Movement Disorders
CLINICAL PRACTICE
REVIEW

Clozapine in Parkinsonian Rest Tremor: A Review of Outcomes, Adverse Reactions, and Possible Mechanisms of Action

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Abstract: **Background:** The pathogenesis of rest tremor in Parkinson's disease (PD) is incompletely understood. This symptom can be resistant to typical anti-PD medications. Therefore, new treatments are needed given the concern that this symptom causes to patients and family. Limited experience suggests that clozapine can have an important antitremor effect in PD. The mechanism(s) underlying this effect is not well understood, but could provide insight and impetus to the development of more-effective and safer antitremor therapies.

Methods and Results: Exemplifying the antitremor effects of clozapine, we describe a patient with tremor-predominant PD who obtained prominent reduction of rest tremor with clozapine treatment. We review the responses to this treatment in another 7 of our PD patients with treatment-resistant rest tremor. We also review the published literature on clozapine for tremor in PD and discuss its potential mechanisms of action and possible adverse effects. In our case series, there was a 64% reduction of tremor score after clozapine was initiated. The mechanism of tremor reduction remains unclear with possible involvement of anticholinergic, serotonergic, antihistaminergic, antiadrenergic, and antidopaminergic effects. Clozapine does have potential serious adverse effects.

Conclusions: Clozapine may be effective in controlling rest tremor in PD. Given the potential fatal side effects, if clozapine is to be initiated in PD patients, it has to be used cautiously with proper monitoring, preferably in specialized centers. We acknowledge that the number of patients in this case series is small. Further studies are needed to understand clozapine's mechanism of action in reducing tremor.

Rest tremor is one of the most common symptoms and a cardinal feature of Parkinson's disease (PD). Tremor has been shown to be a major impairment of quality of life, especially in the early stages of the disease.[1] Clinical experience indicates that rest tremor is not as responsive to dopaminergic medication as rigidity and bradykinesia, questioning its relationship with a pure dopaminergic deficit and encouraging research into other mechanisms of tremor generation. Animal studies involving selective dopaminergic lesions, such as with MPTP, produce akinetic syndromes, but generally not the characteristic tremor of PD.[2] Neuroimaging studies with PET and single-photon emission computed tomography demonstrate dopaminergic deficiency in early PD[3,4] that correlates with bradykinesia and rigidity; however, there is poor correlation between rest tremor and dopaminergic deficit.[5,6] In addition, a study by Doder et al. found that rest tremor correlates well with a decreased binding capacity of the $5HT1_A$ receptor in the median raphe nuclei, suggesting an involvement of the serotonin system.[7] These clinical, neuroimaging, and animal studies suggest that nigrostriatal dopaminergic deficit alone is insufficient to produce rest tremor, and that other neural networks may be involved.

Clozapine is a dopamine D2 receptor antagonist that is used to treat psychosis in PD, without worsening parkinsonian motor features (so called "atypical" antipsychotic action).[8] Clozapine

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acts on multiple receptor classes and has binding affinity for serotonergic, cholinergic, adrenergic, and histaminergic receptors in addition to dopaminergic receptors.[9] Clinical studies have also shown that clozapine is effective in treating rest and postural tremors in PD.[10–12] However, the exact mechanism of action underlying the antitremor effect of clozapine remains unclear. The multiple neurotransmitter systems that are potentially influenced by clozapine could all be implicated in this antitremor activity. This combined antitremor and anti-psychotic action of clozapine may be particularly useful in clinical practice, for example, in PD patients with disabling tremor in which increasing dopaminergic medication triggers or exacerbates psychotic symptoms. However, we find that in addition to its underutilization for psychosis,[13,14] clozapine is also rarely considered in the treatment of parkinsonian rest tremor. In hopes of encouraging better understanding of the mechanism of action of clozapine, which might lead to consideration of its use in PD tremor and also to the development of newer, more-effective, and safer treatments for tremor in PD, we describe a case exemplifying profound antitremor effect of clozapine and review the literature on potential mechanism of action in PD tremor. On the flipside, we also review the potential adverse effects of clozapine in order to give a broader picture on the profile of clozapine to assist in the decision of whether to initiate this treatment.

Case Report

A 75-year-old man had a 20-year history of tremor-dominant PD that began with lip and left-hand tremor. His main concern was his bothersome rest and action tremor that had restricted his activity. He was taking levodopa/carbidopa (LD/CD) 100/25 3.5 tabs t.i.d. and pramipexole 0.75 mg daily. Other medication included zopiclone, perindopril, terazosin, and aspirin. Previous adjustments to his dopaminergic medication which included increasing the LD/CD 100/25 to 4 tabs t.i.d. and addition of entacapone caused bothersome orofacial dystonia. Attempts to increase the pramipexole had caused impulsive gambling. There was no clear relationship between his tremors and the timing of his dopaminergic medication. His total tremor score on the UPDRS was 6 (items 20 and 21). He was started on clozapine with a clear improvement in his tremor at a dose of 25 mg Q.h.s. His tremor score improved after starting clozapine to 4 at 6 months, 2 at 12 months, and 1 at 18 months. With the reductio of his tremors, his L-dopa dose could be decreased substantially to LD/CD 100/25 2 tabs t.i.d. (total L-dopa reduction of 450 mg) with an improvement in his dystonia. He did not encounter any major side effects from the addition of clozapine.

Over the past 5 years, we have treated 8 PD patients with tremor as the primary indication for clozapine, including the above illustrated case. As shown in Table 1, clozapine was able to reduce tremor scores by an average of 64% (range, 0–100%); and in 3 individuals, tremor was abolished.

Review of Mechanism of Action

The antitremor effect experienced by the majority of our small number of patients is consistent with animal studies, open-label case series, and also double-blinded studies published in the literature (Table 2). Clozapine has also been shown to improve

TABLE 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*	Total tremor Score (UPDRS) Postclozapine Treatment at Last Assessment*
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[a]	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

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

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the postural tremor of PD, in addition to improving rest tremor.[15] The mechanism of action of clozapine tremor is unclear. Nonspecific sedation may be a factor; however, Bonucelli et al. have shown that the antitremor effect persists after long-term administration of clozapine, even when the sedative effects have waned.[16] Clozapine could exert an antitremor action through numerous receptor mechanisms, which include anticholinergic, serotonergic, and antihistaminergic effects (Tables 3 and 4).

Anticholinergic Effects

Anticholinergic drugs have long been used in the treatment of the motor aspects in PD, in particular, tremor. Clozapine has high affinity for the muscarinic M1 and M4 receptors that are located in the caudate-putamen (Table 3). A study by Friedman et al. comparing clozapine to benztropine, a well-established anticholinergic agent, showed equal efficacy of the two agents in reducing the mean UPDRS tremor score in PD.[17] However, alternative explanations for clozapine's mechanism of action other than its anticholinergic effect need to be considered for a variety of reasons. First, the patients who took clozapine in this study experienced fewer anticholinergic side effects, compared to the patients who took benztropine. Second, a case series from the same senior author demonstrated efficacy of clozapine for tremor in PD despite failure of pure anticholinergics agents in the same patients.[10] More recent studies have used muscarinic receptor knockout mice to delineate the physiological roles of the muscarinic cholinergic system[18] and the use of M4 receptor antagonist tropicamide to suppress a model of parkinsonian tremor in rodents.[19] In these studies, M4 receptor blockade resulted in improvement of motor function and suppression of tremor. Because benztropine and trihexyphenidyl have greater binding affinities for the M4 receptor than clozapine[9] (Table 3), the suppression of tremor in patients who failed to respond to these anticholinergics cannot be adequately explained by clozapine's antimuscarinic effects. Therefore, we must consider mechanisms of action involving other neurotransmitter systems.

Serotonergic Effects

Clozapine binds to multiple serotonin receptors. It is a 5-HT_{1A} receptor agonist and a 5-$HT_{2A/2C}$ receptor antagonist (Table 3). 5-HT_{1A} receptors are found presynaptically as somatodendritic autoreceptors in the midbrain raphe nucleus, and their activation inhibits the release of serotonin.[20] A PET study showed correlation between decreased 5-HT_{1A} binding in this region with severity of tremor in patients with PD, suggesting a role for serotonin in PD tremor.[21] 5-$HT_{2A/2C}$ receptor antagonism may also play an important role in the antitremor effect of clozapine. 5-HT_2 receptor antagonists have been shown to reduce tremor in rodent models of PD tremor.[22–24] The site of action is thought to be in the substantia nigra pars reticulata (SNr). Thus, Carlson et al. evaluated the effect of mianserin, a

TABLE 2 Clinical studies evaluating the effect of clozapine on tremor in PD patients

Authors	No. of Patients	Duration of Study	Nature of Study	Outcome
Friedman et al.[15]	19	14 weeks, 6 weeks in each arm with a 2-week washout period in between	Double-blind crossover study of benztropine vs. clozapine	Equal significant effectiveness of clozapine and benztropine UPDRS tremor score (4.1 ± 0.6 to 2.75 ± 0.58) and Fahn-Tolosa-Marin tremor score (7.05 ± 1.01 to 4.83 ± 3.26) before and after clozapine intervention; mean effective dose of clozapine was 39 mg
Trosch et al.[12]	172	Retrospective	Retrospective analysis of cohort of PD patients treated with clozapine	Of the 106 patients with rest tremor, 72.4% reported improvement on a standardized 61 items questionaire. Mean dose of clozapine was 31.4 mg + 44.8 SD
Bonucelli et al.[11]	17	Responders moved on to a chronic phase of 15.5 ± 8.3 months	Double-blind, placebo-controlled study followed by an open-label, long-term use of clozapine	15 of the 17 patients experienced more than 50% reduction in UPDRS tremor score severity with an acute administration of clozapine (12.5 mg); benefit was sustained in the open-label study with an average dose of 45 ± 9.6 mg
The Parkinson Study Group[8]	60	14 months	Randomized, double-blind, placebo-controlled trial of low-dose clozapine in patients with PD and drug-induced psychosis	There was a statistically significant beneficial effect of clozapine on tremor as measured by UPDRS tremor score (−1.5 ± 0.5 clozapine vs. −0.2 ± 0.4 placebo); mean dose of clozapine was 24.7 mg/day
Klein et al.[28]	32	Retrospective	Retrospective study of PD patients treated with clozapine for PD psychosis	3 patients had marked improvement of their tremor as reported in the Discussion. Mean daily dose of clozapine was 50 mg

SD, standard deviation.

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TABLE 3 Binding profile of clozapine on various pharmacological receptors, compared to quetiapine and the anticholinerigcs, trihexyphenydyl and benztropine

Receptor	Ki Clozapine[a]	Ki Quetiapine[a]	Ki Trihexyphenidyl	Ki Benztropine
5-HT2A	13	366		
5-HT2B	7.15[b]			
5-HT2C	29	1,500		
5-HT1A	105	431		
M1	14	858		
M4	29	542	2.6[c]	1.1[a,c]
H1	2	7.5		
α1	6.8[d]	8.1[d]		
α2	15[d]	80[d]		
D2	431	567		
D4	39	1,202		

[a]Reference number [9].
[b]Reference number [29].
[c]Reference number [30].
[d]Reference number [65].

nonselective 5-$HT_{2A/2C}$ antagonist and demonstrated that whereas injections into the SNr reduced jaw tremor induced by tacrine, injections into the ventrolateral striatum did not achieve the same result.[25] Further support for this possibility comes from another preclinical study by Bruggeman et al., who showed that acute intravenous administration of risperidone induced a dose-dependent inhibition of the firing rate of the SNr neurons, which was partially blocked by quipazine, a 5-HT2 receptor agonist, strengthening the potential role that antagonism of 5-HT_2 receptors play in inhibiting activity of the SNr.[26] This latter effect could then disinhibit thalamocortical input involved in the pathophysiology of motor symptoms in PD, including tremor. Thus, 5-HT_{1A} agonism and 5-$HT_{2A/2C}$ antagonism or a combination of the two could contribute to the antitremor effects of clozapine.

Antihistaminergic Effects

Literature on antihistaminergics as antitremor agents is sparse. Diphenydramine, usually classified as an "antihistamine,"[27] has been shown to be effective in relieving motor symptoms of PD. However, diphenydramine also has moderate antimuscarinic activity. The role of antagonism of these two receptors in the antitremor effect of diphenydramine has been addressed in a study comparing diphenydramine, doxepin, and mepyramine in treating tacrine-induced tremulous jaw movement in rats.[28] Doxepin and mepyramine were chosen for their higher affinity for H1 receptors, but lower and no antimuscarinic activity, respectively, compared to diphenydramine. In this study, dephenydramine improved the tremulous jaw movements, but doxepin and mepyramine did not, suggesting that dephenydramine largely exerts its antitremor effect through its muscarinic antagonist properties. Thus, the antitremor effects of clozapine may have little to do with its influence on H1 receptors.

Antiadrenergic Effects

To our knowledge, the only studies evaluating the effects of antiadrenergic agents involve β-adrenergic receptor blocking agents (e.g., oxprenolol[29]). Clozapine has negligible β-adrenergic binding.[9] Whether its influences on α_1 or α_2 receptors play a role in clozapine's antitremor effects is unknown.

Antidopaminergic Effects

Clozapine is a dopamine D2 and D4 antagonist (Table 3).[9] This property is unlikely to contribute to the antitremor effect of clozapine given that blockade of dopamine receptors in the basal ganglia would be expected to aggravate the rest tremor of PD,[30] unless the usual low doses of clozapine used in PD have greater presynaptic effects in selected circuits involved in tremor. Many patients experience a diphasic worsening of rest tremor in response to L-dopa (i.e., tremor increases before it improves and then may rebound again as the effects of L-dopa wear off). It is interesting to consider the possibility that an antidopaminergic effect of clozapine might act through whatever mechanism induces this phenomenon.

Adverse Reactions

The cases in Table 1 and the literature reviewed support the potential beneficial effects of clozapine on disabling rest tremor in PD. However, clozapine is clearly infrequently used for this indication. Indeed, clozapine has been underutilized even for the treatment of psychosis in PD,[13,14] where its benefits have been well established and are more widely appreciated.[8,31] This could be owing to the fact that clozapine has been associated with a myriad of side effects, which can be severe and life threatening and require cumbersome monitoring. Table 5 lists some of the common and severe adverse reactions that may occur with clozapine usage and its reported incidence in psychiatric and PD patients.

Metabolic Adverse Reactions

Weight gain is a common consequence in psychiatric patients treated with clozapine. Comparison studies found that clozapine was the antipsychotic with the highest risk of weight gain.[32–34] The exact mechanism of this weight gain is not well under-

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TABLE 4 Studies evaluating the possible roles of various pharmacological receptors in suppressing tremor in animal models of PD and in PD patients

No.	Author	Possible Mechanism of Antitremor Effect	Nature of Study	Outcome
I. Preclinical studies				
a.	Betz et al.[17]	Antimuscarinic	Use of moderately selective muscarinic-4 receptor antagonist, tropicamide in tremulous jaw movements in rodent model of PD tremor	Tropicamide suppresses tremulous jaw movements induced by muscarinic agonist pilocarpine and dopamine antagonist pimozide
b.	Carlson et al.[20]	Antiserotonergic	Injection of mianserin, a 5-HT2A receptor antagonist into SNr and ventrolateral striatum in tremulous jaw movements in rats	Injection of mianserin into SNr and not ventrolateral striatum reduced tacrine-induced tremulous jaw movements
c.	Vanover et al.[21]	Antiserotonergic	ACP-103 (pimavanserin), a 5-HT2A receptor inverse agonist in tacrine-induced jaw tremulous movements	Significant reduction of tacrine-induced tremulous jaw movements
d.	Bruggeman et al.[22]	Antiserotonergic	Effects of risperidone, clozapine, and haloperidol on extracellular recordings of SNr neurons in rat brain	Intravenous administration of risperidone and clozapine decreases SN activity, which is partially blocked by preadministration of quipazine in the risperidone group
e.	Carlson et al.[23]	Antihistaminergic	Effects of histamine H1 receptor antagonists, diphenydramine, doxepin, and mepyramine in tacrine-induced tremulous jaw movements in rats	Diphenydramine reduces tremulous jaw movements significantly compared to doxepin and mepyramine (argues against a role for antihistaminic effects)
II. Clinical studies				
a. PD				
i.	Friedman et al.[15]	Antimuscarinic	Double-blind, crossover trial comparing clozapine and benztropine in 19 patients	Clozapine as effective as benztropine in treating tremor in PD, but fewer anticholinergic side effects. UPDRS tremor score (4.1 ± 0.6–2.75 ± 0.58; $P < 0.013$) and Fahn-Tolosa-Marin tremor score (7.05 ± 1.01–4.83 ± 3.26; $P < 0.0034$) before and after clozapine intervention
ii.	Koller[66]	Antimuscarinic	Double-blind study of amantadine, trihexyphenidyl, and L-dopa in 9 PD patients	Trihexyphenidyl and L-dopa equally efficacious in suppressing PD rest tremor amplitude as measured by a 60-second epoch spectral analysis
iii.	Gordon et al.[64]	Serotonergic	Open-label, prospective trial with mirtazapine in 25 PD patients	UPDRS tremor scores were improved by an average of 7%, which was statistically significant.
b. Other parkinsonism syndromes				
i.	Wirshing et al.[67]	Antimuscarinic	Anticholinergics in drug-induced parkinsonism	Anticholinergics significantly superior to placebo in suppressing tremor as measured by the changes in energy in the 4-Hz band by the resting hand platform device
ii.	Bersani et al.[19]	Antiserotonergic	Double-blind study comparing ritanserin, a 5-HT antagonist, ophenadrine, and placebo in 36 patients with neuroleptic-induced parkinsonism	Tremor assessed by Mindham rating scale significantly reduced in ritanserin and ophenadrine groups compared to placebo

stood. Several factors may be involved, such as increased appetite, metabolic and endocrine alterations, and reduced energy expenditure. Weight gain may be more pronounced in patients who are treated with higher doses of clozapine.[35] This adverse effect could potentially be advantageous for PD patients given that they commonly lose weight during the course of their illness.[36,37] However, in a study by Sitburana et al. comparing PD patients before and after starting atypical antipsychotics, including clozapine, patients continued to lose weight after initiation of treatment, suggesting a unique alteration of weight homeostasis in PD.[38]

Clozapine has the propensity to cause increase in triglyceride, total cholesterol levels, and glucose levels; this effect combined with weight gain mentioned above are constituents of metabolic syndrome.[39] Recent studies comparing atypical antipsychotics have shown that clozapine had the propensity of producing the greatest increase in cholesterol and glucose levels compared to other atypical neuroleptics, such as risperidone and quetiapine.[40] This could be hazardous because metabolic syndrome is associated with increased risk of developing cardiovascular disease and diabetes mellitus. Fortunately, metabolic syndrome in PD is relatively lower than those in studies involving psychiatric patients. In a study by Alissa et al., only 4 of 61 (6.5%) parkinsonism patients reported weight gain and 1 patient (1.6%) reported increased blood glucose levels.

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TABLE 5 Common and severe side effects of clozapine

Adverse Effects of Clozapine	Reported Incidence in All Studies Including Psychiatric Patients	Reported Incidence in PD Subjects
Metabolic adverse effects, %		
Weight gain	50–75[68,69]	0.0–6.5[8,12,28,70–72]
Metabolic syndrome	48–50[39,73]	0.0–1.6[8,12,28,70–72]
Cardiac adverse effects, %		
Myocarditis	0.7–1.2[42]	No reported incidence[8,12,28,70–72]
Blood dyscrasias, %		
Agranulocytosis/neutropenia requiring cessation of clozapine treatment	0.38–0.8[26,46]	0.8 at 1 year[46,47]
Clozapine-induced seizures, %	1.0–4.4[56]	No reported incidence[8,12,28,70–72]
Other common adverse effects, %		
Sedation	39[50]	29–45[8,12,28,70–72]
Orthostatic hypotension	9[50]	9.9 from 1 study[71]
Hypersalivation	30–80[59,60]	11–16[8,12,28,70–72]

Cardiac Adverse Reactions

Clozapine is also associated with numerous adverse cardiac events. Kilian et al. reported 23 cases of myocarditis and cardiomyopathy among 8,000 patients treated with clozapine voluntarily reported to the Australian Adverse Drug Reaction Committee.[41] This represented a relative risk of 1,000 to 2,000 compared to the general population. Of these 23 cases, 6 deaths were reported, 5 cases from myocarditis and a case from cardiomyopathy. All cases of myocarditis occurred within 3 weeks of initiating clozapine with dosages ranging from 100 to 725 mg daily. A more recent study that looked into 116 cases of suspected myocarditis found that the median time to develop myocarditis was 16 days and the clozapine dosages ranged from 100 to 450 mg daily.[42] Risk factors for the development of myocarditis are unclear. It had been suggested that rapid dose titration contributes to its development. To the best of our knowledge, there had been no reported cases of myocarditis in PD patients treated with clozapine to date. This could possibly be owing to the low doses used and gradual titration schedule typically employed in treating PD (psychosis or tremor).

Blood Dyscrasias

One of the most worrisome adverse reactions of clozapine is its propensity to induce blood dyscrasias. Clozapine is associated with various hematological adverse effects, including leukopenia, neutropenia, agranulocytosis, leukocytosis, anemia, eosinophilia, thrombocytopenia, and thrombocythaemia.[43–45] Among these, agranulocytosis is a serious side effect that may cause significant mortality if undetected. The incidence of agranulocytosis in clozapine-treated patients has been reported to be 0.8% over 15 months,[46] with the majority of cases occurring within 18 weeks of initiating clozapine.[47] This hazard can be reduced by close monitoring of the white cell count; clozapine should be stopped when leukopenia is detected before progressing to agranulocytosis and neutropenia.[48] Early detection and drug discontinuation when leucopenia is detected usually leads to rapid recovery of white cell count.[48] In the 8 PD patients who we treated with clozapine for tremor in PD, none experienced a reduction in white blood cell count that required intervention.

Clozapine-Induced Sedation and Orthostatic Hypotension

Sedation and orthostatic hypotension are common adverse reactions of clozapine that warrant attention. Sedation is generally more common with clozapine than with other atypical neuroleptics, such as olanzapine, quetiapine, and risperidone.[49] It had been reported to occur in 39% of patients treated with clozapine[50] and was common even at low doses used in PD.[51] In some patients, the sedation is intolerable and clozapine has to be withdrawn.[49,51]

Orthostatic hypotension is common especially in advanced PD.[52,53] This orthostatic hypotension can be worsened by clozapine[54] and can lead to somnolence, lightheadedness, and syncope.[53,55] In a study conducted by Friedman et al., 9.9% of 172 PD patients treated with clozapine had orthostatic hypotension.[12]

Clozapine-Induced Seizures

Clozapine has also been associated with a dose-related increase risk of seizures. In a study by Devinsky et al., doses of lower than 300 mg, between 300 and 600 mg, and above 600 mg had a seizure rate of approximately 1%, 2.7%, and 4.4%, respectively.[56] In the same study, rapid upward titration was associated with increased seizure risk. In another study by the same investigators, seizures tended to occur during the titration phase and at high doses of more than 600 mg. Seventy-eight percent of these patients who had seizures were successfully rechallenged with the medication, but with a lower dose and a more gradual titration schedule or an addition of an antiepileptic.[57,58] In PD patients, clozapine-induced seizures were rare, with no reported incidence in several publications. In our small cohort of patients, patient 6 had a seizure during the titration phase on a

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very low dose of clozapine, which warranted drug discontinuation. He was not rechallenged with clozapine.

Clozapine-Associated Hypersalivation

Clozapine-associated hypersalivation is another common adverse effect. It occurs in around 30% to 80% of patients treated with clozapine for non-PD-related psychosis[59,60] and had also been commonly reported complicating clozapine treatment in PD patients.[61,62]

Conclusion

Clozapine may be effective in reducing tremor in PD patients. In our series of 8 patients with bothersome rest tremor, tremor score had been reduced by an average 64% and 3 patients had their tremor abolished. One could argue that the reduction in tremor is a result of the natural progression of PD in which increased rigidity dampened the tremor. However, it is unlikely that progression of PD or increased rigidity is the main reason for improvement in tremor score in our series given that the tremor assessment postclozapine initiation was within 6 months from the baseline assessment. Furthermore, the rigidity score did not differ pre- and postclozapine initiation. We have also had the anecdotal experience in patients treated for psychosis who also obtained a pronounced antitremor effect that the tremor returned to its pretreatment severity when they were later withdrawn from clozapine.

It is also interesting to note that in our case report, the patient also had an improvement in his orofacial dystonia after introduction of clozapine with concurrent reduction in L-dopa dose. Another potential beneficial effect of clozapine is the reduction of L-dopa-induced dyskinesia in PD, as described in the study by Durif et al.,[63] which showed that clozapine improved dyskinesias in PD.

We have noted that clozapine does have a myriad of serious adverse reactions that warrant attention and make its usage cumbersome or difficult. However, tremor in PD can be disabling even with the best medical therapy and may warrant a brain surgery (either a thalamotomy or DBS), which could potentially lead to more-serious complications than the adverse reactions of clozapine. Therefore, before subjecting a patient to surgery, we suggest considering a trial with clozapine. Furthermore, from Table 2, only low doses of were needed for resting tremor reduction, and incidence of dose-related side effects, such as seizures and hypersalivation, were generally lower than reported among the psychiatric patients. However, given the potential fatal side effects of this drug, a detailed discussion about these potential adverse effects and required monitoring is needed before initiating the patient on clozapine. If clozapine is to be initiated in PD patients, it has to be used cautiously with proper monitoring, preferably in specialized centers.

The mechanisms underlying the antitremor effect of clozapine remain unclear. It is possible that multiple mechanisms act concurrently for clozapine to be effective in treating tremor in PD. It is interesting to note that there are no reports of tremor reduction in response to quetiapine, another atypical antipsychotic frequently used in PD psychosis, and one study even showed worsening of tremor in a patient switched from clozapine to quetiapine.[64] This could probably be explained by the fact that binding of quetiapine to the various types of receptors that we have postulated might be involved in the antitremor effect of clozapine being weak (Table 3).

We acknowledge that the number of patients in this case series is small. A well-designed prospective trial is required in order to determine the effective dose and the actual frequency of associated side effects of clozapine when used for resting tremor and dyskinesia in PD. Further studies are also needed to understand the exact mechanisms underlying the antitremor effects of clozapine, which will be important to spur research into the development of new drugs capable of treating tremor in PD more safely and effectively.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

T.K.Y.: 1B, 1C, 3A
A.E.L.: 1A, 1B, 3B
S.H.F.: 1B, 3B

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