Methylphenidate for gait hypokinesia and freezing in patients with Parkinson's disease undergoing subthalamic stimulation: a multicentre, parallel, randomised, placebo-controlled trial

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Summary

Background **Despite optimum medical management, many patients with Parkinson's disease are incapacitated by gait disorders including freezing of gait. We aimed to assess whether methylphenidate—through its combined action on dopamine and noradrenaline reuptake—would improve gait disorders and freezing of gate in patients with advanced Parkinson's disease without dementia who also received subthalamic nucleus stimulation.**

Methods **This multicentre, parallel, double-blind, placebo-controlled, randomised trial was done in 13 movement disorders departments in France between October, 2009, and December, 2011. Eligible patients were younger than 80 years and had Parkinson's disease, severe gait disorders, and freezing of gate despite optimised treatment of motor fluctuations with dopaminergic drugs and subthalamic stimulation. We randomly assigned patients (1:1 with a computer random-number generator in blocks of four) to receive methylphenidate (1 mg/kg per day) or placebo capsules for 90 days. Patients, their carers, study staff, investigators, and data analysts were masked to treatment allocation. To control for confounding effects of levodopa we assessed patients under standardised conditions with an acute levodopa challenge. Our primary outcome was a change in the number of steps during the stand-walk-sit (SWS) test without levodopa. We compared the respective mean numbers of steps at day 90 in the methylphenidate and placebo groups in a covariance analysis and adjusted for baseline differences. This trial is registered with ClinicalTrials.gov, number NCT00914095.**

Findings **We screened 81 patients and randomly assigned 35 to receive methylphenidate and 34 to receive placebo. 33 patients in the methylphenidate group and 32 patients in the placebo group completed the study. Efficacy outcomes were assessed in the patients who completed the study. Compared with patients in the placebo group (median 33 steps [IQR 26–45]), the patients in the methylphenidate group made fewer steps at 90 days (31 [26–42], $F_{(1, 62)}$=6·1, p=0·017, adjusted size effect 0·61). Adverse events were analysed in all randomly assigned patients. There were significantly more adverse events in the methylphenidate group compared with placebo. Patients on methylphenidate had a significant increase in heart rate (mean 3·6 [SD 7·2] beats per min) and decrease in weight (mean 2·2 [SD 1·8] kg) compared with the placebo group.**

Interpretation **Methylphenidate improved gait hypokinesia and freezing in patients with advanced Parkinson's disease receiving subthalamic nucleus stimulation. Methylphenidate represents a therapeutic option in the treatment of gait disorders at the advanced stage of Parkinson's disease. The long term risk–benefit balance should be further studied.**

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Introduction

From the early disease stages onwards, Parkinson's disease can be treated with dopaminergic drugs. When drug-induced response fluctuations develop later in the course of the disease, deep brain stimulation of either the subthalamic nucleus (STN) or the internal globus pallidus is an option for selected patients.[1] Although these treatments improve the quality of life and autonomy of patients, the long-term benefits of treatment are often reduced by the development of incapacitating gait disorders.[1] These disorders include gait hypokinesia (slow walking with a reduced step length) and freezing of gait (a brief, episodic absence or notable reduction of forward progression of the feet, despite the intention to walk[2]). Gait disorders in patients with advanced Parkinson's disease can be very debilitating, because they increase the risk of falls and injuries, which can lead to a high risk of long-term institutional care.[2] Unfortunately, treatment of gait disability in people with advanced Parkinson's disease is generally disappointing.[2] Optimisation of dopaminergic drugs remains the main treatment option,[2] but dose increases needed to control gait disorders and freezing of gait are often complicated by worsening of response fluctuations, confusion, or sleepiness. Moreover, dopaminergic drugs lose their efficacy as the disease progresses, presumably owing to the development of

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extranigral, non-dopaminergic lesions. Specifically, lesions within the noradrenergic system have a suspected involvement in the pathophysiology of gait disorders in late-stage Parkinson's disease.[3,4]

In view of this presumed contribution by both dopaminergic and non-dopaminergic lesions, we were interested to investigate the therapeutic potential of combined modulation of dopamine and noradrenaline bioavailability. Methylphenidate, which is used to treat attention deficit hyperactivity disorder in Europe and the USA,[5] blocks dopamine and noradrenaline reuptake through inhibition of the presynaptic dopamine transporter[5] and the noradrenaline transporter—particularly in the striatum and prefrontal cortex.[6–8] Three open-label studies assessing methylphenidate in parkinsonian gait disorders showed some benefits,[9–11] but these were not identified in a double-blind, placebo-controlled study with a crossover design in patients given high daily doses of levodopa.[12]

We aimed to assess the clinical value of 90 days of high-dose methylphenidate treatment in a large sample of patients with advanced Parkinson's disease who had received deep brain stimulation of the STN and were experiencing gait disorders with freezing of gait. These problems are often evident after several years of STN deep brain stimulation and are difficult to manage.

Methods

Participants

Between Oct 15, 2009, and Dec 16, 2011, patients were prospectively enrolled at 13 movement disorders departments in France. We included people with Parkinson's disease in accordance with Gibb's criteria,[13] who were aged less than 80 years, and had received STN stimulation (resulting in at least a 40% improvement in the unified Parkinson's disease rating scale [UPDRS] part III in an acute test after 1 year and without worsened gait and posture during the first year of stimulation, with a subsequent decline in the control of axial signs), and had mild to severe gait disorders (including freezing of gait). We defined gait disorders as gait hypokinesia (subscore ≥2 for UPDRS part II item 15) and freezing of gait (subscore ≥2 for UPDRS part II item 14) in the off-levodopa condition, and score of 2 or greater for UPDRS part III item 30 on gait in the on-levodopa condition. Gait disorders had to have a moderate to severe effect on activities of daily living (ie, score ≥2 for the third question in the freezing of gait questionnaire[14]), despite optimised dopaminergic therapy and STN stimulation. Our exclusion criteria were gait disorders possibly induced by STN stimulation, any change in STN stimulation variables or dopaminergic therapy 90 days before or during the study, inability to walk without continuous ambulatory assistance (walker or wheelchair) while on treatment, dementia diagnosed in accordance with the Movement Disorders Society criteria,[15] progressing axis I psychiatric disorders (psychosis, hallucinations, compulsive disorders, substance addiction, bipolar disorder, severe depression) as assessed in a semistructured interview with a psychiatrist (in accordance with the *Diagnostic and Statistical Manual of Mental Disorders*[16]), serious or unstable medical disorders, and ongoing treatment with sympathomimetics, monoamine oxidase inhibitors, or opiates. All patients provided written, informed consent before random allocation. Our study was approved by the local independent ethics committee in 2008.

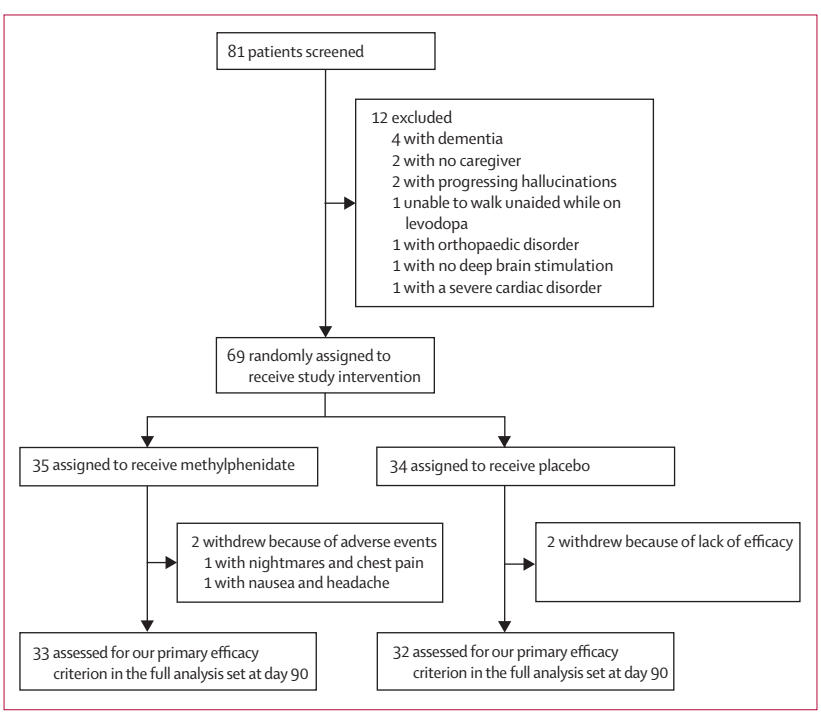

Figure: **Trial profile**

Randomisation and masking

Randomisation was balanced by centre. The 1:1 randomisation sequence (based on a block size of four and the use of a computer random-number generator) was produced by the statistics department at Lille University Hospital (Lille, France). The randomisation list was sent to an independent contract research organisation (LC2, Lentilly, France), which prepared and distributed identical capsules of methylphenidate and placebo. Assignment was masked from the patients, carers, study staff, investigators, and data analysts.

Procedures

Patients received placebo or 1 mg/kg per day methylphenidate (four to eight 10 mg capsules) divided into three doses (at 0800 h, 1200 h, and 1600 h). We used a 4 week titration period with 0·25 mg/kg increments per week. We checked tolerability (assessed by interview and examination) and compliance (assessed by interview and capsule counts) every 2 weeks; interviews were of patients

and caregivers and were administered by the investigators at each site. In the event of poor tolerance, we delayed the titration phase by 1 week, the dose was reduced to 0·8 mg/kg per day, and we asked centres to achieve and maintain the highest possible tolerated dose (at least 0·8 mg/kg per day).

The efficacy criteria we measured at inclusion (day 0) and at day 90 were the mean change in the number of steps (primary outcome) and the completion time during the stand-walk-sit (SWS) test—ie, standing up, making a 14 m round trip, and sitting down as quickly as possible.[17] We rated the number of freezing of gait episodes with the more sensitive trajectory, which features specific triggers for freezing of gait: gait initiation, stopping, rapid 360° and 510° turns, a narrow passage, and dual tasking.[18] The UPDRS and the dyskinesia rating scale were scored. To control for confounding effects of levodopa, we assessed these criteria under standardised conditions, with an acute levodopa challenge in the fasting state (ie, under off-levodopa and on-levodopa conditions before and after 90 days of treatment). The off-levodopa condition was done first (at 0830 h) after overnight withdrawal of levodopa and 24 h withdrawal of dopaminergic agonists. We assessed the on-levodopa condition at 0930 h. The levodopa dose (given at 0900 h) corresponded to 150% of the usual morning levodopa equivalent dose used by patients to relieve their symptoms. We gave the last dose of study treatment at 0700 h on day 90. All measures were reported on a case report form in each centre and double-checked with masked video assessment by two neurologists (CM and AD). If the video data differed from the case report form data, the mean offline video rating was assessed. Secondary endpoints on questionnaires were Giladi's questionnaire,[14] the rating scale for gait evaluation (RSGE parts I–III),[19] the activity-specific balance confidence scale,[20] the Parkinson's disease quality of life scale (PDQ39),[21] and the patients' 2 week falls diary. To detect psychiatric disorders, trained psychiatrists administered, at day 0 and at day 90, a series of assessments to patients taking their usual dopaminergic treatments (ie, not under standardised conditions): the French version of the mini-international neuropsychiatric interview, brief psychiatric rating scale, addiction research center inventory,[22] modified Minnesota impulsive disorders interview, Bech–Rafaelsen mania rating scale,[23] Montgomery Asberg depression rating scale, Lille apathy rating scale,[24] UPDRS part I, Epworth sleepiness scale,[25] and Parkinson's disease sleep scale.[26] Attention was assessed with a computer-controlled reaction time method that included a simple reaction time task for measuring processing speed and four choice reaction tasks for the other attentional subcomponents (appendix).

We assessed each patient's general health status, weight, prone and standing arterial blood pressures, heart rate, and electrocardiogram every 2 weeks after randomisation. We analysed standard blood biochemistry profile (including thyroid hormones) and urinary opiate, tetrahydrocannabinol, amphetamine, cocaine, and barbiturate concentrations monthly. The data safety monitoring board examined adverse event reports periodically. The masking code was not broken.

In an exploratory study, we used ^{123}I-2β-carbomethoxy-3β-(4-iodophenyl) tropane and single photon emission CT (^{123}I-FP-CIT SPECT) to establish whether methylphenidate reduced dopamine transporter binding in the striatum of patients with Parkinson's disease—a finding that would suggest a dopaminergic, pharmacodynamic action[5] on gait in advanced Parkinson's disease (appendix). We also tested patients for the effect of the catechol O-methyltransferase Val158Met polymorphism on the effects of methylphenidate on gait because this polymorphism seems to affect basal dopaminergic prefrontal activity and interact with the levodopa response (appendix).[27–29]

Statistical analysis

We calculated the sample size from our pilot study;[11] we set the expected difference of the primary criteria to 3 steps (SD 5) and, with a power of 80% and a type I error of 5%, the total number of participants needed for this trial was calculated to be 45 patients per group (assuming a dropout rate of 10%). We planned to use an adjustment for the baseline value (covariance analysis), in which case considering a correlation coefficient of 0·5 between the baseline and the end-of-study measurement and a planned

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See **Online** for appendix

	Placebo group (n=34)	Methylphenidate group (n=35)
Age (years)	64 (60–68)	63 (58–68)
Sex ratio (women:men)	0·7	0·6
Height (cm)	169 (163–174)	168 (161–174)
Bodyweight (kg)	80 (72–85)	79 (65–91)
Heart rate (beats per min)	70 (60–76)	70 (60–81)
Systolic arterial pressure (mm Hg)	130 (121–140)	127 (119–140)
Diastolic arterial pressure (mm Hg)	76 (71–86)	77 (69–83)
Disease duration (years)	17 (13–20)	17 (15–21)
Stimulation duration (years)	5 (3–8)	6 (3–9)
Mattis DRS (score <130)	136 (132–140)	137 (134–140)
Levodopa dose for acute tests (mg)	250 (200–300)	250 (200–300)
Levodopa daily dose equivalent (mg)	900 (512–1044)	800 (618–1200)
Dopaminergic agonists	21 (62%)	22 (63%)
Apomorphine pump	2 (6%)	2 (6%)
Entacapone	10 (29%)	11 (31%)
Amantadine	11 (32%)	9 (26%)
Bilateral subthalamic nucleus stimulation		
Mean voltage (V)	3·5 (0·7)	3·3 (0·8)
Mean energy level (TEED)	101 (77–149)	102 (69–157)
High frequency (>130 Hz)	24 (70%)	24 (69%)
Medium frequency (60–80 Hz)	10 (30%)	11 (31%)

Data are median (IQR), n (%), or mean (SD). We calculated the mean total electrical energy delivered (TEED) as TEED=(V^2×frequency×pulse width)/2.[30] These variables (and notably the use of a medium or high frequency for subthalamic stimulation) did not seem to affect the results. DRS=dementia rating scale.

Table 1: **Baseline characteristics**

dropout rate of 10%, we estimated the required sample size to be 38 patients per group (appendix). Our primary efficacy criterion was the change in the number of steps in the SWS test at day 90 versus baseline. We compared the respective mean numbers of steps at day 90 in the methylphenidate and placebo groups in a covariance analysis and adjusted for baseline differences in all patients who completed the day 90 visit. The safety analysis was completed in all patients who were randomly assigned to study groups. If we identified a non-normal distribution the robustness of our results was checked after log transformation. For statistically significant results, we computed the effect size (adjusted for baseline differences). We did the same analysis for the secondary criteria. The numerical safety data, gathered every 2 weeks, were assessed with ANOVA. All significance tests were

	Placebo group		Methylphenidate group		Covariance analysis, p value (adjusted effect size)
	Baseline (n=34)	90 days (n=32)	Baseline (n=35)	90 days (n=33)	
Stand-walk-sit test					
Number of steps off levodopa	33 (26–45)	33 (26–45)	33 (29–47)	31 (26–42)	$F_{(1, 62)}$=6·1, p=0·017 (0·61)
Completion time (s) off levodopa	25 (16–38)	24 (17–54)	24 (18–47)	20 (17–27)	$F_{(1, 62)}$=6·9, p=0·01 (0·65)
Number of steps on levodopa	29 (23–36)	29 (23–32)	29 (24–37)	27 (23–32)	$F_{(1, 62)}$=0·7, p=0·41
Completion time (s) on levodopa	19 (15–25)	19 (15–21)	18 (15–20)	17 (15–22)	$F_{(1, 62)}$=1·5, p=0·2
Freezing of gait trajectory					
Number of freezing episodes off levodopa	6 (4–10), 30 (88%)	7 (1–12), 29 (91%)	6 (3–10), 30 (86%)	4 (0–8), 22 (67%)	$F_{(1, 62)}$=6·2, p=0·02 (0·58)
Number of freezing episodes on levodopa	4 (2–8), 23 (68%)	5 (2–8), 22 (69%)	5 (3–7), 24 (69%)	3 (0 –5), 20 (61%)	$F_{(1, 53)}$=6·3, p=0·015 (0·63)
UPDRS part III off levodopa	29 (22–39)	28 (22–38)	27 (22–38)	24 (18–33)	$F_{(1, 62)}$=7·4, p=0·002 (0·79)
UPDRS part III on levodopa	18 (11–24)	18 (11–26)	18 (10–26)	18 (9–26)	$F_{(1, 62)}$=0·17, p=0·6

Data are median (IQR) and number of patients (% of patients) having freezing episodes.The p values correspond to intergroup comparisons at day 90 (adjusted for baseline) in a covariance analysis. All variables were assessed in 32 patients in the placebo group and 33 patients in the methylphenidate group, apart from the number of freezing episodes on levodopa, which was assessed in 23 patients in the placebo group and 24 patients in the methylphenidate group. UPDRS part III=united Parkinson's disease rating scale, motor part.

Table 2: **Gait and motor assessment before and after an acute challenge with levodopa**

	Placebo group		Methylphenidate group		Covariance analysis, p value (adjusted effect size)
	Baseline (n=34)	90 days (n=32)	Baseline (n=35)	90 days (n=33)	
Gait and freezing					
Giladi questionnaire	28 (25–34)	29 (24–32)	29 (24–35)	27 (19–33)	$F_{(1, 62)}$=3·9, p=0·045 (0·51)
RSGE part I	8 (5–9)	8 (5–10)	8 (6–10)	7 (3–9)	$F_{(1, 62)}$=10·5, p=0·002 (0·78)
RSGE part II	3 (2–4)	3 (2–4)	4 (3–5)	3 (2–4)	$F_{(1, 62)}$=2·1, p=0·1
RSGE part III	6 (4–7)	6 (3–7)	6 (3–7)	5 (2–6)	$F_{(1, 62)}$=5·7, p=0·02 (0·56)
Cognition and behaviour					
Simple reaction time (ms)	356 (321–393)	396 (358–511)	347 (291–391)	353 (314–443)	$F_{(1,56)}$=2·0, p=0·13
Epworth sleepiness scale	10 (5–15)	11 (5–13)	11 (6–15)	8 (4–12)	$F_{(1, 62)}$=6·4, p=0·0041 (0·74)
UPDRS part I	2 (1–3)	2 (1–3)	2 (1–4)	1 (0–2)	$F_{(1, 62)}$=9·1, p=0·0045 (0·73)
Quality of life					
PDQ39	64 (55–72)	63 (51–72)	65 (53–72)	61 (41–70)	$F_{(1, 62)}$=4·1, p=0·02 (0·57)
Dopamine transporter density (ancillary study)					
Binding potential (^{123}I-FP-CIT SPECT; n=28)	0·35 (0·20–0·47)	0·35 (0·19–0·48)	0·34 (0·21–0·38)	0·22 (0·10–0·25)	$F_{(1, 28)}$=14·7, p<0·0001 (1·54)

Data are median (IQR). Our gait and freezing of gait analyses were based on the Giladi questionnaire and the rating scale for gait evaluation (RSGE; part I=functional capacity; part II=long-term complications; part III=socioeconomic consequences). We monitored the potential cognitive and behaviour effects of methylphenidate in terms of attentional performances (with a simple reaction time test), sleepiness (on the Epworth scale), and the unified Parkinson's disease rating scale (UPDRS) I score (four items: cognition, depression, apathy, and hallucinations). We assessed quality of life with the Parkinson's disease quality of life (PDQ39) disease-specific self-questionnaire. Our statistical analyses for all but one of the cited parameters were done on the population as a whole—ie, the set of patients with data for day 90 (33 patients in the methylphenidate group and 32 patients in the placebo group). We assessed the data on the simple reaction time for 59 patients only. Our ancillary study of the dopamine transporter density (with ^{123}I-2β-carbomethoxy-3β-[4-iodophenyl] tropane and single photon emission CT [^{123}I-FP-CIT SPECT]) was done in 28 patients (taking their usual dopaminergic treatments) before and after receipt of the study drug (14 patients in the methylphenidate group and 14 in the placebo group).

Table 3: **Secondary endpoints and exploratory analyses**

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two-tailed. We set the threshold for statistical significance to p=0·05 in all analyses (with SPSS-15.0 software).

This trial is registered with ClinicalTrials.gov, number NCT00914095.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We screened 81 patients with Parkinson's disease. Of these patients we prospectively enrolled 69 who had severe gait disorders and freezing of gait despite receiving an optimised, stable dose of levodopa and STN stimulation (figure, appendix). The groups were balanced in terms of baseline characteristics (table 1). Based on interviews with patients and caregivers and pill counts every 2 weeks, treatment compliance was greater than 90%, with the exception of three patients in the placebo group and two in the methylphenidate group, who had compliance values between 70% and 90% (all patients were included in the analyses). Mean doses were 71 mg/day (SD 9·8) in the methylphenidate group and 72 mg/day (10) in the placebo group. These values did not differ significantly from the mean final doses (methylphenidate 71 [10], placebo 71 [10]). The data we obtained from the case report forms did not differ substantially from those in the video assessment: only two patients in each group who had a high number of steps displayed a difference of one or two steps between the case report form and the video. Our covariance analysis showed a significant positive effect of methylphenidate, relative to baseline values, in the primary outcome of the number of steps in the off-levodopa condition, recorded in the video assessment, and in some of the secondary criteria: the SWS completion time, the number of freezing of gait episodes, the motor UPDRS score (in the off-levodopa condition); the number of freezing of gait episodes in the on-levodopa condition (table 2,); and Giladi questionnaire, RSGE part I, RSGE part III, and PDQ39 scores (table 3).

When compared with placebo, methylphenidate significantly affected the Epworth sleepiness scale and UPDRS part I scores but did not improve attention (table 3). Neuropsychological and psychiatric examinations did not reveal any significant induction of behavioural disorders (appendix). Seven patients in the methylphenidate group with moderate apathy displayed a significant improvement at day 90 (appendix).

Our covariance analysis showed a significant effect of methylphenidate on heart rate and bodyweight relative to baseline, and significantly greater total number of adverse events in the methylphenidate group (table 4). Adverse events prompted five patients to decrease their dose. In the methylphenidate group, two patients decreased the dose by 30 mg (because of nausea or ventricular extrasystoles) and another decreased it by 10 mg (because of headache). In the placebo group, one patient decreased the dose by 20 mg (owing to nausea) and another decreased it by 10 mg (owing to headache). Two patients in the methylphenidate group withdrew owing to adverse events and two patients in the placebo group withdrew owing to lack of efficacy (figure).

We recorded a decrease in striatal dopamine transporter density in the methylphenidate group (table 3). The proportion of patients with a reduction in the number of freezing of gait episodes in the on-levodopa condition was significantly higher in the catechol O-methyltransferase Val/Val subgroup than in the catechol O-methyltransferase Met/Met subgroup. We noted the opposite effect in the off-levodopa condition (table 5).

	Placebo group (n=34)	Methylphenidate group (n=35)	Covariance analysis, p value
Mean heart rate (beats per min)			$F_{(1, 62)}$=4·5, p=0·037
Baseline	70 (60–76)*	70 (60–81)†	
90 days	70 (62–77)‡	74 (67–84)§	
Mean bodyweight (kg)			$F_{(1, 62)}$=9, p=0·004
Baseline	80 (72–85)*	79 (65–91)†	
90 days	80 (70–85)‡	76 (63–88)§	
Serious adverse events			
Gait worsening and depression	1	0	
Cutaneous infection	1	0	
Isolated first seizure episode	1	0	
Nausea, vomiting, gastritis	2	10	
Hypomania episode	0	1	
Enhancement of a pre-existing, hidden, sexual addiction on receipt of a dopamine agonist	0	1	
Anorexia	0	1	
Ventricular extrasystoles	0	1	
Isolated chest pain	0	2	
Erectile dysfunction	0	2	
Transient slight confusion	0	1	
Transient illusions	0	1	
Asthenia	3	3	
Headache	1	2	
Insomnia	1	2	
Isolated myoclonus	0	1	
Nightmares	1	1	
Constipation	1	0	
Dizziness (orthostatic hypotension)	1	0	
Arterial hypertension	1	0	
Dyspnoea	1	0	
Total number of adverse events	15	29	p=0·0008¶

Data are mean (range) or number of patients with the adverse event. We did the analyses on the population that entered randomisation. *n=34. †n=35. ‡n=32. §n=33. ¶χ^2 test.

Table 4: **Adverse events**

Discussion

Our findings show an improvement of gait in the off-levodopa phase, motor symptoms in the off-levodopa

	Val/Val (n=9)	Val/Met (n=15)	Met/Met (n=9)	Dominant effect of Val allele (Val/Val or Val/Met; n=24)	Dominant effect of Met allele (Met/Met or Val/Met; n=24)	p value, Fisher's exact test
Number of steps (off levodopa)	7 (78%)	13 (87%)	7 (78%)	20 (83%)	20 (83%)	1
Completion time (off levodopa)	7 (78%)	12 (80%)	7 (78%)	19 (79%)	19 (79%)	1
Freezing (off levodopa)	3 (33%)*†	12 (80%)	8 (89%)*	16 (67%)	20 (83%)†	0·049,* 0·01†
Freezing (on levodopa)	8 (89%)*	12 (80%)	2 (22%)*‡	20 (83%)‡	14 (58%)	0·015,* 0·002‡

We assessed the effect of the polymorphisms on the primary and secondary gait variables that differed significantly between the methylphenidate and placebo groups. The efficacy variables (the number of steps in the SWS tests, the SWS test completion time, and the number of freezing episodes) were obtained under standardised conditions in the absence of levodopa (off levodopa) and in the presence of levodopa (on levodopa). We defined improvement as a decrease (≥1 episode) in the number of freezing of gait episodes at the freezing of gait trajectory after 90 days of methylphenidate. At the baseline, these variables were not significantly affected by the catechol O-methyltransferase polymorphism. We present the values for the 33 patients in the methylphenidate group, including nine patients with catechol O-methyltransferase Val/Val (Val-Val homozygotes with high catechol O-methyltransferase activity), nine patients with catechol O-methyltransferase Met/Met (Met-Met homozygotes with low catechol O-methyltransferase activity), and 15 patients with catechol O-methyltransferase Val/Met (Val/Met heterozygotes with intermediate catechol O-methyltransferase activity). The allele distribution was the same in the placebo group and in the study population as a whole.[27-29] The dominant effect assesses the effect of the presence of at least one of each allele: Val allele (ie, patients with Val/Val and patients with Val/Met compared with patients with Met/Met) or Met allele (ie, patients with Met/Met and patients with Val/Met compared with patients with Val/Val). The polymorphism did not have a significant effect on the simple reaction time in the methylphenidate group or on any of the parameters in the placebo group. *Fisher's exact test to test for a significant difference between Val/Val and Met/Met. †Fisher's exact test to test for a significant difference between either Met/Met or Val/Met and Val/Val (to assess a dominant effect of the Met allele). ‡Fisher's exact test to test for a significant difference between either Val/Val or Val/Met and Met/Met (to assess a dominant effect of the Val allele).

Table 5: **Number of patients with improvement of gait as a function of the catechol O-methyltransferase Val158Met polymorphism**

Panel: **Research in context**

Systematic review

We identified four studies with PubMed in May, 2012; our search terms were "methylphenidate", "Parkinson's disease", and "gait". We did not limit our search by date or language. In the first, gait speed and stride time variability improved after a single 20 mg dose given to 21 patients.[9] In the second, total walking, non-freezing walking, freezing time, and number of freezing episodes improved after a single 10 mg dose given to five patients.[10] Additionally, our open-label study with blinded video assessment showed an improvement in gait and freezing of gait after 90 days of 1 mg/kg per day methylphenidate in 17 patients who underwent stimulation of the subthalamic nucleus (STN) receiving a median daily levodopa equivalent dose of 675 mg.[11] However, a 6 month, double-blind, placebo-controlled trial recently showed no improvement in gait in 17 patients who completed the crossover study.[12]

Interpretation

Our results confirm the findings of open-label studies,[9-11] but contrast with the double-blind trial.[12] Several aspects of their methods might explain this discrepancy. First, the population in the last study[12] did not undergo STN stimulation. Second, the investigators of this study used an electronic walkway, which might not have elicited freezing of gait sufficiently, when compared with the freezing of gait trajectory used in our study. Third, the high dropout rate of 26% within the small population (*vs* our 6%) might have reduced their statistical power. Fourth, the 6 month period in their crossover design might have biased their results because of the worsening of axial disorders at this advanced disease stage. Thus, methylphenidate could be a new therapeutic option to improve the gait disorders with freezing of gait in patients with Parkinson's disease receiving STN stimulation.

phase, and the number of freezing of gait episodes before and after an acute levodopa challenge. Treatment with methylphenidate had positive effects on activities of daily living (freezing of gait Giladi questionnaire), quality of life (PDQ39), and socioeconomic aspects (RSGE part III). Our patients underwent detailed psychiatric and neuropsychological screening to identify manic episodes, hallucinations, and addictive disorders. Overall, in this elderly population with advanced Parkinson's disease the dropout rate was low and no serious adverse events were observed in the methylphenidate group.

In addition to its effect on gait, methylphenidate decreased excessive daytime sleepiness without worsening sleep quality. This is important, because sleepiness affects up to 50% of patients and worsens with dopaminergic treatments.[31] Methylphenidate also slightly improved the UPDRS part I score (including the depression, cognition, and apathy items). This effect might be related (at least in part) to a reduction in apathy, as suggested by the Lille apathy rating scale score in the subgroup of apathetic patients and by a previous case report.[32]

Methylphenidate might have acted in two ways. First, methylphenidate might have produced a pharmacological blockade of dopamine transporters, as shown by the 35% reduction in striatal radioligand binding compared with baseline value and placebo; this finding suggests the presence of high extracellular dopamine concentrations in the striatum. Gait disorders with freezing of gait might need higher dopaminergic doses for control than symptoms affecting adjacent parts of the body, as suggested by the improvement of freezing of gait only under methylphenidate and levodopa. The catechol O-methyltransferase Val158Met polymorphism seemed to interact with methylphenidate and levodopa and affected the number of freezing of gait responders. Patients with catechol O-methyltransferase Met/Met might have greater basal dopaminergic prefrontal activity than patients with Val/Val, which would increase still further with methylphenidate and thus reduce freezing of gait. Conversely, catechol O-methyltransferase Val/Val patients with low basal dopaminergic prefrontal activity might need more

dopaminergic stimulation (ie, methylphenidate and levodopa) if freezing of gait is to be reduced. The effect of this polymorphism should now be assessed in a larger population. Second, extracellular noradrenaline enhancement in the striatofrontal loops (via inhibition of noradrenaline transporters) might also be involved and would exert direct, noradrenergic effects.[4–8] The central noradrenergic effects of methylphenidate might relate to the noted reduction in sleepiness and the lack of change in reaction times. Peripheral noradrenergic effects might have been evident in the increase in heart rate and weight loss.

Our study had several limitations. The positive short-term risk–benefit balance we note here has yet to be assessed in the long term (especially in terms of the worsening of axial signs and the potential cardiovascular risk in the elderly; panel). Ideally, we should have assessed attention and executive functions under standardised off-levodopa and on-levodopa conditions, to check for interactions with dopaminergic treatments. Under these conditions, we might have been able to identify an improvement in attentional performances after 90 days of methylphenidate and could have established more direct correlations between attention, executive functions, and freezing of gait. We did not assess postural stability but it could have provided us with explanatory information on the lack of a reduction in the number of falls. Lastly, the effects we report apply to only a selected population of patients with Parkinson's disease receiving STN stimulation. Further work is needed to establish whether other patients without previous surgery or in less advanced disease stages might also benefit.

Contributors

CM and AD were involved in the conception, organisation, and execution of the research project and writing of the first draft of the report. LD and KD were involved in the conception, organisation, and execution of the research project and review and critical comment of the report. AD did the biostatistical analysis. GP, IV, J-CC, CB-C, FO-M, DG, AE, VF, P-JS, OL-B, FD, MF, CG, SD, DM, CT, J-LH, BD, J-PA, FT, OR, MV, AD, and BRB were involved in the execution of the research project and review and critical comment of the report. RB was involved in the conception and organisation of the research project and review and critical comment of the report. DD was involved in the conception, organisation, and execution of the research project and writing, review, and critical comment of the first draft of the report.

Parkgait-II study group

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Conflicts of interest

We declare that we have no conflicts of interest.

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