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Treatment of Parkinson's disease with piribedil: Suggestions for clinical practices

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Abstract

With rapidly growing rates of prevalence, disability, and mortality, Parkinson's disease (PD) has become a global healthcare burden. Increasing elderly population increases the incidence of neurodegenerative diseases in China. Hence, PD poses a huge burden to Chinese economic and healthcare system. PD is a movement disorder that affects the motor and nonmotor functions. Dopamine agonists are used in the management of PD. Piribedil is an antiparkinsonian drug and piperazine derivative, which acts as D2/D3 receptor agonist. Piribedil is one of the non-ergot dopamine receptor (DR) agonists and has been used in China for many years as monotherapy or in combination with levodopa. In this paper, we present a review of clinical application of piribedil, management of adverse events, and drug interactions, and discuss the results of clinical trials of piribedil on motor and non-motor symptoms of PD.

Keywords: Neurodegenerative disease; Levodopa; Dopamine receptor; Non-ergot dopamine receptor agonists; α2-adrenoreceptor; Dyskinesia; Hypotension orthostatic

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1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease[1]. PD affects 41 and 107 persons/100,000 people who were in the fourth and fifth decade of age, respectively[2]. It affects 1903 persons/100,000 people who were aged above 80 years, with peak age group between 85 and 89 years[3].

According to the reports of Global Burden of Disease Study 2016, the prevalence of patients with PD in 2016 was approximately 6.10 million in 2016 compared with 2.50 million in 1990. China reports a higher rate of incidence of PD compared with the rest of the world. The prevalence of PD is higher in men (52.5%) than in women (47.5%). It is estimated that in China, nearly 23.9 – 26.9% of the population will be aged above

65 years by 2050. This will result in an expansion of aging population[4], which might further increase the incidence of PD in China. It is expected that by 2030, China will contribute to over half of the world's PD patients[5]. The global burden of PD has been doubled as the age and life expectancy of the population increases. PD resulted in approximately 3.2 million disability-adjusted life years and caused >210,000 deaths worldwide[6].

Motor symptoms such as akinesia and bradykinesia, tremor, and rigidity[7], and non motor symptoms such as depression, fatigue, altered gait, psychosis, apathy, sleep disorders, and sensory abnormalities[8,9] affect the patient and caregiver's quality of life. Thus, PD causes heavy economic burden to families and society[10,11]. Levodopa, dopamine receptor agonists (DRA), monoamine oxidase B inhibitors, catechol-O-methyltransferase inhibitors, anticholinergic agent, and amantadine are the most common first-line therapy for PD. In patients with chronic PD, the long-term use of levodopa would result in decreased response to the drug, dose adjustments, and frequent emergence of motor complications. DRA have multiple advantages, such as direct dopamine receptor (DR) agonistic effect, long half-life, and antidepressant effect. No evidence of oxidative metabolism and interactions with food amino acids with DR agonists was observed. Daytime somnolence and behavioral changes are some of its drawbacks. DR agonists have been increasingly recognized in the treatment of PD, of which non-ergot DR agonists are highly recommended because of their less adverse effects[12].

Non-ergot DR agonists were approved as the first-line medications for the treatment of PD according to multiple national and international authoritative guidelines. Piribedil has been used as the first non-ergot DR agonist in China. Piribedil improves patient's motor and non-motor symptoms, and prevents motor complications in an advanced stage of PD with minimal adverse reactions such as somnolence[12-16].

However, there is no standardized guideline for the use of piribedil in PD. Based on the evidence-based medical research and domestic practical experience, experts put together comprehensive and reliable instructions on piribedil administration for clinicians. In this review article, we highlight the pharmacological properties of piribedil and its clinical applications in PD, management of adverse events and drug interactions.

2. Pharmacological properties of piribedil

2.1. Pharmacological mechanism

Clinical manifestations of patients with PD are mainly characterized by the degeneration of nigral dopaminergic cell bodies in the substantia nigra pars compacta (SNc) and dysfunction of neurons, which produces dopamine (DA)[17]. It is commonly regarded that the death of dopaminergic neurons in SNc is influenced by DA metabolism, oxidative stress and mitochondrial dysfunction, endoplasmic reticulum stress, impaired protein degradation mechanisms, and neuroinflammation. Dopaminergic neurons are susceptible to mitochondrial oxidative stress induced by DA oxidation. Mitochondrial oxidative stress leads to an accumulation of oxidized DA that suppresses the activity of glucocerebrosidase, lysosomal dysfunction, and α-synuclein accumulation in PD neurons[18,19]. The accumulation of DA in cytoplasm is neurotoxic, resulting in selective death of neurons in SNc[20]. Endoplasmic reticulum stress also causes neuronal death, which is caused by the accumulation of misfolded or unfolded proteins[21,22]. In addition, PD pathology affects autophagy, and stimulation of autophagic activities may be a compensatory mechanism induced by persistent reticulum stress. Impairment of autophagy tends to accumulate abnormal α-synuclein in the Lewy bodies which subsequently causes parkinsonism[23,24].

DA binds to G-protein coupled receptors or DA receptors. These receptors can be classified as D1-like receptors (D1 and D5) and D2-like receptors (D2, D3, D4). These receptors mediate all physiological functions of catecholaminergic neurotransmitter, DA. D4 and D5 receptors may have limited effects on motor or cognition function[25,26]. DR agonists can stimulate DR to produce dopaminergic-like effects, thus improving motor and non-motor symptoms. D2 and D3 receptors are the DRs mainly related to PD. Stimulating the D2 receptors can improve motor function and cognitive functions, such as learning and memory, through prefrontal cortical regulation. D3 receptors can slightly regulate cognitive functions through hippocampal and play a key role in reward and reinforcement mechanisms. Evidence shows that D1 receptors might be related to motor function. Piribedil is a D2-like agonist but the D1 agonist (S584) is one of its metabolites[27]. Relevance of D1 agonistic activity remains speculative but it is thought to have consequences regarding efficacy and tolerability of piribedil. A combined stimulation of D1 and D2 receptors in animal model potentiates antiparkinsonian responses of piribedil and participates in the pathophysiology of dyskinesia[28].

DRA acts as adjuncts to levodopa. DAs can be divided into ergot derivatives and non-ergot derivatives. Piribedil, pramipexole, apomorphine, ropinirole, and rotigotine are the common non-ergot DR agonists. These will bind to DA D2-like family of DA receptors[12,17]. Neuroprotection conferred by DA agonists is thought to be provided by

different mechanisms. They decrease DA turnover and free radical generation in the substantia nigra, and possess antioxidant properties. Pathological conditions were reversed by piribedil in a dose-dependent manner, which showed to increase the expression of lactate dehydrogenase and reduce the expression of tyrosine hydroxylase positive/total neurons ratio after infusion[29]. The mechanisms and pharmacokinetics of non-ergot DR agonists are shown in Table 1[12]. In 1969, piribedil was marketed as the first non-ergot partial DA D2/D3-selective agonist. Piribedil 1-(2-pyrimidyl)-4 piperonyl piperazine is a non-catechol analog of DA[29].

Mechanisms of piribedil include the following:

i. Acting as signal-specific partial agonists at D2/D3 receptors. Partial agonism is sufficient to improve motor dysfunction in PD. While improving motor dysfunction, the avoidance of potentially excessive stimulation of D2/D3 receptors may reduce the incidence of complications, such as cognitive dysfunction and abnormal prolactin excretion. The combined stimulation of D1 and D2 receptors can increase the anti-PD effect and reduce the intensity of dyskinesia[17].
ii. α2-adrenoreceptor antagonistic effects. Piribedil blocks the α2-adrenoreceptor and reinforces dopaminergic, adrenergic, and cholinergic transmission. This effect may decrease the incidence of dyskinesia, improve the motor function and cognition, elevate the mood, and reduce the risk of daytime somnolence[30].
iii. Low affinity to multi-subtype 5-HT receptors. Piribedil may decrease serotonergic 5-HT1-related and 5-HT2-related side effects, such as valvular heart diseases[17].
iv. Minimal interaction with histaminergic and cholinergic receptors[12].

2.2. Pharmacokinetics

Piribedil is used as an oral medication. It reaches maximum concentration 1 hour after single oral dose with rapid absorption. Oral bioavailability is low due to an extensive first-pass metabolism. Hepatic metabolism produces many metabolites, which are excreted through kidney. The elimination of piribedil follows biphasic kinetics and is composed of a first phase characterized by a half-life of 1.7 h and a second, slower phase characterized by a half-life of 6.9 h[12,30]. A sustained-release formulation has a half-life of up to 21 h once steady state is attained, which is longer than levodopa and multiple DR agonist-like pramipexole (8 – 12 h) and ropinirole (6 – 8 h)[30,31]. According to Chinese Guidelines for the Treatment of PD (4th Edition), piribedil sustained-release tablets can be split in half in special cases to reduce the side effects. Continuous dopaminergic stimulation of DA receptors will delay the motor complications. Piribedil has a longer half-life than that of levodopa. It stimulates DA in a less pulsatile manner and avoids adverse effects due to DR-pulsed stimulations[12,32,33].

3. Clinical applications of piribedil in the treatment of PD

The goal of PD treatment is to effectively improve patients' motor and non-motor symptoms, prevent complications, and improve patient's workability and quality of life[15]. The International Parkinson and Movement Disorder Society considered piribedil efficacious and clinically useful for the treatment of PD[29].

A meta-analysis only involving randomized controlled trial (RCTss) showed that the combination of piribedil and levodopa is more effective compared with levodopa monotherapy (mostly focused on motor symptoms and few on mood) without significant worsening of drug-related adverse reactions that include gastrointestinal tract reactions and neuropsychiatric disorders[34]. Although this meta-analysis on RCTs revealed that the combination of piribedil and levodopa did not significantly increase the drug-related adverse reactions of patients with PD, these adverse reactions can still happen in clinical practice.

3.1. Motor symptoms

Piribedil can improve motor symptoms in patients with PD by increasing DR excitability[34]. In early untreated or levodopa-treated non-fluctuating PD patients, piribedil has shown superiority to placebo (level 1 evidence) for the alleviation of all cardinal motor symptoms. The typical

Table 1. Mechanisms and pharmacokinetics of non-ergot DR agonists

Parameters	Piribedil	Pramipexole IR	Ropinirole IR	Rotigotine transdermal patches
DR effects	D_2, D_3	D_3>D_2, D_4	D_2>D_3, D_4	D_1, D_2, D_3>D_4, D_5
Half-life (h)	1.7 – 6.9	8 – 12	6	5 – 7
Dose (mg/day)	150 – 250	1.5 – 4	8 – 24	8 – 16
Excretion pathway	68% through kidneys; 25% through bile	90% through kidneys	88% through kidneys	71% through kidneys; 23% through small intestine

DR: Dopamine receptor; IR: Immediate-release

piribedil dosage advised is 150 – 300 mg/day, usually taken 3 times daily[29]. Studies have demonstrated piribedil efficacy as monotherapy and in combination therapy. In this section, the results of clinical trials of piribedil on motor symptoms are reviewed. Table 2 summarizes the evidence for the improvement of motor symptoms by piribedil[34-42].

3.1.1. Monotherapy for early patients with PD

Piribedil monotherapy may improve motor symptoms, such as tremor, rigidity, and bradykinesia, in patients with early PD, and delay the need for levodopa[30,40].

A 7-month, randomized, double-blind, placebo-controlled trial (REGAIN study) showed that the piribedil monotherapy (150 – 300 mg/day) could achieve comprehensive control over motor symptoms, with proportion of both responders and patients remaining on monotherapy significantly higher than that of the placebo group. Researchers presumed that the treatment effect of piribedil monotherapy (effect size of 7.26 points for UPDRS III score) may be higher than or comparable with other dopaminergic agonists, including ropinirole (effect size of about 5 points), pramipexole (effect size of about 6 points), pergolide (effect size of about 5 points), and rotigotine (effect size of about 4 points)[39].

3.1.2. Patients with early PD insufficiently controlled by levodopa

A 6-month, open-label, multicenter trial showed that piribedil (150 mg/day) in early combination with levodopa and then a switch to piribedil monotherapy may improve motor symptoms and was well tolerated[41]. A 6-month RCT showed that piribedil (150 mg/day) as adjunct to levodopa may significantly improve motor symptoms, with a good safety and tolerance profile[42]. A 12-month multicenter RCT showed that the early combination of piribedil (150 mg/day) or bromocriptine (25 mg/day) and levodopa resulted in a similarly significant improvement of all motor symptoms in patients with PD; however, less dose of levodopa is required when piribedil is used, as compared to bromocriptine[38].

3.1.3. Patients with moderate and advanced PD

A previous review on piribedil indicates that the PD treatment generally requires long-term medication, and the long-term use of piribedil may not aggravate motor complications, with low incidence of dyskinesia[30]. Due to the restrictions of the number of cited papers, these results may be not comprehensive.

3.1.4. Patients with advanced PD treated with levodopa

An Asian phase IV, open-label, clinical study showed that an 8-week short-term combination therapy of piribedil (up to 150 mg/day) and levodopa may improve motor symptoms, such as tremor, with good tolerance. Moreover, piribedil reduces the dose of levodopa and prolongs the duration of its effect and may help to decrease the risk for levodopa-induced motor complications, and prolong the "ON" time[36]. Due to the limitations of the design in this study, the results need to be cautiously interpreted.

3.2. Non-motor symptoms

Studies on patients with early PD showed that piribedil monotherapy or as an adjunct to levodopa both resulted in some improvement in patient's non-motor symptoms, including mental state, depression, and sleep disorders. The early combination of piribedil may improve patients' quality of life[29]. Table 3 summarizes the evidence for the improvement of non-motor symptoms by piribedil.[35,38,40,43-47]

3.2.1. Apathy

Apathy is a common feature in end-stage PD that affects up to 42% of patients with PD. Apathy is associated with cognitive impairment and depression[48]. Many studies have shown that they are two different but commonly co-occurring syndromes, and depression can occur simultaneously with or after apathy[12,49].

A 12-week, randomized, double-blind, and placebo-controlled trial showed that (n=37) treatment of piribedil (maximum dose 300 mg/day) may effectively reverse postoperative apathy symptoms (Starkstein Apathy Scale score: -34.6% vs. -3.2%, P = 0.015, Robert Inventor score: improved by 46.6% vs. worsened by 2.3%, P = 0.005) after deep brain stimulation of the subthalamic nucleus. The remission rate of clinical symptoms was also higher than the control group (47.4% vs. 16.7%), and the treatment response was usually achieved in the first 6 weeks after treatment. It was suggested that piribedil should be initiated quickly in patients with postoperative apathy. Moreover, the piribedil group presented a trend towards improvement in symptoms of anhedonia[47].

3.2.2. Cognitive and executive functions

In a 12-month, multicenter, randomized, double-blind, Phase IV trial, and 425 patients with incomplete levodopa response were enrolled, and a subgroup analysis (n = 178) showed that only the combination of piribedil (150 mg/day) and levodopa may significantly improve the scores of Wisconsin Card Sorting Test (WCST) rather than other scales in patients with PD compared with bromocriptine (25 mg/day) and levodopa. The cognitive and executive functions were tested by the widely used WCST, which requires the participation of all cognitive processes needed

Table 2. Evidences for piribedil in treatment of motor symptoms of PD

Study, year	Region	Trial design	Patients	Treatment	Primary outcome	Main results	Evidence levela
Rondot and Ziegler, 1992[40]	France	Multicenter, open-label, single-cohort study	Patients with PD, mainly I–II stages (n = 113)	Piribedil monotherapy (150 – 250 mg/day)	NA	Three-month treatment with piribedil monotherapy may significantly improve motor symptoms, such as tremors, bradykinesia, and rigidity	IV
Ziegler *et al*., 2003[42]	France	Multicenter, randomized, double-blind, placebo-controlled trial	Non-fluctuating PD patients insufficiently controlled by levodopa (n = 115)	Piribedil (150 mg/day, n = 61) as adjunct to levodopa placebo group (n = 54)	The percentage of responders defined by a 30% decrease from baseline on the UPDRS III score and the change from baseline	In 6 months, the response rateb in the piribedil group was significantly higher than that in the placebo group (61.8 vs. 39.6%; P = 0.02)	I
Suwantamee *et al*., 2004[41]	Thailand	Multicenter, open-label, single-cohort clinical trial	Patients with early PD, poorly controlled by levodopa (n = 29)	Piribedil (150 mg/day, combined with levodopa in the first 3 months, and later switched to monotherapy)	The change in UPDRS part III score versus baseline and the percentage of responders defined by at least 30% decrease from baseline of the total UPDRS part III score	Through 6-month treatment of piribedil, UPDRS III scores were decreased significantly by 13.3±10.3 points (P < 0.0001), response rate was 93.1%b	IV
Evidente *et al*., 2004[36]	Philippines	Phase IV, open-label, prospective clinical trial	Advanced PD patients with fluctuating symptoms (n = 49)	Piribedil (up to 150 mg/day) combined with levodopa	Part III of UPDRS	An 8-week treatment of piribedil may improve UPDRS scores by 48% (tremors are improved mostly) and daily living ability by 43%, and may decrease the dose of levodopa and increase its duration of effect	IV
Rascol *et al*., 2006[39]	Multi-national	Multicenter, randomized, double-blind, placebo-controlled clinical trial (REGAIN)	Patients with early PD (n = 401)	Piribedil monotherapy (150 – 300 mg/day, n = 197) Placebo group (n = 204)	UPDRS III score as the last observation on monotherapy over 7 months was the primary outcome	After 7 months, UPDRS III scores were improved (–4.9 points) in the piribedil group, and exacerbated in the placebo group (+2.6 points; P<0.0001), and the response rateb in the piribedil group was also higher than that in the placebo (42% vs. 14%, P < 0.001)	I

(Cont'd...)

Table 2. ***(Continued)***

Study, year	Region	Trial design	Patients	Treatment	Primary outcome	Main results	Evidence levela
Castro-Caldas *et al*., 2006[38]	Multi-national	Multicenter, randomized, double-blind, controlled clinical trial	Patients with stages I–III PD, poorly controlled by levodopa (n = 425)	Piribedil (150 mg/day, n = 210) or Bromocriptine (25 mg/day, n = 215) combined with levodopa	Improvement of the UPDRS III score from baseline over 12 months, expressed as the change from baseline to the last observed value, and second as the response rate defined by a 30% or more decrease on the UPDRS III score at the last value	A 12-month treatment in the piribedil or bromocriptine group may fully improve motor symptoms of patients with PD, and the dose increase requirement of levodopa was less in the piribedil group	I
Xiao-ying *et al*., 2016[71]	China	Retrospective cohort study	PD patients (n = 140)	Compound levodopa combined with piribedil (100 – 150 mg/day, n = 76); compound levodopa monotherapy (n = 64)	NA	The overall effective rate in the piribedil combined group was significantly higher than that in the control group (92.10 vs. 62.50%, P < 0.05), and the decrease of UPDRS scores was significantly larger than that in the control group (P < 0.05)	III
Peihua and Jianqin, 2018[34]	China and France	Meta-analysis involving 11 studies	PD patients	Piribedil combined with levodopa (50~300 mg/day, n = 433); levodopa monotherapy (NA)	NA	The combination therapy group showed greater overall improvement of response rate and UPDRS scores than levodopa monotherapy group	I

[a]The evidence's levels were made with reference to the 2004 EFNS Guideline. [b]Defined as at least 30% decrease from baseline of UPDRS III score.
NA: Not available; PD: Parkinson's disease; UPDRS: Unified Parkinson's disease rating scale.

for executive functions during the test. The WCST can recognize early cognitive impairments and has a good sensitivity to identify frontal cortical dysfunction. This finding was more prominent in younger patients aged 50 – 70 years based on age stratification[38].

Pilot clinical trials demonstrated that piribedil may improve the frontal lobe dysfunction of patients with PD. Randomized, placebo-controlled, and double-blind clinical trials also showed that patients with mild cognitive disorder achieved some improvement in the overall cognitive function after receiving piribedil treatment (63.3% vs. 26.7%, P < 0.01); however, this requires to be further investigated by large-sample studies involving patients with PD[46,50].

3.2.3. Depression

Patients with depression show distinctly negative mood, which causes emotional suffering.

This is different from apathy, which is a mental disorder characterized by decreased goal-directed speech, motor activity, and emotion. Patients with apathy have indifference, but their mood is neutral[51].

Depression is the most common psychiatric non-motor symptom in PD patients with a high prevalence rate of

Table 3. Evidences for piribedil in the treatment of non-motor symptoms of PD

Study, year	Region	Trial design	Patients	Treatment	Primary outcome	Main results	Evidence level[a]
Mentenopoulos *et al.*, 1989[45]	Greece	Open-label, single-cohort clinical study	Stage II–IV PD patients (n = 30)	Piribedil (200 mg/day) combined with prior anti-PD drugs	NA	Through 20-week treatment, tremor showed greatest change, and an improvement of depression was observed in 14 patients	IV
Rondot and Ziegler, 1992[40]	France	Open-label, multicenter, single-cohort study	PD patients, mainly I–II stages (n = 113)	Piribedil monotherapy (150 – 250 mg/day)	NA	The depression score was decreased from 10.2 to 7.3 (P < 0.001), and moods were improved obviously (28%, P < 0.01)	IV
Nagaraja and Jayashree, 2001[46]	Indian	Randomized, double-blind, placebo-controlled clinical trial	Healthy elderly patients with mildly cognitive impairment (n = 60)	Piribedil group (50 mg/day, n = 30); placebo group (n = 30)	Change in MMSE score	Through 3-month treatment, the cognition scores in the piribedil group were improved more significantly (63.3% vs. 26.7%, P < 0.01)	II
Castro-Caldas *et al.*, 2006[38]	Multi-national	Multicenter, randomized, double-blind, controlled clinical trial	Stages I–III PD patients, poorly controlled by levodopa (n = 425); subgroup analysis on cognitive function (n = 178)	Piribedil (150mg/day,n=210) or bromocriptine (25 mg/day, n = 215) combined with levodopa	Improvement of the UPDRS III score from baseline over 12 months, expressed as the change from baseline to the last observed value, and second as the response rate defined by a 30% or more decrease on the UPDRS III score at the last value	A 12-month piribedil treatment may significantly improve cognitive function in PD patients	I
Yan-Bo *et al.*, 2007[72]	China	Prospective cohort study	Patients with early PD (n = 67)	Piribedil monotherapy group (n = 25, 50 – 100 mg/day); piribedil adjunct to compound levodopa (n = 20); and compound levodopa monotherapy (n = 22)	NA	UPDRS scores, depression, sleep quality and quality of life in the combination group were improved significantly at each follow-up time point; the depression scores in the piribedil group were decreased from baseline in any observation window	III
Thobois *et al.*, 2013[47]	France	Randomized, double-blind, placebo-controlled clinical trial	Patients with mid-stage and advanced PD presenting with apathy after deep brain subthalamic nucleus stimulation (n = 37)	Piribedil group (maximum dose 300 mg/day, n = 19); placebo group (n = 18)	The improvement of apathy under treatment, as assessed by the reduction of the Starkstein Apathy Scale score, in both treatment groups	After 12 weeks, the apathy scores in the piribedil group were decreased more significantly (34.6% vs. 3.2%, P = 0.015), and apathy symptom was also improved more (improved by 46.6% vs. worsened by 2.3%, P = 0.005). Piribedil also has a tendency to improve quality of life and anhedonia	II

(Cont'd...)

Table 3. ***(Continued)***

Study, year	Region	Trial design	Patients	Treatment	Primary outcome	Main results	Evidence level[a]
Eggert *et al.*, 2014[44]	Germany	Prospective, multicenter, randomized, active-controlled, rater-blinded phase III study	White men and women aged 35 – 80 years with a diagnosis of PD in Hoehn and Yahr stages 1 – 4 (n = 80)	Piribedil (213.2 mg/day), pramipexole (2.7 mg/day) or ropinirole (10.9 mg/day)	Median reaction time during the second half of the subtest "vigilance," test condition "moving bar" of the test battery for attention performances at the end of treatment	After 11 weeks of study, piribedil reduced daytime sleepiness with lower Epworth Sleepiness Scale scores at the end of treatment compared with the comparator (−4 vs. −2 points; P = 0.01)	I

[a]The evidence levels were made with reference to the 2004 EFNS Guideline

MMSE: Mini-mental state examination; NA, N = Not available; PD: Parkinson's disease; UPDRS: Unified Parkinson's disease rating scale

up to 35%[52], which may impact patients' quality of life and may lead to suicide. Piribedil produced significant antidepressant effects in multiple behavior models of depression, and its antidepressant effects are comparable with or better than those of multiple antidepressant drugs (e.g., imipramine, tricyclic antidepressant drugs, and selective serotonin reuptake inhibitors)[30].

A few open clinical studies have shown that piribedil may significantly relieve depression symptoms in an effective dose for motor symptoms control; however, these studies have no placebo control group[40,45]. More randomized, placebo-controlled, and double-blind studies are needed to verify these results.

3.2.4. Somnolence

A few studies revealed that piribedil may improve the somnolence in patients with PD. A RCT showed that switching from pramipexole or ropinirole to piribedil could decrease daytime sleepiness to a clinically relevant degree in PD patients with excessive daytime sleepiness[44].

3.3. Dyskinesia

The REGAIN study demonstrated that the incidence of dyskinesia in piribedil is comparable with placebo (8% vs. 7.5%)[17]. A RCT showed that the incidences of dyskinesia in piribedil and bromocriptine were 2.9% and 4.7%, respectively[38]. An animal-model study revealed that switching from levodopa to piribedil decreased the dyskinesia intensity without changing the improvement in motor deficits; however, switching from piribedil to levodopa resulted in a rapid increase in dyskinesia[53]. Animal models also demonstrated that α2-adrenoreceptor antagonists counter the dyskinesia induced by acute and chronic treatment of D2/D3 receptors agonists, such as piribedil, and while retaining or strengthening restoration of motor function[17,35]. No data are available to show that the incidence of dyskinesia on piribedil is different from that of other DRA.

3.4. Recommendations for dosage of piribedil

Piribedil is used in clinical practice since 1969 as 50 mg tablets. However, because of the limitations such as very low (< 10%) oral bioavailability due to extensive first pass metabolism and short biological half-life, piribedil is prescribed in high dosing frequencies with 3 – 5 tablets/day[54]. The dosage of sustained release formulation is 50 mg per tablet and the therapeutic effect will be lasting for 20 h. It is recommended to start with 50 mg once daily and an addition of 50 mg/week. Generally, the average effective dose is 150 – 200 mg/day, and the maximum dose is 250 mg. In combination therapy, the daily recommended maintenance dose of piribedil is 50 – 150 mg/day[55].

4. Management of adverse events caused by piribedil

Piribedil is generally safe and well tolerated. Most adverse reactions of piribedil overlap with those of all DRAs. The most commonly reported adverse reactions were gastrointestinal and cardiovascular responses. Neuropsychiatric disorder or daytime somnolence was also reported[29,30]. Thirteen percent of patients have to change the medication due to adverse effects. Suggesting the management of adverse reactions is highly important[12].

4.1. Gastrointestinal tract reactions

Gastrointestinal tract reactions, including nausea, vomiting, anorexia, and constipation, are the most common adverse reactions during treatment. The incidence ranges from 0% to 33%, but most of those are not severe[12]. During the 12-month follow-up, the gastrointestinal adverse reaction rate of piribedil was similar to that of bromocriptine, but

the latter had a higher risk of drug withdrawal due to gastrointestinal adverse events[38].

Piribedil-induced gastrointestinal tract reactions are short-term conditions and tend to disappear gradually. The undesired effect can be relieved by dose titration control or by administration of food. If the symptoms cannot be relieved, then domperidone, a peripheral DR inhibitor, could be used, but it is prohibited in patients with arrhythmia due to the risk of CT interval prolongation[56].

4.2. Daytime somnolence and sleep attack

As piribedil has α2-adrenoreceptor antagonistic effects, its incidence of daytime somnolence might be lesser than that of other DR agonists. The incidence of piribedil-related daytime somnolence is approximately 2% to 30%; however, it rarely results in drug withdrawal[12]. In over 30 years of clinical use, few cases of sudden sleep onset associated with piribedil have been reported. A position statement from the European Medicines Agency on sleep events and dopaminergic medications indicated that piribedil is "very rarely" associated with the incidences of excessive daytime somnolence[30]. A RCT showed that in patients with PD who developed daytime somnolence on pramipexole or ropinirole, switching to piribedil significantly reduced daytime somnolence compared with those continued on original treatment[44].

Patients should be informed of the potential adverse reactions. Caution must be taken while driving or operating the machine and while taking this drug. Those who have experienced this adverse reaction should avoid driving or operating the machine, and consider to reduce the dose or discontinue the treatment. It is suggested to reduce the dose to achieve satisfying response, keep sleep hygiene, and treat actively, if necessary, with modafinil or amantadine drugs[14,57].

4.3. Neuropsychiatric disorders

Piribedil-induced neuropsychiatric disorders, such as psychosis and hallucination, have an incidence of 4 – 23% and are more frequent in patients with preexisting cognitive deficits[12]. This phenomenon may be dose-dependent, and elderly and advanced patients with PD are at a higher risk[30]. Hallucination is a major cause for drug withdrawal[39]. However, a double-blind RCT showed that there was no significant difference in the incidence of neuropsychiatric disorders through 7-month treatment of piribedil compared with placebo[57]. As only 35 patients were enrolled in this trial, the insignificant results may be due to insufficient power.

It is not recommended for the elderly patients with neuropsychiatric symptoms to take piribedil if they have never used piribedil. If neuropsychiatric symptoms are well tolerated by patients and family members, they may not need to be actively treated, or a reduction of the drug dose that might have triggered psychosis syndrome can be considered under the guidance of experts. For PD patients without cognitive disorder, quetiapine may be used for the treatment of hallucination and delusion, although the risk of deterioration in motor function cannot be excluded. If standard therapy failed, clozapine may be considered by carefully monitoring the blood cell count. Olanzapine or other antipsychotic drugs (phenothiazines or butyrophenones) are not recommended because they may result in confused symptoms or deterioration of parkinsonian motor symptoms[14]. Bromocriptine is not in use anymore because it is an ergot derivative.

4.4. Hypotension orthostatic

Hypotension orthostatic is common at the onset of therapy and caused by the agonistic effect on DA receptors at the presynaptic level of the orthosympathetic system, and usually becomes tolerable over time. It mainly occurs in the 1st week after the use of piribedil, accounting for 5% of the adverse drug reactions[58,59].

Animal experiments showed that intravenous injection of piribedil may decrease hypertension and heart rate[30]. During the clinical use of piribedil, decreased systolic pressure and a slight decrease of heart rate and body temperature may also occur especially in patients with advanced PD[29].

The antihypertensive drug history should be traced, including antihypertensive drugs (including diuretics), dopaminergic drugs, alpha-blockers, and antidepressant drugs. These drugs may be tapered or stopped, if possible. Midodrine, an alpha-1 agonist, could be used. If there are contraindications for midodrine, using the mineralocorticoid fludrocortisone can be considered; however, attention should be paid to cardiac risk factors[14].

Droxidopa is "clinically useful" for the short-term treatment of orthostatic hypotension, whereas no data from RCTs on treating PD with droxidopa for a longer treatment time are available[60]. If there are concurrent cardiovascular reactions, such as heart rate change, it is suggested to stop medication and adopt fluid infusion measures[59]. Other patient's management includes education, advice and training on factors influencing blood pressure, and special aspects to be avoided (i.e., foods, habits, and positions). Physical measures include leg crossing, squatting, elastic abdominal binders, and stockings. Furthermore, careful exercise will improve the orthostatic hypotension[61].

4.5. Impulse-control disorders

Impulse-control disorders (ICDs) occur in 2% to 13.7% of patients with PD and are more prevalent at a high dose;

moreover, the use of dopaminergic agonists is considered one of the main pathogenic factors[62-64]. Among dopaminergic agonists, pramipexole was more frequent with ICD[62]. Impulse behaviors caused by piribedil are rarely reported and also tended to be dose-related[65,66]. According to epidemiological survey and spontaneous reports system of adverse reactions in France, no obvious increased risk of ICDs was observed after piribedil intake, and the risk was lower than other DR agonists, such as ropinirole or pramipexole[63,67].

Although the risk of ICDs with piribedil might not be as important as with other DR agonists, definite conclusions can only be achieved with head-to-head comparisons due to the method limitations of the study.

The hazard for switching to another DR agonists is unknown and needs further investigation. Only in some infrequent cases, symptoms were relieved by dose reduction or switching to another drug. Dose reduction to cessation of DR agonists, compensated by a concomitant increase in levodopa dose, is a preferred option to resolve ICD[68]. For patients who have developed impulse behaviors, caution must be taken before resuming piribedil, considering the potential risk of ICD relapse[62,63,69].

5. Drug interactions

Combination treatment with any drug that blocks DA receptors is contraindicated. Antiemetic drugs that do not cross the blood-brain barrier (e.g., domperidone) should be recommended. Using antiemetics that can cross blood-brain barrier in patients with PD is generally contraindicated due to worsening of Parkinsonism. As PD patients with psychosis or hallucination are difficult to be managed, antipsychotics, such as quetiapine, clozapine, and pimavanserin, have been approved for treating PD psychosis[70]. DRA must be tapered gradually until the complete discontinuation of the drug[53].

6. Conclusion

Piribedil is the first and unique non-ergoline, primarily partial D2/D3 receptor agonist among the first generation of DRA. It is the only drug used for about half of the century, which has unique pharmacodynamic profiles with α2-adrenoreceptor antagonistic effects. Many clinical studies have demonstrated that both piribedil monotherapy or combination of piribedil and levodopa may effectively improve the motor and some non-motor symptoms of PD patients at any stage, with a good safety and tolerance. Hereby, piribedil is recommended by multiple authoritative guidelines as the first-line therapy for patients with PD. This clinical suggestion may help neurologists to appropriately use piribedil in patients with PD.

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