

## Pergolide mesylate can improve sexual dysfunction in patients with Parkinson's disease: the results of an open, prospective, 6-month follow-up

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### Keywords:

Parkinson's disease, sexual dysfunction, pergolide

Received 28 July 2003

Accepted 26 December 2003

One of the most disabling problems in males suffering from advanced Parkinson's disease (PD) is complex sexual dysfunction. The effect of dopamine replacement or dopaminergic stimulation on sexual dysfunction has been recently examined and described in patients treated by L-DOPA or apomorphine. Pergolide mesylate is another dopamine agonist with a known high affinity to hD(2S) subtype and a lower affinity to hD(2L) subtype of D2 dopaminergic receptors. It has been repeatedly shown to be a highly effective treatment of the complicated and advanced stages of PD. The current study has been designed to assess its efficacy in the treatment of sexual dysfunction, which frequently accompanies the complicated stage of PD in males. Fourteen male patients suffering from PD, each of whom had been treated with L-DOPA, and in whom additional treatment with peroral dopaminergic agonist (DA) was needed, were followed for a 6-month period. Pergolide mesylate (Permax) was given to each patient, and titrated to a total daily dose of 3 mg. All of the patients were taking L-DOPA. The assessments performed before the start of pergolide treatment consisted of a neurological examination, including Unified Parkinson's Disease Rating Scale (UPDRS) III and IV subscales scoring, Mini Mental State Examination (MMSE) scoring, the neuropsychological examination including Zung scale scoring to exclude depression, biochemical and haematological examinations including the examination of prolactin serum levels; and a sexological examination during which the patients filled-in the International Index of Erectile Function (IIEF) questionnaire. These examinations were repeated during the control assessments at months 1, 3 and 6. To compare the examination results, ANOVA, Friedmann's ANOVA (non-parametric) and Tukey *post hoc* tests were used. There were statistically significant differences between the values of UPDRS III motor subscale, UPDRS IV (complications of therapy) subscale and all subscales of IIEF when months 0 and 1 were compared with the results obtained at months 3 and 6. The differences between months 0 and 1 and months 3 and 6 (in these items) were virtually insignificant. In conclusion, pergolide substantially improved sexual function in the younger male patients who were still interested in sexual activities. In such cases, the introduction of pergolide might be a better choice than treatment with sildenafil, which usually meets several contraindications in common PD male population.

### Introduction

Pergolide mesylate is an ergolinic dopamine agonist with a known high affinity (100% when compared with natural dopamine) to hD(2S) subtype, and a lower affinity (80%) to hD(2L) subtype of D2 dopaminergic receptors (Millan *et al.*, 2002; Newman-Tancredi *et al.*,

2002). It has been repeatedly shown to be a highly effective and relatively safe treatment of the complicated and advanced stages of Parkinson's disease (PD) (Olanow and Alberts, 1987). Recently, its efficacy and tolerability have also been proven when it is used as a monotherapy in the early stage of the disease (Hundemer *et al.*, 2000; Nausieda *et al.*, 2002). Its pharmacological profile, more than 8-hour duration of action on dopamine receptors, and general tolerability create pergolide's most important advantages (Bareš *et al.*, 2001; Thalamas *et al.*, 2002).

One of the most disabling problems in males suffering from advanced PD is complex sexual dysfunction

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(Melis and Argiolas, 1995). The effect of dopamine replacement or dopaminergic stimulation on sexual dysfunction has been examined and described in patients treated by L-DOPA (Uitti *et al.*, 1989; Cummings, 1991; Rosen and Ashton, 1993; Weinman and Ruskin, 1995; Jimenez-Jimenez and Tallon-Barranco, 1999) and apomorphine (O'Sullivan and Hughes, 1998). Sildenafil, phosphodiesterase (PDE-5) – five selective inhibitor, probably the most commonly used drug for the treatment of erectile dysfunction, can meet several contraindications in common PD population, i.e. the hypertension or coronary heart disease with angina pectoris (Lim *et al.*, 2002).

In the 1990s, a study was published that focused on the sexual functions (or rather dysfunctions) of young patients suffering from PD, both male and female (Wermuth and Stenager, 1995). The method (already validated) of a structured interview and structured questionnaire was used. There were 15 males and 10 females examined, all over 36-years old. The most important finding was that the females were significantly more affected: a decrease of libidinous functions was reported by 40% of male patients, but, interestingly, by 70% of female patients. Similarly, a significant reduction of common daily sexual activities was reported by 30% of male patients, but these activities were reported to be significantly reduced by more than 80% of female patients.

Another important study also reviewed sexual dysfunction in PD, although the role of dopaminergic medication was only briefly mentioned (Lambert and Waters, 1998). Several years later, a psychosocial study was published that dealt with the impact of PD on all aspects of the daily activities (including sexual activity) of young women affected by the disease (Posen *et al.*, 2000). Probably the deepest insight into sexual dysfunction in PD patients was brought by a study published last year, in which sexual life quality was assessed in more than 90 patients (Moore *et al.*, 2002). For the evaluation of sexual functions, the structured Quality of Sexual Life Questionnaire (QoSL-Q) was used. The quality of life was assessed using the Parkinson's Disease Quality of Life (PDQ-39) questionnaire. The quality of the sexual life, as assessed by the QoSL-Q, was significantly decreased in all patients. It significantly worsened with the disease progression and with aging. However, no correlation between the results revealed using the PDQ-39 and those revealed by QoSL-Q has been found. The authors recommended implementing the QoSL-Q into the common QOL test battery, because PDQ-39 does not sufficiently address this aspect.

When these findings were published, we had observed the phenomenon of sexual dysfunction and its dimin-

ishment following dopaminergic treatment in seven of 32 patients treated with dopaminergic agonist pergolide (Kaňovský *et al.*, 2002). This observation kindled a greater interest in this phenomenon, and we prepared an open, prospective study. To assess male sexual functions, we decided to use the validated questionnaire 'International Index of Erectile Function' (IIEF), which is also available in national language, and which is, in our opinion, better and less biased than the QoSL-Q (Rosen *et al.*, 1997, 1999, 2002; Lukacs, 2001).

## Patients and methods

All of the patients were well acquainted with the study, and they all gave their informed consent. The study protocol was approved by the institute's ethical committee.

Fourteen male patients participated in the study. All of the patients suffered from PD, and were diagnosed on the basis of the UK–Parkinson's Disease Brain Bank criteria (Hughes *et al.*, 1992); another inclusion criteria were the normal cognition, assessed by neuropsychological examination, existing sexual relationship, current treatment with L-DOPA (Isicom®, Desitin Arzneimittel, Hamburg, Germany; Nalcoh®, CEK Pharma, Ljubljana, Slovenia), and the intent to treat the patients with dopaminergic agonist.

The mean age of patients was 58.2 (SD = 9.9) years; the mean age at the disease onset was 50.8 years (SD = 10.1); the mean duration of disease was 7.3 years (SD = 3.6). All of the patients were treated with L-DOPA; the mean duration of L-DOPA treatment was 5.9 years (SD = 2.7), and the mean daily dose of L-DOPA was 783.6 mg (SD = 412.7).

All of the patients were in the advanced, fluctuating stage of disease, and all of them experienced frequent daily 'on-off' fluctuations with dyskinesias or 'wearing-off' of the L-DOPA dose. The mean duration of this advanced, complicated stage of disease (measured from the first occurrence of the mentioned symptoms) was 2.9 years (SD = 1.7). This situation led to the introduction of pergolide mesylate to the treatment.

Prior to the start of pergolide treatment (month 0), the following examinations were performed: clinical neurological examination, magnetic resonance imaging (MRI) examination of the brain, biochemical and haematological examinations, plasma prolactin level, neuropsychological examination and Zung scale scoring (to exclude dementia, depression, or significant cognitive decline), Mini Mental State Examination (MMSE), Unified Parkinson's Disease Rating Scale (UPDRS) III and UPDRS IV scoring, and all subscales of the International Index of Erectile Function questionnaire (IIEF). The IIEF subscales and their point

ranges are presented in Appendix. The side effects of treatment were also recorded using a checklist.

Pergolide mesylate (Permax®, Eli Lilly, Basingstoke, UK) was added to the stable L-DOPA dose and was titrated in all patients to a total daily dose of 3 mg. The titration lasted (according to the classical schema) 28 days. The control visits were carried out at month 1 (at the end of titration period), at month 3 (titration period + 2 months) and at month 6 (titration period + 5 months). The examinations performed at month 0 were repeated at each control visit, except the brain MR. The examination of the prolactine plasma levels were done only at months 3 and 6. Treatment continued after the month 6 visit. The study protocol decreed that in case of side-effects, the withdrawal of pergolide was possible at any moment during the follow-up.

The mean values of the items being tracked were calculated at each follow-up visit. ANOVA, non-parametric Friedman's ANOVA, and *post hoc* Tukey tests were used for the statistical analysis of the results.

## Results

The results are presented in Table 1 and Figs 1–5.

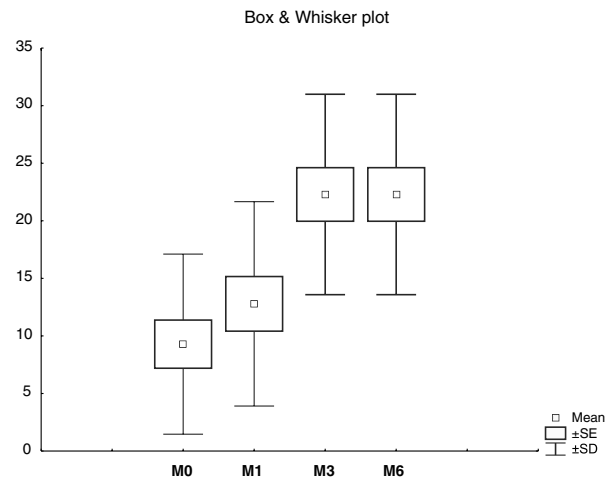
There were no biochemical or haematological value abnormalities present in any patient during the study. The prolactine plasma level varied in all patients

**Table 1** The mean values of UPDRS III and IV, L-DOPA daily dose, MMSE, Zung scale, prolactine level, and IIEF subscores at months 0, 1, 3, and 6

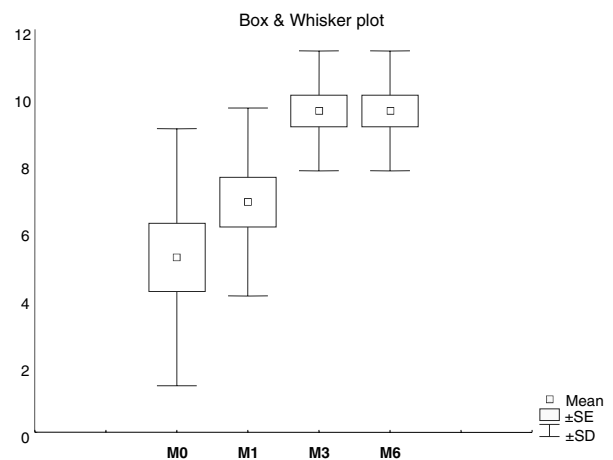
Item	Month 0	Month 1	Month 3	Month 6
UPDRS III	35.7	21.9	17.1*	18.6
UPDRS IV	9.8	7.2	5.6	5.0
L-DOPA Dose	783.6	783.6	617.9	648.2
MMSE	29.5	29.5	29.5	29.5
Zung	32.6	32.6	28.1	29.4
Prolactine	3.9	–	<0.5	<0.5
IIEF 1	9.3	12.8	22.3*	22.3
IIEF 2	5.2	6.9	9.6*	9.6
IIEF 3	4.6	5.1	7.6*	7.6
IIEF 4	6.2	7.3	10.6*	10.6
IIEF 5	5.2	5.6	8.3*	8.3

\*The values, which are significantly different at the level  $P < 0.00000$ , when months 0 and 3 are compared.

UPDRS III, Unified Parkinson's Disease Rating Scale – Motor Subscore (III); UPDRS IV, Unified Parkinson's Disease Rating Scale – Complications Subscore (IV); L-DOPA Dose, daily dose of L-DOPA preparation (Sinemet®, Madopar®, Isicom®, or Nakom®) expressed in milligrams of L-DOPA only (without dopa-decarboxylase inhibitor); MMSE, Mini Mental State Examination (according to Folstein *et al.*); Zung, Zung depression scale; Prolactine, prolactine levels in ng/ml in the blood plasma; IIEF, International Index of Erectile Function.



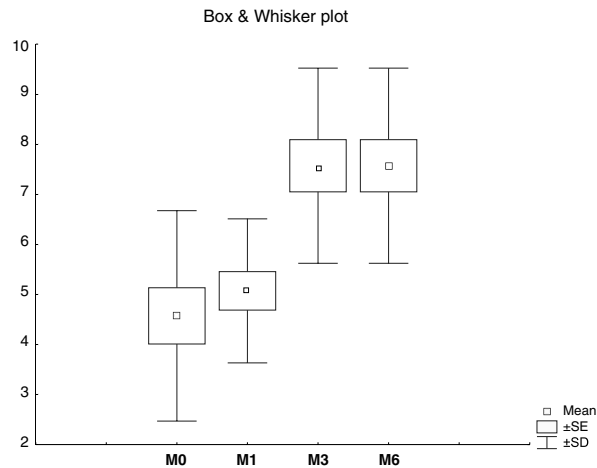
**Figure 1** The figure illustrating the changes in the mean value of IIEF subscale 'erectile function'. SE, standard estimation; SD, standard deviation; M, months.



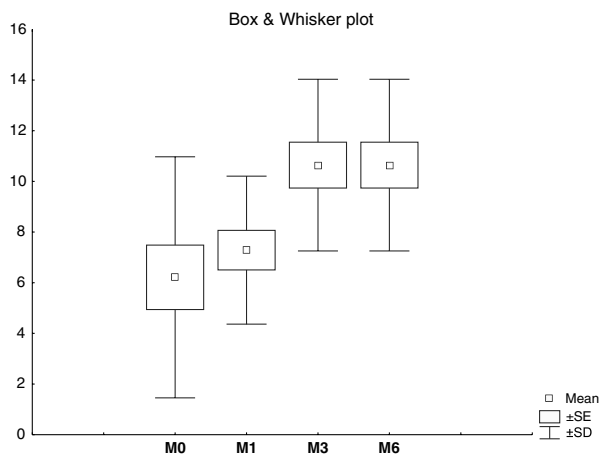
**Figure 2** The figure illustrating the changes in the mean value of IIEF subscale 'orgasmic function'. SE, standard estimation; SD, standard deviation; M, months.

between 0.9 and 7.1 ng/ml (mean 3.9, SD = 3.3) prior to pergolide treatment. There was a decrease of mean prolactine levels when the values between months 0, 3 and 6 were compared. There was no possibility of establishing statistical significance, because the prolactine levels at months 3 and 6 reached <0.5 ng/l (under which the laboratory methods are not able to differentiate); thus, the plasma level of prolactine was practically unmeasurable.

The UPDRS III score (measured when the patients were 'ON') at month 0 was 35.7 points, and there was a statistically significant ( $P < 0.001$ ) difference when it was compared with the value at month 1. Nevertheless, the level of statistical significance was  $P < 0.00000$

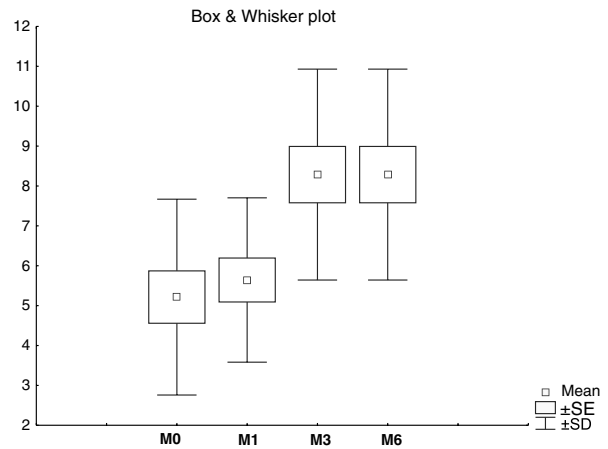


**Figure 3** The figure illustrating the changes in the mean value of IIEF subscale 'sexual appetite'. SE, standard estimation; SD, standard deviation; M, months.



**Figure 4** The figure illustrating the changes in the mean value of IIEF subscale 'satisfaction with sexual intercourse'. SE, standard estimation; SD, standard deviation; M, months.

when the values at month 3 and 6 were compared with the value at month 0 (measured also when the patients were 'ON'). The UPDRS IV subscore, measuring mainly the presence and duration of dyskinesias and 'OFF' periods was improved at months 3 and 6; the difference was statistically significant only when the mean value at month 0 was compared with values at months 3 and 6. There was a slight tendency to decrease the daily L-DOPA intake in all patients; however, the differences of mean L-DOPA daily doses were not significant when the values at months 0, 1, 3, and 6 were compared. The mean value of the MMSE score remained stable. The mean values of the Zung score remained practically identical as before treatment, showing no tendency to increase or decrease.



**Figure 5** The figure illustrating the changes in the mean value of IIEF subscale 'overall satisfaction with sex life'. SE, standard estimation; SD, standard deviation; M, months.

There were statistically significant changes in the mean values of all subscales of International Index of Erectile Function (the subscales and their point ranges are listed in the Appendix). The differences between the values at month 0 and month 1, and also between the values at month 3 and month 6 were minimal, without statistical significance. In contrast, there were differences at statistical level  $P < 0.00000$  in the mean values of all subscales when comparing month 0 and month 3, and also month 0 and month 6.

The differences between mean IIEF values (and their SD) are illustrated in Figs 1–5.

Practically no adverse or side-effects were reported that might have led to the withdrawal of pergolide. Two patients reported increased daily sleepiness (without sleep attacks) during the first month of the pergolide treatment, which disappeared within following 3 weeks.

## Discussion

The results of our prospective (albeit open) study confirmed our initial observation, that pergolide can impressively improve disturbed sexual functions in men suffering from PD (Kaňovský *et al.*, 2002). From our clinical experience, it seems that action of pergolide in this field is the best of the commonly used peroral dopamine agonists (however, such evidence still cannot be found in any medical database). Why pergolide produces such results is not completely clear. It is probably not due to pergolide-induced suppression of prolactin secretion, because in all of our patients the plasma levels of prolactin prior to pergolide treatment were below the usual mean levels, and at the lower end of the normal laboratory range (2.8–19.2 ng/ml). It is not clear whether this was caused by the disease itself,

or by the previous L-DOPA treatment. Such effect of L-DOPA has been repeatedly described, but its clinical relevance is (at least) doubtful (Franchimont *et al.*, 1976). Nevertheless, the behaviour and the role of prolactin and its plasma levels in males under stressful conditions (which chronic disease undoubtedly is) has only rarely been studied (Sivik *et al.*, 1997), and deserves deeper physiological research in the future.

From the neuropharmacological point of view, the more probable hypothesis is that pergolide acts well in sexual dysfunction because of its unique action on specific subtypes of dopaminergic receptors. It has been already speculated by other authors that dopamine agonists act in male sexual dysfunction by the direct stimulation of dopaminergic receptors in the paraventricular nucleus in the hypothalamus (Fine and Lang, 1999). Being aware of the specific action of pergolide on the subtypes of dopaminergic receptors mentioned in the Introduction (Millan *et al.*, 2002; Newman-Tancredi *et al.*, 2002), it should be possible that a specific subtype of D-2 dopamine receptor exists also in the human paraventricular nucleus. In such a case, pergolide may have a specific affinity for this receptor, and can thus improve sexual dysfunction in this way better than other peroral and parenteral dopamine agonists. However, to support this hypothesis, we would need, together with animal studies, clinical evidence from a large number of male patients, studied in a double-blind and placebo-controlled trial.

What remains as a proven clinical observation generated by our study is the fact that pergolide improves all of the aspects of complex sexual dysfunction that are usually seen in PD patients. This is the main difference when the effect of currently used drugs (for instance sildenafil or sublingual apomorphine) is compared with the effect of pergolide in male patients (Zesiewicz *et al.*, 2000; Allard and Giuliano, 2001; Raffaele *et al.*, 2002). Therefore, the introduction of pergolide in the situation of dopamine agonist treatment need should be carefully considered, preferably in male patients for whom sexual dysfunction more impressively affects their quality of life, and who (because of that) might be interested in a sexual relationship. In these cases, the introduction of pergolide might be a better choice than the treatment with sildenafil, which usually meets several contraindications in common PD population (Zesiewicz *et al.*, 2000; Raffaele *et al.*, 2002).

## Acknowledgement

This study was supported by Research Project MSMT CR No. 112801.

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## Appendix

The subscales of the International Index of Erectile Function and their point ranges

- IIEF I: erectile function (range 0–30)
- IIEF II: orgasmic function (range 0–10)
- IIEF III: sexual appetite (range 0–10)
- IIEF IV: satisfaction with sexual intercourse (range 0–15)
- IIEF V: overall satisfaction with sex life (range 0–10)