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Review

# Tremor-Dominant Form of Parkinson's Disease

**Z. A. Zalyalova,[1,2] E. A. Katunina,[3,4] D. V. Pokhabov,[5,6] S. E. Munasipova,[1,2] and M. M. Ermakova[1]**

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This review addresses tremor, which is among the maladaptive and difficult-to-treat symptoms of Parkinson's disease (PD). Along with classical resting tremor, patients with PD may experience postural and kinetic types of tremor, reflecting the multimodal mechanism of its formation, which involves multiple neurotransmitter systems. Unpredictable therapeutic responses and mixed responses to levodopa also reflect the roles of multiple underlying pathophysiological processes. Among medication-based methods for tremor correction, preference is given to dopamine receptor agonists because of their wide range of pharmaceutical effects and high efficacy in relation to the major motor and various non-motor manifestations. Evidence of the efficacy of advanced neurosurgical and non-invasive treatment methods is not always convincing; there have been no large-scale comparative studies assessing their efficacy in patients with tremor-dominant forms of PD.

**Keywords:** Parkinson's disease, tremor, resting tremor, postural tremor, kinetic tremor, tremor pathogenesis, dopamine receptor agonists, piribedil.

Parkinson's disease (PD) is a progressive neurodegenerative disease characterized by a constellation of features including bradykinesia, tremor, rigidity, and postural instability [1, 2]. Tremor is among the commonest motor symptoms in PD, being seen in 75% of patients. Tremor may be the most maladaptive of the movement disorders [3, 4]. Although patients with PD may experience several forms of tremor, the most common is the characteristic resting tremor (RT) of the "pill-rolling" type [5]. RT can be combined with both kinetic tremor (KT) and secondary postural tremor (PT), which can lead to significant functional impairments [4–7]. Compared with other clinical subtypes, tremor-dominant PD tends to progress more slowly, has less disabling non-motor symptoms, and is characterized by a lower risk of developing levodopa-induced dyskinesia and resistance to dopaminergic drugs [8, 9].

The pathogenesis of tremor in PD is complex and not fully understood. It has been suggested that the onset, severity, and progression of tremor are caused by multiple factors and its pathogenesis goes beyond the classical ideas of depletion of dopamine stores in the nigrostriatal system [10–13]. The dimmer (from *dimmer-switch*) model of tremor generation in PD suggests the occurrence of synchronous oscillatory activity in two distinct but partially overlapping central pathways [14, 15]. Dysfunction of the cerebellothalamocortical and subcortical-cortical circuits produces changes in physiological central neural oscillations, ultimately leading to the development of tremor [14]. This model is based on results from neurophysiological, neuroimaging, and intraoperative studies during functional stereotactic neurosurgical procedures [11, 16–18]. In particular, tremor is suppressed by stereotaxic interventions targeting anatomical structures associated with both pathways (the subthalamic nucleus (STN), ventral intermediate nucleus (Vim), and globus pallidus interna (GPi)) [19]. The

[1] Kazan State Medical University, Russian Ministry of Health, Kazan, Russia; e-mail: z.zalyalova@gmail.com.
[2] Republican Consultative-Diagnostic Center for Extrapyramidal Pathology and Botulinum Therapy, Military Veterans' Hospital, Kazan, Russia.
[3] Pirogov Russian National Research Medical University, Russian Ministry of Health, Moscow, Russia.
[4] Federal Center for the Brain and Neurotechnologies, Russian Federal Medical Biological Agency, Moscow, Russia.
[5] Center for Innovation in Neurology, Extrapyramidal Diseases, and Botulinum Therapy, Krasnoyarsk, Russia.
[6] Voyno-Yasenetskii Krasnoyarsk State Medical University, Russian Ministry of Health, Krasnoyarsk, Russia.

model suggests that the basal ganglia constitute the key structure whose activation causes tremor and which functions as a switch [15, 20]. Oscillatory activity in the striatum increases the inhibitory output in the thalamus, which, in addition to spike activity in the GPi, can generate rhythmic discharges in the anterior ventrolateral nucleus of the thalamus (VLa) [21]. The primary motor (M1) and premotor areas of the cortex are the main areas where convergence of the two circuits occurs [22, 23]. Convergence at this level activates the cerebellar-thalamo-cortical circuit, which modulates tremor amplitude, acting as a dimmer [23, 24].

The origin of RT and PT was studied using non-invasive transcranial magnetic stimulation of M1 and the cerebellum. Suppression of both RT and PT was achieved by stimulation of M1, whereas cerebellar stimulation suppressed only the postural component [25, 26]. These data suggest that M1 controls the amplitude and rhythm of RT and PT in PD, while modulation of RT is more related to the cerebellum.

Tremor in PD is associated less with degeneration of dopaminergic neurons in the substantia nigra pars compacta than with degeneration in the retrorubral area (RRA) of the midbrain [27]. Loss of dopaminergic projections from the RRA to the subthalamic region, basal ganglia, and VLa leads to depletion of dopamine in these regions and represents one of the main neurochemical causes of tremor in PD [22, 28]. The severity of tremor has been found to be related to the density of dopamine transporters (DAT) in the pallidum, while other motor symptoms are correlated with the density of DAT in the striatum [22]. This suggests a more selective depletion of pallidal dopamine reserves in tremor in PD.

It has been suggested that, in addition to dopamine, other neurotransmitters may also play an important role in the pathogenesis of tremor in PD. In patients with PD dominated by tremor, degeneration of locus coeruleus interneurons is relatively less marked, and the receptor binding of noradrenaline receptors is enhanced [28, 29]. The amplitude and severity of tremors are related to serotonin deficiency. Thus, loss of serotonin transporters in the raphe nuclei of the midbrain correlates with more severe tremor [4, 11]. More marked manifestations of tremor are associated with lower values levels of serotonin transporter availability in the raphe nuclei as compared with the availability of the dopamine transporter [30]. In addition, patients with tremor-dominant PD tend to mount relatively small responses to dopaminergic therapy. Both conclusions indicate that more severe and dopamine-resistant tremor is indicative of more widespread neurodegeneration with severe raphe nucleus dysfunction [4, 30, 31]. The fact that anticholinergic drugs suppress tremor in PD has led to the suggestion that acetylcholine contributes to the development of tremor in PD [21, 24]. Dopamine deficiency is thought to lead to hyperactivity of striatal cholinergic interneurons, which in turn reduces dopamine release and aggravates the symptoms of PD, including tremor [11, 32].

An asymmetric resting tremor with a frequency of 4–6 Hz is predominant in PD and is often suppressed by voluntary movements [7, 33]. RT is often combined with KT or PT [33–35]. KT appears during hand movements, for example when writing or when performing the finger-tapping test. PT occurs when the subject holds the arms extended in front of himself while holding the limbs against gravity [34]. Secondary PT is a form of PT occurring after a short latent period (a few seconds) while holding the arms in an antigravity position [35].

The mean prevalence of RT in PD is 58.2%, while isolated RT occurs in only 14.5%. In contrast, the prevalences of action-related tremor overall and pure action tremor are 36.6% and 9.6% respectively. The prevalences of PT and isolated PT are 49.7% and 4.0% respectively; KT overall and isolated KT occur in 52.3% and 8.1% respectively. The proportion of patients without tremor is only 19.9%. Mild, weak, moderate, and severe tremor were reported by 52.8%, 21.4%, 5.3%, and 1.0% of patients respectively [36]. All types of tremor decrease on dopaminergic therapy, which is consistent with the conventional view regarding the effects of levodopa and dopamine agonists on tremor in PD [37–39]. The prevalence of KT is high in PD patients with RT. Patients with KT have more severe RT than patients without KT [40]. This suggests that KT may be part of a broader tremor-dominant syndrome in PD. It is of note that the MDS-UPDRS does not assess PT, secondary PT, or isometric tremor, and does not capture PT or KT of the lower extremities or tremor of the head [35].

An early classification suggested that akinetic-rigid, tremulous, and mixed forms of PD should be discriminated. Later, the concept of "benign tremulous parkinsonism" appeared, in which limb tremor is asymmetrical. Although tremor progresses over time, bradykinesia and rigidity are minimal or absent. In some patients, RT is combined with PT. Most first-degree relatives of these patients have tremor or PD [41]. Currently, the concept of "benign tremulous parkinsonism" is virtually unmentioned in the literature.

The tremor-dominant form of PD has more recently been divided into four categories based on clinical phenomenology: type I, in which tremor is pure RT with a frequency of 4–6 Hz; type II, when RT is associated with an action tremor component at the same frequency; type III, in which patients experience isolated action tremor; and type IV, in which mixed RT and action tremor coexist, each with a different frequency, and the patient may have signs of essential tremor (ET) [7, 42].

Another classification of types of PD with tremor discriminates between a tremor-dominant subtype, an indeterminate (mixed) subtype, and postural instability/gait disturbances [43], which are linked with different rates of disease progression. Particular subtypes of the tremulous form of BP are identified by assessment of eight or 11 tremor indicators on the UPDRS or MDS-UPDRS scales, which are then correlated with assessment of postural instability/gait

disturbance [36, 43]. The identification of tremor-dominant PD with postural instability and gait difficulty changes our understanding of the more favorable course of PD when associated with tremor.

**Treatment of Patients with Tremor-Dominant PD.** Levodopa and other dopaminergic drugs remain the first-line treatment for all motor symptoms in PD, including tremor [44–46]. The choice of pharmacotherapy is determined by circumstances related to the characteristics of both the disease (severity of tremor and levodopa sensitivity) and the patient (age, functional and cognitive status, etc.) [44]. The effect of levodopa is most marked in relation to bradykinesia, while its effect on tremor severity is variable [46, 47]. Beneficial effects are more obvious for RT and secondary PT than KT or isolated PT [35, 48]. The intensity of the effect varies widely, from the absence of any objective clinical response to an 80% reduction in tremor intensity [49]. These differences in treatment efficacies have led to the proposal that three subtypes of tremor should be discriminated: dopamine-sensitive, dopamine-resistant, and partially sensitive (intermediate) [50, 51]. Unfortunately, the drug dose and treatment duration required for tremor to be regarded as dopamine-resistant have not been determined. Based on this classification, dopamine resistance is defined according to the response obtained in the levodopa challenge test, which uses higher doses of the drug. The definition of dopamine-resistant tremor is based on the absence of clinical and electrophysiological responses despite a twofold increase in drug dose [50].

Insufficient responses in some patients may be due in part to pseudoresistance, a phenomenon in which levodopa-sensitive symptoms are falsely resistant [51–53]. This occurs due to a number of factors which contribute to a suboptimal response [51, 54]. Factors leading to pseudoresistance include gastrointestinal dysfunction associated with poor food absorption and a high-protein diet. Cognitive stress is also a factor known to weaken the therapeutic effect of dopamine [15, 51, 53]. As the tremor-controlling effect of levodopa is dose-dependent, increased doses may be necessary even if other symptoms show sustained responses to lower doses [55]. However, the possibility of increasing the dose is often limited because of possible dose-dependent side effects (nausea, vomiting, dyskinesia, or hallucinations). Some studies have shown that tremor may, paradoxically, increase with higher doses of levodopa [56].

Dopamine agonists (DAA) can be used as initial monotherapy or adjuvant therapy to levodopa [46, 57]. DAA may enhance the effect of levodopa, thereby providing greater control of tremor [58, 59]. Both selective (pramipexole) and non-selective (pergolide) DAA produce the same degree of suppression of resting tremor in monotherapy, though with different tolerabilities [60]. The addition of an DAA to levodopa decreases UPDRS tremor scores by 45% and produces a significant reduction in the frequency of waking tremor as measured by long-term electromyography [58]. Apomorphine is a potentially highly effective short-acting DAA; given via by continuous subcutaneous infusion with a pump or by intermittent sublingual or subcutaneous injections, it can have effects on tremor comparable to those of levodopa, albeit with a shorter duration [61, 62].

Among DAA, piribedil has a particular spectrum of activity, characterized by a triple binding profile: balanced affinity for D2- and D3-dopamine receptors, selective antagonism of $\alpha$2-adrenergic receptors, and minimal interaction with serotoninergic receptors [63]. D2 receptors in PD are hypersensitive, with the result that partial agonism is sufficient to relieve motor dysfunction (increased activity in the nigrostriatal pathway) while limiting undesirable effects due to an excess of normosensitive D2 receptors in other dopaminergic pathways. In addition, antagonism of $\alpha$2-adrenergic receptors enhances adrenergic, dopaminergic, and cholinergic transmission, with beneficial effects on motor and cognitive functions, mood, and the preservation of dopaminergic neurons [63, 64]. Piribedil is effective against all major motor symptoms (tremor, rigidity, bradykinesia, and postural instability) [65–67]. Piribedil has the advantage that its major effect is on tremor, decreasing it by 70% [68, 69]. The marked reduction in tremor with piribedil may be due not only to stimulation of D2 and D3 receptors on dopaminergic neurons, but also to direct effects on dopaminergic and cholinergic receptors on cholinergic neurons [70].

The most common dose-related side effect associated with DAA is impulse control disorder [71]. The moderate activity of piribedil against D3 receptors, combined with its lack of affinity for D1 receptors, gives a low risk of developing impulsive-compulsive disorders, which contrasts with other DAA drugs [63]. In contrast to pramipexole, there are no descriptions of increases in or the development of camptocormia during treatment with piribedil [72, 73]. Treatment of the early stages of PD with DAA is associated with a reduction in the risk of motor fluctuations in the first five years after treatment initiation, especially in younger patients [74, 75].

The use of anticholinergic drugs can be considered if tremor is not adequately controlled by dopaminergic agents [52, 76]. Anticholinergics are effective in reducing tremor and other motor symptoms of PD, though they have a high risk of psychiatric and cognitive adverse events [77]. Because of the potential side effects, anticholinergic drugs should only be used in young patients with tremor-dominant PD where dopaminergic drugs have failed to provide improvement [52, 76]. If necessary, drug doses can be reduced slowly, as rapid treatment discontinuation may result in exacerbation of parkinsonism [78].

Monoamine oxidase B (MAO-B) inhibitors work by increasing the bioavailability of central monoamines, including dopamine. They may be effective in relieving motor and non-motor symptoms in the early stages of PD, thereby delaying the need for levodopa [79]. The positive effects of MAO-B inhibitors are noticeably higher in akinetic-rigid

PD than in tremor-dominant PD [80]. Rasagiline has been studied as monotherapy or adjuvant therapy to levodopa in patients with tremor, and significant reductions in tremor were found after 10 weeks of treatment [81, 82].

Clozapine is an antipsychotic drug used to treat patients with schizophrenia and drug-induced psychosis in PD [83]. The exact mechanism of its antitremor effect is not completely clear, though the explanation may lie in its anticholinergic and antiserotoninergic properties [84]. Clozapine decreased RT and PT in 72% of patients with PD, with a 64% reduction in severity [85]. In addition to its antitremor effect, the advantage of its antipsychotic action may be important in patients with psychosis [84]. One of the main limitations of the use of clozapine is the risk of developing agranulocytosis, so monitoring of blood cell composition is required [86].

Non-selective β-blockers, particularly propranolol, are widely used in the treatment of ET. The efficacy and safety of propranolol and other β-blockers for tremor in PD have not been confirmed [86]. Propranolol may reduce the postural component of tremor in PD and may be useful in the context of associated anxiety, which increases tremor [87]. The efficacy of propranolol is generally not sustained, with a large proportion of patients eventually discontinuing the drug due to poor tolerability, loss of an initial positive response, and increased risk of orthostatic hypotension [88].

Like anticholinergic drugs, β-blockers should be tapered gradually to prevent withdrawal symptoms [89]. Other therapeutic approaches include clonazepam, budipine, zonisamide, amantadine, and mirtazapine, which have shown different levels of efficacy [90]. Botulinum neurotoxins (BoNT) act on cholinergic presynaptic nerve terminals by cleaving and inactivating SNARE proteins and inhibiting acetylcholine release. This in turn prevents muscle contraction and leads to paralysis of the injected skeletal muscles. BoNT type A (BoNT-A) is widely used to treat tremor and other movement disorders [91–93]. The efficacy of injections depends on the dose, the muscles selected, and the doctor's technique and experience. The long-term effect of BoNT injections was demonstrated at a mean follow-up period of 29 months, with more than 80% of patients reporting moderate or marked improvement [94, 95]. The severity of RT and KT decreased significantly from baseline; more than half the patients experienced transient weakness in the injected muscles [95].

Deep brain stimulation (DBS) is the most common surgical treatment for PD. Its long-term efficacy in improving refractory and poorly controlled motor symptoms and fluctuations makes DBS indispensable [96, 97]. The therapeutic mechanism of DBS is not well understood, though placing electrodes within structures with oscillatory activity (the basal ganglia and cerebellothalamocortical circuits) may suppress their ability to generate tremor [98, 99]. The selection of DBS targets for patients with tremor-dominant PD is individual. Electrode placement in the STN, ventral intermediate Vim, GPi, and posterior subthalamic region has been reported to be effective in reducing tremor in PD [100–102]. The STN and GPi have an obvious advantage over other targets, in that targeting these structures reduces the severity of all movement disorders [100]. STN-DBS may be superior to GPi-DBS in controlling dopamine-resistant tremor [103]. Selection of the Vim is preferred for patients with long-lasting and mostly unilateral tremor as the main symptom when there are no other significant motor disturbances or fluctuations. Dual stimulation of the GPi and Vim can also be used in patients with dopamine-resistant tremor who have other significant motor symptoms or fluctuations [103]. Bilateral Vim-DBS is potentially associated with the risks of dysarthria, loss of balance, and impaired coordination [104].

MRI-guided focused ultrasound (FUS) destruction, gamma knife (GK) treatment, and radiofrequency thermal ablation are accessible methods for thermal destruction [105, 106]. Although thermal ablation has fallen out of favor with the advent of DBS, interest in this approach has been growing in recent years with the advent of non-surgical treatments such as FUS or GK. The advantage of these methods is that they do not require general anesthesia and, as compared with DBS, have fewer of the side effects associated with surgical interventions [106]. They may provide an alternative to DBS for treating patients in remote areas where access to DBS treatment and monitoring is limited. The advantage of FUS is that it provides real-time assessment of results during procedures to achieve optimal clinical effects [105]. Unlike DBS, any thermal destruction method results in irreversible damage, which is regarded as a serious drawback. Furthermore, the evidence for the long-term efficacy of DBS in PD is overwhelming compared with existing studies on the efficacy and safety of thermal destruction, which have been relatively small and short-term [107].

FUS is a promising treatment for refractory tremor in PD. The safety and efficacy of FUS were first demonstrated in the treatment of ET, with the result that it was approved by the Food and Drug Administration (FDA) as a treatment for drug-resistant tremor [108]. Thalamotomy with FUS provides an average improvement of 7 UPDRS tremor points as compared with preintervention levels [109, 110]. Subthalamotomy using FUS leads to improvements in UPDRS-III scores (including tremor), as well as quality of life on the UPDRS-II scale [109]. At present, this method is mainly used for unilateral lesions to control the most affected side [111]. Bilateral ablation in PD remains controversial, though a growing number of reports on ET have indicated good efficacy and safety [112]. Most side effects are transient, usually disappearing 3–12 months after the procedure [113], and include reversible ataxia, paresthesia, and weakness [108, 112, 113]. FUS subthalamotomy may lead to dyskinesia in the off state [112].

Non-invasive stimulation techniques offer new possibilities for reducing tremor. Stimulation has been seen to produce therapeutic effects using high-frequency repetitive transcranial magnetic stimulation and anodal transcranial

direct current stimulation [114], along with peripheral functional electrical stimulation, sensory electrical stimulation, and transcutaneous electrical nerve stimulation [115]; further study and standardization of the methodology are required.

**Conclusions.** Tremor is one of the most common symptoms of PD. Along with classic RT, patients with PD may experience tremor of other modalities, reflecting multimodal mechanisms of tremor formation involving multiple neurotransmitter systems. Unpredictable treatment responses and mixed responses to levodopa also reflect the roles of multiple underlying processes. Among drug treatments, preference should be given to drugs which are effective against motor and non-motor symptoms, with broad profiles of selective binding to dopaminergic, adrenergic, and cholinergic receptors. Evidence for advanced neurosurgical and noninvasive modalities is mixed, and there are not enough comparative studies for their efficacies to be evaluated in patients with tremor-dominant forms of PD.

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