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The long-lasting improvement of sexual dysfunction in patients with advanced, fluctuating Parkinson's disease induced by pergolide: evidence from the results of an open, prospective, one-year trial

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Abstract

Fourteen male patients suffering from Parkinson's disease, each of whom had been treated with L-DOPA, and in whom additional treatment with oral dopamine agonist (DA) was needed, were followed for a period of one year. 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 neurological examination, 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, biochemical and hematological examinations including 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, 6 and 12. ANOVA, non-parametric Friedmann's ANOVA and Tukey post hoc tests were used for the statistical analysis. There were statistically significant differences between the values of UPDRS III motor subscale and all subscales of IIEF when months 0 and 1 were compared with the results obtained at months 3, 6 and 12. Pergolide mesylate, when added to L-DOPA, significantly improved all sexual functions in younger male Parkinsonian patients who were still interested in sexual activities. The treatment with pergolide in these cases might be more beneficial than with short-acting PDE-5 inhibitor sildenafil. Nevertheless, the relationship between pergolide treatment and incidence of restrictive valvular heart disease must be considered.

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1. Introduction

Pergolide mesylate is an ergolinic dopamine agonist with a known high affinity to hD(2S) subtype, and substantially lower affinity to hD(2L) subtype of D2 dopaminergic receptors. These affinities were calculated as 100% for hD(2S) subtype and about 80% for hD(2L) subtype (1, 2). Pergolide has been in the past reported to be effective

and safe treatment in Parkinson's disease (PD) either in the early or advanced stage of disease [3–7].

As it has been repeatedly described in last two decades, the complex sexual dysfunction is one of the most disabling non-motor symptoms in patients suffering from PD [8]. There were several prospective epidemiological studies, which used the method (already validated) of a structured interview and structured questionnaire [9–12]. The quality of sexual functions was significantly decreased in all patients examined in these studies, both males and females. The effect of dopamine replacement or dopaminergic stimulation on this sexual dysfunction in parkinsonian patients has been examined and described in patients treated with L-DOPA [13–17] or apomorphine [18]. Several years later we observed the phenomenon of sexual dysfunction improvement following dopaminergic treatment in 7 of 32

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113 male patients treated with oral dopamine agonist pergolide
 114 [19], and subsequently designed an open, prospective study.
 115 To assess the male sexual functions, we decided to use the
 116 validated questionnaire ‘international index of erectile
 117 function’ (IIEF) in national language [20–23]. Our recent
 118 report showed excellent improvement of complex sexual
 119 dysfunction in all patients during the first 6 months of
 120 treatment [24], comparable to that seen with sildenafil
 121 treatment [25]. In the presented follow-up, we aimed to
 122 assess whether the pergolide-induced improvement can be
 123 sustained, i.e. whether it will continue without necessity to
 124 change the drug dose or dosing regime during the period of
 125 1 year.

128 2. Patients and methods

129
 130 The protocol of the study was approved by the hospital
 131 ethical committee, all participating subjects were
 132 acquainted with the study and protocol and gave their
 133 informed consent.

134 Fourteen males suffering from Parkinson’s disease
 135 participated in the study. Parkinson’s disease was diagnosed
 136 on the basis of UK-Parkinson’s disease brain bank criteria
 137 [26]. Inclusion criteria were the normal cognition, existing
 138 sexual relationship, current treatment with L-DOPA, and
 139 finally, the doctor’s intent to treat the patient with newly
 140 introduced dopamine agonist. All patients were in the
 141 advanced, fluctuating stage of disease, all of them
 142 experienced daily ‘wearing-off’ of the L-DOPA dose and
 143 daily ‘on-off’ fluctuations with dyskinesias.

144 The mean age of patients was 58.2 (SD=9.9) years; the
 145 mean age at the Parkinson’s disease onset was 50.8 (SD=
 146 10.1) years; the mean duration of disease was 7.3 (SD=3.6)
 147 years. The mean duration of complicated disease stage (the
 148 time from the very first occurrence of abovementioned
 149 symptoms) was 2.9 (SD=1.7) years. All patients were
 150 treated with L-DOPA. At the start of follow-up, the mean
 151 duration of L-DOPA treatment was 5.9 (SD=2.7) years,
 152 and the mean daily dose of L-DOPA was 783.6 (SD=
 153 412.7) mg.

154 Prior to the introduction of pergolide (Month 0), these
 155 examinations were done: complete neurological examin-
 156 ation, MRI imaging of the brain, biochemical and
 157 haematological examinations including the plasma prolac-
 158 tine level, neuropsychological examination, mini mental
 159 state examination (MMSE) and Zung scale scoring, UPDRS
 160 III and UPDRS IV scoring, and all subscales of the
 161 international index of erectile function questionnaire-IIEF
 162 (the IIEF subscales and their point ranges are presented in
 163 Appendix 1). Treatment side effects were recorded using a
 164 checklist.

165 Pergolide mesylate (Permax[®]) was added to the stable
 166 L-DOPA dose and was titrated in all patients to a total daily
 167 dose of 3 mg. The titration lasted 28 days. Control visits
 168 were planned at Month 1 (M1, end of titration period),

Month 3 (M3, titration period+2 months) Month 6 (M6, 169
 titration period+5 months) and Month 12 (M12, titration 170
 period+11 months). The examinations done at M0 (except 171
 MR) were repeated at each control visit. Treatment 172
 continued after reaching the M12 visit. The study protocol 173
 decreed that in case of any side effects, the withdrawal of 174
 pergolide was possible during the follow-up period. 175

The mean values of the items being tracked were 176
 calculated at each follow-up visit. ANOVA, non-parametric 177
 Friedmann’s ANOVA, and post hoc Tukey tests were used 178
 for the statistical analysis of the results. 179

182 3. Results

183
 184 The results are presented in Table 1. All patients had 185
 normal brain MRI, and virtually no abnormalities of 186
 biochemical or haematological values were present in any 187
 patient during the whole study period. The prolactine 188
 plasma level prior to pergolide treatment varied between 0.9 189
 and 7.1 ng/ml (mean 3.9, SD=3.3); and there was a steep 190
 decrease of its mean level at M3, M6 and M12. There was 191
 no possibility of neither comparison nor establishing 192
 statistical significance, because the prolactine levels at 193
 M3, M6 and M12 fall to a value $0.5 < \text{ng/l}$. The laboratories 194
 are not able to differentiate these extremely low values; 195
 thus, from the practical point of view, the plasma level of 196
 prolactine was unmeasurable. 197

The UPDRS III score (measured when the patients were 198
 ‘ON’) at M0 was 35.7 points, and there was a statistically 199
 significant difference ($p < 0.001$) when compared with M1. 200
 The significance was $p < 0.00000$ when the M3, M6 and 201
 M12 were compared with M0. The UPDRS IV subscore 202
 (assessing and scoring the presence and duration of 203
 dyskinesias and ‘OFF’ periods) was improved at M3, M6 204
 and M12; the difference was statistically significant when 205
 the M0 mean value was compared with values at M3, M6 206
 and M12. A tendency to decrease the daily L-DOPA intake 207
 was present in all patients; however, the differences of mean 208
 L-DOPA daily doses at M0, M1, M3, M6 and M12 were not 209
 significant. The mean values of MMSE score and Zung 210
 score remained practically unchanged. 211

The statistically significant changes were present when 212
 the mean values of all subscales of international index of 213
 erectile function were compared (the subscales and their 214
 point ranges are listed in the Appendix 1). The differences of 215
 all subscale values between M0 and M1, and also mutually 216
 between M3 and M6 and M12 did not show any statistical 217
 significance. The differences at statistical level $p < 0.00000$ 218
 in the mean values of all IIEF subscales were present when 219
 values at M0 and M3, M0 and M6; and M0 and M12 were 220
 compared. 221

Two patients reported increased daily sleepiness (with- 222
 out sleep attacks) during the first month of the pergolide 223
 treatment. This feature disappeared within several weeks. 224

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, 6 and 12

Item	Month 0	Month 1	Month 3	Month 6	Month 12
UPDRS III	35.7	21.9	17.1 ^a	18.6	20.2 ^a
UPDRS IV	9.8	7.2	5.6	5.0	4.8
L-DOPA Dose	783.6	783.6	617.9	648.2	669.6
MMSE	29.5	29.5	29.5	29.5	29.5
Zung	32.6	32.6	28.1	29.4	29.3
Prolactine	3.9	–	<0.5	<0.5	<0.5
IIEF 1	9.3	12.8	22.3 ^a	22.3	23.9 ^a
IIEF 2	5.2	6.9	9.6 ^a	9.6	10.3 ^a
IIEF 3	4.6	5.1	7.6 ^a	7.6	8.1 ^a
IIEF 4	6.2	7.3	10.6 ^a	10.6	11.3 ^a
IIEF 5	5.2	5.6	8.3 ^a	8.3	8.7 ^a

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.

^a The values, which are significantly different at the level $p < .00000$, when months 0/3 and 0/12 are compared.

Such a side effects, which might lead to the withdrawal of pergolide, were not reported throughout the study.

4. Discussion

The presented results of our 12-months open, prospective study add further evidence to our recently published observations [19,24]. Certainly, we are aware of the limitations of open studies. However, from the view of our experience and results, the impact of pergolide treatment on the disturbed sexual functions in parkinsonian men is extraordinary among currently used dopamine agonists, probably including parenteral apomorphine. We presume that this effect is not caused by the impressive pergolide-induced suppression of prolactine secretion and, consequently, its plasma level. All patients in our study had the plasma levels of prolactine (already prior to pergolide treatment) below the usual mean levels, rather low within the laboratory range (which is, depending on the laboratory, 2.8–19.2 ng/ml). It cannot be answered, whether these low plasma levels are caused by the Parkinson's disease, or whether they are a consequence of the previous L-DOPA treatment. This effect of L-DOPA has been repeatedly reported, although its clinical relevance is still leak [27]. Nevertheless, the role of prolactine plasma levels and its fluctuations in males under chronic stressful conditions has (to our knowledge) been only once studied [28] and deserves deeper research in the future.

In our opinion, it seems to be more probable that pergolide has such a beneficial effect on complex male sexual dysfunction because it has such an unique action on specific subtypes of dopamine receptors. It has been already speculated by other authors that dopamine agonists act in male sexual dysfunction by the direct stimulation of dopamine receptors in the paraventricular nucleus in

the hypothalamus [29]. Pergolide acts exclusively and differently on the subtypes of D2 dopamine receptors [1,2]. Then it should be presumed that a specific subtype of D-2 dopamine receptor can exist also in the human paraventricular nucleus. Pergolide then may have a specific affinity to this receptor, and can improve sexual dysfunction better than other D2 dopamine agonists. Nevertheless, we will need data from both animal and clinical studies to more strongly support this hypothesis.

From the clinician's point of view, our 12-months follow-up demonstrated that pergolide improves all symptoms or features of complex male sexual dysfunction in Parkinson's disease, and that this improvement has a long-lasting character. Other dopamine agonists were only rarely mentioned in this context, and if, their effect was beneficial only in selected subfields of sexual functions [29–32]. Then in male patients, in whom sexual dysfunction affects their quality of life and who are still interested in active sexual relationship, the introduction of pergolide should be considered, particularly in patients in whom the treatment with short-acting PDE-5 inhibitors meets any contraindication [30,32]. On the other side, the introduction of PDE-5 inhibitors should be a better choice, mainly in the light of recent observations, which reported the increased incidence of restrictive valvular heart disease in patients treated with ergoline dopamine agonists, namely pergolide [33].

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Appendix 1

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 apatence (range 0–10)
- IIEF IV: satisfaction with sexual intercourse (range 0–15)
- IIEF V: overall satisfaction with sex life (range 0–10)

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