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Parkinsonian apathy responds to dopaminergic stimulation of D2/D3 receptors with piribedil

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Apathy is one of the most common symptoms encountered in Parkinson's disease, and is defined as a lack of motivation accompanied by reduced goal-directed cognition, behaviour and emotional involvement. In a previous study we have described a delayed withdrawal syndrome after successful motor improvement related to subthalamic stimulation allowing for a major decrease in dopaminergic treatment. This withdrawal syndrome correlated with a diffuse mesolimbic dopaminergic denervation. To confirm our hypothesis of parkinsonian apathy being related to mesolimbic dopaminergic denervation, we performed a randomized controlled study using piribedil, a relatively selective D2/D3 dopamine agonist to treat parkinsonian apathy, using the model of postoperative apathy. A 12-week prospective, placebo-controlled, randomized, double-blinded trial was conducted in 37 patients with Parkinson's disease presenting with apathy (Starkstein Apathy Scale score > 14) following subthalamic nucleus stimulation. Patients received either piribedil up to 300 mg per day ($n = 19$) or placebo ($n = 18$) for 12 weeks. The primary end point was the improvement of apathy under treatment, as assessed by the reduction of the Starkstein Apathy Scale score in both treatment groups. Secondary end points 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 in changes of the Robert Inventory score and Hamilton depression scales. An intention to treat analysis of covariance analysis was performed to compare treatment effects ($P < 0.05$). The number of premature study dropouts was seven in the placebo and five in the piribedil groups, mostly related to intolerance to hypodopaminergic symptoms. At follow-up evaluation, the apathy score was reduced by 34.6% on piribedil versus 3.2% on placebo ($P = 0.015$). With piribedil, modifications in the Beck depression and anxiety scores were −19.8% and

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−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% versus +6.7% on placebo; $P = 0.08$) and anhedonia (−49% versus −5.6% on the placebo; $P = 0.08$). Apathy, assessed by the Robert Inventory score, improved by 46.6% on piribedil and worsened by 2.3% on placebo ($P = 0.005$). Depression, measured by the Hamilton score, improved in the piribedil group ($P = 0.05$). No significant side effects were observed. The present study provides a class II evidence of the efficacy of the dopamine agonist piribedil in the treatment of apathy in Parkinson's disease.

Keywords: Parkinson; apathy; piribedil; dopamine agonist; subthalamic nucleus

Introduction

Non-motor neuropsychiatric manifestations in Parkinson's disease encompass various manifestations (Aarsland *et al*., 2009; Chaudhuri and Schapira, 2009). Apathy is one of the most common symptoms encountered in patients with Parkinson's disease and is defined as a lack of motivation accompanied by reduced goal-directed cognition, behaviour and emotional involvement (Levy and Dubois, 2006; Dujardin and Defebvre, 2012; Starkstein, 2012). Its prevalence in Parkinson's disease varies from 16 to 42% across studies because of different methods of assessment (Pluck and Brown, 2002). Apathy may be observed at all stages of the disease, in isolation or more frequently in association with dementia, depression or anxiety (Aarsland *et al*., 2009; Barone *et al*., 2010). Apathy can also appear after subthalamic nucleus deep brain stimulation, often associated with depression and anxiety (Krack *et al*., 2003; Funkiewiez *et al*., 2004; Czernecki *et al*., 2008; Witt *et al*., 2008). Convergent data suggest that apathy, depression and anxiety observed after subthalamic nucleus deep brain stimulation are part of a hypodopaminergic syndrome related to mesolimbic dopaminergic lesions (Remy *et al*., 2005; Czernecki *et al*., 2008; Thobois *et al*., 2010). Given the predominance of dopamine D3 receptors in the mesolimbic dopaminergic system, there is a clear rational in targeting these receptors using dopamine agonist to improve hypodopaminergic manifestations (Sokoloff *et al*., 2006). This hypothesis is further supported by non-controlled studies showing an improvement in parkinsonian apathy following the reintroduction of dopaminergic agonists such as ropinirole (Czernecki *et al*., 2008; Rektorova *et al*., 2008). Other authors have also shown that pramipexole alleviates depression in Parkinson's disease or patients without Parkinson's disease (Leentjens *et al*., 2009; Barone *et al*., 2010). One of the first demonstrations of the efficacy of this strategy to treat depression was provided by Post *et al*. (1978) using piribedil, another D2/D3 dopamine agonist (Millan, 2010). However, no controlled study permitting definite confirmation of this strategy of treatment of apathy and depression in Parkinson's disease exists to date. This is a crucial issue owing to the frequency of these manifestations and their consequences in terms of increased incidence of suicide attempts in operated patients and their impact on quality of life (Schrag *et al*., 2000; Voon *et al*., 2008; Chaudhuri and Schapira, 2009).

The present placebo controlled study aims to demonstrate the efficacy of piribedil, a non-ergot D2/D3 dopamine agonist, in the treatment of postoperative parkinsonian apathy.

Materials and methods

The trial was designed as a prospective, randomized, double blind, placebo-controlled study, with 50/50 allocation ratio.

Patients

Inclusion criteria

One hundred and two consecutive patients with Parkinson's disease operated on for bilateral subthalamic nucleus deep brain stimulation in two centres (Grenoble and Lyon) were enrolled. Patients <70 years without surgical contraindications underwent bilateral subthalamic nucleus stimulation because of severe L-DOPA related motor complications (Limousin *et al*., 1998; Deuschl *et al*., 2006; Odekerken *et al*., 2013). Surgical implantation of the leads bilaterally in the subthalamic nucleus and of the neurostimulator (leads 3389 and Kinetra, Medtronic) was performed as previously described (Krack *et al*., 2003). A detailed neuropsychological assessment was performed before surgery (Thobois *et al*., 2010). After surgery, dopamine agonists were suppressed and levodopa was reduced as much as allowed by the motor state. Then, monthly assessments of apathy and depression on stimulation and under chronic medication with very low doses of levodopa were carried out by telephone, using the Starkstein Apathy Scale and the Beck Depression Inventory to detect patients who became apathetic and/or depressed after surgery.

The present study concerned all patients, who became apathetic during the first year following deep brain stimulation whatever the delay between surgery and the occurrence of apathy. Apathy was defined as a Starkstein Apathy Scale score >14 or if the Starkstein Apathy Scale score increased by five points with clinically significant apathy as judged by both the patient and neurologist between the preoperative and postoperative monthly telephone evaluations. Apathy occurred after a mean of 4.7 months (3.3–8.2) after surgery and represented the main inclusion criteria being the most prevalent symptom of postoperative withdrawal syndrome of dopamine replacement therapy.

Apathetic patients were then randomized as soon as possible (typically within a few days) in the piribedil versus placebo double blind pharmacological study evaluating the effects of piribedil, a D2/D3 agonist, on parkinsonian apathy. The trial protocol was registered on www.clinicaltrials.gov (N° NCT01020682). The ethics committee of Grenoble University approved the study, and all patients gave written informed consent.

Exclusion criteria

Surgical contraindications, dementia or any major ongoing psychiatric illness constituted general exclusion criteria (Krack *et al*., 2003). Patients presenting, in the preoperative ON-drug evaluation condition, apathy as defined by a Starkstein Apathy Scale (Starkstein *et al*., 1992)

score ⩾14 or the presence of moderate to severe depression (score ⩾20) on Beck Depression Inventory (Beck *et al.*, 1961) were excluded.

Intervention

Before starting the pharmacological study, neuropsychological and motor assessments were performed. These included evaluations of depression [Beck Depression Inventory (Beck *et al.*, 1961) and Hamilton scale (Hamilton, 1960)], apathy [Starkstein Apathy Scale (Starkstein *et al.*, 1992) and Robert Inventory (Robert *et al.*, 2002)], anxiety (Beck Anxiety Inventory (Beck *et al.*, 1988), anhedonia [Snaith-Hamilton Pleasure Scale, (Snaith *et al.*, 1995)], mania (Young *et al.*, 1978), hyperdopaminergic behaviour (Ardouin *et al.*, 2009) (mean for the following hyperdopaminergic items in the Ardouin Scale: punding, risk-taking behaviours, creativity, compulsive buying, pathological gambling, addiction to levodopa, hypersexuality, binge eating, nocturnal hyperactivity and hobbyism). In addition, motor status was assessed using the Unified Parkinson's Disease Rating Scale part III in on stimulation/OFF medication condition in order to assess the motor benefit of subthalamic stimulation and indirectly a correct lead placement. Daily life activities were assessed with Unified Parkinson's Disease Rating Scale II, and motor complications with Unified Parkinson's Disease Rating Scale IV subscores. Quality of life was assessed using the PDQ39 scale. Robert apathy inventory, Hamilton and Ardouin scales were administered in the chronic treatment condition. Starkstein Apathy Scale, Snaith-Hamilton Pleasure Scale, Beck Depression Inventory, Beck Anxiety Inventory and Young scales were administered in the on stimulation/chronic treatment condition.

Patients received domperidone (60 mg/day) and were randomly assigned to either the placebo or the piribedil group. Both the patients and investigators were blinded after assignment to interventions.

Throughout the protocol, when severe depression appeared as defined per protocol by a Beck Depression Inventory depression score >28, patients were excluded from the pharmacological study and received open treatment with an antidepressant drug and/or a dopamine agonist according to individual decision of the treating investigator. Piribedil/placebo dosages were increased in 50 mg steps per week in the first 2 weeks, then every 2 weeks to a maximum of 200 mg/day. After 6 weeks, the patient had a neurological evaluation and assessments of apathy and mood (Starkstein Apathy Scale and Beck Depression Inventory) in the on stimulation/chronic treatment condition. If apathy score remained >14, the piribedil/placebo daily dose was increased in 50 mg steps every 2 weeks to a maximum of 300 mg/day.

After 12 weeks of pharmacotherapy, baseline neuropsychological and motor assessments were repeated. Thus three visits were performed for evaluations (baseline, 6 weeks and 12 weeks). After completion of the pharmacological protocol, piribedil was prescribed in an open-label fashion to all the patients. As neurologists were blinded, they disposed of the possibility to prescribe run-out study medication over 2 weeks before replacing the study medication with open treatment with piribedil to avoid side effects of a too rapid increase in medication. The duration of this run out period could be reduced based on patient's tolerance to piribedil. The design of the study is presented in Fig. 1.

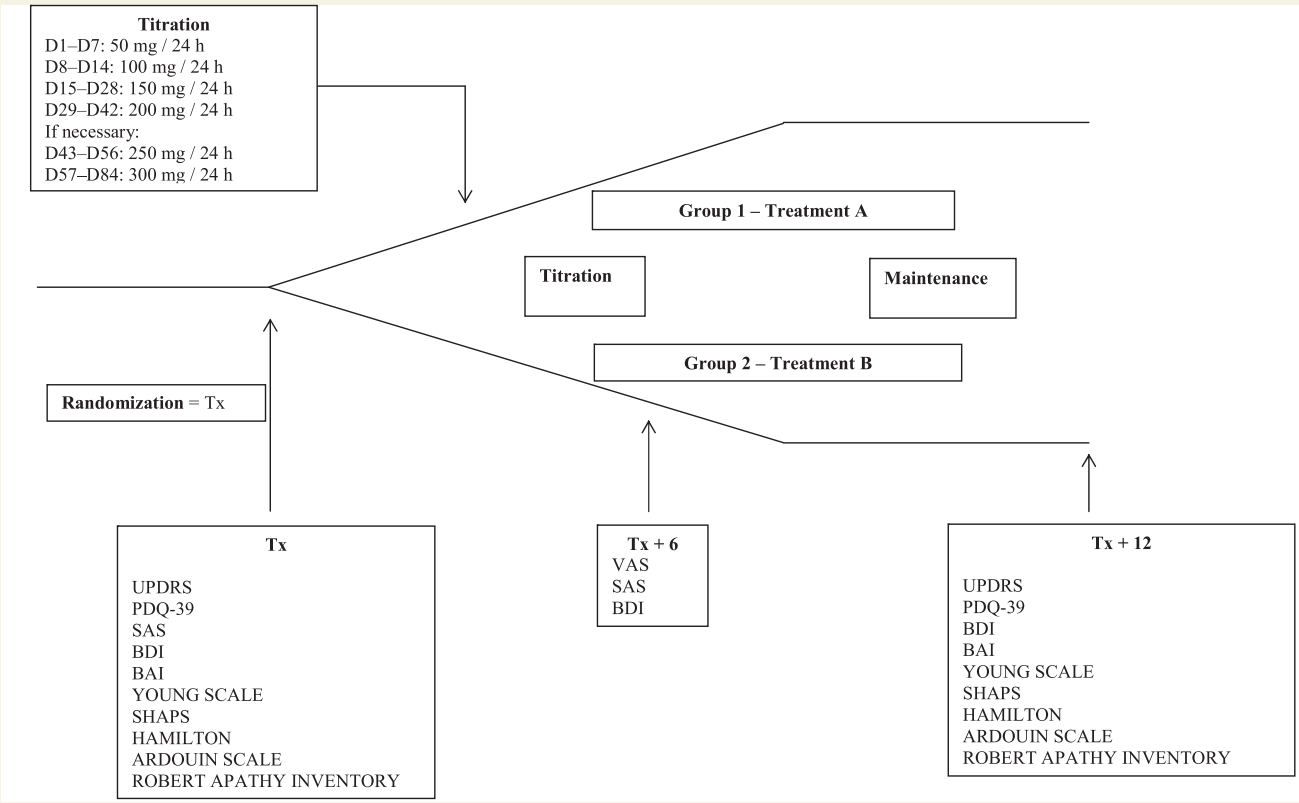

Figure 1 Design of the study.
BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; D = Day; SAS = Starkstein Apathy Score; UPDRS = Unified Parkinson's Disease Rating Scale; VAS = Visual Analogue Scale.

Sample size

The sample size was calculated taking into account an expected difference of efficacy of 30% (5.1 points on the Starkstein Apathy Scale) between the two groups in the primary endpoint (change of Starkstein Apathy Scale Score between baseline and 12 weeks) later corresponding to a large effect size of 1.02, using a two-tailed test with an alpha risk of 5% and a power of 80%. Seventeen patients per group were necessary based on an estimated variance of 25.

Randomization

The randomization list was generated by the company Eutherapie with an in-house validated application software. Randomization was stratified and balanced by centre. The hospital pharmacies were delivered blinded encapsulated treatments (placebo or piribedil) by Eutherapie. Blinded treatments could be identified only by a randomization number, the significance of which was known only to Eutherapie until the end of the study and statistical analysis.

Outcomes

Primary outcome consisted in the Starkstein Scale score (Starkstein Apathy Scale) assessed in the on stimulation/chronic treatment condition and tested using ANCOVA analysis adjusted by baseline Starkstein Apathy Scale values to allow comparison of treatment effects between Weeks 1 and 12 ($P < 0.05$).

Secondary (Beck Depression Inventory, Beck Anxiety Inventory, Snaith-Hamilton Pleasure Scale, PDQ39 Summary Index) and exploratory (Hamilton score, Robert's Inventory Apathy Scale, Unified Parkinson's Disease Rating Scale I to VI, Young mania scale) outcomes were analysed using ANCOVA analysis adjusted by baseline values to allow comparison of treatment effects between Weeks 1 and 12 or Mann-Whitney test for non-Gaussian assumption ($P < 0.05$).

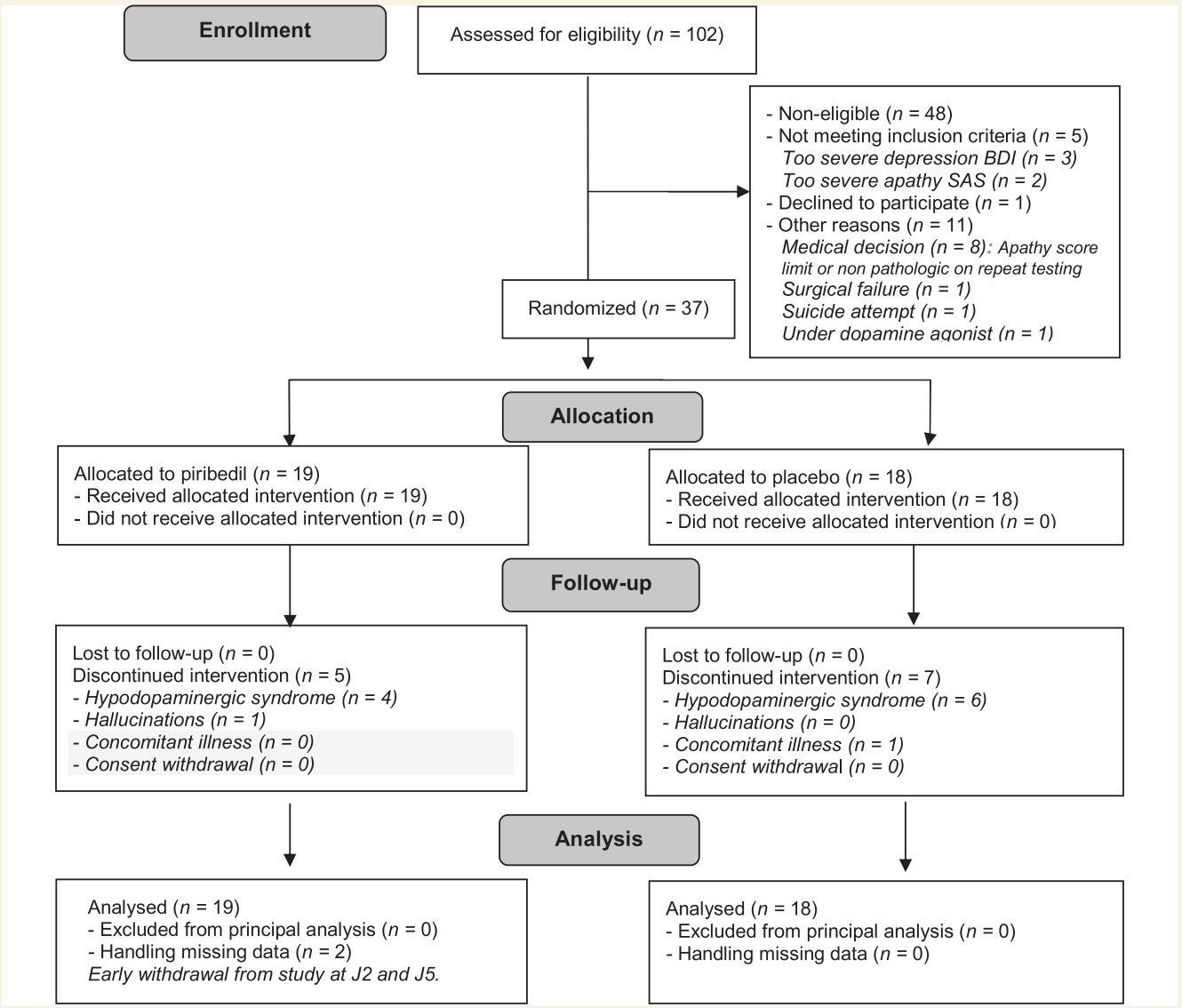

Figure 2 Flow chart of the study.
BDI = Beck Depression Inventory; SAS = Starkstein Apathy Score.

Statistical analysis

The analysis was conducted using the intent to treat population, with last observation carried forward imputation for any missing values at Week 12. This analysis was performed blind to the treatment received.

Data were summarized in terms of size and frequency for categorical parameters, and by means and standard deviations for continuous parameters, or by median and 25th, 75th percentiles where necessary.

Baseline characteristics were compared using Student's *t*-test for continuous parameters. A Mann-Whitney test was applied for non-Gaussian assumption. Independence between qualitative parameters was assessed using either the chi-square test or Fisher's exact test. Statistical analyses were performed using STATA release 12 (StataCorp) PC-Software.

Results

Patients

The trial flow chart is presented in Fig. 2. Recruitment was performed between January 2005 and October 2010. Of the operated patients, 65 of 102 were not enrolled in the pharmacological study. Most were ineligible because they did not develop apathy ($n = 48$). Seventeen did not participate despite a Starkstein Apathy Scale score >14. Six of these were not included because of excessively severe and subjectively intolerable apathy, typically accompanied with anxiety and irritability ($n = 2$) or depression ($n = 3$) or an impulsive suicide attempt ($n = 1$). Owing to the severity of this hypodopaminergic syndrome, patients required open-label prescription of dopamine agonists and/or an antidepressant drug. Other reasons for non-participation in the study were: surgical failure preventing drug decrease ($n = 1$); reduced activity due to hip pain, affecting the apathy score in the absence of clear-cut clinical apathy ($n = 1$); spontaneous fluctuation of the apathy score around the cut-off on repeat testing without clinically relevant apathy ($n = 8$); non-compliance with self-prescription of a dopamine agonist ($n = 1$).

Thirty-seven patients were included in the pharmacological trial. The delay between the occurrence of apathy and the inclusion in the trial was typically within a few days, the maximum duration being 2 weeks. Thirty-six patients presented a Starkstein Apathy Scale score >14 and one a clinically relevant 5-point increase of Starkstein Apathy Scale score between the preoperative and postoperative evaluations. Among these 37 patients, 28 were not depressed. Eighteen were assigned to receive placebo and 19 piribedil. The two groups did not differ in terms of age, equivalence of levodopa dose, motor symptoms and motor complication severity, stimulation parameters, apathy, depression and anxiety scores at baseline. All the patients were treated either by levodopa monotherapy or a combination of levodopa and entacapone with a minimal per protocol dose of 3×25 mg of levodopa. In case a patient required an increase in anti-parkinsonian medication because of an increase in motor symptoms that could not be compensated by an increase in stimulation parameters, only an increase in L-DOPA or L-DOPA/entacapone were allowed. No patient was prescribed amantadine or a monoamine oxidase B inhibitor or any other dopamine agonist apart from study medication. The levodopa equivalent doses at baseline and the end of the study are indicated in Table 1. Patients' baseline clinical characteristics are presented in Table 1.

Seven patients in the placebo group failed to complete the full study. The reasons for premature withdrawal were: intolerance of the hypodopaminergic syndrome ($n = 6$) within the first 6 weeks of the study; prostate adenocarcinoma surgery ($n = 1$). Four subjects in the piribedil group withdrew from the study within the first 6 weeks of the study because of intolerance of the hypodopaminergic syndrome, and one was excluded because of hallucination. Intent to treat analysis was performed in 19 patients on piribedil (14 evaluated at 12 weeks and five evaluated at the moment they discontinued the protocol) and 18 patients on placebo (11 evaluated at 12 weeks and seven evaluated at the moment they discontinued the protocol). The mean dose received of piribedil at the end of the study was 239.2 + 154.8 mg/24 h.

Table 1 Clinical characteristics of the patients at baseline

	Piribedil group ($n = 19$)	Placebo group ($n = 18$)
Age (years)	58.6 ± 6.5	55.6 ± 8
Sex	10 M/9 F	11 M/7 F
Disease duration (years)	12 ± 3.5	11.1 ± 2.6
Starkstein Apathy Scale	21.1 ± 4.8	18.9 ± 4.2
Beck depression inventory	16.7 ± 5.9	14.3 ± 6.6
Beck anxiety inventory	14.9 ± 10.5	8.4 ± 6.2
UPDRS motor score (/108) (OFF medication/on stimulation)	19.3 ± 9.8	14.9 ± 5.1
UPDRS motor complications score	1.5 ± 2.1	1.1 ± 1.6
L-DOPA dose (mg/day; range)	200 [75; 300]	150 [75; 250]
Percentage of anti-parkinsonian treatment reduction after surgery (levodopa equivalent; mg /day; range)	87% [65; 90]	89% [80; 95]
Stimulation parameters [V/pulse width (μs)/Hz]	2.77/60/130	2.78/60/130

UPDRS = Unified Parkinson's Disease Rating Scale.

Neuropsychological status

Primary endpoint: evolution of the apathy score

Apathy clearly improved on piribedil. The Starkstein Apathy Scale score was reduced by 34.6% on piribedil compared with 3.2% on placebo ($P = 0.015$) (Fig. 3). Furthermore, the number of patients in whom apathy disappeared (i.e. Starkstein Apathy Scale strictly inferior to 14) was significantly greater under piribedil (47.4 versus 16.7%). The therapeutic response was usually achieved within the first 6 weeks of treatment. After piribedil re-introduction or introduction in all the patients in an open fashion, the improvement of apathy was preserved in the patients who received piribedil in the double blind study, while patients treated with placebo typically experienced an improvement of their apathy, once they had open treatment with piribedil. These data are not presented as they were not analysed, all the statistics being done before unblinding the randomization.

Secondary endpoints

Evolution of anxiety (Beck Anxiety Inventory) and depression (Beck Depression Inventory) scores was not statistically different in the two groups despite a greater reduction in anxiety and depression scores in the piribedil group. There was a trend ($P = 0.08$) for greater improvement of quality of life and anhedonia (Snaith-Hamilton Pleasure Scale scale) on piribedil.

Exploratory endpoints

Apathy, assessed by the Robert Inventory score, fell by 46.6% on piribedil and increased by 2.3% on the placebo ($P = 0.005$). Depression, measured by the Hamilton score, improved in the piribedil group (−34% versus −2%; $P = 0.05$). No significant changes on the Young mania scale or in hyperdopaminergic behaviours (Ardouin scale) were noted in either the piribedil or the placebo group. No significant differences of changes in Unified Parkinson's Disease Rating Scale motor and motor complication scores were observed. Unified Parkinson's Disease Rating Scale daily life activity was improved in the piribedil group. Results are summarized in Table 2.

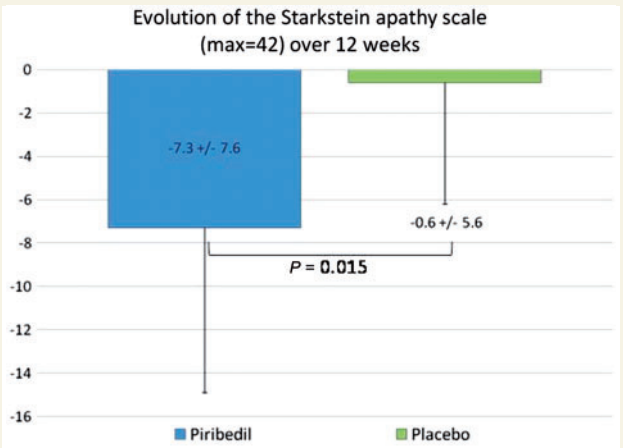

Figure 3 Changes of the Starkstein Apathy Score (SAS) in both groups between baseline and 12 weeks follow-up.

Side effects

Frequency of side effects observed during the protocol did not differ between groups and are summarized in Table 3.

Classification of evidence

Because of a high dropout rate, this interventional study provides class II level of evidence that piribedil, a D2/D3 dopamine agonist, significantly alleviates postoperative apathy in patients with Parkinson's disease implanted with bilateral subthalamic nucleus deep brain stimulation, as measured with the Starkstein apathy scale (34.6% on piribedil compared with 3.2% on placebo; $P = 0.015$) (Sackett *et al.*, 1991).

Discussion

The present randomized controlled study demonstrates for the first time, that piribedil, a D2/D3 dopamine agonist, significantly alleviates postoperative apathy in patients with Parkinson's disease implanted with bilateral subthalamic nucleus deep brain stimulation, as measured with either the Starkstein Apathy Scale (−34.6%) or the Robert Apathy Inventory (−46.6%). This efficacy was also proven by a significantly greater number of patients, in whom apathy disappeared (i.e. Starkstein Apathy Scale strictly <14) under piribedil (47.4 versus 16.7%). Alleviation of depression was shown with the Hamilton scale and the Beck depression scale but the difference between groups was significant only on the Hamilton scale. A trend for improvement in anhedonia accompanied improvement in apathy and mood. Although there was no difference in motor scores and motor complications, daily life activities improved slightly, and there was a trend towards improvement in quality of life on piribedil.

Our study is in line with a previous non-controlled study showing the benefits of ropinirole, another D2/D3 dopamine agonist, in the treatment of postoperative apathy in patients with Parkinson's disease (Czernecki *et al.*, 2008). The present controlled study reinforces this treatment strategy with piribedil, another dopamine agonist. Although not marketed in several countries, piribedil was chosen in this study because of its broad use in France over several decades with well known safety profile and relatively low cost compared with more recent dopamine agonists, the fact that it is a non-ergot drug, its known efficacy on motor symptoms in Parkinson's disease but also based on early studies indicating a benefit on depression (Post *et al.*, 1978; Castro-Caldas *et al.*, 2006; Rascol *et al.*, 2006, 2010). Most importantly, in a previous study (Thobois *et al.*, 2010) we had shown that dopamine withdrawal syndrome is related to mesolimbic dopaminergic denervation and we hypothesized that a D2/D3 agonist should be beneficial on non-motor psychic symptoms that we have classified as hypodopaminergic (Ardouin *et al.*, 2009). As the D3 subtype is the main dopamine receptor of the mesolimbic dopaminergic system (Sokoloff *et al.*, 2006) the efficacy should be relatively

Table 2 Evolution of the neuropsychological parameters between baseline and 12 weeks follow-up

Scales		Piribedil group ($n = 19$)	Placebo Group ($n = 18$)	*P*-value
Primary endpoint				
Starkstein apathy scale	Baseline	21.1 ± 4.8	18.9 ± 4.2	
	12 weeks	13.8 ± 7.5	18.3 ± 5.4	
	Difference between baseline and 12 weeks	−7.3 ± 7.6 (−34.6%)	−0.6 ± 5.6 (−3.2%)	0.015
Secondary endpoints				
Beck depression inventory	Baseline	16.7 ± 5.9	14.3 ± 6.6	
	12 weeks	13.4 ± 9.6	14.6 ± 8.6	
	Difference between baseline and 12 weeks	−3.3 ± 8.8 (−19.8%)	0.2 ± 7.3 (+1.4%)	0.29
Beck anxiety inventory	Baseline	14.9 ± 10.5	8.4 ± 6.2	
	12 weeks	11.5 ± 10.1	7.5 ± 6.1	
	Difference between baseline and 12 weeks	−3.4 ± 8.1 (−22.8%)	−0.8 ± 4.6 (−8.3%)	0.41
Anhedonia: SHAPS	Baseline	3 ± 2.3	2.2 ± 3.1	
	12 weeks	1.5 ± 1.9	1.9 ± 3.6	
	Difference between baseline and 12 weeks	−1.5 ± 2.4 (−49%)	−0.4 ± 1.4 (−15.6%)	0.08
Quality of life: PDQ39 (summary index)	Baseline	7.2 ± 2.5	5.7 ± 2.3	
	12 weeks	6 ± 2.9	6.1 ± 2.1	
	Difference between baseline and 12 weeks	−1.2 ± 1.9 (−16.2%)	0.4 ± 2 (+6.7%)	0.08
Exploratory endpoints				
Hamilton depression scale	Baseline	12.6 ± 5.6	9.5 ± 5.5	
	12 weeks	8.3 ± 6.2	9.2 ± 5.9	
	Difference between baseline and 12 weeks	−4.3 ± 4.4 (−34.1%)	−0.2 ± 5.1 (−2.1%)	0.05
UPDRS motor score	Baseline	19.3 ± 9.8	14.9 ± 5.1	
	12 weeks	16.3 ± 7	16 ± 8.3	
	Difference between baseline and 12 weeks	−3.1 ± 8.2 (−15.8%)	1.1 ± 8.1 (7.1%)	0.5
UPDRS motor complication score	Baseline	1.5 ± 2.1	1.1 ± 1.6	
	12 weeks	2.2 ± 2.1	1.4 ± 1.7	
	Difference between baseline and 12 weeks	0.7 ± 1.9	0.3 ± 0.8	0.23
UPDRS activities of daily living	Baseline	11.7 ± 6	8.3 ± 4.4	
	12 weeks	10.5 ± 5.6	9.6 ± 4.7	
	Difference between baseline and 12 weeks	−1.2 ± 6.3 (−10.3%)	1.3 ± 3.3 (15.7%)	0.03
UPDRS Mentation, behaviour and mood	Baseline	3.7 ± 1.7	3.9 ± 1.4	
	12 weeks	2.6 ± 2.2	3.6 ± 1.9	
	Difference between baseline and 12 weeks	−1.2 ± 6.3 (−30.7%)	−0.2 ± 2 (−6.2%)	0.14
Young mania scale	Baseline	0.11 ± 0.32	0.06 ± 0.24	
	12 weeks	0.32 ± 1	0.06 ± 0.24	
	Difference between baseline and 12 weeks	0.21 ± 1	0	0.56
Hyperdopaminergic behaviour (Ardouin scale)	Baseline	0.07 ± 0.08	0.11 ± 0.19	
	12 weeks	0.13 ± 0.09	0.11 ± 0.14	
	Difference between baseline and 12 weeks	0.06 ± 0.14	0 ± 0.19	0.49
Apathy: Robert Inventory	Baseline	12.3 ± 5.3	12.3 ± 7.6	
	12 weeks	6.6 ± 6	12.6 ± 8.1	
	Difference between baseline and 12 weeks	−5.7 ± 5.7 (−46.6%)	0.3 ± 7.4 (+2.3%)	0.005

SHAPS = Snaith-Hamilton Pleasure Scale; UPDRS = Unified Parkinson's Disease Rating Scale.

Table 3 Side effects

	Piribedil group ($n = 19$)	Placebo group ($n = 18$)
Dyskinesia	2 (9.5%)	0 (0%)
Gastric pain	0 (0%)	1 (5.6%)
Hallucinations	1 (5.3%)	0 (0%)
Irritability	1 (5.3%)	0 (0%)
Prostatic carcinoma	0 (0%)	1 (5.6%)

selective on non-motor symptoms without inducing too much dyskinesia, which can be a problem after surgery when using D1/D2 agonists such as apomorphine or when using levodopa. Interestingly pramipexole, which also stimulates D2/D3 receptor selectively has been shown to have an effect on parkinsonian depression (Barone *et al.*, 2010) arguing for a class effect, and we would suggest the use of any other of the available non-ergot D2/D3 agonist to treat hypodopaminergic symptoms in case piribedil, for which we now have class 2 evidence for its efficacy on parkinsonian apathy, is not available. Our findings provide further

arguments in favour of the 'hypodopaminergic hypothesis' explaining both apathy and depression in Parkinson's disease after drastic reduction of dopamine replacement therapy after subthalamic nucleus stimulation (Thobois *et al*., 2010) or because of abrupt withdrawal of a dopamine agonist in the context of psychosis, impulse control disorder or dopamine dysregulation syndrome (Rabinak and Nirenberg, 2010; Pondal *et al*., 2013). It adds the notion that anhedonia may also be part of the hypodopaminergic spectrum, consistent with the notion that anhedonia is one aspect of apathy (Levy and Dubois, 2006; Dujardin and Defebvre, 2012). Mesolimbic dopaminergic denervation could well mediate apathy, depression and anxiety, as shown by PET studies (Remy *et al*., 2005; Thobois *et al*., 2010) albeit dopaminergic denervation is not the exclusive aetiology of apathy (Levy and Dubois, 2006; Gallagher and Schrag, 2012). This fits well with the role of the dopaminergic system in motivated behaviour (Voon *et al*., 2009). From a therapeutic point of view, it is interesting to note that the reduced novelty-seeking personality trait in *de novo* drug-naïve patients with Parkinson's disease can be reversed by dopaminergic agonists (Bódi *et al*., 2009) and that depression in Parkinson's disease can also be improved by dopamine agonists such as pramipexole (Barone *et al*., 2010). In addition, we demonstrated in a previous ^{11}C-raclopride PET study performed before and after methylphenidate that apathetic patients experienced an improvement in asthenia and affective subscores of the Norris visual analogue scale after intake of methylphenidate, a relatively selective mesolimbic dopamine reuptake inhibitor (Thobois *et al*., 2010). Similarly, in another study analysing the benefits of methylphenidate on freezing of gait in Parkinson's disease, the authors noted an improvement of the scores of the Lille Apathy rating scale in a subpopulation of apathetic patients (Moreau *et al*., 2012). The present controlled study extends these findings and demonstrates that piribedil can also reverse postoperative apathy in patients with advanced Parkinson's disease treated with subthalamic nucleus stimulation.

Improvement in depression only reached statistical threshold when the Hamilton clinician rated scale was used, but failed to do so when depression was assessed by the Beck Depression Inventory self questionnaire. Before discussing this result, it should be acknowledged that depression was not assessed by a structured interview and we can only speak about depressive symptoms without formal diagnosis of depression. The lack of robust effect of piribedil on depressive manifestations can be explained by the exclusion of the most severely depressed patients. Indeed the efficacy of antidepressant drugs is more difficult to demonstrate in moderately severe depression (Fournier *et al*., 2010). In addition, depression in Parkinson's disease is only partly responsive to dopaminergic drugs and other neurotransmitters are also involved in its pathophysiology, which could explain the less robust efficacy of piribedil for depression (Even and Weintraub, 2012). Beyond this, a lack of power and the relatively small number of subjects with depression are likely to explain this inconclusive result. Given these limitations the tendency for depression improvement by piribedil should not be totally neglected but remains to be demonstrated in a study that is properly powered.

The same explanation can be applied to the absence of statistically significant effect of piribedil on anhedonia and anxiety. This result could be linked to the absence of depression improvement. Indeed, there is a clear association between depression and anhedonia, and dopaminergic agonists such as pramipexole preferentially improve anhedonia in depressed patients with Parkinson's disease (Lemke *et al*., 2005).

In the present study we also observed a trend for improvement in quality of life, which, in the absence of motor improvement, is likely related to the improvement of apathy, which is one of the key factors of reduced quality of life in patients with Parkinson's disease (Schrag *et al*., 2000; Chaudhuri and Schapira, 2009; Barone *et al*., 2010; Benito-Leon *et al*., 2012). However, in this relatively small series, this improvement did not reach significance level. Overall, there is a need to carry out studies in larger patient populations, selected for the presence of depression, anhedonia and anxiety, in order to study the effects of dopamine agonists on these symptoms and on quality of life.

In terms of side effects, it is of great interest to note that the improvement of apathy by piribedil was associated with a very limited increased incidence of hyperdopaminergic behavioural manifestations despite the use of high doses of a dopamine agonist (one patient developed an excessive irritability under piribedil). This supports the relative safety of treating postoperative apathy with the D2/D3 dopamine agonist piribedil and the limited risk of developing hyperdopaminergic behaviours after subthalamic nucleus deep brain stimulation in a patient population presenting with apathy and having a marked decrease in pulsatile L-treatment and in non-motor fluctuations (Lhommée *et al*., 2012) even if one of the patients had to be excluded from the study because of hallucinations. However, this relative safety should be taken with caution as the follow-up period in the double-blind study was relatively short and the sample size was limited.

Overall, the present study shows that when apathy does occur after subthalamic nucleus deep brain stimulation, the best strategy is to increase or reintroduce a D2/D3 dopamine agonist. This treatment option should be performed in a rapid manner. Indeed, some patients in the piribedil arm of the present study had to be excluded from the pharmacological protocol shortly after entering it due to lack of quick improvement. The demonstration of an effective strategy of treatment and the impact of apathy on quality of life highlight the importance of carefully monitoring motivation in surgical patients, as apathy is the most prominent symptom of the hypodopaminergic syndrome (Thobois *et al*., 2010).

In conclusion, this study demonstrates the efficacy of the D2/D3 dopamine agonist piribedil in the reversal of parkinsonian apathy occurring after subthalamic nucleus deep brain stimulation and points to the importance of the mesolimbic dopaminergic system in human motivated behaviour. It provides clear indications on how to handle apathy observed in patients with Parkinson's disease operated on with subthalamic nucleus deep brain stimulation. However, these results cannot, without further studies, be extended in general to apathy in Parkinson's disease. In particular, apathy in the elderly demented patient should not be managed in the same way as relatively sudden onset apathy in a context of withdrawal of dopamine replacement treatment in a young and

non-demented patient. This effect is probably a class effect of dopamine agonists that are relatively selective for the mesolimbic D3 receptor, but further controlled studies are needed to extend these findings to other dopamine agonists. In the future, it would be of great interest to study whether apathy can also be improved by treatment with a dopamine agonist in *de novo* patients with Parkinson's disease who constitute another model of parkinsonian apathy without the confounding effects of concurrent dopaminergic treatment or deep brain stimulation.

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