gradually increased dose to an average daily dose of 282 +/- 203 mg for approximately 20 days. Out of 139 patients delirium was diagnosed in 14 (10.1% incidence). A sum up report has shown that in 10 % of clozapine-treated inpatients delirium occurred.

Delirium as complication has higher rate of occurrence in patients who mostly are older, patients who mainly are exposed to other central anticholinergics, or have other medical co-morbidity though delirium was also clinically recognized in milder cases with clozapine alone and was associated with increased length-of-stay and higher costs, and lower clinical outcome. There are also cases of delirium with clozapine withdrawal, even low dose of clozapine as well as an increasing dosage of clozapine has been noted to precipitate delirium, and what is more, few case studies report the complication after restarting clozapine. Delirium despite being a fatal complication is an under-recognized potential adverse effect of clozapine therapy treatment and has been poorly studied.

With all this data we might conclude that mostly clozapine-induced encephalopathy risk escalates with rapid dosage increases, high dose therapies, and when the patient takes many medications in combination with clozapine however these don't exclude clozapine-induced delirium in milder cases.

Neuroleptic malignant syndrome (NMS) is a life-threatening complication of antipsychotic drugs and is characterized by high fever, altered mental status, peripheral muscle rigidity and autonomic dysfunction, irregular pulse, tachypnea, tachycardia. Clozapine was initially thought not to cause NMS. But over time some cases report NMS with the association of clozapine as a single agent that developed NMS. Case report of a 28-year-old male with nine-year history of paranoid schizophrenia and no prior history of NMS was receiving only aripiprazole for seven months; however because of resistance, treatment with clozapine was started. On day 8 the patient developed confusion, high fever, tachypnea,

yet no general muscle stiffness was noted on the exam. Creatinine levels increased one day later. Patients oral medications were discontinued except as needed-lorazepam, the patient received intravenous hydration and supportive measures. He recovered within ten days (Andrew Farah, Department of Psychiatry, UNC). The features of clozapine-induced NMS may be somehow different, with fewer muscle rigidity and a lower rise in creatine kinase levels. Waiting for muscle rigidity or fever may delay or even prevent the diagnosis and treatment of NMS.

NMS usually occurs within two weeks after starting clozapine however may occur at any time. Significant risk factors of developing this complication increases in patients using other mood stabilizer along with clozapine (The combination of clozapine and aripiprazole has induced NMS in five case reports, including the one above) and in patients who had a previous history of NMS (found to reoccur in 50% of those patients) however it may occur de-novo without any previous history or aggravating factors.

## Conclusion

Varma et al. found a relationship between mean clozapine levels and EEG changes but Kikuchi et al. failed to find a statistical significance that we believe is due to their small number of cases studied. Clozapine plasma levels and EEG changes were found to be in relation. Although higher clozapine dose is correlated with higher risk of seizures, Varma et al. did not find significance. As for clozapine plasma levels and seizure occurrence, significant relationship was found [1]. Other common acute adverse effects include: Parkinsonism, acute akathisia, acute dystonia while chronic ones are: tardive dystonia, chronic akathisia, tardive dyskinesia. We have listed some common extrapyramidal adverse effects of Clozapine and also brought some interesting studies which show comparison to other antipsychotics, association with movement disorders and controversial theories about using the drug. Clozapine's ocular side effects are similar to those observed with chlorpromazine use. As for the cataplexy, it is still controversial whether it is a true cataplexy or negative myoclonus. Sedation significantly decreases the patient's quality of life. Speaking of sleep disturbances, clozapine increases the number of awakenings, but at the same time the total sleep period is significantly prolonged. Patients report being more refreshed and relaxed upon waking up. The strong association between clozapine and hypersalivation is reported by a great deal of studies. Finally, as other neuroleptics, clozapine is prone to elicit psychiatric side effects such as emotional indifference, depression, restlessness however among all these are several severe complications that should be emergently recognizes and treated, those are clozapine induced obsessive-compulsive symptoms, delirium and the neuroleptic malignant syndrome.

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