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REVIEW ARTICLE

Piribedil for the Treatment of Motor and Non-motor Symptoms of Parkinson Disease

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Abstract Dopamine agonists are well-established symptomatic medications for treating early and advanced Parkinson disease (PD). Piribedil was one of the first agonists to be marketed (1969) and is widely used as an extended-release oral formulation in European, Latin-American, and Asian countries. Piribedil acts as a non-ergot partial dopamine D_2/D_3-selective agonist, blocks alpha2-adrenoreceptors and has minimal effects on serotoninergic, cholinergic, and histaminergic receptors. Animal models support the efficacy of piribedil to improve parkinsonian motor symptoms with a lower propensity than levodopa to induce dyskinesia. In PD patients, randomized double-blind studies show that piribedil (150–300 mg/day, three times daily) is superior to placebo in improving motor disability in early PD patients. Based on such evidence, piribedil was considered in the last Movement Disorder Society Evidence-Based Medicine review as "efficacious" and "clinically useful" for the symptomatic treatment of PD, either as monotherapy or in conjunction with levodopa, in non-fluctuating early PD patients. This effect appears comparable to what is known from other D_2 agonists. However, randomized controlled trials are not available to assess the effect of piribedil in managing levodopa-induced motor complications. Pilot clinical studies suggest that piribedil may improve non-motor symptoms, such as apathy, but confirmatory trials are needed. The tolerability and safety profile of piribedil fits with that of the class of dopaminergic agonists. As for other non-ergot agonists, pneumo-pulmonary, retroperitoneal, and valvular fibrotic side effects are not a concern with piribedil. The original combination of piribedil D_2 dopaminergic and alpha-2 adrenergic properties deserve further investigations to better understand its antiparkinsonian profile.

Key Points

Randomized double-blind studies show that piribedil (150–300 mg/day, three times daily) is superior to placebo in improving motor disability in early Parkinson disease patients. This effect appears comparable to what is known from other dopamine D_2 agonists.

Randomized controlled trials are not available to assess the effect of piribedil in managing levodopa-induced motor complications.

Pilot clinical studies suggest that piribedil may improve non-motor symptoms, such as apathy, but confirmatory trials are needed.

The tolerability and safety profile of piribedil fits with that of the class of dopaminergic agonists.

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1 Introduction

Parkinson disease (PD) is a progressive neurodegenerative disorder affecting about 1 person every 1000 in the fifth decade and 19 in every 1000 above 80 years of age [1]. The core motor parkinsonian syndrome includes bradykinesia, rigidity, tremor, and postural abnormalities [2], frequently associated with other motor symptoms such as gait abnormalities, micrographia, and speech problems [3]. Non-motor features, such as mood and cognitive dysfunction, sleep abnormalities, or autonomic disturbances, are also frequent and disabling [4]. Some non-motor symptoms, such as constipation, olfactory dysfunction, visual abnormalities, sleepiness, rapid eye movement behavior disorder, mood disorders, or cognitive dysfunction can even be present before the motor symptoms [5].

Levodopa remains the 'gold standard' antiparkinsonian treatment [6]. Nevertheless, its initial unequaled therapeutic efficacy is frequently confounded within a few years by the emergence of motor complications (fluctuations, abnormal movements) and other problems [7, 8]. Because of such limitations, the treatment of patients with PD has expanded to incorporate additional pharmacologic approaches, including drugs such as dopamine receptor agonists, monoamine oxidase B inhibitors, and catechol-*O*-methyl-transferase inhibitors.

Ten different dopamine agonists have been marketed during the last 4 decades for the treatment of PD [9]. Five of them are ergot compounds (bromocriptine, cabergoline, dihydroergocryptine, lisuride, and pergolide) and as such are not used anymore because of the risk of drug-induced fibrosis [10], while the five others are non-ergot derivatives and are still commonly used to manage PD patients (apomorphine, piribedil, pramipexole, ropinirole, and rotigotine). Three are used as oral medications (piribedil, pramipexole, and ropinirole), while apomorphine is used as subcutaneous injections or infusions and rotigotine as a transdermal patch.

Piribedil is an orally active dopamine agonist that has been one of the first of this class to be marketed for the treatment of PD patients, since 1969 [11, 12]. It is chemically unrelated to other non-ergolinic agonists and displays some specific pharmacological characteristics [11, 13]. At the present time, an oral extended-release formulation of piribedil is available worldwide [14]. In this article, pharmacological characteristics, results on animal PD models, and the clinical efficacy and safety of piribedil will be reviewed.

For this purpose, a bibliographical research was conducted in PubMed with the following string "piribedil AND (Parkinson's disease OR motor symptoms OR cognitive OR motor fluctuations OR dyskinesias)". Studies published in English, French, or Spanish before June 2015 were selected for further review. Reference sections from retrieved papers were searched for new references. Abstracts submitted to the International Movement Disorders Congresses from 2013 were also searched for studies involving piribedil.

2 Pharmacological Properties

2.1 Pharmacodynamics

Piribedil (1-(2-pyrimidyl)-4 piperonyl piperazine) (Fig. 1), synthesized initially by Regnier and co-workers during the 1960s, is a non-catechol analog of dopamine [15]. It shares with other marketed non-ergot dopamine agonists such as pramipexole and ropinirole the property of being more selective for the dopamine D_2/D_3 receptors than for the D_1-like family. Despite its simplistic appellation as a 'dopamine agonist', piribedil interacts with other receptors [13]: it has antagonistic effects at alpha2-adrenoreceptors, low affinity for serotonin 5-HT receptors, and negligible affinity for the histaminergic and cholinergic receptors. Such a profile may confer, at least theoretically, a specific efficacy/tolerability antiparkinsonian profile as opposed to other agents of the same pharmacological class. Binding affinities for piribedil and other non-ergolinic dopamine agonists are summarized in Table 1.

2.1.1 Partial D_2/D_3 Agonism

Piribedil behaves as a partial agonist of D_2 and D_3 receptors (affinity for the D_3 receptor being higher than for the D_2 receptor), with lower affinities than those of ropinirole and pramipexole [13, 16]. The consequence of partial agonism referring to clinical response remains a matter of debate. This could theoretically lead to reduced antiparkinsonian potency, as compared with full agonists. This does not seem however to be the case and, despite the lack of head-to-head comparisons, the magnitude of the clinical antiparkinsonian response to piribedil in animal models and clinical trials is in the range of what is reported

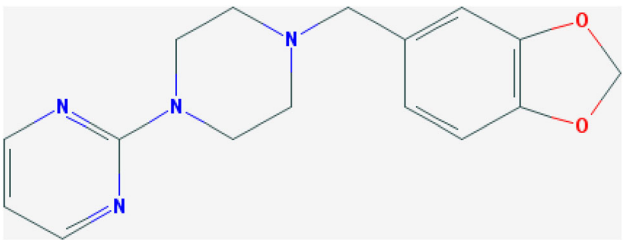

Fig. 1 Chemical structure of piribedil

Table 1 Binding affinities for piribedil and other non-ergolinic dopamine agonists. Adapted from [9, 13, 16]

	D_1 like	D_2 like	5-HT	α1	α2
Apomorphine	++	++	0/+	0/+	0/+
Piribedil	0/+	++	0	0/+	++
Pramipexole	0/+	+++	0/+	0/+	0/+
Ropinirole	0	+++	0	0	0/+
Rotigotine	0	+++	+	+	0/+

+++ indicates strong, ++ indicates moderate, + indicates mild, 0 indicates no effect

with other agonists (see below). Furthermore, there might be some potential theoretical advantages for partial over full agonistic properties to treat PD [16]. For example, it has been speculated, although not proven, that avoiding a full and potentially excessive stimulation of dopaminergic receptors could reduce the incidence and/or intensity of dyskinetic movement. Partial agonism might also offer potential benefits regarding cognitive function, as cortical dopaminergic hyperstimulation might induce cognitive deterioration as much as blockade of the same receptors would do [16]. In other words, it has been speculated that partial stimulation of dopaminergic receptors should be sufficient for piribedil to develop its clinical efficacy in situations when intrinsic levodopa stimulation is reduced, while under conditions where D_2 and D_3 receptors are saturated, piribedil would 'reduce' stimulation by competing with the neurotransmitter. In this sense, it might help keep dopaminergic stimulation within the boundaries of a 'therapeutic window'.

2.1.2 D_1/D_2 Agonism

As previously mentioned, piribedil is a D_2-like agonist. Nevertheless, another theoretical original and interesting property of the drug is that one of its metabolites is a D1 agonist (S584) [12]. The relevance of this compound regarding piribedil global effects remains speculative, but this may have some consequences regarding efficacy and tolerability, as many experimental results in animal models of PD suggest that a combined stimulation of D_1 and D_2 receptors potentiates antiparkinsonian responses and participates in the pathophysiology of dyskinesia [17].

2.1.3 Alpha2-adrenoreceptor Antagonistic Effects

As mentioned earlier, piribedil behaves as an alpha2-adrenoreceptor antagonist [18, 19]. This provides a specific profile to the drug. In animal models, this causes increased cerebral turnover of noradrenaline owing to increases in firing rate of the neurons of the locus coeruleus [20]. Striatal GABAergic interneurons display alpha2-adrenoreceptors, and their activation enhances the activity of the 'direct' pathway [21], a player in the genesis of dyskinesias [22]. This action would be blocked by piribedil. In addition, alpha 2-adrenoreceptor antagonists, by stimulating endogenous noradrenaline release [18], potentially promote alertness, selective attention, learning, and memory consolidation [23]. Furthermore, by acting on alpha 2-adrenoreceptors on cholinergic terminals, piribedil reinforces indirectly fronto-cortical release of acetylcholine, as shown in freely moving rats [19, 24]. By acting at two interrelated substrates, alpha2-adrenoreceptor antagonists might also exert an antidepressant effect. First, blockade of alpha2-adrenergic autoreceptors may increase activation of cortico-limbic monoaminergic projections [25, 26]. Second, they may also promote neurogenesis at the hippocampus [27, 28].

2.2 Pharmacokinetics

Piribedil is absorbed rapidly. The maximum concentration is reached 1 h after oral administration [29]. Piribedil has a low oral bioavailability owing to an extensive first-pass metabolism [29]. Hepatic metabolism (primarily demethylation, p-hydroxylation, and N-oxidation) produces many metabolites, one of which is an active D_1 agonist (see above) [12]. Metabolites are excreted mainly via the kidney. Urinary excretion is approximately 50 % at the 24th hour and is total at the 48th hour. In a study with single intravenous infusions of piribedil in fluctuating PD patients, pharmacokinetics was found to be linear, with a half-elimination time of 12 h [30]. The extended-release pharmaceutical form of piribedil allows in vivo gradual absorption and release of the active ingredient. The kinetic studies conducted in humans with tablets of sustained-release piribedil show extension of the therapeutic coverage for more than 24 h [14]. However, in clinical practice, sustained-release piribedil is prescribed three times daily, as opposed to other extended-release formulations of other dopamine agonists such as pramipexole and ropinirole, which are used once daily.

Other administration routes have been used for piribedil in the clinical experimental setting. Preparation of micron and submicron particles using solid lipid carriers suggested enhanced efficacy in in vivo-in vitro models [31]. A sublingual formulation capable of providing rapid relief of motor symptoms in PD has also been tested in patients [32], as discussed latter on in this review.

3 Data on PD Animal Models

In this section, studies with piribedil in animal models of PD will be reviewed. Studies are summarized in Table 2.

3.1 Parkinsonian Symptoms

The bulk of animal and clinical evidence suggest that dopamine agonists are effective for the relief of motor symptoms in PD [9]. In an early pilot study, Jenner and Marsden studied the effects of piribedil in the reserpinized rat [33]. Piribedil and levodopa caused a reversal of akinesia, which was significantly enhanced by concurrent administration of clonidine. Interestingly, the effects of levodopa but not those of piribedil were antagonized in part by the pre-administration of an adrenergic receptor blocker, suggesting that effects on motility of the former but not of the latter are related to the stimulation of adrenergic receptors. Although piribedil increased the level of noradrenaline metabolites in the brain, it was considered that the drug stimulated the release of the neurotransmitter by acting at presynaptic alpha2-adrenergic sites. Results on 6-hydroxydopamine (6-OHDA) lesioned rats also showed positive antiparkinsonian effects of piribedil [34, 35].

Oral administration of a solution of piribedil also produced a dose-related reversal of locomotor and behavioral deficits in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned marmoset [36]. Pretreatment with the peripheral dopamine receptor antagonist domperidone prevented nausea and retching. In addition, piribedil increased vigilance and awareness.

A transdermal formulation of piribedil was developed in an attempt to produce more continuous and stable drug concentrations. The antiparkinsonian efficacy of this formulation was also tested in the MPTP-lesioned common marmoset [37]. The antiparkinsonian actions of piribedil occurred within 10 min of drug administration and lasted as long as 10 h. A dose–response relationship could be established.

In subsequent studies, antiparkinsonian effects of piribedil were compared with those of levodopa in MPTP-lesioned common marmosets [38, 39]. Administration of piribedil produced a similar reversal of MPTP-induced motor deficits than levodopa. Interestingly, in these studies, the duration of the motor response was longer with piribedil than with levodopa (400 vs. 190 min) [39].

In summary, piribedil showed consistent antiparkinsonian effects across all studied species. Results were dose dependent and similar to those of levodopa in magnitude, but lasted longer.

3.2 Levodopa-induced Dyskinesias

Levodopa-induced dyskinesias (LIDs) are a frequent complication of levodopa therapy, affecting about 17 % of the patients after only 40 weeks of treatment [40, 41]. LIDs remain an important unmet need for the management of PD. The effects of piribedil on LIDs have been studied in a variety of PD animal models.

Smith and colleagues studied the ability of piribedil to generate dyskinesia in MPTP-lesioned levodopa-naïve marmosets [39]. LIDs developed progressively after the administration of levodopa, while the administration of

Table 2 Most relevant studies in animal Parkinson disease models with piribedil

Study	Piribedil administration	Comparators	Main results
Reserpinized mice			
Jenner [33]	50 mg/kg i.p.	Levodopa and apomorphine	Reversal of akinesia with piribedil, apomorphine or levodopa
6-OHDA lesioned rat			
Turle-Lorenzo et al. [43]	0.3 mg/kg i.p.	Levodopa	Improved cognitive performance to levels comparable to status before lesioning with piribedil alone or in combination with levodopa
Lane and Dunnett [35]	1 mg/kg i.p.	Ropinirole, bromocriptine	Increased turning behavior without overt dyskinesias with bromocriptine, ropinirole or piribedil
Gerlach et al. [42]	5–40 mg/kg i.p	Levodopa, idazoxan, clonidine	Reduced turning behavior with levodopa-related dyskinesias in rats under piribedil. This effect was blocked by idazoxan
MPTP-lesioned marmoset			
Smith et al. [36]	1.25–12.5 mg/kg p.o.	Vehicle	Improvements in locomotion, vigilance, and awareness
Smith et al. [37]	2.5–10 mg/day td	Vehicle	Increases in locomotor activity and reversal of motor deficits
Smith et al. [39]	4–5 mg/kg p.o.	Levodopa	Similar increases in locomotor activity and reversal of motor deficits with less dyskinesia in the piribedil group
Smith et al. [38]	3–4 mg/kg p.o.	Levodopa	Similar increases in locomotor activity and reversal of motor deficits with less dyskinesia in the piribedil group

6-OHDA 6-hydroxydopamine, *i.p.* intraperitoneal, *MPTP* 1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridil, *p.o.* oral, *td* transdermal

piribedil produced a significantly lower degree and intensity of LIDs.

In a subsequent study, the effects of piribedil on LIDs were studied in MPTP-lesioned marmosets previously treated with levodopa, so that the animals had been already 'primed' for LIDs [38]. Priming refers to long-lasting exacerbation of abnormal dopaminergic responses after the first exposure to dopaminergic drugs owing to receptor and post-receptor changes [44]. When switching from levodopa to piribedil, the intensity of LIDs decreased. On the contrary, when switching from piribedil to levodopa, a very rapid increase in LIDs was observed. The occurrence of such LIDs was so rapid that the authors concluded that piribedil had generated underlying neuronal changes that were not sufficient to produce by themselves a full expression of the abnormal motor behavior, but had 'primed' the brain of the animals. In a similar study in 6-OHDA-lesioned rats, the administration of levodopa after a period during which piribedil, ropinirole, or bromocriptine had been administered to the animals as monotherapy, also induced marked and rapid LIDs, suggesting that this phenomenon is shared among other, if not all, dopamine agonists [35].

The contribution of the alpha2-adrenoreceptor blocking properties of piribedil to the modulation of LIDs remains a challenging topic. It has been explored in 6-OHDA-lesioned rats [42]. In this study, LIDs were classified into four different subtypes: locomotive dyskinesia (LD) defined as increased locomotion with contralateral side bias; axial dystonia (AD) defined as contralateral twisted posturing of the neck and upper body; oro-lingual dyskinesia (OD) defined as stereotyped jaw movements and contralateral tongue protrusion; forelimb dyskinesia (FD) defined as repetitive rhythmic jerks of dystonic posturing of the contralateral forelimb and/or grabbing movements of the contralateral paw. Piribedil reduced turning behavior, AD, OD, and FD, but increased LD at the 40-mg/kg doses compared with the levodopa group. Clonidine, an alpha2 agonist, blocked the effect of piribedil on AD, OD, and FD. Surprisingly, idazoxan, another alpha2 antagonist, also blocked the effect of piribedil on AD and FD. Such results are difficult to interpret. Authors proposed that alpha2-adrenergic receptors might affect differently the actions of piribedil on different subclasses of LIDs. Further experiments are warranted to clarify the contribution of adrenergic versus dopaminergic mechanisms in the effects of piribedil on dyskinesia.

In summary, piribedil was able to 'prime' the basal ganglia of PD animal models for LIDs, but the clinical expression of such abnormal movements was less marked when the animals were exposed to piribedil than levodopa. The potential involvement of alpha 2-adrenoreceptors blocking properties in influencing the clinical expression of LIDs remains to be further evaluated.

3.3 Non-motor PD Symptoms

Non-motor symptoms of PD are common, occur across all stages of PD, are under-reported, and are a key determinant of the patients' quality of life [4]. Their management is an important unmet need in PD. The effects of piribedil on some non-motor features have been explored in animal models of PD.

As discussed earlier, the pharmacological alpha 2-adrenergic antagonistic properties of the drug may offer potential beneficial effects on some domains, namely vigilance and attention, memory, and mood.

Piribedil was first reported to increase vigilance and alertness in initial studies assessing motor behavior in the monkey [36, 37]. Such effects were confirmed later by studies measuring these variables more precisely; piribedil producing a positive effect on alertness and head checking movement subscore items, and surprisingly was superior to L-dopa in these items related to vigilance [39]. The hypothesis that this effect may be related to blockade of alpha2-adrenoreceptors is consistent with the findings that piribedil blocks in vivo the hypnotic–sedative activity of the alpha2-adrenoreceptor agonist xylazine [18].

The effects of piribedil on attentional deficits were studied in the 6-OHDA-lesioned rat [43]. Before treatment, rats were trained to depress a lever, detect a stimulus occurring after variable foreperiods, and release the lever quickly afterward. Successful completion of the task requires that the rats are attentive to the presentation of the stimulus. The 6-OHDA lesion produced deficits in the timing of foreperiods and prolonged reaction times. Piribedil 0.3 mg/kg administered for 3 weeks significantly reversed the akinetic deficits produced by the striatal dopamine depletion and progressively improved attentional deficits. These effects were potentiated by the co-administration of levodopa. The authors proposed that the mechanism explaining this effect may involve the release of acetylcholine in the basal forebrain, induced by the blockade of the alpha2-adrenoreceptors. Indeed, attentional deficits in PD are known to be related to cholinergic degeneration in these regions [44, 45].

The effects of piribedil on memory have been studied in several memory paradigms in the rodents [46]. Paradigms included the spontaneous object recognition to measure memory formation, a two-stage radial-maze discrimination test to assess memory flexibility, and a working memory test. Piribedil enhanced spontaneous object recognition in young adult rats and displayed beneficial effects against aging-related memory impairments in two radial-maze experiments in mice. Working memory was also improved by piribedil in the aged mice. Authors suggested again that the release of acetylcholine induced by blockade of alpha2-adrenoreceptors might be the mechanism accounting for these effects.

Finally, the potential antidepressant properties of piribedil have also been studied in a forced-swim test in mice [47]. Piribedil reduced immobility in a dose-dependent manner when acutely administered. Similar results were obtained with short- and long-term administration of the drug to rats subjected to the same test. Both in mice and in rats, the D_2/D_3 receptor antagonist, raclopride, and the D_2 receptor antagonist, L741,626, dose dependently blocked the antidepressant properties of piribedil, whereas the selective D_3 receptor antagonists, S33084 and SB277,011, were ineffective [47]. At the doses used in these antidepressant trials, piribedil did not stimulate locomotor behavior. These data support a role for D_2 receptor stimulation in the antidepressant actions of piribedil in animal models. Whether these are reinforced or not by its alpha2 antagonist properties remains to be clarified.

In summary, there is experimental evidence in animal models suggesting that piribedil might be effective for the treatment of somnolence, attention deficit, cognitive dysfunction, or depressed mood in PD. The effects on attention and cognition may be mediated by the stimulation of acetylcholine release induced by blockade of alpha2-adrenergic presynaptic receptors. Conversely, the antidepressant properties appear to be more dependent on the activation of the D_2 receptor.

3.4 Neuroprotection

The lack of efficacious 'disease-modifying' therapies probably represents the most important unmet need in the current management of PD [48]. Dopamine agonists have been speculated to provide neuroprotection by different mechanisms, including that they decrease DA turnover rate and free radicals generation in the substantia nigra, and also have antioxidant properties. However, clinical proof is lacking.

Pilot results suggested that piribedil has an anti-peroxidative effect in the brain [49]. In a recent study, dopaminergic cell cultures obtained from embryonic Wistar rats were instilled with cerebrospinal fluid from a PD patient or from patients without neurological conditions [50]. Results showed increased expression of lactate dehydrogenase and reductions in the expression of tyrosine hydroxylase positive/total neurons ratio after infusion of PD cerebrospinal fluid but not in control cultures. Piribedil reversed these changes in a dose-dependent manner. The potential clinical relevance of such observations remains unknown.

4 Clinical Efficacy in Patients with PD

Generally speaking, dopamine agonists are known to be effective in improving PD motor symptoms in early and advanced PD, to reduce the duration of the time spent in the OFF condition in levodopa-treated patients experiencing motor fluctuations, and to delay the occurrence of levodopa-induced motor complications (ON–OFF and dyskinesia) when used early in the course of the disease [9]. Piribedil was considered by the International Parkinson and Movement Disorder Society Evidence-Based Medicine (MDS-EBM) Task Force as "efficacious" and "clinically useful" for the symptomatic treatment of PD, either as monotherapy or in conjunction with levodopa, in non-fluctuating patients with early PD [51]. Conversely, the same MDS-EBM Task Force stated that "insufficient evidence" was available to conclude on piribedil efficacy and usefulness on motor fluctuations (treatment and prevention) because of the lack of placebo-controlled randomized clinical trials in such conditions.

In this section, the results of clinical trials regarding the efficacy of the drug on motor and non-motor symptoms will be reviewed.

4.1 Motor Symptoms

In a first pilot study by Rondot and colleagues, intravenous infusions of piribedil stopped tremor within 10–50 min in 9 of 13 PD patients [52]. Uncontrolled studies subsequently documented further the effect of the drug in relieving parkinsonian tremor and other motor symptoms, although to a lesser extent than levodopa [52–55]. Mentenepoulos and colleagues studied the efficacy of piribedil in 13 de novo PD patients and 17 others on levodopa, with the Hoehn and Yahr score between II and III [56]. There was no control group and the study was open label. The great majority of patients (84 %) responded 'favorably' to the treatment. Among the cardinal symptoms of parkinsonism, tremor was reported to have responded the best. Depression also appeared to respond favorably. Further results from another open-label study on 133 de novo PD patients, of whom 90 completed the trial, showed similar effects of piribedil on PD cardinal symptoms and mood [57, 58]. Similar results were also observed in Thai, Filipino, and Spanish PD patients insufficiently controlled with levodopa [59–61]. However, the lack of a comparative placebo-controlled double-blind design of these first studies precludes any robust conclusion to be drawn.

A first randomized, double-blind, placebo-controlled, crossover trial, was conducted in nine PD patients taking levodopa and six others taking amantadine [62]. Greater improvement with piribedil was reported in akinesia, gait, speech, facial expression, and finger dexterity, but the small size of the study and the heterogeneity of the patients limit the conclusions of this trial.

A second set of randomized, double-blind, placebo-controlled clinical trials was then subsequently conducted during the 2000s, to provide more robust evidence,

according to methodological standards complying with modern international regulatory recommendations and guidelines [63]. In a first study, 108 non-fluctuating PD patients with insufficient motor control under levodopa were randomized to piribedil (up-titrated for up to 150 m/days three times daily) or placebo and followed up for 6 months [64]. Adjustment to levodopa dose was allowed during the last 2 months. At month 4, the rate of response, defined as a 30 % decrease from baseline on the Unified PD Rating Scale (UPDRS) III motor score, was significantly greater on piribedil compared with placebo (56.4 vs. 37.7 %; $p < 0.04$). At month 6, the better efficacy of piribedil was maintained and a significant reduction in the UPDRS III score was also noted.

In a second study, 405 untreated patients with early PD were randomly assigned to piribedil up to 300 mg/day or placebo and followed up for 7 months (REGAIN study) [65]. Administration of levodopa was possible after week 6 if needed, but data were censored after levodopa introduction. The primary endpoint was the mean change from baseline to endpoint (as the last observation on monotherapy over 7 months) of the UPDRS III score. At endpoint, the mean daily dose of piribedil was 240 ± 55 mg/day. UPDRS III improved on piribedil (−4.9 points) versus a worsening on placebo (+2.6 points; estimated effect = 7.26 points, $p < 0.0001$). A significantly greater reduction in the UPDRS II (activities of daily living) score in patients on piribedil was also detected. Piribedil was effective for the relief of all cardinal motor symptoms.

Piribedil efficacy has also been compared with bromocriptine in a third randomized study conducted in non-fluctuating patients insufficiently controlled with levodopa [66]. Follow-up was 12 months and piribedil and bromocriptine doses were 150 mg/day and 25 mg/day, respectively. A similar improvement in the UPDRS III (i.e., the primary outcome) over the 12-month study duration was observed both in the piribedil and bromocriptine groups (−7.9 ± 9.7 vs. −8.0 ± 9.5, respectively).

The effects on tolerability and PD symptoms of switching from bromocriptine to piribedil have been assessed in a randomized single-blind crossover trial in patients with mild to moderate PD already treated with stable doses of bromocriptine and levodopa [67]. Patients were randomized to two groups of 10 patients each, to receive piribedil based on 1:5 or 1:10 conversion ratios. Nineteen of the twenty patients (95 %) completed the study without major adverse events (except one case of sleep attack in the 1:10 group). Secondary efficacy outcomes showed a greater improvement in the UPDRS total score after 1 month of treatment in the 1:10 group. Notwithstanding, values were higher in this group at baseline, complicating the interpretation of these results.

Finally, a randomized placebo-controlled study has also been conducted in Russian patients, with positive results, but the article is not available in English [68].

A skin patch formulation of piribedil has also been tested in a 3-week, randomized, double-blind, placebo-controlled study conducted in 27 PD patients insufficiently controlled by levodopa. [69]. The piribedil patch did not prove to be superior to placebo based on UPDRS findings.

In summary, piribedil has been shown to be superior to placebo (level 1 evidence) for the relief of all cardinal motor symptoms in early untreated or levodopa-treated non-fluctuating PD patients. The usual dose that is recommended is 150–300 mg/day, using a three-times-daily regimen. Table 3 summarizes the design and results of studies reviewed in this section.

4.2 Motor Fluctuations

No randomized placebo-controlled trial is available to assess the efficacy of the currently available oral extended-release formulation of piribedil in levodopa-treated patients with advanced PD and motor fluctuations (ON–OFF problem). This is unfortunate, as other antiparkinsonian medications, including dopamine agonists, catechol-*O*-methyltransferase, and mono-amino-oxidase-B inhibitors have proven to significantly reduce the daily time spent 'OFF' by fluctuating PD patients in placebo-controlled conditions, and similar effects can be expected from a D_2 agonist such as piribedil [51]. Similarly, levodopa-controlled randomized trials are lacking to assess if the early use of piribedil delays the incidence of motor complications, while such results are available with other agonists [51].

Findings obtained using non-oral formulations of piribedil support the concept that piribedil can improve the symptoms of PD patients in the advanced stage of the disease. Simon and colleagues studied the effects of single intravenous infusions of piribedil for end-of-dose akinesia in 10 fluctuating PD patients by means of a randomized, double-blind, placebo-controlled trial [30]. Piribedil was reported to be effective in reducing the UPDRS III score at the first evaluation timepoint of 15 min, and in reversing the OFF state in 7 of 10 patients. In another study, the efficacy of an oro-dispersible sublingual formulation of piribedil for aborting OFF episodes was studied in 30 fluctuating PD patients by means of a randomized, double-blind, placebo-controlled crossover trial [32]. The primary endpoint was the maximal change versus baseline in UPDRS III assessed after drug administration following an overnight withdrawal of antiparkinsonian medications. Piribedil was superior to placebo on the change in UPDRS III (−13 ± 12 versus −7±9 respectively; estimated difference −5.2, 95 % confidence interval [−10.4 to 0.05], $p = 0.05$).

Table 3 Clinical studies with piribedil extended-release oral formulation for motor or non-motor symptoms

Study	Design	Sample	Piribedil maximum daily dose (mg)	Comparator	Duration	Main results
Motor symptoms						
Rondot et al. [52]	OL, UC	14 p	1–3 i.v.	–	Acute	Tremor relief in 10–50 min
Callaghan et al. [62]	DB, R, CO	15 p on levodopa	200	Placebo	12 weeks	Significant improvement of motor symptoms compared to placebo
Mentenopoulos et al. [56]	OL, UC	20 p under levodopa or other	200	–	20 weeks	30–50 % motor improvement, better mood
Rondot and Ziegler [57]	OL, UC	113 p not on levodopa	200	–	3 months	25–50 % motor improvement, better mood
Evidente et al. [60]	OL, UC	49 fluctuating p on levodopa	150	–	8 weeks	47 % improvement in UPDRS III score. 17 % reduction in levodopa dose
Ziegler et al. [64]	DB, R, C	115 fluctuating p on levodopa	150	Placebo	4 months	Improvement of 56.4 % vs. 37.7 % in UPDRS III
Tan et al. [67]	OL, R	20 p on levodopa and bromocriptine	1:5 or 1:10 b:p ratios	–	2 months	Essentially equivalent results on both agonists and ratios
Suwantamee et al. [59]	OL, UC	29 p on levodopa insufficiently treated	150	–	6 months	33 % improvement in UPDRS III
Salazar et al. [61]	R, C	62 p on levodopa insufficiently treated	?	Placebo	9 months	63% improvement in UPDRS III (p <0.01 vs. placebo)
Rascol et al. [65]	DB, R, C	401 untreated PD	300	Placebo	7 months	20 % improvement vs. 10 worsening in UPDRS III. Delayed introduction of levodopa
Castro-Caldas et al. [66]	DB, R, C	425 p on levodopa insufficiently treated	150	Bromocriptine 25 mg/day	1 year	33 % improvement in UPDRS III in both groups. Cognitive improvement with piribedil
Non-motor symptoms						
Thobois et al. [71]	DB, R, C	37 p with apathy (SAS > 14 p)	300	Placebo	12 weeks	Improvements in apathy of 34.6 % vs. 3.2 %
Eggert et al. [72]	DB, R, C	80 p with somnolence (ESS > 11)	300	Ropinirole or pramipexole	11 weeks	ESS reduced by 27 % vs. 15 %

b:p bromocriptine:piribedil, *C* controlled, *CO* crossover, *DB* double-blind, *ESS* Epworth Sleepiness Scale, *i.v.* intravenous, *OL* open-label, *p* patients, *PD* Parkinson's disease, *R* randomized, *UC* uncontrolled, *UPDRS* Unified PD Rating Scale, *SAS* Starkstein Apathy Scale

In summary, pilot positive results obtained using sublingual and intravenous formulations in fluctuating PD patients suggest that piribedil should be efficacious in this category of patients with advanced PD. Nevertheless, adequate trials remain to be conducted to document and confirm the effects of an oral formulation at this stage of the disease.

4.3 Non-motor Symptoms

Our knowledge on piribedil effects on non-motor PD symptoms relies mainly on the analysis of secondary outcome measures or post hoc analyses of trials designed to assess primarily motor efficacy. However, some studies have been specifically designed to assess directly the effect of piribedil on non-motor symptoms in PD patients and in non-PD subjects.

Apathy is a behavioral symptom commonly observed in PD patients. It is defined as a lack of motivation accompanied by reduced goal-directed cognition, behavior, and emotional involvement [70]. Piribedil efficacy on this disabling symptom has recently been studied in a 12-week, randomized, double-blind, placebo-controlled study conducted in 37 PD patients who became apathetic during the first year after deep brain stimulation of the subthalamic nucleus (STN DBS) for PD treatment [71]. The primary endpoint of that study was the improvement of apathy as assessed by the reduction in the Starkstein Apathy Scale score. Secondary endpoints included alleviation in depression (Beck Depression Inventory), anxiety (Beck Anxiety Inventory), improvement of quality of life (PDQ39), and anhedonia (Snaith–Hamilton Pleasure Scale). Exploratory endpoints consisted of changes of the Robert Inventory score and Hamilton depression scales. At follow-up evaluation, the apathy score was reduced by 34.6 % on piribedil versus 3.2 % on placebo ($p = 0.015$). Consistent with this finding, apathy assessed by the Robert Inventory score also significantly improved by 46.6 % on piribedil versus 2.3 % worsening on placebo ($p = 0.005$). With piribedil, modifications in the Beck depression and anxiety scores were −19.8 and −22.8 %, respectively versus +1.4 and −8.3 % with placebo, without reaching significance level. Piribedil led to a trend towards improvement in quality of life (−16.2 vs. +6.7 % on placebo; $p = 0.08$) and anhedonia (−49 vs. −5.6 % on placebo; $p = 0.08$).

The effects of piribedil on vigilance have been studied in an 11-week, randomized, double-blinded (except for neuropsychological testing) study conducted in 80 PD patients experiencing excessive daytime sleepiness on pramipexole or ropinirole. Patients were randomly assigned to either switch to piribedil or to continue on pramipexole or ropinirole [72]. Equivalent doses for the switch to piribedil were: piribedil 100 mg = pramipexole ≤ 0.7 mg, ropinirole 4–8 mg; piribedil 150 mg = pramipexole 0.7–1.4 mg, ropinirole 8–12 mg; piribedil 200 mg = pramipexole 1.4–2.1 mg, ropinirole 12–16 mg; piribedil 250 mg = pramipexole 2.1–2.8 mg, ropinirole 16–20 mg; and piribedil 300 mg = pramipexole > 2.8 mg, ropinirole > 20 mg. The primary outcome was the median reaction times during the second 15 min of the subtest 'vigilance' of the Test battery for Attention Performances (TAP). Secondary outcomes included the Epworth Sleepiness Scale, UPDRS, and neuropsychological testing. The study was negative, as no differences in reaction times were observed. However, patients randomized to piribedil had a greater reduction in Epworth Sleepiness Scale scores at the end of treatment compared with those who remained on pramipexole or ropinirole (−4 vs. −2 points; $p < 0.01$). No differences were observed in UPDRS scores or neuropsychological tests.

Castro-Caldas and colleagues compared the effects of piribedil and bromocriptine on cognitive function in a subset of 178/428 patients with early PD assessed primarily for motor response (see above) [66]. At both 6 and 12 months, there was a significant effect of piribedil on the Wisconsin Card Sorting Test in younger (aged < 70 years) patients, with no effect of bromocriptine [0.2 points improvement on piribedil vs. 0.3 worsening on bromocriptine ($p = 0.03$)]. However, the clinical importance of this finding is questionable, as it was observed in a subset of the subjects only, and statistical analysis did not report differences in the five other tested domains. Piribedil also showed some positive effects in memory in non-parkinsonian subjects [73, 74]. Furthermore, two randomized double-blind placebo-controlled studies conducted in young or older healthy subjects suggest that piribedil could enhance cognitive performance as measured with reaction times, recall of words and pictures, working memory, or problem solving [75, 76]. The relevance of such findings referring to PD patients is unknown.

The evidence supporting a possible antidepressant effect of piribedil comes mainly from uncontrolled studies. In the study by Mentenopoulos and colleagues, the Beck Depression Inventory score after piribedil dropped by 29 % ($p < 0.01$), without major effects on memory tests, but the lack of comparative design cannot exclude a placebo effect [56]. Depression score also decreased by 30 % after treatment with piribedil in another open-label study by Rondot and colleagues, but the same concern exists regarding the placebo bias [57].

Table 3 summarizes the design and main results of the studies reviewed in this section. In summary, the effects of piribedil on apathy are to be emphasized as very few drugs have proven to be efficacious in this condition [77] and these results have been obtained in randomized double-

blind placebo-controlled conditions. The down-titration of dopaminergic medications following STN DBS (50 % reduction in levodopa-equivalent daily dose on average) may have contributed to the emergence of apathy in the patients enrolled in this trial [78]. This poses the question whether the observed piribedil anti-apathetic effect resulted from its alpha 2-antagonistic property, or from a more generic D_2/D_3 dopaminergic response that might be shared with other dopaminergic antiparkinsonian agents. Further trials are therefore needed to better explore and understand these findings, and to extend them to a larger population of PD patients not restricted to those having undergone STN DBS. The effects of piribedil on depressive symptoms should deserve also further exploration. For the moment, they can only be considered as exploratory because of the lack of placebo control or adequately powered studies. More attention should be paid in the future in studying potential relationships between apathy, depression, and cognitive dysfunction, as there are frequent overlaps in the clinical assessment of these symptoms, and as other dopamine agonists, namely pramipexole, improved depressive symptoms better than placebo in PD patients [79]. The available data of the effects of piribedil on cognition and memory remain difficult to interpret and their clinical importance is unclear. Here again, more studies are needed.

5 Safety Data

Adverse drug reactions (ADRs) to dopamine agonists typically include central and peripheral dopaminergic events, and non-dopaminergic reactions [9]. Central dopaminergic effects include reduced prolactin secretion, hallucinations, delusions, impulse-control disorders (ICDs), daytime somnolence, and aggravation of LIDs. Peripheral dopaminergic reactions include nausea and vomiting, cardiovascular reactions, such as orthostatic hypotension and peripheral edema. The most typical non-dopaminergic reaction refers to valvular, pleural, or retroperitoneal fibrosis, which is almost exclusively observed with ergot dopamine agonists [10]. These are therefore unlikely to occur with a non-ergot agent such as piribedil, as the drug does not interact with the serotoninergic 5-HT_{2A} or 5-HT_{2C} receptors, which is the proposed mechanism to account for this complication [80].

5.1 Tolerability as Assessed in Clinical Trials

A summary of safety findings in clinical studies with piribedil is offered in Table 4. The most frequent adverse events were gastrointestinal and orthostatic hypotension, in line with observation from trials with other dopamine agonists [9]. The hypotensive effects of piribedil were tested specifically in 10 normotensive PD patients after single intravenous infusions of the drug [79]. Results showed a drop in blood pressure of 12 mmHg, a reduction in heart beats of 9 per minute, and a slight drop in body temperature of 0.4 °C. These effects were not observed after the infusion of a placebo and were blocked by pretreatment with haloperidol, a dopamine, serotonin, noradrenaline, acetylcholine, and histamine antagonist. These results were confirmed in a subsequent clinical study, in which orthostatic systolic blood pressure fall increased after 30 and 90 days of treatment with piribedil ($p < 0.05$) [56].

Worsening of dyskinesia is an ADR frequently caused by dopamine agonists in levodopa-treated PD patients [9]. Dyskinesia was infrequently observed on piribedil over 1 year in patients with early PD (2.9 % of the patients) [66]. The same applied to bromocriptine (4.7 %), which was used as the active comparator in this study. Such findings are not surprising, as LIDs are uncommon at this stage of the disorder. As mentioned previously, very few studies have been published regarding the use of piribedil in patients with advanced PD (see the above section on motor fluctuations). Thobois and colleagues, however, studied the effect of piribedil on apathy in 37 patients with advanced PD (see above) [71]. Dyskinesias occurred in that study in significantly more patients randomized to piribedil (9 %) than to placebo (0 %), suggesting that piribedil worsens dyskinesia in levodopa-treated patients, as do other dopaminergic medications. This observation is consistent with the fact that 47 % of 30 patients with advanced PD who switched 'ON' after an acute sublingual piribedil challenge experienced dyskinesia [33]. There is however not enough information from longer and larger studies to allow definite conclusions. This is unfortunate, considering the potentially interesting alpha-2 antagonistic properties of the drug observed in dyskinetic animal models (see above).

Neurospychiatric adverse reactions (hallucinations, psychosis) are also expected adverse reactions with any dopamine agonists. In a 7-month randomized double-blind placebo-controlled trial conducted in 405 patients with early PD, psychiatric disorders were reported with the same prevalence on piribedil (23 % of the patients) and placebo (18 %) [32]. Nevertheless, in the same study, hallucinations were among the most common reasons for discontinuation in the active group (4 patients, 1 %) as compared with placebo (none). In a 12-month randomized double-blind trial aimed at assessing the efficacy of piribedil (150 mg/day) versus bromocriptine (25 mg/day) as early combination therapy with levodopa, the incidence of hallucinations was 8.1 % for piribedil and 2.8 % for bromocriptine, and treatment discontinuations because of hallucinations were 2.9 % for piribedil and 1.4 % for bromocriptine [66].

Table 4 Safety findings in clinical trials with piribedil

Study	Treatments	Nausea/ vomiting, *n* (%)	Somnolence, *n* (%)	Sleep disorders, *n* (%)	Edemas, *n* (%)	Hypotension/ dizziness, *n* (%)	Hallucinations, *n* (%)
Mentenopoulos et al. [56]	Piribedil ($n = 20$)	6 (30)	6 (30)	–	–	6 (30)	1 (5)
Rondot and Ziegler [57]	Piribedil ($n = 200$)	66 (33)	–	–	–	–	7 (4)
Ziegler et al. [64]	Piribedil ($n = 61$)	5 (8)	–	–	–	3 (5)	–
	Placebo ($n = 54$)	1 (2)	–	–	–	2 (4)	–
Evidente et al. [60]	Piribedil ($n = 49$)	0	4 (8)	3 (6)	–	5 (10)	10 (20)
Tan et al. [67]	Piribedil ($n = 20$)	3 (15)	4 (20)	–	–	3 (15)	2 (10)
Suwantamee et al. [59]	Piribedil ($n = 29$)	8 (28)	–	–	–	4 (14)	2 (7)
Castro-Caldas et al. [66]	Piribedil ($n = 210$)	36 (17)	14 (7)	10 (5)	10 (5)	31 (15)	8 (4)
	Bromocriptine ($n = 215$)	40 (19)	9 (4)	11 (5)	10 (5)	30 (14)	3 (1)
Rascol et al. [65]	Piribedil ($n = 200$)	24 (12)	12 (6)	13 (7)	10 (5)	19 (10)	<5 %
	Placebo ($n = 205$)	8 (4)	6 (3)	6 (3)	7 (3)	9 (4)	<5 %
Rascol et al. [32]	Piribedil orodispersible ($n = 30$)	2 (7)	–	–	–	–	–
	Apomorphine ($n = 30$)	1 (3)	–	–	–	4 (13)	–
	Placebo ($n = 30$)	1 (3)	–	–	–	1 (3)	–
Thobois et al. [71]	Piribedil ($n = 19$)	–	–	–	–	–	1 (5)
	Placebo ($n = 18$)	–	–	–	–	–	0 (0)
Eggert et al. [72]	Piribedil ($n = 44$)	7 (16)	1 (2)	–	–	4 (9)	–
	Pramipexole or ropinirole ($n = 36$)	0 (0)	1 (3)	–	–	0 (0)	–

Most clinical trials assessing piribedil in PD patients have been conducted before daytime somnolence, impulse control disorders, and behavioral changes have been identified as 'expected' adverse reactions to dopaminergic medications. Little informative data are then available from published trials. Somnolence was however reported more commonly on piribedil than placebo in a trial in early PD (6.0 vs. 2.9 %) [32]. Similarly, one out of 10 patients who were switched from bromocriptine to piribedil in a 1:10 ratio developed 'sleep attacks', leading to premature drop-out from the trial [66].

5.2 Post Marketing Surveillance

Case reports show that ICDs can occur with piribedil, as observed with other dopamine agonists [81–83]. In a recent survey conducted in 200 PD patients, we observed a non-significant increased risk of ICDs with piribedil (odds ratio [OR] = 2.18, 95 % confidence interval 0.56–8.53), which was lower than the risks observed with other agonists like ropinirole (OR = 6.05) or pramipexole (OR = 6.02) [84]. Interestingly, a study on spontaneous Adverse Drug Reaction reports to the French Health Authority also conducted by our group, showed a non-significantly lower risk of ICDs on piribedil as compared with ropinirole [85]. It is however impossible to exclude in such retrospective analyses a potential bias in spontaneous reporting, as piribedil has been marketed in France many years before ropinirole. A serious delusional state has also been reported after piribedil therapy onset [86], and this is in line with the expected risk of neuro-psychiatric adverse reactions known with dopamine agonists.

Sleep attacks and somnolence caused by dopaminergic medications, and especially dopamine agonists, are

common in PD patients. Case reports of piribedil-induced sleep attacks can be found in the literature [87], and 23/124 (18.5 %) cases of sleep events related to dopamine agonist therapy were associated with piribedil in a review of publications between 1999 and 2001 [88]. In a sample of 50 PD patients seen at the Department of Neurology, Singapore General Hospital, three (6 %) were reported as having manifested sleep attacks [89]. Among the French spontaneous ADR reports, the risk of diurnal somnolence with piribedil was found to be significantly lower compared with ropinirole, but again, it is not possible to exclude an under-reporting bias, as both drugs have been put on the market at very different times [85]. Sleep attacks after piribedil have also been observed in non-parkinsonian patients [90].

Regarding, peripheral edema, one study suggested that its prevalence may be up to 15 % in patients on piribedil [91]. In the study of the French Pharmacovigilance Database, the risk was lower than for ropinirole [85].

Isolated cases of hepatic dysfunction, with increases in serum alkaline phosphatase and transaminases, have also been reported with piribedil [29].

In summary, the safety profile of piribedil is in the range of what has been reported with other non-ergot dopamine agonists. Most frequent ADRs are gastrointestinal and cardiovascular. Dyskinesias and neuro-psychiatric events, such as ICDs, inappropriate day-time somnolence, or hallucinations can occur. It is impossible from the available data to decide if piribedil is at greater or lower risk than the other agonists for such side effects. Antagonism of alpha2-adrenoreceptors might help explain for example a lower risk of somnolence or cardiovascular problems. Interestingly, atipamezole, another alpha2-adrenoreceptor antagonist, reversed apomorphine-induced orthostatic hypotension and somnolence in rats [92]. Our retrospective analysis of spontaneous ADR reports to the French Health Authority also suggests that the risk of ICDs, somnolence, and peripheral edemas might be lower than with other dopamine agonists [85]. However, as already emphasized, under-reporting may have induced a bias and these preliminary findings require further confirmation from prospective studies.

Three studies further exploring piribedil safety in the real clinical setting have been recently completed and hopefully results will be published in the near future (NCT01519856, NCT00727727, and NCT00725478).

6 Conclusions

The bulk of level I evidence, based on randomized placebo-controlled trials, demonstrates that piribedil is efficacious and clinically useful for the control of motor symptoms as monotherapy or in combination with levodopa in non-fluctuating patients with early PD [51, 64–66]. Conversely, in the absence of randomized clinical trials in the later stages of PD, the use of piribedil to treat motor fluctuations is only based on level III evidence, while more robust data are available for other dopamine agonists [50]. Meaningful comparisons between dopamine agonists are difficult because motor effects are dose dependent, dose-equivalences between dopamine agonists are based on empirical and incomplete data, and there are no head-to-head studies comparing dopamine agonists at multiple doses.

Regarding non-motor PD symptoms, the piribedil alpha 2-antagonistic effect may offer an interesting clinical profile as compared with other agonists, but definite conclusions are difficult to draw at this stage. Piribedil improved apathy in a placebo-controlled study in patients who developed this symptom after STN DBS [71], but it remains to be assessed if this is an effect shared with other dopaminergic medications and if it may be observed in other populations of PD patients. Piribedil can induce abnormal daytime somnolence in PD patients. It is possible that the risk might be less than with other agonists, but data are insufficient to conclude definitely. The same is true for other adverse reactions such as peripheral leg edemas and ICDs [84, 85]. If these results could be confirmed, then piribedil might offer an advantage over other agonists, especially in patients at risk for these conditions.

Compliance with Ethical Standards

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