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Most Common Side Effects of Clozapine and Their Management

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ABSTRACT: *Clozapine is a novel, unique and oldest second generation (atypical) antipsychotic agent, first introduced in 1970s in the European market in under trade name, Leponex but has been withdrawn years in 1974 due to development of severe neutropenia (agranulocytosis) resulting in cluster of deaths. It was reintroduced in the early 1990s in United States under trade name, Clozaril by U.S. Food and drug Administration (FDA) for use in treatment resistant schizophrenia in adults and for reduction of risk of persistent suicidal ideation or aggressive behavior in schizophrenic patients. As of today, Clozapine remains the most effective antipsychotic available in reducing both positive and negative symptoms in patients with schizophrenia who fail to respond to typical antipsychotic agent, treating affective disorders, some neurological disorders, aggression, as well as psychosis in patients with dementia and parkinsonism. Most side effects associated with clozapine in general are typically benign, tolerable, and manageable.*

Keywords: *Clozapine, Atypical antipsychotics, Schizophrenia, Side effects*

INTRODUCTION

Schizophrenia is a chronic, disabling mental illness that affects individuals and devastates families. About 1 in 100 adults in the United States (approximately 1.5 million) suffer from this disease (Kessler et al., 1994; Rosentein, Milazzo-Sayre & Manderscheid, 1989). An estimated 30% to 60% of patients with schizophrenia respond poorly to typical and atypical antipsychotic drugs. This leads to repeated hospital admissions and warrants treatment with clozapine; an atypical anti-psychotic drug very cautiously, given its several side-effects (National Institute For Clinical Excellence, 2002; Feltus & Gardner, 1999).

Clozapine is a dibenzodiazepine antipsychotic with strong affinity for D_4-dopaminergic receptors and potent serotonergic (including 5-HT_2, 5-HT_3, 5-HT_6 and 5-HT_7 subtypes), noradrenergic, histamine and cholinergic (muscarinic A_1 and A_2) receptor blocking ability. Moreover, it also has significant effects on GABA-ergic and glutamatergic systems. It differs from traditional antipsychotic drugs in that it has relatively weak D_2-receptor activity and therefore it may cause fewer extrapyramidal side effects than other antipsychotics with D_2 receptor blocking properties (Domenico et al., 2012).

Clozapine-therapy can lead to significant improvements in mental state, productivity and quality of life for patients (Carol Paton & Raadiyya Esop, 2005). In addition to its proven efficacy on both positive and negative symptoms in refractory schizophrenia, clozapine is useful in reducing aggressive behavior, hostility and excitement, comorbid use of alcohol and drugs, as well as reducing suicidality in schizophrenia. A review that identified six animal studies, four randomized controlled trials, 12 prospective non-controlled studies and 22 retrospective studies, with four case studies found considerable evidence in support of clozapine's ability to reduce violent and aggressive behavior. (Frogley, Taylor, Dickens & Picchioni, 2012). It is also efficacious in severe mood disorders, drug-induced psychosis in Parkinson's disease, without worsening Parkinsonism; and reducing drug-induced tardive dyskinesia. However, the therapeutic journey with this drug is fraught with several side-effects, and is perhaps therefore not considered first-line despite its exceptional effectiveness.

Clozapine has significant dopaminergic, serotonergic, adrenergic, muscarinic and histaminic blocking properties; and thus most of its adverse effects can be predicted on the basis of its pharmacological profile. These side effects often lead either to non-compliance or discontinuation of treatment by patients.

The most serious side-effects associated with this drug, such as agranulocytosis, myocarditis and neuroleptic malignant syndrome, are fortunately rare. In routine clinical practice, the most commonly encountered side-effects of clozapine are excessive salivation (drooling), somnolence, tachyarrhythmia, weight gain, dizziness, orthostatic hypotension, vertigo and constipation. This review article covers the overview of these most common side effects of clozapine and their management (Table 1).

Drooling

Drooling (also known as sialorrhea or hypersalivation) is a very common, socially stigmatizing adverse effect of clozapine that usually occurs early in the course of treatment. It has been reported to occur in 30-80% of patients on clozapine (Macfarlane et al., 1997; Davydov & Botts, 2000; Bird, Smith & Walton, 2011). Hypersalivation tends to be worse at night and is often dose-dependent and may thus improve with dose reduction. Patients on clozapine complain of excessive drooling, wet pillows, choking sensation at night and aspiration of excessive saliva (Davydov & Botts, 2000; Young, Bowers & Mazure, 1998). Salivary gland swelling and aspiration pneumonia have been reported as a result of excessive salivation (Robinson, Fenn & Yesavage, 1995; Hinkes, Quesada, Currier & Gonzalez-Blanco, 1996; Brodkin, Pelton & Price, 1996).

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Table 1.
Side-effect profile of Clozapine

System	Side-effect
Central nervous system	Drowsiness, sedation, somnolence, fatigue, dizziness, vertigo, headache, tremor, disturbed sleep (insomnia) or nightmares, restlessness, agitation, rigidity, lethargy, ataxia, slurred speech, confusion, myoclonus, neuroleptic malignant syndrome, seizure, delirium, tardive dyskinesia, akathisia, tremor, obsessive compulsive disorder [6-14].
Cardio vascular system	Myocarditis, cardiomyopathy, deep venous thrombosis, orthostatic hypotension, tachyarrhythmia, pericardial effusion, sudden cardiac death, syncope and rarely cardiac arrest [6,15-18]
Endocrine/metabolic systems	Excessive salivation, weight gain, hyperglycemia, hypercholesterolemia (6,19-24)
Gastrointestinal system	Constipation, bowel obstruction, colitis, necrotizing fecal impaction, gastrointestinal hypomotility, ischemic bowel disease, pancreatitis, paralytic ileus, perforation of intestine, nausea, vomiting, xerostomia [14,25,26,27]
Genito-urinary system	Urinary frequency or urgency, urine retention, incontinence [28,29]
Hematologic	Agranulocytosis, drug-induced eosinophilia, neutropenia [30-33]
Dermatologic	Rash, sweating
Respiratory	Pulmonary thromboembolism, respiratory arrest [18]
Hepatic	Hepatitis, hepatic failure [34-36]

Although the mechanism of hypersalivation is not well understood, several possible mechanisms have been suggested. These include activation of muscarinic receptor M_4 (Zorn, Jones, Ward & Liston, 1994; Szabadi, 1997), blockade of alpha-adrenoceptors (Berlan, Montastruc & Lafontan, 1992), decreased peristalsis (Raja, 2011), and/or interference with the swallowing reflex causing pooling of saliva (Bird, Smith & Walton, 2011; Pearlmen, 1994).

It is a good clinical practice to let all patients know that they are likely to experience sialorrhea early in the course of their treatment, and in some instances hypersalivation will be voluminous, especially at night and that it can be managed, even though there is no single-most effective therapy to treat it. There have been several pharmacological and non-pharmacological approaches described in literature. These include chewing sugarless gum to induce swallowing during the day and placing a towel over the pillowcase at night to prevent soaking the pillow and are usually tried first for patients with mild clozapine induced sialorrhea. (Bourgeois, Drexler & Hall, 1991).

Pharmacotherapy is considered when hypersalivation is severe. Pharmacological approaches focus primarily on antimuscarinic and adrenergic agents and benzamide derivatives (not available in the United States). Studies consist mainly of case reports and small controlled and uncontrolled trials (Bird, Smith & Walton, 2011). There have been multiple drugs used based on case reports or open-label studies includes antimuscarinic agents such as benztropine, trihexyphenidyl, diphenhydramine, amitriptyline (75mg-100mg/day), glycopyrolate, atropine sulfate, sublingual or intranasal ipratropium bromide spray and scopolamine (Bird, Smith & Walton, 2011; Raja, 2011; Bourgeois, Drexler & Hall, 1991; Rogers & Shramko, 2000; Copp, Lament & Tennent, 1991; Fitzsimons et al., 2005). Also used pirenzepine (selective muscarinic receptor antagonist, not available in US), doxepine, and alfa-$_2$ adrenergic agonists (clonidine patch, guanfacine, lofexidine) (Raja, 2011; Bourgeois, Drexler & Hall, 1991; Rogers & Shramko, 2000; Copp, Lament & Tennent, 1991) to treat clozapine induced sialorrhea.

A recent literature review reported that low cost atropine (1 drop of 1% ophthalmic solution at night) administered sublingually is a reasonable place to start for pharmacological management since it offers relatively low systemic absorption potentially limiting adverse effects (Bird, Smith & Walton, 2011). Glycopyrrolate demonstrated significant reduction of hypersalivation in a randomized controlled trial (Mier et al., 2000). However, use of any antimuscarinic agents has to be weighed against the risk of potentiating the anticholinergic effects of clozapine.

Unfortunately, treating sialorrhea with anticholinergics often leads to additive adverse and drug reactions, including blurry vision, confusion, nausea and constipation (Joseph & Lieberman, 2004). In some instances, it may impair the gag reflex and thereby increase the risk of aspiration. Patients using clonidine should have frequent blood pressure checks because of antihypertensive effects resulting from clonidine withdrawal. In refractory cases, Botulinum injections into the parotid glands have shown successful result (Mier et al., 2000).

Sedation, Drowsiness, Fatigue and Grogginess

Several clinical trials that have found between 10% and 58% of patients treated with clozapine experience sedation, drowsiness and fatigue (Fitzsimons et al., 2005; Joseph & Lieberman, 2004; Steinlechner et al., 2010; Baldessarini & Frankenburg, 1991). These are the most common reported side effects of clozapine. Usually sedation occurs at the beginning of the treatment, gradually diminishes over 4-6 weeks and can be managed by giving higher doses at night, doing a slower titration or decreasing the dose. Sedation is related to clozapine's potent antihistaminergic effects (Kane, Honigfeld, Singer & Meltzer, 1988). Certain medications with dopaminergic activating effect such as stimulants (dextroamphetamine, methylphenidate or modafinil), bupropion and L-dopa, reduces sedation and improve wakefulness state (Kane, Honigfeld, Singer & Meltzer, 1988; Claghorn et al., 1987; Chen, 1992). These medications are reserved only for severe and persistent cases and may cause psychosis and/or movement disorder (Kane, Honigfeld, Singer & Meltzer, 1988; Claghorn et al., 1987; Chen, 1992) (Table 1).

Tachycardia

Approximately 25% of patients taking clozapine experience dose-dependent tachycardia which is rare, if any, clinical significance. (Chen, 1992; Kraus et al., 1999). Usually doses greater than 300mg/day effect an increase of about 10-25 beats per minute (Meltzer, 1995; Haddad & Sharma, 2007; Safferman et al., 1991). Tachyphylaxis typically is seen within 4-6 weeks of initiation of treatment (Bird, Smith & Walton, 2011; Kane, Honigfeld, Singer & Meltzer, 1988). Tachycardia is related to anticholinergic effects that exert vagal inhibition rather than simply a reflex increase secondary to clozapine-induced hypotension (Ereshefsky, Watanabe & Tran-Johnson, 1989).

Management of persistent tachycardia usually only includes lowering the dose or slower upward titration of clozapine. As with hypotension, tolerance usually occurs over 4 to 6 weeks (Rechlin, Claus & Weis, 1994). Thus, tachycardia need not be treated at all if the patient is not symptomatic. In some cases tachycardia can be persistent (>110 bpm) and distressing at rest. For patients with distressing tachycardia, a beta-blocker, especially a cardio-selective agent such as atenolol or metoprolol is prescribed which may also minimize orthostatic hypotension secondary to alpha blockade (Kane, Honigfeld, Singer & Meltzer, 1988; Marinkovic et al., 1994). Atenolol is generally preferred since it is not metabolized by the liver and so has little effect on clozapine metabolism, and is relatively cardio-selective; often making it a suitable choice for patients with asthma or diabetes. If atenolol is not effective, consider the use of a

non-selective beta blocker such as propranolol. (Cleophas & Kauw, 1988). If symptoms are associated with fever, hypotension, sedation or chest pain/pressure, myocarditis is suspected. In this case, patient needs to undergo a 12-lead EKG, troponin and WBC with differential to rule out myocarditis. (Stryjer et al., 2009).

Weight Gain

Unwanted weight gain is one of the most bothersome and disturbing adverse effects of clozapine, especially in young adults when compared to the elderly (Nielsen, Correll, Manu & Kane, 2013). It is most frequently noticed in the first 4 to 12 weeks but further weight gain can occur during prolonged treatment with clozapine treatment (Wetterling, 2001; Leadbetter et al., 1992). In fact, some studies have found greater than 10% weight gain from baseline in one in five patients treated with clozapine at 12 weeks to 12 months (Leadbetter et al., 1992; Bustillo, Buchanan, Irish & Breir, 1996; Wirshing et al., 1999). The average weight gain is reported to be 8 kg or 17.6 pounds (Raja, 2011). The risk of weight gain with clozapine is similar to that with Olanzapine (Zyprexa) and is likely higher than that associated with other antipsychotics (Hummer et al., 1995; Marder et al., 2004).

The mechanism of clozapine induced weight gain is not clearly understood. Some of the pharmacological properties of clozapine may have a role in weight gain, although there is no clear evidence for this hypothesis (Nielsen, Correll, Manu & Kane, 2013). Possible mechanisms include antagonism of the D_2 receptor which is involved in feeding regulation, antihistaminergic activity, anticholinergic effects on M_4 receptors and antagonism of 5-HT_2 receptor. (Leadbetter et al., 1992; Allison & Casey, 2001; Megna, Schwartz, Siddiqui & Herrera Rojas, 2011). Other factors associated with increased body weight such as increased leptin secretion, cessation of smoking, decreased ghrelin and adiponectin serum levels may also be involved. (Raja, 2011; Allison & Casey, 2001; Wetterling & Mussigbrodt, 1999). Above mechanism that caused weight gained lead to increased appetite, energy intake and storage, metabolic and endocrine alterations, decreased energy expenditure and lower physical activity**.**

Leptin is produced by fat cells and is thought to signal the size of adipose tissue to the brain. Increased leptin secretion is associated with over eating and is seen in clozapine treatment. Reduced smoking as a result of clozapine treatment (Wetterling, 1996) may be yet another cause of weight gain since 80% of patients with schizophrenia are smokers (George, Sernyak, Ziedonis & Woods, 1995) and cessation or reduction in smoking is strongly associated with weight gain (Wetterling & Mussigbrodt, 1999).

Weight gain can be prevented by close monitoring, engagement in an exercise-based weight management program, life style modifications, dietary intervention, or changes in patient's antipsychotic medication (Hummer et al., 1995). Consensus guidelines developed by the American Diabetes Association (ADA), the American Psychiatric Association (APA) and the American Association for Clinical Endocrinologists for antipsychotic monitoring recommends weight measurements at baseline and monthly thereafter; as well as fasting glucose and lipid panel at baseline and after 3 months of any antipsychotic trial. The metabolic parameters most impacted by most second generation antipsychotics (SGA) including Cozaril are weight, serum triglycerides and measures of glycemic control, considerably more so than serum high density lipid (HDL) and blood pressure (Hughes, Hatsukami, Mitchell & Dahlgren, 1986).

A strict dietary regimen should be started if weight gain occurs at high rate (>2 kg within 2 weeks) (Wetterling & Mussigbrodt, 1999). However, compliance with behavioral interventions is often poor. Despite interventions, weight gain due to clozapine treatment tends to persist (Nielsen, Correll, Manu & Kane, 2013). The first treatment approach for significant weight gain (weight gain more than 5% during therapy- (Newcomer, 2007) should be switching to another medication with a lower tendency to cause weight gain. Referral to an endocrinologist may also be warranted, and patients should be advised on healthy life style adjustments including dietary suggestions and behavioral strategies (Allison & Casey, 2001).

Metabolic Syndrome

Metabolic Syndrome (MS) is a collection of risk factors-including disturbances in glucose and lipid metabolism, obesity and hypertension-that are associated with increased morbidity and mortality resulting cardiovascular disease. Recently research has established any second-generation anti-psychotic (SGA) use as an independent risk factor for developing metabolic syndrome (MS). The prevalence of MS among patients receiving clozapine is slightly over two times more than that found in the general population (Newcomer, 2007; American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists & North American Association for the Study of Obesity, 2004).

A study of 468 patients taking clozapine with and without metabolic syndrome revealed that mean levels of homocysteine in patients with metabolic syndrome were significantly higher than those without it. Additionally, their findings suggested a potential association between rs4680 in COMT and elevated TG levels (corrected $P=0.024$), particularly among female patients ($P=0.009$) (Lamberti et al., 2006; Hagg, Lindblom, Mjorndal & Adolfsson, 2006).

Adjunctive drug treatments have been tried to counteract clozapine induced weight gain when dietary, exercise and behavioral strategies fail. Several medications have been investigated for the prevention or treatment of antipsychotic-associated weight gain. Medications are most effective when combined with diet and lifestyle changes. The various medications that can be considered are fenfluramine, orlistat, amantadine, sibutramine, reboxetine, histamine H2 antagonists (nizatidine, cimetidine), rosiglitazone, aripiprazole and topiramate (Allison & Casey, 2001; Zhang et al., 2014; Schwartz et al., 2004; Floris, Lejeune & Deberdt, 2001; Baruch et al., 2002; Stoa-Birketvedt, 1993; Sacchetti, Guarneri & Bravi, 2000; Dursun & Devarajan, 2000; Chengappa et al., 2001). Among these, Orlistat is the only medication with specific FDA approval for weight loss (Allison & Casey, 2001; Zhang et al., 2014). Many patients find the gastro-intestinal side effects of orlistat, including flatulence and steatorrhea, to be unpleasant, and these side effects should be discussed with patients in whom orlistat is being considered.

The findings from a study that followed 520 non-diabetic individuals treated with clozapine (N=73), olanzapine (N=190), quetiapine (N=91) or risperidone (N=166) as predictors of post-challenge insulin secretion in non-diabetics suggested that the diabetogenic risk of clozapine may persist even after weight reduction (Manu et al., 2013).

Dizziness, Orthostatic Hypotension and Vertigo

About 9% of patients on clozapine may develop orthostatic hypotension usually observed in the first week of treatment. Fortunately, orthostasis with clozapine is usually temporary, gradually diminishes with tolerance developed by 4-6 weeks but may also develop with a rapid dosage increase (Kane, Honigfeld, Singer & Meltzer, 1988; Haddad & Sharma, 2007; Rechlin, Claus & Weis, 1994). Orthostatic hypotension results from by blocking alpha-1 adrenergic receptor (Kane, Honigfeld, Singer & Meltzer, 1988).

It is important to warn patients about orthostatic hypotension and to reassure them that it will improve with time. Blood pressure

should be checked before patient starting taking clozapine afterward. Patients should be counseled to rise slowly from the sitting or lying position to standing position and increased fluid and salt intake in-order to prevent orthostasis which should be first measure. Patients should be warned about the seriousness of the risk from falls associated with clozapine-induced orthostasis. It is always better to increase the dose slowly rather than higher dosages.

If the patient's symptoms are severe or the risk of fall is high, increases in dose may be slowed or the current dose may be maintained for a few days to allow time to adjust. It is good clinical practice to examined patient's all medications list that may exacerbate orthostasis. Using support stockings and tilting the head of the bed at night are the second measure in the management of orthostasis hypotension (Marinkovic et al., 1994).

If non-pharmacological measures fail, medications such as fludrocortisones (Testani, 1994) or ephedrine (Patterson, 1992; Flanagan & Ball, 2011) can be used but caution is recommended due to their side effects. If hypotension is severe and refractory and cannot be managed by the above measures, consider discontinuation of clozapine. While discontinuing clozapine, dose should be tapered slowly over 2 week period to prevent cholinergic rebound and switched to alternative agents.

Constipation

Gastrointestinal hypomotility is an under-recognized life-threatening adverse effect of clozapine as it may cause death due to intestinal necrosis and/or perforation, or pulmonary aspiration (Lieberman, Safferman & Pollack, 1994). 15% to 60% of patients taking Clozapine experience constipation as common side effects (Young, Bowers & Mazure, 1998; Raja, 2011). Lieberman et. al (Hayes & Gilber, 1995) reported a rate of 33.3% constipation in the acute treatment phase with Clozapine and 22.8% in the maintenance phase. Hayes and Gilber (Lennard-Jones, 1993) reported a prevalence of 60% of constipation with Clozapine in their patient population along with three deaths from severe ileus and obstipation as well (Chukhin et al., 2013). Often the onset of constipation is heralded not by complaints of difficult bowel movements, but by complaints of nausea and vomiting. This nausea and vomiting is the result of severe constipation that must be managed urgently. This side effect is more likely to occur in sedentary patients or in patients taking other constipating drugs.

Clozapine is highly anticholinergic and is thought to be the primary mechanism behind decreased gastrointestinal peristalsis and clozapine induced constipation but 5-HT antagonism may also be implicated. The treatment of clozapine induced constipation is directed towards softening the stool and increasing transit time through gastrointestinal tract. High fiber diet, adequate fluid intake and exercise are recommended to prevent constipation in general. Mild constipation is effectively managed with fiber supplements such as psyllium or unprocessed bran. Stool softeners and osmotic laxatives e.g., docusate sodium and milk of magnesia can be used for more distressing symptoms. In severe case, stimulant cathartics such as senna, phenolphthalein and bisacodyl are used (Young, Bowers & Mazure, 1998). Finally, if necessary, enemas can be given (Lieberman, Safferman & Pollack, 1994). In a 16 week randomized placebo-controlled add-on study, orlistat significantly reduced clozapine-induced constipation (p=0.035) (Chukhin et al., 2013).

CONCLUSIONS

For almost 25 years now, clozapine has been and likely will continue be an invaluable drug treatment-resistant schizophrenia, suicide risk in schizophrenia spectrum disorders, aggressiveness or violence in psychiatric patients, psychosis in Parkinson's disease, prevention and treatment of tardive dyskinesia. Its association with many purportedly serious side effects and monitoring requirements have played a major role in discouraging clozapine use. Therefore, the drug is underused. The only way to avoid the underuse of clozapine is full awareness of its side effects and competence to minimize them. Only a good knowledge of these side effects and of the core strategies to prevent their occurrence or minimize their impact might allow overcoming the under-utilization of this effective drug. The article describes the clinical and epidemiological features of the non-motor side effects of clozapine including drooling, sedation, fatigue, drowsiness, weight gain, metabolic syndrome, dizziness, orthostatic hypotension, vertigo and constipation. The paper suggests several strategies, supported by scientific evidence, in the management of these side effects.

Most recent reviews indicate that prompt discontinuation of clozapine without rechallenge is indicated for agranulocytosis, myocarditis, cardiomyopathy, and a QTc interval > 500 milliseconds that is confirmed and derived using the appropriate correction method. Clozapine discontinuation with potential rechallenge (provided there is appropriate surveillance and management or prophylactic therapy) is indicated for ileus or subileus, neuroleptic malignant syndrome, venous thromboembolism, and diabetic ketoacidosis or hyperosmolar coma. Neutropenia, leukocytosis, seizures, orthostatic hypotension, severe constipation, and weight gain and metabolic abnormalities, including metabolic syndrome and its components, as well as moderately prolonged myocardial repolarization, need to be managed but do not generally warrant clozapine discontinuation. Eosinophilia, leukocytosis, drug-induced fever, and tachycardia (provided that myocarditis and neuroleptic malignant syndrome are ruled out) can be managed and should rarely lead to clozapine discontinuation. (Stryjer et al., 2009). We hope that this review clarifies that Clozapine's seemingly benign commonly occurring side effects need to be minimized.

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