

Patient-Perceived Retrospective Outcome of Duodenal Levodopa Infusion in Advanced Parkinson's Disease

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ABSTRACT

Patients with advanced Parkinson's disease (PD) are dependent on adequate dopaminergic therapy to treat motor and non-motor fluctuations. Continuous duodenal levodopa/carbidopa infusion is effective in relieving such complications, but patient-perceived outcome has not been thoroughly investigated so far. The present study retrospectively examined the patient-perceived frequency, as well as the discomfort, from both motor and non-motor symptoms before and after levodopa infusion initiation. A questionnaire ($n=68$) and a semi-structured interview ($n=25$) were used. A factor analysis was performed on the assembled discomfort data to show which symptoms are more likely to occur simultaneously. The subjects were relieved from symptoms significantly more than having acquired a symptom after initiating levodopa infusion. There was a significant ($P<0.01$) decrease in discomfort in 17 of 44 symptoms. Different aspects of pain coincided with anxiety, depression, nightmares, cramps, restless legs, and freezing of gait. A strong correlation was found between activities of daily living (ADL) functions and mood. Indexation of questions concerning ADL, sleep, and social relations showed significant improvements after initiation of levodopa infusion therapy. Ninety-six percent of the 25 patients interviewed strongly recommend the infusion to someone else. The foundation for the patients' ability to cope with PD relies heavily on adequate dopaminergic stimulation. The duodenal levodopa infusion enhances such a regime by improving ADL function, and thereby mood.

Keywords: Parkinson's disease, duodenal levodopa infusion, symptom profile, activities of daily living (ADL), social functioning, quality of life, patient-perceived discomfort

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INTRODUCTION

Parkinson's disease (PD) is a multisymptomatic illness beyond the three cardinal symptoms that were first described in "An essay on the shaking palsy", by Dr. James Parkinson: bradykinesia, tremor, and rigidity [1]. In addition to these symptoms, over time, many other symptoms develop and create a more complex clinical picture. Examples of such additional symptoms include both motor and non-motor problems such as postural instability, depression, and sleep disturbance [2, 3]. The inevitable development of treatment-induced dyskinesias further complicates the situation in the long-term management of PD [4]. Quality of life is decreased in patients with motor and non-motor fluctuations [5]. The negative effect of advanced PD on social relations is well documented [6–8]. In a questionnaire study concerning symptom profiles vs gender, 948 subjects with PD were retrospectively asked about their symptoms at disease onset and at present. Both occurrence and discomfort measures were assessed [6]. The overall results demonstrated small differences between genders. What the result did show was that the subjects had doubled the amount of symptoms from PD onset to the present time (about eight symptoms at onset to 16 at present). The results also showed that the annoyance due to PD progress had worsened.

The progression of the disease requires refinement of treatment as symptoms and functional impairments become

more difficult to control. Advanced PD is currently treated with drug therapy alone or with a combination of drug therapy and surgical intervention such as deep brain stimulation (DBS) [3]. Continuous duodenal/jejunal infusion of levodopa/carbidopa has been shown to be an effective alternative in advanced PD [9, 10]. Both motor and non-motor symptoms can be significantly better controlled with infusion therapy compared with conventional pharmacotherapy [11–15]. Quality of life can be improved by the levodopa infusion, as demonstrated using PDQ-39 and electronic diaries [11, 14–17], but patient-perceived outcome has not been analyzed in detail.

The present study retrospectively aimed at capturing detailed patient-perceived outcome of the introduction of duodenal levodopa infusion (DLI) therapy with regard to the occurrence and discomfort of a large number of symptoms. A questionnaire was sent to 95 patients on levodopa infusion. A second part of the study involved a semi-structured interview with 25 patients to investigate what effect the treatment had on daily functioning in terms of activities of daily living (ADL), sleep, and social relations.

SUBJECTS AND METHODS

The study had two phases. In phase 1, a questionnaire format was used, in which the occurrence and the discomfort of various symptoms likely to emerge in advanced PD were examined. In phase 2, subjects were randomly selected from the questionnaire

study sample. These subjects were interviewed, and the questions concerned ADL, sleep, and social relations. The study was deemed not to require any ethical approval from the local ethics committee (Etikprövningsnämnden, Uppsala, Sweden) because no interventions were made.

Subjects

In phase 1, subjects with PD were identified who were on DLI and who were all members of the Swedish PD Association. A total of 95 questionnaires were mailed out from the PD Association, of which 75 were returned. Of the 75 subjects who did return their questionnaire, seven had to be excluded. One subject was deceased (the questionnaire was returned empty), three did not use the DLI, and the remaining three subjects had not succeeded in filling in the questionnaire. Thus, the number of analyzed questionnaires was 68 (75% of the eligible patients). Data were gathered during autumn 2007. All subjects in the questionnaire study were asked if they would like to participate in the interview (phase 2) and, from the subjects who accepted, 25 subjects were picked randomly. The interviewer had no knowledge of the subjects' answers to the questionnaire used in phase 1.

Phase 1 (questionnaire)

In phase 1, data were gathered through a modified questionnaire containing questions about PD symptoms and perceived discomfort stemming from each symptom. The original version of this questionnaire was used in an earlier study [6]. The occurrence of symptoms was indicated by a "yes" or "no" answer, and the discomfort of each specific symptom was assessed on a five-point scale where one (1) indicated no problems, "not at all" and five (5) indicated maximal discomfort. The questionnaire consisted of a list of 44 symptoms that were selected based on symptoms expected in subjects who have had PD for a longer time [6]. They indicated the occurrence and the discomfort of symptoms that they had before (Pre) and after (Post) initiation of DLI. They also answered questions about age, gender, and the duration of DLI. The questions were answered anonymously. After a reminder was sent out to the subjects who had declined to answer, the data were coded. All results are reported on a group level.

The questionnaire constructed for this study aimed at capturing the specific problems linked to advanced stage of PD. By doing this, a higher degree of face validity is obtained, and thereby an increased willingness to answer the questions. Further, the discomfort measure used in an earlier study [6] has shown good psychometrical values. Therefore, the same strategy was used in the present study. The construction of the questions was outlined in such a fashion that the patient could answer them single-handedly while the measures traditionally used need a professional to fill them in [2].

Phase 2 (interview)

In phase 2, data were gathered via telephone interviews. The collected data focused on different aspects of functional impairments that occur in advanced PD. Subjects described their situation before and after DLI. The interview was

conducted using a semi-structured form with questions with a predetermined choice of answers. The interviewer interpreted the responses and filled in the forms. As with the questionnaire responses, these answers were coded immediately after the data-gathering process. Most of the PD subjects answered the interview questions themselves (72%), relatives answered the questions in 12% of the cases, while the remaining 16% represent a collaborative response.

Subjects were asked nine questions concerning ADL such as buttoning clothing, preparing food, and cleaning. Four questions were assigned to sleeping problems. They also answered questions concerning their social situation. Eight questions were assigned to measure social relations. Subjects were also given the opportunity to add personal functional impairments and how they coped with them. Responses were on a scale of 1 to 5 where one (1) indicates "no problem at all" and five (5) "constant problems". The results from the specific questions as well as a formed index (mean values calculated per category) covering ADL (nine questions), sleep (four questions), and social relations (eight questions) are presented. Further, subjects answered five hypothetical statements where the responses included "agree completely", "agree in part", and "disagree completely". These statements involved mood, quality of life, activity, and functioning in general terms. One question related to the family's perception of the patient's functioning. Thereafter, subjects answered one question each about degree of activity expressed as a percentage, about daytime and nighttime use of the levodopa infusion pump, and whether they would recommend the pump to others. Finally, subjects were asked to state the three worst and the three best characteristics of levodopa infusion treatment.

Statistical analysis

Questionnaire data were analyzed using dependent t-test, χ^2 , and factor analysis (Statistica, Statsoft Inc., Tulsa, OK, USA). In order to avoid mass significance errors, the P-level was set at $P < 0.01$ except for some calculations where repeated calculations were not used, e.g., difference in mean number of symptoms Pre to Post DLI. Interview data were analyzed using the dependent, independent t-test, and product-moment correlations. Owing to the small number of subjects which require marked effects to reach significance, P-levels from $P < 0.05$ were used.

RESULTS

Phase 1 (questionnaire)

Among the 68 subjects who filled in the questionnaire, 63% were men and 37% were women. The average age was 66.9 years (range 47–80 years). Age differences between genders were small (men 66.6 years, women 67 years). A majority (64%) had been treated with DLI for more than 2 years, 17% had used DLI for 1–2 years, 13% had used DLI for 6 months to 1 year, and 6% had used DLI for less than 6 months. No significant gender differences were found in duration of DLI use.

Occurrence of symptoms

The mean, \pm standard deviation, of the number of symptoms occurring before DLI was 28 ± 7.8 (range 9–44), whereas the mean after initiation of DLI was 26 ± 8.9 (range 8–44). This decrease in the mean number of symptoms from Pre to Post DLI was significant ($P < 0.05$). **Table 1** shows the occurrence of symptoms Pre and Post DLI. The span of occurrence Pre DLI ranged between 98% (stiffness) to 30% (pain—headache). The proportional distribution of yes—no answers Pre and Post DLI can be seen in **Table 1**.

Tremor, shaking (inner shivering), and insomnia were the symptoms that most subjects indicated had disappeared Post DLI. The percentage change (symptom is gone) was led by tremor (29% of patients), followed by shaking (inner shivering 25%), and insomnia (23%). For each of the symptoms, constipation, sweats, communication problems, difficulties alternating with arm/leg, clumsiness, and nightmares, 18% indicated that the symptom was eliminated Post DLI. For the symptoms easily irritated, and involuntary movements of face/mouth/head, 17% stated they no longer had these symptoms Post DLI. Of all 44 symptoms, 73% (32/44) had improved from Pre to Post DLI.

Table 1 also shows the results for symptoms that were not reported Pre DLI but had developed Post DLI. Nineteen percent had developed vision problems, followed by 16% for memory problems. Problems with balance, fatigue, and seborrhea also show a small but increased percentage when compared with subjects reporting a decline in the symptom.

Only three symptoms had equal amounts of subjects who reported having lost as having gained the symptom. The most common symptoms occurring both Pre and Post DLI were stiffness, fatigue, hyperkinesias, and coordination problems (93% to 75%).

The least frequent symptoms both Pre and Post DLI were pain—headache, loss of appetite, seborrhea, irritation/anger, dizziness, and numbness (64% to 45% were not affected).

Perceived discomfort from symptoms

Results are presented in **Table 2**. Of all symptoms studied, statistically significant positive differences in discomfort Post DLI were shown in 61% of the symptoms at the level of $P < 0.05$ or 39% at $P < 0.01$.

To detect any gender differences, an independent t-test was used on the Post DLI discomfort measure. The analyses show that women were significantly more annoyed by hallucinations ($P < 0.01$) than men, but men were significantly more annoyed by urinary and sexual problems ($P < 0.01$).

Factor analysis

In order to see which discomfort symptoms tend to cluster, a factor analysis (Varimax rotation) of the discomfort measures was conducted on the Post measure. Two factors were found with an Eigenvalue exceeding 1. Only symptoms with factor loadings ≥ 0.50 are presented in **Table 3**. The most prominent symptoms showing factor loadings > 0.60

explain 10.1% of the variance. The factor loadings exceeding > 0.60 forming factor two contribute prominently to the explained variance of 7.9%.

Phase 2 (interview)

The average age of the 25 patients in phase 2 was 67.4 years (range 53–80 years). In this group, 66% were men and 34% were women. A majority (68%) had been using DLI for 2 years or longer, 12% had used DLI for 1–2 years, 16% had used DLI for 6 months to 1 year, while 4% had used DLI for less than 6 months. The majority of subjects (80%) disconnected the pump at night, whereas 20% used the DLI around the clock.

Tables 4–6 show the effects of DLI treatment on ADL, sleep, and social relations, i.e., the magnitude of differences in effect that were reported Pre and Post DLI.

The results of the ADL questions showed that the subjects were significantly improved in the ability to dress themselves, buttoning clothing, and slicing bread (**Table 4**). Brushing teeth and personal hygiene did not reach significance ($P < 0.06$). When an index of the ADL questions (**Table 4**) was conducted and then tested (ADL-index-Pre and ADL-index-Post), a significant difference was found ($t(24) = 3.05$, $P < 0.01$).

Table 5 shows the results concerning sleeping problems. Improvement in getting out of bed in the morning reached significance. Problems falling asleep and waking up during the night were improved but not statistically significant ($P < 0.06$). The index of sleep questions was tested Pre–Post, and a significant difference was found ($t(24) = 2.68$, $P < 0.01$).

All the questions but one concerning social relations (**Table 6**) showed positive trends for DLI when Pre and Post measures were compared. The only question showing a negative direction was driving a car. The indexation of these questions reached significance ($t(24) = 2.61$, $P < 0.05$).

Hypothetical statements and other questions

The results of the hypothetical statements (**Table 7**) show that the majority of subjects “agree completely” with the statements that quality of life and functioning had increased after DLI. It is noteworthy that no subjects answered “disagree completely” with these statements.

As for the two statements, increased activity and improved mood, the responses were distributed more evenly between the response alternatives.

On the question of whether the subject can recommend the pump to others, 96% strongly recommend the DLI pump to someone else.

In response to the question about how active the subjects considered themselves during the day, 20% answered active all day, a little more than half (52%) indicated three-quarters of the time, and the remaining 28% stated half the time.

Regarding the advantages of the pump, a majority of patients appreciated a more even dose regime during the waking hours and the benefit of not having to handle tablets. Increased mobility (e.g., being able to participate in social

Table 1. The Distribution (%) of “Yes” Answers at Pre and Post Duodenal Levodopa Infusion (DLI)

Symptom	Yes at Pre DLI % (n)	Yes at Pre and no at Post DLI % (n)	No at Pre and yes at Post DLI % (n)	Yes at both Pre and Post DLI % (n)	No at both Pre and Post DLI % (n)	N
Tremor	58 (38)	29 (19)	9 (6)	29 (19)	33 (21)	65
Shaking (inner shivering)	66 (43)	25 (16)	6 (4)	42 (27)	27 (18)	65
Insomnia	73 (48)	23 (15)	7 (5)	50 (33)	20 (13)	66
Constipation	72 (49)	18 (12)	4 (3)	54 (37)	24 (16)	68
Sweats	68 (44)	18 (12)	5 (3)	49 (32)	28 (18)	65
Communication problems	63 (38)	18 (11)	7 (4)	45 (27)	30 (18)	60
Problems alternating arms/legs	72 (44)	18 (11)	8 (5)	54 (33)	20 (12)	61
Clumsiness	91 (62)	18 (12)	4 (3)	74 (50)	4 (3)	68
Nightmares	60 (40)	18 (12)	2 (1)	42 (28)	38 (25)	66
Easily irritated/anger	42 (27)	17 (11)	8 (5)	25 (16)	50 (33)	65
Involuntary movements, face/head	61 (36)	17 (10)	9 (5)	44 (26)	31 (18)	59
Freezing of gait	70 (44)	16 (10)	8 (5)	54 (34)	22 (14)	63
Initiating movement, etc.	89 (57)	16 (10)	6 (4)	73 (47)	5 (3)	64
Involuntary movements, arm/leg	88 (50)	16 (9)	5 (3)	72 (41)	7 (4)	57
Hallucinations	47 (31)	15 (10)	11 (7)	32 (21)	42 (28)	66
Dryness of the mouth	80 (53)	15 (10)	9 (6)	65 (43)	11 (7)	66
Loss of appetite	35 (23)	15 (10)	9 (6)	20 (13)	56 (36)	65
Cramps, leg/calf	76 (50)	14 (9)	5 (3)	62 (41)	19 (13)	66
Restless legs/paresthesias	65 (42)	14 (9)	3 (2)	51 (33)	32 (21)	65
Pain—back	57 (37)	14 (9)	3 (2)	43 (28)	40 (26)	65
Dizziness	43 (28)	14 (9)	11 (7)	29 (19)	46 (30)	65
Pain—headache	30 (19)	13 (8)	6 (4)	17 (11)	64 (41)	64
Pain—arm/leg	67 (43)	13 (8)	5 (3)	55 (35)	27 (18)	64
Handwriting problems	82 (56)	10 (7)	5 (3)	72 (49)	13 (9)	68
Dysphoria/depression	68 (44)	12 (8)	5 (3)	55 (36)	28 (18)	65
Worry/anxiety	70 (44)	11 (7)	9 (6)	59 (37)	21 (13)	63
Coordination problems	86 (54)	11 (7)	6 (4)	75 (47)	8 (5)	63
Hyperkinesia	89 (59)	11 (7)	4 (3)	79 (52)	6 (4)	66
Urinary problems	66 (44)	10 (7)	5 (3)	55 (37)	30 (20)	67
Pain—neck/shoulder	65 (42)	9 (6)	6 (4)	56 (36)	29 (19)	65
Numbness	48 (32)	8 (5)	6 (4)	41 (27)	45 (30)	66
Stiffness	98 (64)	5 (3)	2 (1)	93 (61)	0 (0)	65
Vision problems	52 (32)	3 (2)	19 (12)	49 (30)	29 (18)	62
Memory problems	53 (34)	6 (4)	16 (10)	47 (30)	31 (20)	64
Increased salivation	54 (35)	8 (5)	15 (10)	46 (30)	31 (20)	65
Swallowing problems	51 (33)	9 (6)	15 (10)	42 (27)	34 (22)	65
Sexual dysfunction	63 (38)	2 (1)	15 (9)	61 (37)	22 (13)	60
Weight problems	55 (36)	11 (7)	15 (10)	44 (29)	30 (20)	66
Problems with balance	73 (45)	8 (5)	10 (6)	64 (40)	18 (11)	62
Seborrhea	39 (25)	5 (3)	8 (5)	34 (22)	53 (34)	64

Table 1. Continued

Symptom	Yes at Pre DLI % (n)	Yes at Pre and no at Post DLI % (n)	No at Pre and yes at Post DLI % (n)	Yes at both Pre and Post DLI % (n)	No at both Pre and Post DLI % (n)	N
Fatigue	86 (54)	5 (3)	6 (4)	81 (51)	8 (5)	63
Loss of initiative	81 (52)	9 (6)	9 (6)	73 (46)	9 (6)	64
Speech problems	72 (47)	9 (6)	9 (6)	63 (41)	19 (12)	65
Concentration problems	72 (46)	8 (5)	8 (5)	64 (41)	20 (13)	64

The most frequently occurring symptoms Pre DLI (>80%) are marked in bold.

Symptoms that disappeared Post DLI more frequently than they appeared are sorted in ranking order and marked in bold. The same goes for symptoms that appeared Post DLI more frequently than they disappeared.

events) and security (e.g., getting the medicine at the right time) were also noted. In response to the question, what are the three worst characteristics of the pump, the majority of subjects said that the pump is large, heavy, and bulky. Another problem was that the tubes may become detached.

Correlations between the statements and functional impairment in ADL, sleep, and social relations

When the four hypothetical statements that concern quality of life, mood, activity, and functioning were correlated with ADL-index-Post, sleep-index-Post, and social relations-index-Post, a strong correlation was found between the ADL-index-Post and mood ($r=0.51$, $P<0.01$), suggesting that an enhanced ability to cope with ADL with DLI improved mood levels. The correlation between activity and ADL-index-Post was weaker ($r=0.36$, $P=0.082$). Quality of life and functioning vs ADL-index-Post did not reach significance.

Concerning the statements on quality of life, mood, activity, and functioning vs the sleep-index-Post measure, no correlations reached significance. One correlation was close, mood vs sleep-index-Post, but was not statistically significant ($r=0.36$, $P=0.087$). Further, the social-index-Post measure did not reach significance when correlated with quality of life, mood, activity, and functioning.

Finally, improved ADL significantly correlated with relatives' perception of well-treated PD symptoms ($r=0.45$, $P<0.05$). The sleep-index-Post measure showed a weak but non-significant correlation with relatives' perception of functioning ($r=0.39$, $P=0.063$), whereas the social-index-post measure did not correlate.

Differences in symptom severity rating among subjects participating in the interview compared with subjects not participating in the interview

When the subjects participating in the interview were compared with those not participating regarding how discomforted they were by their symptoms, no significant differences in symptom severity were found when the significance level was set at the 0.01 level.

DISCUSSION

The overall conclusion is that DLI is an effective treatment to alleviate or significantly mitigate several existing symptoms

among individuals with advanced PD. Thus, previous results of efficacy [11–15] are confirmed, but the present study provides more details on patient-perceived occurrence and severity of symptoms, not previously reported. Importantly, the discomfort measures clearly show that subjects have benefited from this treatment regime. However, there was no control group or assessment of patients who discontinued DLI therapy, although discontinuations are rare [18]. The patients may represent a selected group because of their membership of the PD Association, but we believe that the high number of patients (95) covers almost all patients in Sweden on the treatment at the time of the study. Probably, demented or severely disabled patients were excluded among the 20 patients who did not answer the questionnaire, but the answering frequency was high considering the patient group had advanced PD. Further, the study was carried out in a retrospective format, and this can be argued to be a methodological flaw in the interpretation of the results, which is a common problem in studies evaluating subjective outcomes. The retrospective design also includes a risk of recall bias. Many patients reported memory problems. The most common way to evaluate patient-perceived treatment effects is just by asking the subjects shortly after the initiation of treatment regimes. This study offers a more stringent methodological approach by forcing the subjects to consider both the past and the present. The placebo effect, which is common in short-term studies, is probably reduced in the present study, in which 64% of patients had been on DLI therapy for >2 years. There is a risk of exaggeration because the treatment method is an expensive last-line option. By requesting rather high confidence intervals, mass significance errors are reduced. Thus, the results are reliable and create a stable foundation for the conclusions drawn.

Phase 1 (questionnaire)

The results of the questionnaire demonstrate a significant decrease in the average number of symptoms per patient, from 28 to 26, in the entire group after initiation of DLI. Importantly, a significant decrease was reported in the severity of many of the symptoms. Closer scrutiny of symptoms appearing Pre but not Post DLI (Table 1) shows that subjects have been relieved of symptoms proportionally more than having acquired a symptom. This applies to both "classic" motor symptoms as well as to non-motor

Table 2. Mean (M) and Standard Deviations (SD) for Each Symptom in The Discomfort Measure, Pre and Post Duodenal Levodopa Infusion (DLI)

Symptom	Severity Pre DLI		Severity Post DLI		t
	M	SD	M	SD	
Shaking (inner shivering)	3.0	1.3	1.9	0.9	3.7***
Tremor	2.9	1.1	1.8	0.7	4.2***
Stiffness	3.7	1.0	2.3	1.0	7.5***
Clumsiness	3.2	0.9	2.4	1.1	4.4***
Cramps, leg, calf	3.2	1.4	2.2	1.1	4.2***
Initiating movement, etc.	3.4	1.1	2.5	1.3	3.7***
Problems alternating arms and legs	2.9	1.0	2.2	1.2	3.4***
Involuntary movements, arm/leg	3.4	1.1	2.2	1.0	5.6***
Hyperkinesia	3.5	1.1	2.2	1.1	5.6***
Insomnia	3.4	1.0	2.6	1.1	3.5***
Freezing of gait	3.7	0.9	2.7	1.2	3.2**
Restless legs/paresthesias	3.1	1.0	2.3	1.1	2.7**
Sweats	3.3	1.2	2.3	1.1	3.4**
Worry/anxiety	3.3	1.2	2.5	1.2	3.1**
Involuntary movements, face/mouth/head	3.2	1.2	2.2	1.2	2.8**
Nightmares	3.0	1.4	1.9	0.9	3.2**
Dysphoria/depression	2.8	1.1	2.1	1.0	3.4**
Swallowing problems	2.7	1.0	2.1	1.2	2.1*
Fatigue	3.1	1.1	2.6	1.1	2.0*
Loss of initiative	3.2	0.9	2.8	1.0	2.3*
Dryness of the mouth	2.9	1.1	2.5	1.1	2.0*
Pain—arm/leg	3.1	1.1	2.6	1.1	2.1*
Pain—neck/shoulder	2.9	1.1	2.4	1.2	2.5*
Pain—back	3.5	1.1	2.7	1.4	2.2*
Constipation	3.1	1.1	2.5	1.1	2.0*
Concentration problems	3.0	1.0	2.4	1.2	2.3*
Communication problems	2.7	1.1	2.1	0.9	2.5*
Coordination problems	2.9	1.2	2.7	1.3	NS
Handwriting problems	3.5	1.1	3.1	1.4	NS
Numbness	2.4	1.0	2.1	1.0	NS
Speech problems	2.4	1.1	2.4	1.2	NS
Pain—headache	2.5	1.4	2.3	1.2	NS
Increased salivation	2.4	1.1	2.1	1.2	NS
Loss of appetite	2.5	0.9	2.0	0.8	NS
Sexual dysfunction	3.3	1.4	3.5	1.3	NS
Urinary problems	3.1	1.4	3.1	1.3	NS
Problems with balance	2.9	1.3	2.8	1.3	NS

Table 2. Continued

Symptom	Severity Pre DLI		Severity Post DLI		t
	M	SD	M	SD	
Dizziness	2.7	1.2	2.4	1.0	NS
Seborrhea	2.9	1.2	2.5	1.0	NS
Hallucinations	2.3	1.1	2.2	1.1	NS
Easily irritated/anger	2.6	1.1	2.1	1.0	NS
Memory problems	2.5	0.1	2.4	1.1	NS
Weight problems	2.8	1.2	2.3	1.1	NS
Vision problems	3.2	1.3	3.0	1.3	NS

The number of subjects (N) for each symptom varied between 11 and 61. * $P < 0.05$, not considered significant in this study; ** $P < 0.01$; *** $P < 0.001$; NS, not significant.

symptoms. The improvement in quality of life reflected by these reported reductions in symptoms is probably high according to both general quality of life studies [5] and studies of DLI [11, 13–17]. However, it is not the numbers as such that are of highest interest, but rather the severity of the symptoms that disappear or emerge. The questionnaire reveals that DLI has a positive impact on the severity of a majority of symptoms according to the discomfort measures. Both frequently reported symptoms Pre DLI such as stiffness (98%), clumsiness (91%), and initiating movement (89%) and less frequently occurring symptoms such as cramps (76%), insomnia (73%), and problems alternating arms/legs (72%) show a significant decrease in severity at the 0.001 level (Table 2). Thus, the total discomfort from the disease is lower after the introduction of DLI, even if new symptoms may emerge.

In order to establish which symptoms cluster together, a factor analysis was performed on the Post DLI discomfort measure. One factor contained symptoms showing factor loadings > 0.60 such as speech, writing problems, and loss of initiative (Table 3). From a clinical viewpoint, this is an interesting finding because the probability of finding problems with writing, for example, is higher if any of the other symptoms within the factor are present. The second factor found indicates that, if a subject suffers from different aspects of pain, the probability of finding anxiety and depression, or vice versa, is high. This is also an important finding, suggesting that antidepressant therapy could improve pain, and that optimized PD therapy that alleviates pain could improve depressive symptoms and anxiety. The explained variances are not high, but still the findings are consistent and may contribute to a better understanding of the existing symptom profiles.

Phase 2 (interview)

When daily functions in ADL, sleep, and social relations were studied Pre–Post DLI, an overall positive trend in favor of DLI could be found (Tables 4–6). However, not all

Table 3. Factor Loadings for the Symptom Discomfort Measure

Symptom	Factor 1	Factor 2
Speech problems	0.84	
Handwriting problems	0.82	
Loss of initiative	0.78	
Communication problems	0.78	
Coordination problems	0.78	
Fatigue	0.76	
Concentration problems	0.76	
Clumsiness	0.72	
Problems with balance	0.63	
Memory problems	0.63	
Problems alternating arms and legs	0.58	
Stiffness	0.54	
Vision problems	0.52	
Constipation	0.51	
Hallucinations	0.51	
Urinary problems	0.50	
Cramps, legs/calf		0.72
Easily irritated/anger		0.69
Pain—arm/leg		0.67
Depression		0.66
Pain—neck/shoulder		0.65
Worry/anxiety		0.65
Pain—back		0.63
Numbness		0.58
Restless legs		0.57
Shaking (inner shivering)		0.53
Freezing of gait		0.53
Tremor		0.52
Nightmares		0.50
Explained variance	10.1%	7.9%

The symptoms are presented in ranking order starting with the most contributing symptom to the explained variance for each factor.

improvements reached significance. When questions concerning ADL, sleep, and social relations were indexed, significant differences were obtained for all three indices. In order to maintain good mental health, it is important that these areas should be as positively restored as possible [19]. Social relations in particular showed improvement with DLI (Table 6). The increased ability to participate in normal social contexts is an important result by itself.

It is clear that functional impairments, daily irritations in everyday life, play a role in quality of life and functioning at all levels. DLI provides advantages that can scarcely be achieved

Table 4. Mean (M) and Standard Deviation (SD) for Functional Impairment regarding Activities of Daily Living (ADL), Pre-Post Duodenal Levodopa Infusion (DLI)

	Problem Pre DLI		Problem Post DLI		t
	M	SD	M	SD	
Dressing oneself	2.9	1.5	1.9	1.1	4.0***
Buttoning clothing	2.8	1.7	2.2	1.2	2.2*
Personal hygiene	2.3	1.3	1.8	0.9	NS
Brushing teeth	1.9	1.2	1.6	0.8	NS
Preparing food	1.8	1.6	1.4	1.3	NS
Slicing bread, etc.	2.3	1.4	1.8	1.2	2.5*
Opening cans or packages	2.1	1.4	1.7	1.1	NS
Cleaning	2.1	1.7	1.8	1.6	NS
Coping with bathroom visits	1.9	1.1	1.5	1.0	NS

* $P < 0.05$, *** $P < 0.001$, NS, not significant.

through treatment with conventional medications in advanced PD.

When the hypothetical statements related to mood and activity are correlated with the subjects' answers to the functionality questions (ADL, sleep, and social relations), the mood and ADL measures show the most distinct pattern. Apparently, the ability to dress, take care of personal hygiene, and to clean are important features in maintaining a positive mood.

The high agreement percentages in the statement questions (Table 7) further confirm the usefulness of DLI in patients with advanced PD. However, some patients did not agree with improved mood and increased activity, which, again, probably reflects the fact that depression and psychomotor disability are common in this patient group.

The fact that 96% of patients would recommend the pump to someone else despite the disadvantage characteristics is a striking result.

Table 5. Mean (M) and Standard Deviations (SD) for Functional Impairment regarding Aspects of Sleep, Pre-Post Duodenal Levodopa Infusion (DLI)

Sleep	Problem Pre DLI		Problem Post DLI		t
	M	SD	M	SD	
Falling asleep	3.0	1.5	2.3	1.7	NS
Waking up during the night	2.7	1.6	2.1	1.1	NS
Turning over in bed	3.3	1.6	2.8	1.5	NS
Problems getting out of bed in the morning	3.2	1.4	2.4	1.3	2.7**

** $P < 0.01$, NS, not significant.

Table 6. Mean (M) and Standard Deviation (SD) for Functional Impairment in Social Interactions, Pre–Post Duodenal Levodopa Infusion (DLI)

Social relations	Problem Pre DLI		Problem Post DLI		t
	M	SD	M	SD	
Socializing with friends	2.6	1.5	2.0	1.1	2.2*
Talking on the phone	2.6	1.4	1.8	0.9	3.0**
Dinner at friends' home or at restaurant	3.2	1.6	2.1	1.0	3.6***
Driving a car	1.4	1.7	1.5	1.9	NS
Meeting people in different environments	2.5	1.6	2.0	1.3	2.1*
Shopping for groceries	2.0	1.6	1.8	1.5	NS
Shopping, clothes, etc.	2.1	1.6	1.9	1.5	NS
Concerts, movies, etc	2.5	1.7	1.9	1.7	2.3*

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, NS, not significant.

Table 7. The Distribution of Agreement in Statement Questions

	Agree completely (%)	Agree in part (%)	Disagree completely (%)
Improved mood	44	40	16
More active	36	32	32
Improved quality of life	76	24	
Improved functioning	84	16	
Relatives' opinion on improved functioning	80	16 ^a	

^aOne case of attrition i.e., $n = 24$.

Concluding remarks

Two-thirds of the subjects in the study were men. This is noteworthy as there is almost equality between genders in the incidence of PD. The discrepancy between genders in using this treatment is not answered. However, one possible cause could be esthetic. The size and weight of the infusion pump might make women hesitate to choose this treatment. Gender differences have also been found in daily levodopa consumption, where men use higher doses than women [20].

The study highlights the fact that PD patients have, besides their cardinal symptoms, multilateral problems to handle. Many of the symptoms such as depression, anxiety, or insomnia are reported frequently, and are in themselves huge problems to cope with. Any intervention that alleviates or diminishes the different problem symptoms that the PD patients have to cope with is beneficial. We conclude that duodenal levodopa infusion has such a potential in PD patients despite their advanced disease stages.

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