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METHYLPHENIDATE: A TREATMENT FOR PARKINSON'S DISEASE?

--Manuscript Draft--

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Abstract:	Parkinson's disease (PD) affects about 1% of the population over the age of 60 and is characterized by a combination of rest tremor, bradykinesia, rigidity, postural instability, stooped posture and freezing of gait (FoG). However, the clinical spectrum also spans a wide range of non-motor symptoms, such as depression, apathy, cognitive disorders, sleepiness, fatigue and pain. Given that the loss of dopamine in the striatum is the primary pathochemical hallmark in PD, pharmacological treatment of the disease has focused on restoring dopaminergic neurotransmission. The currently licensed dopaminergic treatments for PD modulate all the key steps in the dopamine transmission except the most powerful determinant of extracellular dopamine concentrations: the presynaptic dopamine transporter (DaT). Methylphenidate is a central nervous system stimulant that blocks the DaT and the norepinephrine transporter in the striatum and the prefrontal cortex in particular. Here, we report on and discuss the main open-label studies and randomized controlled trials of methylphenidate' effect on severe gait disorders (e.g. the FoG) and non-motor symptoms in advanced PD. Methylphenidate's various pharmacodynamic effects mean that the drug may have significant value in the treatment of PD. However, there is a lack of randomized controlled trials in this field. Furthermore, more rigorous selection of the types and doses of the associated dopaminergic treatments is required because these parameters may profoundly influence methylphenidate's mechanisms of action and the clinical outcomes. Pharmacogenetic tools could be of use in better defining study patients as a function of their dopaminergic metabolism and drug responsiveness.
Response to Reviewers:	Manuscript reference number: CNS-C-09-01709

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Dear Kathy Fraser, dear Sue Pochon, dear Editors and reviewers

Many thanks for sending us the comments on our manuscript, and for offering us the ability to revise our paper. We would be grateful if you could consider this revised version of our manuscript for publication as an article. Please find enclosed a "clean" copy of the manuscript, a copy of the manuscript in which our revisions are indicated in red type (with the file name 'highlighted") and a separate document listing our point-by-point replies to the editorial and referees' comments.

We have been able to answer all the comments, criticisms and, of course, we remain open to further changes as required. We will send the Author Declaration Forms and the copyright release forms very soon (the number of fax remains busy).

Yours sincerely,

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Answers to the editor’s and reviewers' comments: My comments are below.

Our preferred term is "levodopa" rather than "L-dopa".
Answer: We have replaced L-dopa by levodopa (in red type)

Page 4: please include the name "droxidopa" as an alternative to L-threo-DOPS.
Answer: We have added it in red type

Page 8: regarding the study by Espay et al., the text states the patients were non-fluctuating, but table I states "with motor fluctuations"; please clarify.
Answer: We apologize for this mistake. We have corrected in the text by replacing « non-fluctuation » by « advanced stage » (in red type)

Page 10, section 3.1.1: please divide this section into 2 or 3 paragraphs.
Answer: We have now divided in 3 paragraphs.

Page 17, 2nd paragraph: please provide references for the statement: "It has been reported that confusion and hallucinations..."
Answer: We have provided the references (in red type).

Page 18: please provide a reference for the summary of product characteristics for methylphenidate.
Answer: We have provided the references (in red type).

Table I: Please include the reference citation numbers for each study.
Answer: We have included the reference citation, in brackets, for each study in the first column of the table 1.

Under Pollack et al. 2007, please specify the dosage.
Answer: We have specified the dosage in the Table 1.

This table includes some non-motor findings in the studies, but not other findings that are discussed in the text. Was this intentional?
Answer: Yes, this was intentional; we have put in the Table 1, the main results of each

study and discussed it in the text. Sometimes, some secondary criteria (not presented in the table 1) have been briefly discussed (mainly when there was a lack of data from other study). However, we are ready to add more data in the Table 1 according to your choice (but it might be less readable).

Have the studies been arranged in order of year of publication? If so, the Nutt et al 2004 study should be moved.
Answer: We apologize for this mistake. We have arranged in order of year of publication and indicated in the legend.

Reviewer #1: My comments are below.

This is an interesting review although the authors fail to acknowledge that there may be a good reason for the relative lack of interest in methylphenidate (MPH), namely that the drug has been used for many years without any PD experts being particularly impressed by it. I use it quite frequently for fatigue and cannot recall any patient noting any significant benefit aside from the fatigue or sleepiness. While this certainly is not "scientific", it does suggest that the drug will never have a major effect. From a clinical perspective, I believe that MPH may be beneficial for fatigue, mood, apathy, attention, but very unlikely to be much help in motor symptoms, including gait/FOG.

Answer: We agree that the symptomatic action of methylphenidate is not as much efficient as levodopa. But regarding the strategy to save dopamine by decreasing the metabolism (IMAO and ICOMT), it appears also logical from a « conceptual point of view » to decrease its recapture by inhibiting the DaT. We have published a clinical trial (Moreau et al., 2012) demonstrating a mild but significant motor benefit. We and others in France (Paris, Grenoble, Strasbourg, Marseilles, Nantes, Bordeaux…) have treated a large number of PD patients to improve their gait. Most of them remain under methylphenidate. The benefit of the drug remains even after several years (also non scientific open label observations…). Even if the handicap progresses, the stop of the drug frequently leads to a worsening of the motor handicap.
We agree that we better need to find treatments for the numerous non-motor symptoms. Methylphenidate might help for some of them. We agree your interesting observations on fatigue. Indeed, fatigue is a complex symptom, different from sleepiness. In my experience, fatigue is frequently improved by dopaminergic treatments (dopaminergic agonist and levodopa) but the latter concomitantly worsen sleepiness. Conversely, methylphenidate could improve both. It would be very interesting to lead together a clinical trial on this symptom.

The article, while interesting, is excessively long for a review of a topic that includes only 4 double-blind trials of MPH for more than a week. None of these trials showed much benefit for anything other than the Mendonca study in fatigue.
Answer: We agree that apart from the studies on gait, the studies are largely lacking. We have disclosed it in the conclusion. However, it was asked for a full review and it appears interesting for us to open the discussion on the non-motor symptoms. However, we have decided to report all the published studies obtain from the search in PubMed with the terms "methylphenidate" and "Parkinson's disease" performed in May 2012.” We have reduced the paragraphs where there were only few open label studies. We have slightly reduced the introduction. The editors and the other reviewer did not ask for reducing the text. We remain open to further changes as required.

The authors note the UK warning on MPH in Tourette's but should counter this with the results of actual studies showing no problem (see Kurlan R. Curr Neurol Neurosci Rep 2003;3:285.)
Answer: We have also said “According to the guidelines issued by the United Kingdom's National Institute for Health and Clinical Excellence, Tourette’s syndrome may not be a true contraindication.[72] We have added the reference Kurlan R. Curr Neurol Neurosci Rep 2003;3:285. [73]

The authors might also cite old work on amphetamines showing no motor benefit in PD.
Answer: We apologise, but we did not find this old work, which properly studied the motor benefit under amphetamine in PD patients.

	This article should be greatly shortened. Statements like, "dopamine deficiency is the main cause of PD," need to be deleted. Perhaps you meant "dopamine is the most important neurotransmitter deficiency in PD"? Certainly it is not a "cause." Answer: We apologise. We have corrected (in red type at the top of page 2). The notion that MPH or other stimulants are going to potentially alter the landscape for the treatment of motor function is very unrealistic. Answer: We have withdrawn motor symptoms from the abstract. The introduction deals with all the pharmacological options in the treatment of PD in order to be explicit for every reader. However, we did not mention that methylphenidate will change these strategies. We have slightly reduced this paragraph in the introduction. We agree that a careful interpretation of the results is required. Apart from the results on gait, we have mainly developed the results on non-motor symptoms. At the end of the paragraph on gait we have discussed that long term benefit and the variability of response according to the associated dopaminergic treatments and pharmacogenetic factors should be studied. Reviewer #2: This article reviews the effects of methylphenidate on motor and non-motor function in Parkinson's disease. This is a topic of interest. On a general level it would be important to outline how the areas of methylphenidate's effects were selected. How the literature searches were constructed would be important to include. Answer: We thank you. We have stated (page 5 end of the introduction) “In May 2012, we searched PubMed with the terms "methylphenidate" and "Parkinson's disease".” We have carefully reported all the published studies. One could add effects on autonomic function as a topic for instance. Answer: We agree that methylphenidate could have some interesting effects on autonomic function regarding the hypotension in advanced PD patients. However, the search did not find any study on this topic. The areas where methylphenidate has been studied include generally non-dopamine-responsive symptoms that have been partially attributed to either mesolimbic dopamine dysfunction or effects of nor-adrenergic dysfunction. Answer: We agree. The authors quote one of their own papers examining genetic modulation of methylphenidate's effects yet this isn't discussed in detail. Answer: We have added these informations (in red type page 9 and 10 end of paragraph 2.3). Something that should be mentioned specifically is the potential effect on wearing off. This could be in the introduction. Answer: We have added it (in red type page 3). However, we cannot further develop this hypothesis, regarding the lack of study in this field. Moreover, the reviewer # 1 asked for limiting the hypotheses on the motor symptoms without further evidence. There are occasionally unclear sentences. The authors should go through the text for clarity.Page 3 "they may have effects on severity of motor complications" Answer: We have corrected it (in red type). Page 4 "which probably explains dextroamphetamines the toxicity of amphetamine" The comment on "does not involve the reuptake transporter" should be clarified and referenced. Answer: We have corrected it (in red type).

METHYLPHENIDATE: A TREATMENT FOR PARKINSON'S DISEASE?

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Abstract

Parkinson's disease (PD) affects about 1% of the population over the age of 60 and is characterized by a combination of rest tremor, bradykinesia, rigidity, postural instability, stooped posture and freezing of gait (FoG). However, the clinical spectrum also spans a wide range of non-motor symptoms, such as depression, apathy, cognitive disorders, sleepiness, fatigue and pain. Given that the loss of dopamine in the striatum is the primary pathochemical hallmark in PD, pharmacological treatment of the disease has focused on restoring dopaminergic neurotransmission. The currently licensed dopaminergic treatments for PD modulate all the key steps in the dopamine transmission except the most powerful determinant of extracellular dopamine concentrations: the presynaptic dopamine transporter (DaT). Methylphenidate is a central nervous system stimulant that blocks the DaT and the norepinephrine transporter in the striatum and the prefrontal cortex in particular. Here, we report on and discuss the main open-label studies and randomized controlled trials of methylphenidate' effect on severe gait disorders (e.g. the FoG) and non-motor symptoms in advanced PD. Methylphenidate's various pharmacodynamic effects mean that the drug may have significant value in the treatment of PD. However, there is a lack of randomized controlled trials in this field. Furthermore, more rigorous selection of the types and doses of the associated dopaminergic treatments is required because these parameters may profoundly influence methylphenidate's mechanisms of action and the clinical outcomes. Pharmacogenetic tools could be of use in better defining study patients as a function of their dopaminergic metabolism and drug responsiveness.

1. INTRODUCTION

Parkinson's disease (PD) is the second most frequent neurodegenerative disorder worldwide and affects about 1% of the over-60s.[1] The disease is characterized by association of rest tremor, bradykinesia, rigidity, postural instability, stooped posture and FoG. However, the clinical spectrum also spans a wide range of non-motor symptoms, including sleep disorders, autonomic dysfunction, fatigue and cognitive, behavioral and sensory symptoms.[2] The core neuropathological features of PD are the loss of dopaminergic neurons in the substantia nigra and the deposition of iron and cytoplasmic protein aggregates (Lewy bodies) inside neurons.

The available treatments for PD are limited to symptomatic relief. Given that the loss of dopamine in the striatum as a result of progressive neuronal degeneration in the substantia nigra pars compacta is the primary pathochemical hallmark in PD, pharmacological treatment of the disease has been focused on restoring dopaminergic neurotransmission.[3] Since dopamine itself does not cross the digestive mucosa or the blood-brain barrier, the dopamine precursor L-dopamine (levodopa) has been developed for oral administration. Levodopa is now considered to be the "gold standard" treatment for PD; it improves the patient's motor function, activities of daily living and quality of life. However, levodopa also presents several pharmacokinetic drawbacks – notably its short half-life. Hence, the chronic levodopa regimen required for advanced disease is frequently associated with the development of motor fluctuations and dyskinesia. The prevalence of these motor complications ranges from 40% to 50% after 4 to 6 years of treatment.[4,5] Inhibitors of the dopamine metabolizing enzymes catechol-O-methyltransferase (COMT) and monoamine oxidase-B (MAO-B) have been developed in order to prolong the half-life of levodopa in order to limit the motor fluctuations and the wearing off (i.e. end of dose). Dopamine agonists directly stimulate postsynaptic dopamine receptors in the striatum in order to decrease the need of levodopa and to limit the appearance of motor complications.[4,6,7] However, the dopamine agonists' safety profile provides cause for concern, since they may variously induce impulse control disorders (ICDs, i.e. hypersexuality, pathological gambling, compulsive shopping and compulsive eating), confusion, hallucinations, psychosis, excessive daytime sleepiness and sleep attacks.[4,8] Deep brain stimulation of the subthalamic nucleus or (to a lesser extent) the internal globus pallidus is a proven, effective means of controlling levodopa-related motor complications.[9] However, these techniques involve neurosurgery and, in view of their contraindications, are only appropriate for a small proportion of PD patients. Despite the large number of available treatments, it is clear that there are still major unmet needs in the control of PD symptoms.

We therefore hypothesized that clinical benefit in PD could be achieved by (i) further potentiating dopaminergic transmission via a new mechanism and (i) potentiating other neurotransmitters, such as norepinephrine. Indeed, norepinephrine appears to be involved in the physiopathology of PD.[10] Neuronal loss in the locus coeruleus can be as high as 70%, which leads to a dramatic decrease in the norepinephrine content of the brain- second only to the loss of dopamine production.[11] Administration of an alpha-2 adrenergic antagonist decreased motor handicap in the unilateral 6-hydroxydopamine mouse model of PD.[12] The relationship between norepinephrine depletion and the symptoms of PD remains to be determined. However, norepinephrine is thought to be involved in FoG,[13] since the synthetic precursor L-threo-DOPS (droxidopa) has particularly favorable effects.[14,15,16]

Methylphenidate is a central nervous system stimulant that is licensed for the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy in Europe and the USA. Methylphenidate blocks dopamine and norepinephrine reuptake through inhibition of the presynaptic dopamine transporter (DaT) [17,18,19] and norepinephrine transporter (NeT) [17,20,21] - particularly in the striatum and the prefrontal cortex.[22] The drug has little effect on the serotonin transporter. [17] As with other psychostimulants used to treat ADHD, methylphenidate enhances extraneuronal norepinephrine and dopamine concentrations in the rodent brain *in vivo*. This increase in dopamine efflux is not limited to cortical regions and the onset of action is rapid, with no ceiling on the drug's effect.[23] However, methylphenidate differs from other psychostimulants (such as dextroamphetamine) in terms of the mechanism of action. For example, dextroamphetamine's effects are independent of the neuronal firing rate. The latter drug acts by displacing intraneuronal stores of catecholamines, delaying catecholamine reuptake and inhibiting catabolism by MAO. Thus, dextroamphetamine increases the cytoplasmic concentration of catecholamines which become toxic by auto-oxidation. Conversely, methylphenidate does not induce an accumulation of catecholamines in the cytoplasm (i.e. catecholamines remain largely extracellular and in the vesicules).[23] Methylphenidate's effect is nevertheless almost as powerful as that of dextroamphetamine.[23]

The currently licensed dopaminergic treatments for PD modulate all the key steps in the dopamine transmission other than the most powerful determinant of the extracellular dopamine concentration: the DaT, as demonstrated by studies in DaT knockout mice.[24] Hence, methylphenidate has potential value in the treatment of PD. Oral doses (ranging from 0.5 to 0.8 mg/kg) strongly increased the extracellular dopamine concentration in the brain in general and in the striatum in particular.[22] Methylphenidate may also potentiate levodopa's action via NeT inhibition, as suggested by studies of noradrenergic drugs (e.g. alpha-2

adrenergic receptor antagonists).[25] Since noradrenergic neurons are also involved in dopamine release, methylphenidate may restore the dopaminergic/noradrenergic neurotransmitter balance. [21,26]

Methylphenidate was first assessed in a very small cohort of PD patients in 1961. A dose of 0.5 to 1 mg/kg/day was associated with an improvement in voluntary movements and a decrease in rigidity.[27] However, methylphenidate's effects were mostly attributed to its impact on mood (i.e. its euphorizing action), which was associated with increased restless and insomnia in some patients. This might partly explain the lack of further development of methylphenidate in PD. In fact, methylphenidate has always been considered as a treatment for attention disorders, with potentially valuable effects on cognition and behavior but not (at least directly) on motor symptoms. However, methylphenidate has attracted renewed interest because it was suggested that the gait disorders in PD were profoundly influenced by attention disorders.

Here, we report on the main open-label and double-blind studies (Table 1) of methylphenidate's effects on severe gait disorders (i.e. FoG) and non-motor symptoms in advanced PD. In May 2012, we searched PubMed with the terms "methylphenidate" and "Parkinson's disease". For each symptom or group of symptoms, we shall review the various studies' limitations and potential sources of bias. We then suggest further steps for developing the drug's indications in PD.

2. Gait disorders (Table 1)

The beneficial effects of today's dopaminergic treatments on quality of life and personal independence are often countered over the long term by the appearance of gait disorders (including gait hypokinesia and FOG). Gait disturbances and falls are associated with advanced disease and a longer time since disease onset.[28] The gait disturbances are mainly characterized by abnormal stride length regulation (leading to irregular, small steps) and thus a slower walking speed, i.e. gait hypokinesia.[29] In addition, FoG is defined by a brief, episodic absence of (or a marked reduction in) forward progression of the foot, even though the patient wishes to take a step.[30] The disease mechanism underlying for FoG is not fully understood but is clearly multifactorial. It involves the fundamental control of step scaling and timing (including gait variability), the cognitive and affective state, visual perception disturbances and higher-level motor control.[30] Posture-gait coupling also appears to be abnormal. Clinically, FoG episodes most commonly occur in complex environments that necessitate the integration of many different sensory stimuli. In daily life, FoG particularly

occurs when the patient is starting, turning, walking between obstacles or in confined spaces (e.g. passing a narrow doorway) or upon reaching a destination but can sometimes arise during straight walking in an open space. Turning around appears to be the strongest trigger. The performance of dual tasks and/or the presence of stress may also increase the frequency of occurrence of FoG.[31] Furthermore, FoG episodes tend to be lengthier and more severe once the patient no longer responds to dopaminergic treatment or during an "off-drug" phase. Indeed, gait disorders associated with FoG appear to be mainly related to disease severity and a hypodopaminergic state.[32] Optimization of levodopa treatment is the main therapeutic option under these conditions.[30,32] However, increasing the levodopa dose with a view to controlling gait disorders with FoG may be significantly restricted by (i) the worsening of levodopa-related motor complications, (ii) induction or confusion or sleepiness and (iii) progressive inefficiency as the disease worsens. Patient outcomes may be disappointing, since dopaminergic drugs and deep brain stimulation have a greater effect on limb-related signs than for gait disorders *per se*.[9] There is a need for studies designed to establish whether methylphenidate can improve gait disorders and FoG through the drug's combined action on dopamine and norepinephrine reuptake.

2.1 Open-label studies

An initial, open-label study by Auriel et al. assessed the acute use of methylphenidate (20 mg) in 21 non-demented, non-stimulated PD patients who were free of major postural or gait disorders (Hoehn and Yahr stage II to III) and had stable dopaminergic regimens.[33] The main efficacy criteria for gait hypokinesia were the duration of the timed up-and-go test (TUG: standing up from a chair, walking 3 m, turning round and returning to the seated position), the gait speed, stride time and stride-to-stride variability (assessed by means of foot switches during a two-minute walk). Performance in a tapping task with the dominant hand was also assessed. Evaluations were made under the patients' usual "on-drug" conditions before and then two hours after administration of methylphenidate. The researchers observed significant improvements in all the gait parameters but not in the tapping performance. Methylphenidate was associated with a slightly improvement in attention. These study results agreed with the report by Nutt et al., in which 0.2 or 0.4 mg/kg methylphenidate had no effects on gait or performance of a tapping task when given alone (i.e. after the withdrawal of antiparkinsonian medications).[19]. However, the drug did improve gait when administered two hours after the infusion of levodopa.

A small, open-label study by Pollak et al. [34] examined the effect of low-dose (10 mg)

methylphenidate on FoG in five patients with severe PD (Hoehn &Yahr stage III to IV) during the "off" state. Al the patients were dopa-responsive. All antiparkinsonian medications were withdrawn for at least 12 hours and the patients were evaluated before and then two hours after administration of methylphenidate. Since the study's primary objective was to evaluate methylphenidate's effect on the occurrence of FoG, seated patients were instructed to stand up and walk around two chairs along a figure-of-eight path. The primary efficacy variables were the total walking time, total freezing time and number of FoG episodes. Administration of low-dose methylphenidate was associated with improvements in all these parameters. The study results demonstrated that methylphenidate may improve gait and FoG in advance PD patients, without the need for exogenous levodopa. However, the absence of clinical data on non-axial signs of PD prevents one from drawing conclusions as to a dopaminergic-like action of methylphenidate.

In an open-label study, Devos et al.[35] tested the effect of high-dose (1 mg/kg) methylphenidate on gait disorders, given that low doses of the drug (~0.25 mg/kg) may only occupy half the striatal DaTs in humans.[18] Methylphenidate was administered over a 3-month period to 17 advanced PD patients (mean disease duration: 17 years) undergoing subthalamic nucleus stimulation. Seven of the patients had a clinical diagnosis of dementia. Efficacy was blindly assessed both before and after the course of methylphenidate. The tests were performed following the withdrawal of dopaminergic medications and just after acute administration of the methylphenidate. The primary efficacy parameters were the time to complete the Stand-Walk-Sit (SWS) test (standing up from a chair, walking 7 m, turning around, walk back 7 m and sitting down), the number of steps and the number of FoG episodes. Acute administration of methylphenidate either with levodopa or without levodopa was associated with a lower number of steps and a lower test completion time (relative to the "off-drug, on-stim") condition. The two drugs reduced the parameters to a similar range and had additive effects in this population. Twelve of the 17 patients displayed FoG episodes in either the "off drugs, on-stim") or the "off-stim, on- levodopa" conditions. There was a non-significant trend towards a lower number of FoG episodes in the "on- levodopa, on-methylphenidate" condition. Unlike previous studies, chronic administration of high-dose methylphenidate (in both the presence and absence of dopaminergic medications) indeed had an effect on gait disorders in advanced PD. However, the specific nature of methylphenidate's effects on FoG episodes and other dopasensitive signs in PD remains to be established.

2.2. Randomized controlled trials

Two randomized clinical trials were recently performed.[36,37] The first was a 6-month, double-blind, placebo-controlled, randomized, single-center crossover study in 27 patients. The second was a double-blind, placebo-controlled, randomized, multicenter trial performed in 69 patients. The two studies had similar objectives and are complementary, although methylphenidate's observed effects on gait impairments in PD differed. Espay et al. recruited advanced- stage PD patients with gait impairments (a score of 1 or more for item 29 of UPDRS part III; Hoehn & Yahr stage III). Demented individuals or those undergoing subthalamic stimulation were excluded. The included patients were randomized to 12 weeks of treatment with either placebo or 1 mg/kg methylphenidate. There was a 3-week washout period prior to crossover to the other study medication. Evaluations were made both in the presence and absence of dopaminergic medications. Gait was evaluated using a 144-inch (3.66 m) electronic walkway system. The variables of interests were stride length, gait speed, gait cadence and a composite gait score (including gait speed and stride length). The self-administered Freezing of Gait Questionnaire (FOGQ[38]) and a gait diary were used to evaluate FoG. Relative to placebo, methylphenidate was associated with only a slight improvement in the gait composite score in the "off- levodopa" condition and did not improve the FOGQ score, the freezing diary score or the kinematic variables. The UPDRS motor score was not improved (relative to placebo) by methylphenidate.

In the second study, 69 patients suffering from severe PD (despite the optimization of drug treatments and subthalamic stimulation parameters) and FoG (subscores ≥2 for item 14 of FoGQ, UPDRS part II item 15 for gait in the "on" condition and UPDRS part III item 30 for gait in the "on levodopa" condition) were randomized 1:1 to methylphenidate or placebo for three months. The primary efficacy parameter was the number of steps in the SWS test. Second efficacy parameters included the time to complete SWS test, the number and duration of FoG episodes during the FoG trajectory (which included FoG triggers such as gait initiation and termination, rapid 360° and 540° turns, a narrow passage and dual-tasking,[39]) and questionnaire scores (the FOGQ and a falls diary). All tests were performed following the withdrawal of dopaminergic medications and after the acute administration of levodopa. As in Espay's study, improved gait (the number of steps in the SWS test) was only seen in the "off-dopaminergic drug" condition. However, FoG was less frequent in the methylphenidate group (relative to the placebo group) under both "off-" and "on-dopaminergic drug" conditions. The FOGQ score was lower in the methylphenidate group than in the placebo group. Interestingly, global motor function (the UPDRS III motor score) was slightly greater in the methylphenidate group. The drop-out rate for the study as a whole was low (5.8%).

2.3. Discussion

The disparities between the results obtained respectively by Espay et al. and Moreau et al. may be due to differences in study design (i.e. six months of follow-up in Espay et al.'s study, with the potential for more pronounced progression of axial signs than during the 3-month follow-up period in Moreau et al.)[36,37] , study population (patients undergoing subthalamic nucleus stimulation in Moreau et al.) [37] and the FoG assessment method (questionnaires and an objective assessment in Moreau et al. vs. questionnaires and an electronic walkway (which might not have elicited FoG sufficiently) in Espay et al.).[36] The results can be summarized by saying that administration of methylphenidate in PD was associated with improved gait in the open-label studies and in the second (larger) double-blind, placebo-controlled study.[37] There were fewer motor symptoms in the absence of levodopa and fewer FoG episodes before and after an acute levodopa challenge. This benefit had a positive impact on the activities of daily living and quality of life.[37] Thus, methylphenidate may be a new therapeutic option for alleviating gait disorders with FoG in stimulated PD patients. However, the long-term risk/benefit balance (especially in terms of the worsening of axial signs and the potential cardiovascular risk in the elderly) has not been established. It would be interesting to assess attention and executive functions under standardized off-levodopa and on-levodopa conditions, in order to check for interactions with dopaminergic drugs. This design would perhaps have enabled the identification of improved attentional performance after 90 days of methylphenidate treatment and could have established more direct correlations between attention, executive function and FoG. Lastly, the benefit could be variable from one patient to another regarding notably, the level of associated dopaminergic treatments and some pharmacogenetic factors. Work is needed to establish whether non-stimulated patients (i.e. having higher doses of dopaminergic treatments) or in less advanced stages of PD (i.e. lower doses) might also benefit from methylphenidate treatment. Regarding, the putative pharmacogenetic factors of inter individual variability, the $COMT^{val158met}$ polymorphism appeared to interact with methylphenidate and L-dopa and influenced the number of FoG responders.[37] $COMT^{met/met}$ patients may display greater basal dopaminergic prefrontal activity, which would increase still further with methylphenidate and thus reduce FoG. Conversely, $COMT^{val/val}$ patients with low basal dopaminergic prefrontal activity may require greater dopaminergic stimulation (i.e. methylphenidate and L-dopa) if FoG is to be reduced.[37] The impact of this polymorphism and others should be assessed in a larger population.

3. Non-motor signs (Table 1)

3.1 Depression

Depression is very frequent in PD; 40% of patients show depressive symptoms and 25% have major depression. Indeed, depression often precedes the cardinal motor features of PD and thus is one of the disease's primary symptoms.[40] Moreover, there is no apparent correlation between disease duration and the severity of depression because the latter may sometimes only appear in the later stage of PD.[40,41,42] Many investigators have suspected that depression in PD has a specific etiological mechanism. The condition is often responsive to dopaminergic drugs and is correlated with the degree of anatomic and functional damage to the dopaminergic fibers arising from the ventral-tegmental area (VTA) of the mesencephalon (usually referred as the "mesolimbic dopamine system"). The neuronal circuitries of the noradrenergic and serotoninergic systems and their connections to the prefrontal cortex and the mesolimbic system are also involved.[43,44,45] Serotonin reuptake inhibitors are well tolerated and constitute the gold standard treatment for depression in PD.[46,47] However, in a double-blind, randomized study, it has also been shown that a predominantly noradrenergic/tricyclic antidepressant induced a more intense short-term effect in parkinsonian depression than an serotonin reuptake inhibitor did.[48] By modulating dopamine and norepinephrine reuptake, methylphenidate may have some useful effects on mood in PD.

3.1.1 Double-blind studies of an acute methylphenidate challenge

In the study by Nutt et al., an acute, oral dose of up to 0.4 mg/kg methylphenidate was administrated alone or in combination with a levodopa infusion (0.5 to 1 mg/kg/hour) in eight PD patients. No effects on mood or anxiety were observed, according to self-evaluation on an analog scale ranging from "very depressed" to "very happy").[19] In a double-blind study, Cancello et al. assessed behavioral changes associated with the intravenous injection of methylphenidate or placebo in (i) 13 depressed and 11 non-depressed PD patients, (ii) 14 non-PD sufferers with major depression and (ii) 12 healthy controls. There was at least a three-day interval between slow infusions (0.4 mg/kg over 3 minutes).[49] Changes in psychic status were self-rated on a 0 to 5 scale at the time of methylphenidate injection and 15, 30, 60 and 120 minutes thereafter. The subjects' behavior was also blindly rated by a neurologist. After at least 72 hours of dopaminergic medication, depressed PD patients were less able to distinguish between the active drug and placebo than the non-depressed PD patients and the controls were. Methylphenidate failed to produce any mood change towards a euthymic or

euphoric state; the greater the patients' level of depression, the poorer their response (in terms of mood) to the active drug. In depressed controls, methylphenidate administration was associated with significant relief of depressive symptoms.

In healthy subjects, the intravenous injection of small to medium doses of central sympathomimetics like methylphenidate is followed by a characteristic euphoria syndrome, with a feeling of wellbeing, psychic activation, talkativeness and a general increase in locomotor activity in 50% of the subjects.[50] In PD, methylphenidate appears to have few subjective effects when administered in the absence of levodopa. It has been suggested that a decrease in endogenous dopamine synthesis and release could make PD patients less sensitive to methylphenidate-induced subjective effects.[51] Indeed, the same dose of methylphenidate may have led to a lesser effect in PD patients because their dopamine depletion is greater than in non-PD patients (i.e. PD patients may require higher doses of methylphenidate). Indeed, the more pronounced anhedonia in the depressed parkinsonian group may correlate with degeneration of the VTA/mesolimbic dopaminergic circuitry, which is known to occur in severe PD.[50] Moreover, sustained drug therapy in PD might alter the psychomotor responses to acute challenges with dopaminergic drugs (including methylphenidate and levodopa) and thus cause cross-sensitization.[52] The long-term effects of repeated, pulsatile dopaminergic drug therapy in PD may induce various neural changes, such as dyskinesia, end-dose phenomena, non-motor fluctuations and behavioral abnormalities (stereotypies, ICDs and compulsive self-administration of levodopa, etc.). However, individual patient observations revealed two cases of responsive patients in the depressed PD subgroup, with significant motor and non-motor positive fluctuations 2 hours after intravenous administration and improvements in terms of rigidity, gait, dysarthria and a feeling of wellbeing.[50]

In a double-blind study of 15 medication-naïve patients, Evans et al. assessed mood, psychomotor parameters and the reward potentiating effect of an acute challenge with levodopa plus methylphenidate versus placebo. The test sessions were then repeated in the same patients after a median of 16.7 months of continuous dopaminergic drug therapy.[52] Mood was evaluated on a visual analogue scale every 20 minutes Reward responsiveness was assessed using the Cognitive Arranging Reward Responsivity Objective Test at baseline and then 80 min after methylphenidate administration and 60 min after placebo administration. Under medication-naïve conditions, levodopa improved motor function but not affect. After more than a year of dopaminergic drug treatment, acute methylphenidate improved positive affect (compared with the naïve condition).

3.1.2 Discussion

In terms of design, the above-mentioned studies only assessed acute effects (mainly via self-assessment) and did not use sensitive scales.[53] Additional data are thus required. Pilot studies on the long-term effect of higher doses of methylphenidate on mood would be of value. As a first step, we recommend the use of a double-blind, placebo-controlled, randomized study design and the administration of validated instruments by psychiatrists.

3.2. Apathy

Apathy is characterized by lack of interest, loss of initiative, diminished motivation, effort in performing everyday activities and indifference or flattening of affect. It is frequently considered as a symptom of depression but sometimes occurs in the absence of a mood disorder.[54] Apathy is frequent in PD, with an estimated prevalence of between 13.9% and 60% [55,56], depending on the diagnostic criteria and the inclusion or not of demented and/or depressed patients. In fact, apathy is more frequent in late-stage disease and thus the prevalence has been estimated at 15% in patients with stable disease, 30% in fluctuating patients and 56% in demented patients.[57] Schematically, one can consider at least two different forms of apathy: dopaminergic apathy, with mesolimbic denervation,[58] and a non-levodopa-responsive condition that occurs later in PD and which may be predictive of the occurrence of dementia.[59]. Specific treatments for each of the two types are currently lacking.

3.2.1 Case reports

Chatterjee and Fahn reported the case of a PD patient in whom administration of methylphenidate (5 mg twice per day) sharply reduced severe apathy.[60]

3.2.2 Randomized controlled trials

Moreau et al. reported that chronic administration of high-dose methylphenidate (for 3 months) was associated with a significant reduction in apathy in a subgroup of seven advanced PD patients.[37] Apathy was measured on the validated scale of Lille Apathy Rating Scale (LARS). However, the study was not specifically designed to study apathy; the LARS score was a secondary criterion examined in the few apathetic individuals within a large group of late-stage PD patients with severe gait disorders.

3.2.3 Discussion

There are not enough data for drawing firm conclusions as to the benefit of methylphenidate on parkinsonian apathy - even though this appears plausible. A double-blind, placebo-controlled, randomized clinical trial that uses the LARS to measure dopaminergic apathy is thus required. Indeed, there are no current treatment guidelines for this condition. Given that (i) hyperdopaminergic symptoms (ICDs, etc.) are frequently induced by dopaminergic agonists and (ii), in contrast, hypodopaminergic symptoms (e.g. apathy and depression) are frequently induced by the partial withdrawal dopaminergic treatment associated with the initiation of subthalamic nucleus stimulation, apathy may be relieved by dopaminergic agonists. However, there are serious concerns regarding the induction of ICDs with the latter.[61] Hence, the question of the relative risk of ICD induction by dopaminergic agonists and methylphenidate arises. In the 69 advanced PD patients included in the clinical trial for severe gait disorders, only one reported the enhancement of a pre-existing, hidden, sexual addiction on administration of a dopamine agonist. Furthermore, ICDs did not recur during methylphenidate treatment in the many patients who had experienced an disorder of this type during treatment with dopaminergic agonists earlier in the course of disease.[37]

3.3. Attention

The various studies of methylphenidate and cognitive function have yielded conflicting results. The slight reduction in simple reaction time reported in several open-label studies has not been confirmed by randomized, double-blind studies.

3.3.1 Open-label studies

Auriel et al. studied 21 PD patients before and then two hours after the administration of a single dose of 20 mg of methylphenidate. [33] Attention (measured as a simple reaction time) was significant improved, whereas memory and visuospatial performance were unchanged. Likewise, in another study of 10 non-demented patients (Mattis score ≥ 130), the authors observed that sustained attention was improved by a three-month course of methylphenidate. The mean response time in the simple reaction task significantly decreased and there was no significant change in response accuracy. Performance in the choice reaction task did not change. For the seven demented patients (Mattis score < 130) in this study, sustained attention was not modified by three months of methylphenidate treatment. Moreover, there was a worsening in selective attention, since the mean reaction time on the choice reaction task increased significantly (despite the absence of an effect on accuracy).[35]

3.3.2. Randomized, controlled trials

In a double-blind, randomized, controlled pilot study, Camicioli et al. administered 0.2 mg/kg oral methylphenidate or placebo and (30 minutes later) a one-hour intravenous infusion of levodopa (2 mg/kg per hour) or placebo to five PD patients after withdrawal of antiparkinsonian medications. The researchers observed a lower choice reaction time with methylphenidate (relative to placebo) but failed to see any effects on simple reaction time, attention and executive function (in the Stroop word color test and a digit ordering test).[62]

The absence of an effect on simple reaction time and attention was confirmed by Moreau et al. in a double-blind, placebo-controlled, randomized study of 69 patients.[37]

3.3.3. Discussion

At present, there are data to support a beneficial effect of methylphenidate on attention disorders in PD. Indeed, reaction times have been mainly investigated as a secondary efficacy criterion in small patient populations and/or in non-standardized conditions (i.e. with potentially confounding effects from other dopaminergic drugs, all of which have positive or negative influences on attention and executive performances). We can raise the hypothesis that methylphenidate's effects may differ radically according to the dose of dopaminergic drugs, the patient's cognitive status (at least in demented versus non-demented patients) and the disease stage (i.e. different levels of mesocortical dopaminergic depletion in early-stage versus late-stage disease). Moreover, other pharmacogenetic factors should be also controlled for, such as the COMT val158met status that influences subcorticofrontal cognitive activities.[63]

3.4. Sleepiness

Sleepiness is a disabling symptom that occurs frequently in PD as a result of many different factors: chronic disease, fatigue, drug treatments (e.g. dopamine agonists, levodopa, benzodiazepine, antidepressants, clozapine, quetiapine and cardiovascular agents) and co-morbidities (apnea syndrome and secondary narcolepsy).[64]

3.4.1. Open-label studies

A significant reduction in the Epworth sleepiness scale (ESS) score was noted in 17 PD patients taking 1 mg/kg/day of methylphenidate for 3 months, although there were no sleep attacks.[35]

3.4.2. Randomized, controlled trials

In a recent double-blind study, we observed a three-point decrease in the ESS score (as a secondary criterion) in a group of 35 advanced PD patients after 3 months of high-dose (1 mg/kg/day), when compared with 34 patients on placebo.[37]

3.4.3. Discussion

In view of the lack of validated treatments for sleepiness in PD, the above results could be of great value for the patient. Indeed, modafinil is the sole treatment considered to be probably efficacious in this respect by the Movement Disorder Society, although proof from a randomized, controlled trial is lacking.[64] Hence, there is a need for a randomized, controlled study that considers sleepiness as its primary efficacy criterion. The doses and types of dopaminergic drugs must also be rigorously controlled for. Indeed, adjunction of methylphenidate in patients already taking high doses of dopaminergic agonists may only be effective if the dopaminergic regimen has already been optimized.

3.5. Fatigue

Fatigue is a common non-motor symptom in PD and can have prominent effects on everyday function in between 36% and 56% of patients.[65] Central fatigue is defined as a failure to initiate or sustain tasks that require either mental or physical effort.

3.5.1. Open-label studies

In 2007, Nutt et al. evaluated methylphenidate in 13 fluctuating PD patients in term of the primary motor outcome and a fatigue questionnaire score.[66] Patients took 0.4 mg/kg/day methylphenidate in three doses (morning, noon and 4pm) and levodopa doses were reduced in parallel (to avoid motor fluctuations). Despite a good motor outcome, the effect on fatigue failed to achieve statistical significance; this may have been due to the small sample size, the presence of motor fluctuations and/or the reduction in the levodopa daily dose.

3.5.2. Randomized, controlled trials

Mendonça et al. selected PD patients reporting significant fatigue (despite the treatment optimization of standard anti parkinsonian drug treatments) [67] and randomized them to receive a six week course of either methylphenidate (30 mg per day, n=17) or placebo (n=19). The primary efficacy criterion was the change from baseline in the scores for two separate, self-reported fatigue questionnaires: the Fatigue Severity Scale (FSS) and the

Multidimensional Fatigue Inventory (MFI). Secondary outcomes included the UPDRS motor scores. Fourteen patients in the methylphenidate group and 16 in the placebo group completed the study. In the treatment arm, the mean post-treatment FSS score was 6.5 points lower than the baseline score (43.8) and the mean FSI was 8.4 points lower than the mean baseline score (51). These changes were statistically significant. Reduction in the scores in the placebo was smaller and non-significant. Adverse events were observed more frequently in the placebo group.

3.5.3. Discussion

Apathy is a possible confounding factor for fatigue in PD but was not systematically analyzed in the aforementioned studies. Moreover, depressive symptoms, sleepiness and attention disorders can overlap. Future studies will thus have to control for all these parameters and target one for correct assessment. In an evidence-based review of the efficacy of treatments for the non-motor symptoms of PD, the Movement Disorder Society task force considered that methylphenidate is likely to be effective for fatigue, although there was not enough evidence to recommend treatment with the drug for that purpose.[64]

3.6. Pain

Different types of pain (with differing pathophysiological mechanisms) occur in PD. Setting aside rheumatologic pain (which partly responds to non-steroidal anti inflammatory), two types of neurologic pain have been described: nociceptive pain and neuropathic pain.[68] These symptoms have barely been studied and there are no treatment guidelines other than increasing the dose of dopaminergic medications.

3.6.1. A double-blind study of acute methylphenidate challenge

Intravenous administration of methylphenidate hydrochloride exerted an analgesic effect on primary sensory symptoms in a group of PD patients. [69] In view of methylphenidate's mechanism of action on the central nervous system, the observed adrenergic and serotoninergic mediation of its analgesic effect and the demonstration of impaired central serotonin metabolism in the patient group, one can now conclude that altered noradrenergic and serotoninergic transmission in the spinal cord and central dopaminergic deficiency have a role in the pathophysiology of pain in PD.

3.6.2. Discussion

Methylphenidate may possess analgesic properties that deserve to be investigated in a randomized, controlled clinical trial. Better characterization of the different types of pain encountered in PD will nevertheless be necessary, since they may not all respond in the same way to a given treatment strategy.

4. Safety

Methylphenidate-associated adverse events have been widely described in children (and, to a lesser extent, adults) suffering from ADHD.[70,71] The most frequently reported events are gastrointestinal pain, headache and decreased appetite. Conversely, the data on PD patients have come from a very small number of clinical trials with small sample sizes (other than the latest randomized, controlled trial, which concerned 69 patients).[37] However, the adverse events in the PD population appeared to be similar to those reported in ADHD, with nausea, vomiting, gastritis, decreased appetite and headache. Insomnia was only reported in one patient, although the last dose was taken before 4 pm. The erectile dysfunction reported in previous ADHD trials was also noted in a PD population with dysautonomia and sexual disorders.[37] Overall safety was good, with generally mild, transient events and very few serious adverse events in both patient populations.[37,70] This may have been partly due to compliance with the contraindications listed in the summary of product characteristics for methylphenidate, which are mainly psychiatric, cardiac and (to a lesser extent) neurological (Tourette's syndrome) and endocrinological (hyperthyroidism) phenomena.[71] According to the guidelines issued by the United Kingdom's National Institute for Health and Clinical Excellence, Tourette's syndrome may not be a true contraindication.[72,73]

It has been reported that confusion and hallucinations may arise in at-risk populations with schizophrenia and/or psychotic symptoms.[70,71] PD patients having previously suffered from hallucinations (whether related or not to dopaminergic agonists or parkinsonian psychosis) may therefore represent an at risk population for methylphenidate. Another high psychiatric risk corresponds to mood modulation in patients having already shown suicidal tendencies, severe depression and (in particular) mania/bipolar disorder.[70,71] Indeed, a mild, transient episode of hypomania was observed in a woman suffering from bipolar disorder and PD. The event resolved after a dose reduction.[37] Anorexia nervosa represents also a contraindication. In PD, decreased appetite and a mean weight loss of 2.2 kg over a 3 months period has also been described, with stabilization during a subsequent open-label extension phase.[37] Severe cases of anxiety reportedly worsen during methylphenidate treatment and thus at least require monitoring. In a double-blind trial, none of the 69 PD patients with anxiety reported a

worsening of their condition. However, some adverse events (such as chest pain) may in fact be related to anxiety [37] and require further investigation. Addiction also represents a primary, archetypal psychiatric contraindication mentioned in the summary of product characteristics. As discussed above, only one PD patient reported the enhancement of a pre-existing, hidden, sexual addiction following administration of a dopamine agonist. Furthermore, ICDs did not recur during methylphenidate treatment in the many patients who had experienced an disorder of this type during treatment with dopaminergic agonists earlier in the course of disease.[37] Hence, methylphenidate has to be strongly contraindicated in PD patients with an addiction in progress. Combination treatment with a dopamine agonist may need to be also avoided for the same reason. The hypothesis whereby ICDs are less induced by methylphenidate than by dopamine agonists merits investigation.

Lastly, cardiovascular adverse events may be serious if the drug's contraindications are not rigorously observed - especially in view of the advanced age of the PD population. In ADHD, methylphenidate is contraindicated in cases of severe cardiovascular or cerebrovascular disorders likely to progress as a result of clinically significant increases in blood pressure or heart rate. Six-monthly check-ups with a cardiologist are recommended for non-severe cardiac disorders.[71] In patients with ADHD, heart rate and blood pressure should be monitored and recorded on a centile chart (i) before and after each dose change and (ii) every three months (according to the NICE guidelines)[72] or every 6 months (according to methylphenidate's summary of product characteristics).[71] In the largest clinical trial to date, only mild, transient cardiovascular adverse events were reported; this included one case of ventricular extrasystole and two cases of isolated chest pain.[37] The mean heart rate increased significantly (by three beats per minute) but the blood pressure did not change significantly in a population with prevalent hypotension and hypervariability related to dysautonomia. Hence, in PD, we strongly recommended a careful, comprehensive cardiovascular examination prior to initiation of methylphenidate, in order to identify patients with past or present cardiovascular and ischemic disease. Patient should then be closely monitored, with an electrocardiogram and blood pressure measurement at least every three months.

Most of the descriptions of the adverse events of methylphenidate come from short-duration clinical trials. Since methylphenidate is prescribed as a long-term treatment, there is a need for long-term safety studies. Lastly, there is a need to study the interaction between methylphenidate and MAO-B inhibitors. Although this dual inhibition (i.e. MAO-B inhibition and DaT inhibition) could be of high interest in PD for greater dopaminergic potentiation, the safety profile of this combination has not been evaluated and remains contraindicated.

5. Conclusion

The long-term experience with methylphenidate (a well-characterized drug with a relatively good risk/benefit balance, as long as the contraindications are rigorously observed) suggests that it should be clinically tested for the relief of the various symptomatic disorders in PD. This type of clinical investigation would cost less than the development of novel chemical entities. There is a need for randomized, controlled trials in these possible new indications. The many on-going studies seeking to characterize non-motor symptoms will help to define the best efficacy end points for future trials. Moreover, dopaminergic medications will have to be rigorously controlled in these studies, since the results may be radically different in patients taking low vs. high concomitant doses of levodopa and/or dopaminergic agonists. The recent development of pharmacogenetic tools could also be of use in better defining patient subgroups (either as an inclusion criterion or to analyze the best responders). However, the long-term risk/benefit balance - especially in terms of (i) the maintenance of benefits and (ii) the potential cardiovascular risk (transient ischemic attacks and sudden death/ventricular arrhythmia) in the elderly has yet to be established.

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AUTHORS CONTRIBUTION

1) The research project: a: conception; b: organization; c: execution

2) The manuscript: a: writing of the first draft, b: review and critical comment

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Table 1

(References)	Number of patients	Study design	Methylphenidate	Efficacy criteria	Results
Halliday et al., 1961 (27)	12 PD patients	**Open-label**	Administration of 30 to 100 mg/day	Motor scores (UPDRS III rigidity, bradykinesia)	**Improvement in motor signs**
Cantello et al., 1988 (69)	8 PD patients with pain and paresthesia that were refractory to analgesic treatment	**Randomized, double-blind, placebo-controlled**	2 assessments with 2 acute intravenous administrations of 0.4 mg/kg/day at a 3-day interval	Pain and primary sensory symptoms Cerebrospinal fluid monoamine metabolites: 5-Hydroxyindoleacetic acid	**A short-term analgesic effect**
Cantello et al., 1989 (49)	13 PD patients with severe depression 11 PD patients without mood disorders 14 non-PD controls with severe depression 12 non-PD controls without mood disorders	**Randomized, double-blind, placebo-controlled**	2 assessments with 2 acute intravenous administrations of 0.4 mg/kg/day at a 3-day interval	Depression	**Lack of sensitivity to the euphorizing effects of methylphenidate in depressed PD patients**
Persico et al., 1990 (51)	12 PD patients 12 healthy controls	**Randomized, double-blind, placebo-controlled**	Acute response to placebo versus 15, 20, 25 and 30 mg of oral methylphenidate	Physiological and subjective mood responses	**Drug-induced changes in good affect are attenuated in PD**
Canicioli et al., 2001 (62)	5 PD patients	**Randomized, double-blind, placebo-controlled**	Oral administration of 0.2 mg/kg of methylphenidate or placebo followed 30 minutes later by a 1-hour intravenous infusion of levodopa (2 mg/kg per hour) or placebo	Cognition, attention, mood and anxiety	**Isolated improvement in choice reaction time** No impact on other parameters
Nutt et al., 2003 (19)	17 PD patients	"Triple blind", placebo-controlled trial with two parts: - **PROTOCOL 1**: placebo versus 0.2 to 0.4 mg/kg of methylphenidate in 8 subjects in an "off-drug" condition - **PROTOCOL 2**: levodopa + carbidopa + placebo or 0.5 or 1 mg/kg methylphenidate infusion	**- PROTOCOL 1:** 4 days administration of methylphenidate or placebo between 7 and 10 am and then an oral morning dose of levodopa study of tolerability **-PROTOCOL 2:** levodopa morning doses + methylphenidate or placebo infusions	**Acute evaluations:** Tapping task (alternatively 2 counter keys 20 cm apart for 1 minute with the more affected arm) A 6-meter Stand-Walk-Sit test (walking speed) Tremor score (out of 4) Dyskinesia score (out of 4) Visual analog scales for subjective symptoms: mood, anxiety and energy	**-Methylphenidate alone provided no motor benefits.** **-Potentiation of 10% concerning tapping tasks with 0.4 mg/kg methylphenidate + levodopa** **-20 % increase in gait speed with 1 mg/kg of methylphenidate + levodopa** **-Increase in the duration but not severity of dyskinesia** **Positive effects on mood and fatigue**
Mendonça et al., 2007 (67)	17 PD patients on methylphenidate 19 PD patients on placebo	**Randomized, double-blind, placebo-controlled**	Methylphenidate (30 mg/day) for 3 weeks	Self-questionnaires on fatigue: the Fatigue Severity Scale and the Multidimensional Fatigue Inventory UPDRS III	**Reduction in fatigue** No effect on UPDRS III scores
Devos et al., 2008 (35)	17 patients with subthalamic stimulation	Open-label with **blind, off-line video assessment**	Methylphenidate (1 mg/kg/day) for 3 months	Stand-Walk-Sit test UPDRS III	**Improvement in gait hypokinesia, freezing, motor symptoms and sleepiness**
Pollak et al., 2007 (34)	5 male PD patients	Open-label	Acute assessment with low dose of 10 mg of methylphenidate	Gait and freezing with a figure-of-eight trajectory	**Improvement in walking time and freezing**
Nutt et al., 2007 (66)	- 13 PD patients with motor fluctuations	**Double-blind trial:** 4 days of evaluation in a medical center of methylphenidate 3 times a day (progressive decrease in levodopa to avoid dyskinesia) **2 WEEKS LATER:** same response to 4 days of levodopa + methylphenidate at the same oral doses or placebo	4 days of administration of methylphenidate (0.4 mg/kg) + levodopa in the first part and 4 days of administration of levodopa + methylphenidate or placebo 2 weeks later	-Duration of "on" time between 9am and 8pm: Assessed by an average 10 % increase in tapping speed when comparing on and off conditions A 6-meter Stand-Walk-Sit test (walking speed) Tremor score (out of 4) Dyskinesia score (out of 4) Visual analog scales for subjective symptoms: mood, anxiety and energy	**The effects of 0.4 mg/kg of methylphenidate 3 times per day on the motor response to levodopa were small and variable and judged to be clinically insignificant.**
Auriel et al., 2009 (33)	21 PD patients	**Open-label**	Acute assessment with an oral dose of 20 mg	Attention Gait speed	**Improvements in attention and gait**

					speed
Evans et al., 2009 (52)	15 PD patients	**Randomized, double-blind, placebo-controlled**	2 acute administrations of placebo or methylphenidate at T0 in untreated PD patients and after 18 months of treatment with dopaminergic agents.	Motor (UPDRS III) Mood (analog scale: positive affects) Reward potentiating effects (the CARROT test)	**Methylphenidate was active on mood only when combined with dopaminergic agents. It increased reward responsiveness. Synergistic effect on motor symptoms with dopaminergic agents**
Espay et al., 2011 (36)	PD patients with advanced stage and gait disorders and no subthalamic stimulation (27 screened/17 randomized)	**Randomized, double-blind, placebo-controlled, crossover**	Methylphenidate (1 mg/kg/day) or placebo for 3 months	Gait analysis system (GAITRite®) Self-administered Freezing of Gait Questionnaire and a gait diary	**No changes in the gait composite score. Reduction in depression**
Moreau et al., 2012 (37)	PD patients with subthalamic stimulation (81 screened / 69 randomized)	**Randomized, double-blind, placebo-controlled with two parallel groups**	Methylphenidate (1 mg/kg/day) for 3 months	Number of steps in a Stand-Walk-Sit test in an "off-drug" condition (primary criterion), number of freezing episodes in the FoG trajectory and the UPDRS motor score in "off-" and "on- levodopa conditions, sleepiness (Epworth Sleepiness Scale score) and apathy (Lille Apathy Rating Scale)	**Improvement in gait hypokinesia and reduced freezing of gait Improvement in motor symptoms in the absence of levodopa Reduction in sleepiness. Reduction in apathy in a subgroup of patients.**

Legend: Summary of the main data from trials of methylphenidate in Parkinson's disease.

The studies are arranged in order of year of publication. Abbreviations: PD means Parkinson's disease; UPDRS: Unified Parkinson's Disease Rating Scale; LARS: Lille Apathy Rating Scale; FoG: freezing of gait; ICD: impulse control disorders; MAO: monoamine oxidase

METHYLPHENIDATE: A TREATMENT FOR PARKINSON'S DISEASE?

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Abstract

Parkinson's disease (PD) affects about 1% of the population over the age of 60 and is characterized by a combination of rest tremor, bradykinesia, rigidity, postural instability, stooped posture and freezing of gait (FoG). However, the clinical spectrum also spans a wide range of non-motor symptoms, such as depression, apathy, cognitive disorders, sleepiness, fatigue and pain. Given that the loss of dopamine in the striatum is the primary pathochemical hallmark in PD, pharmacological treatment of the disease has focused on restoring dopaminergic neurotransmission. The currently licensed dopaminergic treatments for PD modulate all the key steps in the dopamine transmission except the most powerful determinant of extracellular dopamine concentrations: the presynaptic dopamine transporter (DaT). Methylphenidate is a central nervous system stimulant that blocks the DaT and the norepinephrine transporter in the striatum and the prefrontal cortex in particular. Here, we report on and discuss the main open-label studies and randomized controlled trials of methylphenidate' effect on severe gait disorders (e.g. the FoG) and non-motor symptoms in advanced PD. Methylphenidate's various pharmacodynamic effects mean that the drug may have significant value in the treatment of PD. However, there is a lack of randomized controlled trials in this field. Furthermore, more rigorous selection of the types and doses of the associated dopaminergic treatments is required because these parameters may profoundly influence methylphenidate's mechanisms of action and the clinical outcomes. Pharmacogenetic tools could be of use in better defining study patients as a function of their dopaminergic metabolism and drug responsiveness.

1. INTRODUCTION

Parkinson's disease (PD) is the second most frequent neurodegenerative disorder worldwide and affects about 1% of the over-60s.[1] The disease is characterized by association of rest tremor, bradykinesia, rigidity, postural instability, stooped posture and FoG. However, the clinical spectrum also spans a wide range of non-motor symptoms, including sleep disorders, autonomic dysfunction, fatigue and cognitive, behavioral and sensory symptoms.[2] The core neuropathological features of PD are the loss of dopaminergic neurons in the substantia nigra and the deposition of iron and cytoplasmic protein aggregates (Lewy bodies) inside neurons.

The available treatments for PD are limited to symptomatic relief. Given that the loss of dopamine in the striatum as a result of progressive neuronal degeneration in the substantia nigra pars compacta is the primary pathochemical hallmark in PD, pharmacological treatment of the disease has been focused on restoring dopaminergic neurotransmission.[3] Since dopamine itself does not cross the digestive mucosa or the blood-brain barrier, the dopamine precursor L-dopamine (levodopa) has been developed for oral administration. Levodopa is now considered to be the "gold standard" treatment for PD; it improves the patient's motor function, activities of daily living and quality of life. However, levodopa also presents several pharmacokinetic drawbacks – notably its short half-life. Hence, the chronic levodopa regimen required for advanced disease is frequently associated with the development of motor fluctuations and dyskinesia. The prevalence of these motor complications ranges from 40% to 50% after 4 to 6 years of treatment.[4,5] Inhibitors of the dopamine metabolizing enzymes catechol-O-methyltransferase (COMT) and monoamine oxidase-B (MAO-B) have been developed in order to prolong the half-life of levodopa in order to limit the motor fluctuations and the wearing off (i.e. end of dose). Dopamine agonists directly stimulate postsynaptic dopamine receptors in the striatum in order to decrease the need of levodopa and to limit the appearance of motor complications.[4,6,7] However, the dopamine agonists' safety profile provides cause for concern, since they may variously induce impulse control disorders (ICDs, i.e. hypersexuality, pathological gambling, compulsive shopping and compulsive eating), confusion, hallucinations, psychosis, excessive daytime sleepiness and sleep attacks.[4,8] Deep brain stimulation of the subthalamic nucleus or (to a lesser extent) the internal globus pallidus is a proven, effective means of controlling levodopa-related motor complications.[9] However, these techniques involve neurosurgery and, in view of their contraindications, are only appropriate for a small proportion of PD patients. Despite the large number of available treatments, it is clear that there are still major unmet needs in the control of PD symptoms.

We therefore hypothesized that clinical benefit in PD could be achieved by (i) further potentiating dopaminergic transmission via a new mechanism and (i) potentiating other neurotransmitters, such as norepinephrine. Indeed, norepinephrine appears to be involved in the physiopathology of PD.[10] Neuronal loss in the locus coeruleus can be as high as 70%, which leads to a dramatic decrease in the norepinephrine content of the brain- second only to the loss of dopamine production.[11] Administration of an alpha-2 adrenergic antagonist decreased motor handicap in the unilateral 6-hydroxydopamine mouse model of PD.[12] The relationship between norepinephrine depletion and the symptoms of PD remains to be determined. However, norepinephrine is thought to be involved in FoG,[13] since the synthetic precursor L-threo-DOPS (droxidopa) has particularly favorable effects.[14,15,16]

Methylphenidate is a central nervous system stimulant that is licensed for the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy in Europe and the USA. Methylphenidate blocks dopamine and norepinephrine reuptake through inhibition of the presynaptic dopamine transporter (DaT) [17,18,19] and norepinephrine transporter (NeT) [17,20,21] - particularly in the striatum and the prefrontal cortex.[22] The drug has little effect on the serotonin transporter. [17] As with other psychostimulants used to treat ADHD, methylphenidate enhances extraneuronal norepinephrine and dopamine concentrations in the rodent brain *in vivo*. This increase in dopamine efflux is not limited to cortical regions and the onset of action is rapid, with no ceiling on the drug's effect.[23] However, methylphenidate differs from other psychostimulants (such as dextroamphetamine) in terms of the mechanism of action. For example, dextroamphetamine's effects are independent of the neuronal firing rate. The latter drug acts by displacing intraneuronal stores of catecholamines, delaying catecholamine reuptake and inhibiting catabolism by MAO. Thus, dextroamphetamine increases the cytoplasmic concentration of catecholamines which become toxic by auto-oxidation. Conversely, methylphenidate does not induce an accumulation of catecholamines in the cytoplasm (i.e. catecholamines remain largely extracellular and in the vesicules).[23] Methylphenidate's effect is nevertheless almost as powerful as that of dextroamphetamine.[23]

The currently licensed dopaminergic treatments for PD modulate all the key steps in the dopamine transmission other than the most powerful determinant of the extracellular dopamine concentration: the DaT, as demonstrated by studies in DaT knockout mice.[24] Hence, methylphenidate has potential value in the treatment of PD. Oral doses (ranging from 0.5 to 0.8 mg/kg) strongly increased the extracellular dopamine concentration in the brain in general and in the striatum in particular.[22] Methylphenidate may also potentiate levodopa's action via NeT inhibition, as suggested by studies of noradrenergic drugs (e.g. alpha-2

adrenergic receptor antagonists).[25] Since noradrenergic neurons are also involved in dopamine release, methylphenidate may restore the dopaminergic/noradrenergic neurotransmitter balance. [21,26]

Methylphenidate was first assessed in a very small cohort of PD patients in 1961. A dose of 0.5 to 1 mg/kg/day was associated with an improvement in voluntary movements and a decrease in rigidity.[27] However, methylphenidate's effects were mostly attributed to its impact on mood (i.e. its euphorizing action), which was associated with increased restless and insomnia in some patients. This might partly explain the lack of further development of methylphenidate in PD. In fact, methylphenidate has always been considered as a treatment for attention disorders, with potentially valuable effects on cognition and behavior but not (at least directly) on motor symptoms. However, methylphenidate has attracted renewed interest because it was suggested that the gait disorders in PD were profoundly influenced by attention disorders.

Here, we report on the main open-label and double-blind studies (Table 1) of methylphenidate's effects on severe gait disorders (i.e. FoG) and non-motor symptoms in advanced PD. In May 2012, we searched PubMed with the terms "methylphenidate" and "Parkinson's disease". For each symptom or group of symptoms, we shall review the various studies' limitations and potential sources of bias. We then suggest further steps for developing the drug's indications in PD.

2. Gait disorders (Table 1)

The beneficial effects of today's dopaminergic treatments on quality of life and personal independence are often countered over the long term by the appearance of gait disorders (including gait hypokinesia and FOG). Gait disturbances and falls are associated with advanced disease and a longer time since disease onset.[28] The gait disturbances are mainly characterized by abnormal stride length regulation (leading to irregular, small steps) and thus a slower walking speed, i.e. gait hypokinesia.[29] In addition, FoG is defined by a brief, episodic absence of (or a marked reduction in) forward progression of the foot, even though the patient wishes to take a step.[30] The disease mechanism underlying for FoG is not fully understood but is clearly multifactorial. It involves the fundamental control of step scaling and timing (including gait variability), the cognitive and affective state, visual perception disturbances and higher-level motor control.[30] Posture-gait coupling also appears to be abnormal. Clinically, FoG episodes most commonly occur in complex environments that necessitate the integration of many different sensory stimuli. In daily life, FoG particularly

occurs when the patient is starting, turning, walking between obstacles or in confined spaces (e.g. passing a narrow doorway) or upon reaching a destination but can sometimes arise during straight walking in an open space. Turning around appears to be the strongest trigger. The performance of dual tasks and/or the presence of stress may also increase the frequency of occurrence of FoG.[31] Furthermore, FoG episodes tend to be lengthier and more severe once the patient no longer responds to dopaminergic treatment or during an "off-drug" phase. Indeed, gait disorders associated with FoG appear to be mainly related to disease severity and a hypodopaminergic state.[32] Optimization of levodopa treatment is the main therapeutic option under these conditions.[30,32] However, increasing the levodopa dose with a view to controlling gait disorders with FoG may be significantly restricted by (i) the worsening of levodopa-related motor complications, (ii) induction or confusion or sleepiness and (iii) progressive inefficiency as the disease worsens. Patient outcomes may be disappointing, since dopaminergic drugs and deep brain stimulation have a greater effect on limb-related signs than for gait disorders *per se*.[9] There is a need for studies designed to establish whether methylphenidate can improve gait disorders and FoG through the drug's combined action on dopamine and norepinephrine reuptake.

2.1 Open-label studies

An initial, open-label study by Auriel et al. assessed the acute use of methylphenidate (20 mg) in 21 non-demented, non-stimulated PD patients who were free of major postural or gait disorders (Hoehn and Yahr stage II to III) and had stable dopaminergic regimens.[33] The main efficacy criteria for gait hypokinesia were the duration of the timed up-and-go test (TUG: standing up from a chair, walking 3 m, turning round and returning to the seated position), the gait speed, stride time and stride-to-stride variability (assessed by means of foot switches during a two-minute walk). Performance in a tapping task with the dominant hand was also assessed. Evaluations were made under the patients' usual "on-drug" conditions before and then two hours after administration of methylphenidate. The researchers observed significant improvements in all the gait parameters but not in the tapping performance. Methylphenidate was associated with a slightly improvement in attention. These study results agreed with the report by Nutt et al., in which 0.2 or 0.4 mg/kg methylphenidate had no effects on gait or performance of a tapping task when given alone (i.e. after the withdrawal of antiparkinsonian medications).[19]. However, the drug did improve gait when administered two hours after the infusion of levodopa.

A small, open-label study by Pollak et al. [34] examined the effect of low-dose (10 mg)

methylphenidate on FoG in five patients with severe PD (Hoehn &Yahr stage III to IV) during the "off" state. Al the patients were dopa-responsive. All antiparkinsonian medications were withdrawn for at least 12 hours and the patients were evaluated before and then two hours after administration of methylphenidate. Since the study's primary objective was to evaluate methylphenidate's effect on the occurrence of FoG, seated patients were instructed to stand up and walk around two chairs along a figure-of-eight path. The primary efficacy variables were the total walking time, total freezing time and number of FoG episodes. Administration of low-dose methylphenidate was associated with improvements in all these parameters. The study results demonstrated that methylphenidate may improve gait and FoG in advance PD patients, without the need for exogenous levodopa. However, the absence of clinical data on non-axial signs of PD prevents one from drawing conclusions as to a dopaminergic-like action of methylphenidate.

In an open-label study, Devos et al.[35] tested the effect of high-dose (1 mg/kg) methylphenidate on gait disorders, given that low doses of the drug (~0.25 mg/kg) may only occupy half the striatal DaTs in humans.[18] Methylphenidate was administered over a 3-month period to 17 advanced PD patients (mean disease duration: 17 years) undergoing subthalamic nucleus stimulation. Seven of the patients had a clinical diagnosis of dementia. Efficacy was blindly assessed both before and after the course of methylphenidate. The tests were performed following the withdrawal of dopaminergic medications and just after acute administration of the methylphenidate. The primary efficacy parameters were the time to complete the Stand-Walk-Sit (SWS) test (standing up from a chair, walking 7 m, turning around, walk back 7 m and sitting down), the number of steps and the number of FoG episodes. Acute administration of methylphenidate either with levodopa or without levodopa was associated with a lower number of steps and a lower test completion time (relative to the "off-drug, on-stim") condition. The two drugs reduced the parameters to a similar range and had additive effects in this population. Twelve of the 17 patients displayed FoG episodes in either the "off drugs, on-stim") or the "off-stim, on- levodopa" conditions. There was a non-significant trend towards a lower number of FoG episodes in the "on- levodopa, on-methylphenidate" condition. Unlike previous studies, chronic administration of high-dose methylphenidate (in both the presence and absence of dopaminergic medications) indeed had an effect on gait disorders in advanced PD. However, the specific nature of methylphenidate's effects on FoG episodes and other dopasensitive signs in PD remains to be established.

2.2. Randomized controlled trials

Two randomized clinical trials were recently performed.[36,37] The first was a 6-month, double-blind, placebo-controlled, randomized, single-center crossover study in 27 patients. The second was a double-blind, placebo-controlled, randomized, multicenter trial performed in 69 patients. The two studies had similar objectives and are complementary, although methylphenidate's observed effects on gait impairments in PD differed. Espay et al. recruited advanced- stage PD patients with gait impairments (a score of 1 or more for item 29 of UPDRS part III; Hoehn & Yahr stage III). Demented individuals or those undergoing subthalamic stimulation were excluded. The included patients were randomized to 12 weeks of treatment with either placebo or 1 mg/kg methylphenidate. There was a 3-week washout period prior to crossover to the other study medication. Evaluations were made both in the presence and absence of dopaminergic medications. Gait was evaluated using a 144-inch (3.66 m) electronic walkway system. The variables of interests were stride length, gait speed, gait cadence and a composite gait score (including gait speed and stride length). The self-administered Freezing of Gait Questionnaire (FOGQ[38]) and a gait diary were used to evaluate FoG. Relative to placebo, methylphenidate was associated with only a slight improvement in the gait composite score in the "off- levodopa" condition and did not improve the FOGQ score, the freezing diary score or the kinematic variables. The UPDRS motor score was not improved (relative to placebo) by methylphenidate.

In the second study, 69 patients suffering from severe PD (despite the optimization of drug treatments and subthalamic stimulation parameters) and FoG (subscores ≥2 for item 14 of FoGQ, UPDRS part II item 15 for gait in the "on" condition and UPDRS part III item 30 for gait in the "on levodopa" condition) were randomized 1:1 to methylphenidate or placebo for three months. The primary efficacy parameter was the number of steps in the SWS test. Second efficacy parameters included the time to complete SWS test, the number and duration of FoG episodes during the FoG trajectory (which included FoG triggers such as gait initiation and termination, rapid 360° and 540° turns, a narrow passage and dual-tasking,[39]) and questionnaire scores (the FOGQ and a falls diary). All tests were performed following the withdrawal of dopaminergic medications and after the acute administration of levodopa. As in Espay's study, improved gait (the number of steps in the SWS test) was only seen in the "off-dopaminergic drug" condition. However, FoG was less frequent in the methylphenidate group (relative to the placebo group) under both "off-" and "on-dopaminergic drug" conditions. The FOGQ score was lower in the methylphenidate group than in the placebo group. Interestingly, global motor function (the UPDRS III motor score) was slightly greater in the methylphenidate group. The drop-out rate for the study as a whole was low (5.8%).

2.3. Discussion

The disparities between the results obtained respectively by Espay et al. and Moreau et al. may be due to differences in study design (i.e. six months of follow-up in Espay et al.'s study, with the potential for more pronounced progression of axial signs than during the 3-month follow-up period in Moreau et al.)[36,37] , study population (patients undergoing subthalamic nucleus stimulation in Moreau et al.) [37] and the FoG assessment method (questionnaires and an objective assessment in Moreau et al. vs. questionnaires and an electronic walkway (which might not have elicited FoG sufficiently) in Espay et al.).[36] The results can be summarized by saying that administration of methylphenidate in PD was associated with improved gait in the open-label studies and in the second (larger) double-blind, placebo-controlled study.[37] There were fewer motor symptoms in the absence of levodopa and fewer FoG episodes before and after an acute levodopa challenge. This benefit had a positive impact on the activities of daily living and quality of life.[37] Thus, methylphenidate may be a new therapeutic option for alleviating gait disorders with FoG in stimulated PD patients. However, the long-term risk/benefit balance (especially in terms of the worsening of axial signs and the potential cardiovascular risk in the elderly) has not been established. It would be interesting to assess attention and executive functions under standardized off-levodopa and on-levodopa conditions, in order to check for interactions with dopaminergic drugs. This design would perhaps have enabled the identification of improved attentional performance after 90 days of methylphenidate treatment and could have established more direct correlations between attention, executive function and FoG. Lastly, the benefit could be variable from one patient to another regarding notably, the level of associated dopaminergic treatments and some pharmacogenetic factors. Work is needed to establish whether non-stimulated patients (i.e. having higher doses of dopaminergic treatments) or in less advanced stages of PD (i.e. lower doses) might also benefit from methylphenidate treatment. Regarding, the putative pharmacogenetic factors of inter individual variability, the $COMT^{val158met}$ polymorphism appeared to interact with methylphenidate and L-dopa and influenced the number of FoG responders.[37] $COMT^{met/met}$ patients may display greater basal dopaminergic prefrontal activity, which would increase still further with methylphenidate and thus reduce FoG. Conversely, $COMT^{val/val}$ patients with low basal dopaminergic prefrontal activity may require greater dopaminergic stimulation (i.e. methylphenidate and L-dopa) if FoG is to be reduced.[37] The impact of this polymorphism and others should be assessed in a larger population.

3. Non-motor signs (Table 1)

3.1 Depression

Depression is very frequent in PD; 40% of patients show depressive symptoms and 25% have major depression. Indeed, depression often precedes the cardinal motor features of PD and thus is one of the disease's primary symptoms.[40] Moreover, there is no apparent correlation between disease duration and the severity of depression because the latter may sometimes only appear in the later stage of PD.[40,41,42] Many investigators have suspected that depression in PD has a specific etiological mechanism. The condition is often responsive to dopaminergic drugs and is correlated with the degree of anatomic and functional damage to the dopaminergic fibers arising from the ventral-tegmental area (VTA) of the mesencephalon (usually referred as the "mesolimbic dopamine system"). The neuronal circuitries of the noradrenergic and serotoninergic systems and their connections to the prefrontal cortex and the mesolimbic system are also involved.[43,44,45] Serotonin reuptake inhibitors are well tolerated and constitute the gold standard treatment for depression in PD.[46,47] However, in a double-blind, randomized study, it has also been shown that a predominantly noradrenergic/tricyclic antidepressant induced a more intense short-term effect in parkinsonian depression than an serotonin reuptake inhibitor did.[48] By modulating dopamine and norepinephrine reuptake, methylphenidate may have some useful effects on mood in PD.

3.1.1 Double-blind studies of an acute methylphenidate challenge

In the study by Nutt et al., an acute, oral dose of up to 0.4 mg/kg methylphenidate was administrated alone or in combination with a levodopa infusion (0.5 to 1 mg/kg/hour) in eight PD patients. No effects on mood or anxiety were observed, according to self-evaluation on an analog scale ranging from "very depressed" to "very happy").[19] In a double-blind study, Cancello et al. assessed behavioral changes associated with the intravenous injection of methylphenidate or placebo in (i) 13 depressed and 11 non-depressed PD patients, (ii) 14 non-PD sufferers with major depression and (ii) 12 healthy controls. There was at least a three-day interval between slow infusions (0.4 mg/kg over 3 minutes).[49] Changes in psychic status were self-rated on a 0 to 5 scale at the time of methylphenidate injection and 15, 30, 60 and 120 minutes thereafter. The subjects' behavior was also blindly rated by a neurologist. After at least 72 hours of dopaminergic medication, depressed PD patients were less able to distinguish between the active drug and placebo than the non-depressed PD patients and the controls were. Methylphenidate failed to produce any mood change towards a euthymic or

euphoric state; the greater the patients' level of depression, the poorer their response (in terms of mood) to the active drug. In depressed controls, methylphenidate administration was associated with significant relief of depressive symptoms.

In healthy subjects, the intravenous injection of small to medium doses of central sympathomimetics like methylphenidate is followed by a characteristic euphoria syndrome, with a feeling of wellbeing, psychic activation, talkativeness and a general increase in locomotor activity in 50% of the subjects.[50] In PD, methylphenidate appears to have few subjective effects when administered in the absence of levodopa. It has been suggested that a decrease in endogenous dopamine synthesis and release could make PD patients less sensitive to methylphenidate-induced subjective effects.[51] Indeed, the same dose of methylphenidate may have led to a lesser effect in PD patients because their dopamine depletion is greater than in non-PD patients (i.e. PD patients may require higher doses of methylphenidate). Indeed, the more pronounced anhedonia in the depressed parkinsonian group may correlate with degeneration of the VTA/mesolimbic dopaminergic circuitry, which is known to occur in severe PD.[50] Moreover, sustained drug therapy in PD might alter the psychomotor responses to acute challenges with dopaminergic drugs (including methylphenidate and levodopa) and thus cause cross-sensitization.[52] The long-term effects of repeated, pulsatile dopaminergic drug therapy in PD may induce various neural changes, such as dyskinesia, end-dose phenomena, non-motor fluctuations and behavioral abnormalities (stereotypies, ICDs and compulsive self-administration of levodopa, etc.). However, individual patient observations revealed two cases of responsive patients in the depressed PD subgroup, with significant motor and non-motor positive fluctuations 2 hours after intravenous administration and improvements in terms of rigidity, gait, dysarthria and a feeling of wellbeing.[50]

In a double-blind study of 15 medication-naïve patients, Evans et al. assessed mood, psychomotor parameters and the reward potentiating effect of an acute challenge with levodopa plus methylphenidate versus placebo. The test sessions were then repeated in the same patients after a median of 16.7 months of continuous dopaminergic drug therapy.[52] Mood was evaluated on a visual analogue scale every 20 minutes Reward responsiveness was assessed using the Cognitive Arranging Reward Responsivity Objective Test at baseline and then 80 min after methylphenidate administration and 60 min after placebo administration. Under medication-naïve conditions, levodopa improved motor function but not affect. After more than a year of dopaminergic drug treatment, acute methylphenidate improved positive affect (compared with the naïve condition).

3.1.2 Discussion

In terms of design, the above-mentioned studies only assessed acute effects (mainly via self-assessment) and did not use sensitive scales.[53] Additional data are thus required. Pilot studies on the long-term effect of higher doses of methylphenidate on mood would be of value. As a first step, we recommend the use of a double-blind, placebo-controlled, randomized study design and the administration of validated instruments by psychiatrists.

3.2. Apathy

Apathy is characterized by lack of interest, loss of initiative, diminished motivation, effort in performing everyday activities and indifference or flattening of affect. It is frequently considered as a symptom of depression but sometimes occurs in the absence of a mood disorder.[54] Apathy is frequent in PD, with an estimated prevalence of between 13.9% and 60% [55,56], depending on the diagnostic criteria and the inclusion or not of demented and/or depressed patients. In fact, apathy is more frequent in late-stage disease and thus the prevalence has been estimated at 15% in patients with stable disease, 30% in fluctuating patients and 56% in demented patients.[57] Schematically, one can consider at least two different forms of apathy: dopaminergic apathy, with mesolimbic denervation,[58] and a non-levodopa-responsive condition that occurs later in PD and which may be predictive of the occurrence of dementia.[59]. Specific treatments for each of the two types are currently lacking.

3.2.1 Case reports

Chatterjee and Fahn reported the case of a PD patient in whom administration of methylphenidate (5 mg twice per day) sharply reduced severe apathy.[60]

3.2.2 Randomized controlled trials

Moreau et al. reported that chronic administration of high-dose methylphenidate (for 3 months) was associated with a significant reduction in apathy in a subgroup of seven advanced PD patients.[37] Apathy was measured on the validated scale of Lille Apathy Rating Scale (LARS). However, the study was not specifically designed to study apathy; the LARS score was a secondary criterion examined in the few apathetic individuals within a large group of late-stage PD patients with severe gait disorders.

3.2.3 Discussion

There are not enough data for drawing firm conclusions as to the benefit of methylphenidate on parkinsonian apathy - even though this appears plausible. A double-blind, placebo-controlled, randomized clinical trial that uses the LARS to measure dopaminergic apathy is thus required. Indeed, there are no current treatment guidelines for this condition. Given that (i) hyperdopaminergic symptoms (ICDs, etc.) are frequently induced by dopaminergic agonists and (ii), in contrast, hypodopaminergic symptoms (e.g. apathy and depression) are frequently induced by the partial withdrawal dopaminergic treatment associated with the initiation of subthalamic nucleus stimulation, apathy may be relieved by dopaminergic agonists. However, there are serious concerns regarding the induction of ICDs with the latter.[61] Hence, the question of the relative risk of ICD induction by dopaminergic agonists and methylphenidate arises. In the 69 advanced PD patients included in the clinical trial for severe gait disorders, only one reported the enhancement of a pre-existing, hidden, sexual addiction on administration of a dopamine agonist. Furthermore, ICDs did not recur during methylphenidate treatment in the many patients who had experienced an disorder of this type during treatment with dopaminergic agonists earlier in the course of disease.[37]

3.3. Attention

The various studies of methylphenidate and cognitive function have yielded conflicting results. The slight reduction in simple reaction time reported in several open-label studies has not been confirmed by randomized, double-blind studies.

3.3.1 Open-label studies

Auriel et al. studied 21 PD patients before and then two hours after the administration of a single dose of 20 mg of methylphenidate. [33] Attention (measured as a simple reaction time) was significant improved, whereas memory and visuospatial performance were unchanged. Likewise, in another study of 10 non-demented patients (Mattis score ≥ 130), the authors observed that sustained attention was improved by a three-month course of methylphenidate. The mean response time in the simple reaction task significantly decreased and there was no significant change in response accuracy. Performance in the choice reaction task did not change. For the seven demented patients (Mattis score < 130) in this study, sustained attention was not modified by three months of methylphenidate treatment. Moreover, there was a worsening in selective attention, since the mean reaction time on the choice reaction task increased significantly (despite the absence of an effect on accuracy).[35]

3.3.2. Randomized, controlled trials

In a double-blind, randomized, controlled pilot study, Camicioli et al. administered 0.2 mg/kg oral methylphenidate or placebo and (30 minutes later) a one-hour intravenous infusion of levodopa (2 mg/kg per hour) or placebo to five PD patients after withdrawal of antiparkinsonian medications. The researchers observed a lower choice reaction time with methylphenidate (relative to placebo) but failed to see any effects on simple reaction time, attention and executive function (in the Stroop word color test and a digit ordering test).[62]

The absence of an effect on simple reaction time and attention was confirmed by Moreau et al. in a double-blind, placebo-controlled, randomized study of 69 patients.[37]

3.3.3. Discussion

At present, there are data to support a beneficial effect of methylphenidate on attention disorders in PD. Indeed, reaction times have been mainly investigated as a secondary efficacy criterion in small patient populations and/or in non-standardized conditions (i.e. with potentially confounding effects from other dopaminergic drugs, all of which have positive or negative influences on attention and executive performances). We can raise the hypothesis that methylphenidate's effects may differ radically according to the dose of dopaminergic drugs, the patient's cognitive status (at least in demented versus non-demented patients) and the disease stage (i.e. different levels of mesocortical dopaminergic depletion in early-stage versus late-stage disease). Moreover, other pharmacogenetic factors should be also controlled for, such as the COMT val158met status that influences subcorticofrontal cognitive activities.[63]

3.4. Sleepiness

Sleepiness is a disabling symptom that occurs frequently in PD as a result of many different factors: chronic disease, fatigue, drug treatments (e.g. dopamine agonists, levodopa, benzodiazepine, antidepressants, clozapine, quetiapine and cardiovascular agents) and co-morbidities (apnea syndrome and secondary narcolepsy).[64]

3.4.1. Open-label studies

A significant reduction in the Epworth sleepiness scale (ESS) score was noted in 17 PD patients taking 1 mg/kg/day of methylphenidate for 3 months, although there were no sleep attacks.[35]

3.4.2. Randomized, controlled trials

In a recent double-blind study, we observed a three-point decrease in the ESS score (as a secondary criterion) in a group of 35 advanced PD patients after 3 months of high-dose (1 mg/kg/day), when compared with 34 patients on placebo.[37]

3.4.3. Discussion

In view of the lack of validated treatments for sleepiness in PD, the above results could be of great value for the patient. Indeed, modafinil is the sole treatment considered to be probably efficacious in this respect by the Movement Disorder Society, although proof from a randomized, controlled trial is lacking.[64] Hence, there is a need for a randomized, controlled study that considers sleepiness as its primary efficacy criterion. The doses and types of dopaminergic drugs must also be rigorously controlled for. Indeed, adjunction of methylphenidate in patients already taking high doses of dopaminergic agonists may only be effective if the dopaminergic regimen has already been optimized.

3.5. Fatigue

Fatigue is a common non-motor symptom in PD and can have prominent effects on everyday function in between 36% and 56% of patients.[65] Central fatigue is defined as a failure to initiate or sustain tasks that require either mental or physical effort.

3.5.1. Open-label studies

In 2007, Nutt et al. evaluated methylphenidate in 13 fluctuating PD patients in term of the primary motor outcome and a fatigue questionnaire score.[66] Patients took 0.4 mg/kg/day methylphenidate in three doses (morning, noon and 4pm) and levodopa doses were reduced in parallel (to avoid motor fluctuations). Despite a good motor outcome, the effect on fatigue failed to achieve statistical significance; this may have been due to the small sample size, the presence of motor fluctuations and/or the reduction in the levodopa daily dose.

3.5.2. Randomized, controlled trials

Mendonça et al. selected PD patients reporting significant fatigue (despite the treatment optimization of standard anti parkinsonian drug treatments) [67] and randomized them to receive a six week course of either methylphenidate (30 mg per day, n=17) or placebo (n=19). The primary efficacy criterion was the change from baseline in the scores for two separate, self-reported fatigue questionnaires: the Fatigue Severity Scale (FSS) and the

Multidimensional Fatigue Inventory (MFI). Secondary outcomes included the UPDRS motor scores. Fourteen patients in the methylphenidate group and 16 in the placebo group completed the study. In the treatment arm, the mean post-treatment FSS score was 6.5 points lower than the baseline score (43.8) and the mean FSI was 8.4 points lower than the mean baseline score (51). These changes were statistically significant. Reduction in the scores in the placebo was smaller and non-significant. Adverse events were observed more frequently in the placebo group.

3.5.3. Discussion

Apathy is a possible confounding factor for fatigue in PD but was not systematically analyzed in the aforementioned studies. Moreover, depressive symptoms, sleepiness and attention disorders can overlap. Future studies will thus have to control for all these parameters and target one for correct assessment. In an evidence-based review of the efficacy of treatments for the non-motor symptoms of PD, the Movement Disorder Society task force considered that methylphenidate is likely to be effective for fatigue, although there was not enough evidence to recommend treatment with the drug for that purpose.[64]

3.6. Pain

Different types of pain (with differing pathophysiological mechanisms) occur in PD. Setting aside rheumatologic pain (which partly responds to non-steroidal anti inflammatory), two types of neurologic pain have been described: nociceptive pain and neuropathic pain.[68] These symptoms have barely been studied and there are no treatment guidelines other than increasing the dose of dopaminergic medications.

3.6.1. A double-blind study of acute methylphenidate challenge

Intravenous administration of methylphenidate hydrochloride exerted an analgesic effect on primary sensory symptoms in a group of PD patients. [69] In view of methylphenidate's mechanism of action on the central nervous system, the observed adrenergic and serotoninergic mediation of its analgesic effect and the demonstration of impaired central serotonin metabolism in the patient group, one can now conclude that altered noradrenergic and serotoninergic transmission in the spinal cord and central dopaminergic deficiency have a role in the pathophysiology of pain in PD.

3.6.2. Discussion

Methylphenidate may possess analgesic properties that deserve to be investigated in a randomized, controlled clinical trial. Better characterization of the different types of pain encountered in PD will nevertheless be necessary, since they may not all respond in the same way to a given treatment strategy.

4. Safety

Methylphenidate-associated adverse events have been widely described in children (and, to a lesser extent, adults) suffering from ADHD.[70,71] The most frequently reported events are gastrointestinal pain, headache and decreased appetite. Conversely, the data on PD patients have come from a very small number of clinical trials with small sample sizes (other than the latest randomized, controlled trial, which concerned 69 patients).[37] However, the adverse events in the PD population appeared to be similar to those reported in ADHD, with nausea, vomiting, gastritis, decreased appetite and headache. Insomnia was only reported in one patient, although the last dose was taken before 4 pm. The erectile dysfunction reported in previous ADHD trials was also noted in a PD population with dysautonomia and sexual disorders.[37] Overall safety was good, with generally mild, transient events and very few serious adverse events in both patient populations.[37,70] This may have been partly due to compliance with the contraindications listed in the summary of product characteristics for methylphenidate, which are mainly psychiatric, cardiac and (to a lesser extent) neurological (Tourette's syndrome) and endocrinological (hyperthyroidism) phenomena.[71] According to the guidelines issued by the United Kingdom's National Institute for Health and Clinical Excellence, Tourette's syndrome may not be a true contraindication.[72,73]

It has been reported that confusion and hallucinations may arise in at-risk populations with schizophrenia and/or psychotic symptoms.[70,71] PD patients having previously suffered from hallucinations (whether related or not to dopaminergic agonists or parkinsonian psychosis) may therefore represent an at risk population for methylphenidate. Another high psychiatric risk corresponds to mood modulation in patients having already shown suicidal tendencies, severe depression and (in particular) mania/bipolar disorder.[70,71] Indeed, a mild, transient episode of hypomania was observed in a woman suffering from bipolar disorder and PD. The event resolved after a dose reduction.[37] Anorexia nervosa represents also a contraindication. In PD, decreased appetite and a mean weight loss of 2.2 kg over a 3 months period has also been described, with stabilization during a subsequent open-label extension phase.[37] Severe cases of anxiety reportedly worsen during methylphenidate treatment and thus at least require monitoring. In a double-blind trial, none of the 69 PD patients with anxiety reported a

worsening of their condition. However, some adverse events (such as chest pain) may in fact be related to anxiety [37] and require further investigation. Addiction also represents a primary, archetypal psychiatric contraindication mentioned in the summary of product characteristics. As discussed above, only one PD patient reported the enhancement of a pre-existing, hidden, sexual addiction following administration of a dopamine agonist. Furthermore, ICDs did not recur during methylphenidate treatment in the many patients who had experienced an disorder of this type during treatment with dopaminergic agonists earlier in the course of disease.[37] Hence, methylphenidate has to be strongly contraindicated in PD patients with an addiction in progress. Combination treatment with a dopamine agonist may need to be also avoided for the same reason. The hypothesis whereby ICDs are less induced by methylphenidate than by dopamine agonists merits investigation.

Lastly, cardiovascular adverse events may be serious if the drug's contraindications are not rigorously observed - especially in view of the advanced age of the PD population. In ADHD, methylphenidate is contraindicated in cases of severe cardiovascular or cerebrovascular disorders likely to progress as a result of clinically significant increases in blood pressure or heart rate. Six-monthly check-ups with a cardiologist are recommended for non-severe cardiac disorders.[71] In patients with ADHD, heart rate and blood pressure should be monitored and recorded on a centile chart (i) before and after each dose change and (ii) every three months (according to the NICE guidelines)[72] or every 6 months (according to methylphenidate's summary of product characteristics).[71] In the largest clinical trial to date, only mild, transient cardiovascular adverse events were reported; this included one case of ventricular extrasystole and two cases of isolated chest pain.[37] The mean heart rate increased significantly (by three beats per minute) but the blood pressure did not change significantly in a population with prevalent hypotension and hypervariability related to dysautonomia. Hence, in PD, we strongly recommended a careful, comprehensive cardiovascular examination prior to initiation of methylphenidate, in order to identify patients with past or present cardiovascular and ischemic disease. Patient should then be closely monitored, with an electrocardiogram and blood pressure measurement at least every three months.

Most of the descriptions of the adverse events of methylphenidate come from short-duration clinical trials. Since methylphenidate is prescribed as a long-term treatment, there is a need for long-term safety studies. Lastly, there is a need to study the interaction between methylphenidate and MAO-B inhibitors. Although this dual inhibition (i.e. MAO-B inhibition and DaT inhibition) could be of high interest in PD for greater dopaminergic potentiation, the safety profile of this combination has not been evaluated and remains contraindicated.

5. Conclusion

The long-term experience with methylphenidate (a well-characterized drug with a relatively good risk/benefit balance, as long as the contraindications are rigorously observed) suggests that it should be clinically tested for the relief of the various symptomatic disorders in PD. This type of clinical investigation would cost less than the development of novel chemical entities. There is a need for randomized, controlled trials in these possible new indications. The many on-going studies seeking to characterize non-motor symptoms will help to define the best efficacy end points for future trials. Moreover, dopaminergic medications will have to be rigorously controlled in these studies, since the results may be radically different in patients taking low vs. high concomitant doses of levodopa and/or dopaminergic agonists. The recent development of pharmacogenetic tools could also be of use in better defining patient subgroups (either as an inclusion criterion or to analyze the best responders). However, the long-term risk/benefit balance - especially in terms of (i) the maintenance of benefits and (ii) the potential cardiovascular risk (transient ischemic attacks and sudden death/ventricular arrhythmia) in the elderly has yet to be established.

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AUTHORS CONTRIBUTION

1) The research project: a: conception; b: organization; c: execution
2) The manuscript: a: writing of the first draft, b: review and critical comment
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Table 1

(References)	Number of patients	Study design	Methylphenidate	Efficacy criteria	Results
Halliday et al., 1961 (27)	12 PD patients	**Open-label**	Administration of 30 to 100 mg/day	Motor scores (UPDRS III rigidity, bradykinesia)	**Improvement in motor signs**
Cantello et al., 1988 (69)	8 PD patients with pain and paresthesia that were refractory to analgesic treatment	**Randomized, double-blind, placebo-controlled**	2 assessments with 2 acute intravenous administrations of 0.4 mg/kg/day at a 3-day interval	Pain and primary sensory symptoms Cerebrospinal fluid monoamine metabolites: 5-Hydroxyindoleacetic acid	**A short-term analgesic effect**
Cantello et al., 1989 (49)	13 PD patients with severe depression 11 PD patients without mood disorders 14 non-PD controls with severe depression 12 non-PD controls without mood disorders	**Randomized, double-blind, placebo-controlled**	2 assessments with 2 acute intravenous administrations of 0.4 mg/kg/day at a 3-day interval	Depression	**Lack of sensitivity to the euphorizing effects of methylphenidate in depressed PD patients**
Persico et al., 1998 (51)	12 PD patients 12 healthy controls	**Randomized, double-blind, placebo-controlled**	Acute response to placebo versus 15, 20, 25 and 30 mg of oral methylphenidate	Physiological and subjective mood responses	**Drug-induced changes in good affect are attenuated in PD**
Camicioli et al., 2001 (62)	5 PD patients	**Randomized, double-blind, placebo-controlled**	Oral administration of 0.2 mg/kg of methylphenidate or placebo followed 30 minutes later by a 1-hour intravenous infusion of levodopa (2 mg/kg per hour) or placebo	Cognition, attention, mood and anxiety	**Isolated improvement in choice reaction time** No impact on other parameters
Nutt et al., 2004 (19)	17 PD patients	"Triple blind", placebo-controlled trial with two parts: - **PROTOCOL 1**: placebo versus 0.2 to 0.4 mg/kg of methylphenidate in 8 subjects in an "off-drug" condition - **PROTOCOL 2**: levodopa + carbidopa + placebo or 0.5 or 1 mg/kg methylphenidate infusion	**- PROTOCOL 1:** 4 days administration of methylphenidate or placebo between 7 and 10 am and then an oral morning dose of levodopa study of tolerability **-PROTOCOL 2:** levodopa morning doses + methylphenidate or placebo infusions	**Acute evaluations:** Tapping task (alternatively 2 counter keys 20 cm apart for 1 minute with the more affected arm) A 6-meter Stand-Walk-Sit test (walking speed) Tremor score (out of 4) Dyskinesia score (out of 4) Visual analog scales for subjective symptoms: mood, anxiety and energy	**-Methylphenidate alone provided no motor benefits.** **-Potentiation of 10% concerning tapping tasks with 0.4 mg/kg methylphenidate + levodopa** **-20 % increase in gait speed with 1 mg/kg of methylphenidate + levodopa** **-Increase in the duration but not severity of dyskinesia** **Positive effects on mood and fatigue**
Mendonça et al., 2007 (67)	17 PD patients on methylphenidate 19 PD patients on placebo	**Randomized, double-blind, placebo-controlled**	Methylphenidate (30 mg/day) for 3 weeks	Self-questionnaires on fatigue: the Fatigue Severity Scale and the Multidimensional Fatigue Inventory UPDRS III	**Reduction in fatigue** No effect on UPDRS III scores
Devos et al., 2007 (35)	17 patients with subthalamic stimulation	Open-label with **blind, off-line video assessment**	Methylphenidate (1 mg/kg/day) for 3 months	Stand-Walk-Sit test UPDRS III	**Improvement in gait hypokinesia, freezing, motor symptoms and sleepiness**
Pollak et al., 2007 (34)	5 male PD patients	Open-label	Acute assessment with low dose of 10 mg of methylphenidate	Gait and freezing with a figure-of-eight trajectory	**Improvement in walking time and freezing**
Nutt et al., 2007 (66)	- 13 PD patients with motor fluctuations	**Double-blind trial:** 4 days of evaluation in a medical center of methylphenidate 3 times a day (progressive decrease in levodopa to avoid dyskinesia) **2 WEEKS LATER:** same response to 4 days of levodopa + methylphenidate at the same oral doses or placebo	4 days of administration of methylphenidate (0.4 mg/kg) + levodopa in the first part and 4 days of administration of levodopa + methylphenidate or placebo 2 weeks later	-Duration of "on" time between 9am and 8pm: Assessed by an average 10 % increase in tapping speed when comparing on and off conditions A 6-meter Stand-Walk-Sit test (walking speed) Tremor score (out of 4) Dyskinesia score (out of 4) Visual analog scales for subjective symptoms: mood, anxiety and energy	**The effects of 0.4 mg/kg of methylphenidate 3 times per day on the motor response to levodopa were small and variable and judged to be clinically insignificant.**
Auriel et al., 2009 (33)	21 PD patients	**Open-label**	Acute assessment with an oral dose of 20 mg	Attention Gait speed	**Improvements in attention and gait**

					speed
Evans et al., 2009 (52)	15 PD patients	**Randomized, double-blind, placebo-controlled**	2 acute administrations of placebo or methylphenidate at T0 in untreated PD patients and after 18 months of treatment with dopaminergic agents.	Motor (UPDRS III) Mood (analog scale: positive affects) Reward potentiating effects (the CARROT test)	**Methylphenidate was active on mood only when combined with dopaminergic agents. It increased reward responsiveness. Synergistic effect on motor symptoms with dopaminergic agents**
Espay et al., 2011 (36)	PD patients with advanced stage and gait disorders and no subthalamic stimulation (27 screened/17 randomized)	**Randomized, double-blind, placebo-controlled, crossover**	Methylphenidate (1 mg/kg/day) or placebo for 3 months	Gait analysis system (GAITRite®) Self-administered Freezing of Gait Questionnaire and a gait diary	**No changes in the gait composite score. Reduction in depression**
Moreau et al., 2012 (37)	PD patients with subthalamic stimulation (81 screened / 69 randomized)	**Randomized, double-blind, placebo-controlled with two parallel groups**	Methylphenidate (1 mg/kg/day) for 3 months	Number of steps in a Stand-Walk-Sit test in an "off-drug" condition (primary criterion), number of freezing episodes in the FoG trajectory and the UPDRS motor score in "off-" and "on- levodopa conditions, sleepiness (Epworth Sleepiness Scale score) and apathy (Lille Apathy Rating Scale)	**Improvement in gait hypokinesia and reduced freezing of gait Improvement in motor symptoms in the absence of levodopa Reduction in sleepiness. Reduction in apathy in a subgroup of patients.**

Legend: Summary of the main data from trials of methylphenidate in Parkinson's disease.

The studies are arranged in order of year of publication. Abbreviations: PD means Parkinson's disease; UPDRS: Unified Parkinson's Disease Rating Scale; LARS: Lille Apathy Rating Scale; FoG: freezing of gait; ICD: impulse control disorders; MAO: monoamine oxidase