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Patient Profile, Indications, Efficacy and Safety of Duodenal Levodopa Infusion in Advanced Parkinson's Disease

David Devos, MD, PhD* for the French DUODOPA Study Group

Department of Neurology, EA2683 IFR114 IMPRT, CHU Lille, France

Abstract: The studies of duodenal infusion of a levodopa on small groups of parkinsonian patients have reported beneficial effects on motor complications. However, little is known about the patient profile and indications for duodenal levodopa infusion. The purpose of this study is to exhaustively investigate the clinical characteristics of the population and indication, efficacy and tolerability of duodenal levodopa infusion in natural care settings. Of the 102 patients treated with duodenal levodopa infusion since 2003, 91 were enrolled in a multicentre retrospective study. The mean age was 72.7 years, with average disease duration of 17 years. Patients were at advanced stage: 91% had gait disorders, 65% had visual hallucinations, and 50% were demented (MMSE: 23). Duodenal levodopa infusion was the last line of treatment for motor complications in 98% of the patients, due to failure of or contraindication for apomorphine pump and neurosurgical treatments. Long-term treatment was observed by 73% of the population. Of these, >90% reported an improvement in motor fluctuations, quality of life, and autonomy. There were few severe adverse events. Technical problems were commonplace. Duodenal levodopa infusion seems to be an effective last-line therapy for motor complications in Parkinson's disease. Hence, technical improvements and earlier introduction should be considered. © 2009 Movement Disorder Society

Key words: Parkinson's disease; levodopa-related motor complications; continuous dopaminergic stimulation; duodenal infusion; Duodopa

The management of disabling, levodopa-related motor complications is at the heart of current therapeutic strategies for Parkinson's disease (PD), since these symptoms occur in one third of patients after 3 to 5 years of levodopa treatment and in almost all patients after 10 to 12 years.[1,2] Apart from oral drug management, apomorphine pump therapy[3,4] and subthalamic nucleus (STN) stimulation[5,6] are effective for controlling motor complications but are only applicable to a very select population free of cognitive and behavioral complications. In patients with advanced PD, enteral infusion of levodopa can decrease fluctuations in plasma levodopa levels and thus the clinical motor symptoms.[7] Duodenal infusion of a levodopa/carbidopa gel via a portable pump and an intestinal tube yields high concentrations of the active substances[8] and has become a feasible alternative treatment for fluctuating patients.[9] A crossover study[10] of constant-rate infusion has shown that the levodopa plasma concentration profile is smoother than that of sustained-release levodopa/carbidopa tablets. A randomized, crossover study of 24 PD patients has demonstrated that infusion of levodopa is clinically superior to a number of individually optimized combinations of conventional oral and subcutaneous drugs.[11] Despite evidence that continuous dopaminergic stimulation via enteral infusion can reduce motor complications in small samples of nondemented patients, there are no exhaustive studies reporting on the indications of duodenal levodopa infusion in a large, nonselected population of users. We therefore retrospectively collected data for all patients having received duodenal levodopa infusion since the technique became available in France. The study sought to investigate (1) the population's characteristics (to establish the "real life" patient profile and determine at what point in the therapeutic strategy duodenal

*Correspondence to: David Devos, Service de Neurologie et Pathologie du Mouvement EA 2683, IFR 114, IMPRT, Hôpital R. Salengro, Clinique Neurologique, CHU de Lille, F-59037 LILLE cedex, France. E-mail: d-devos@chru-lille.fr

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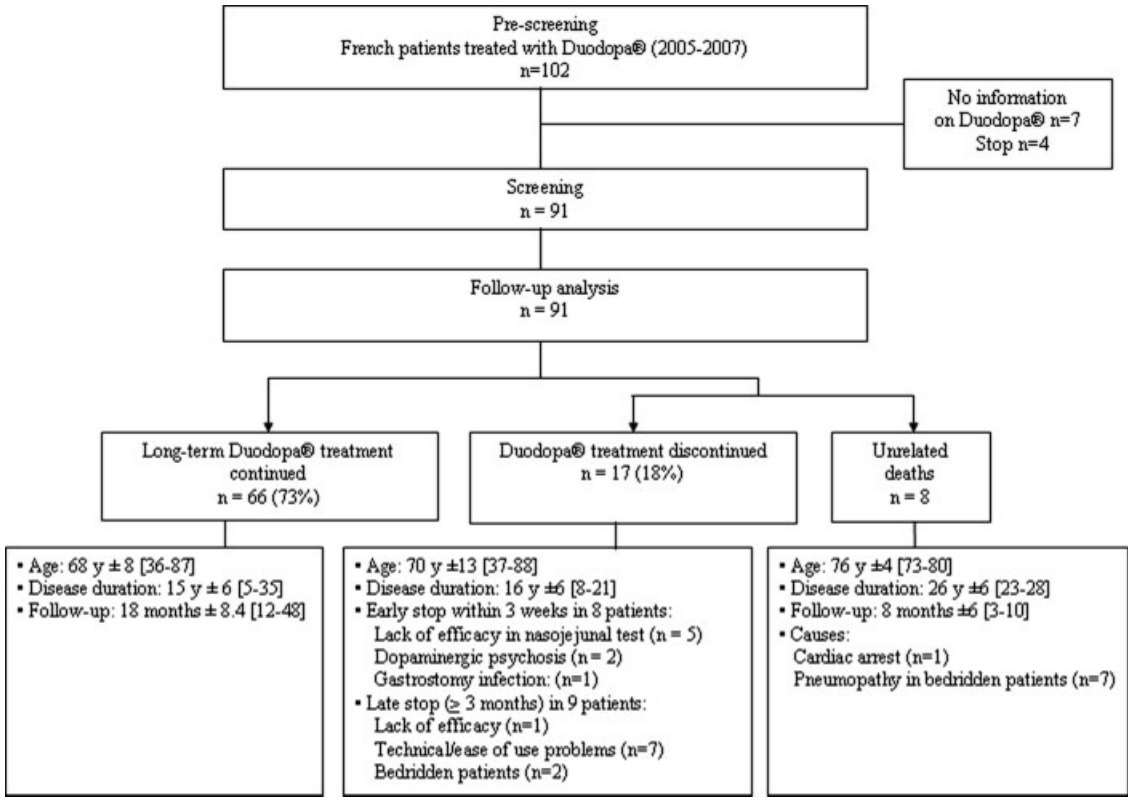
levodopa infusion is considered) and (2) the efficacy and tolerability reported by patients, their caregivers and their physicians.

PATIENTS AND METHODS

Patients

Duodenal levodopa infusion has been used to treat 102 patients, fulfilling the clinical diagnosis criteria of PD,[12] in France, between 2003 and 2007. No information was available for 11 patients (see Flowchart).

Ninety-one patients were analyzed in 24 centers: Aix en Provence (n = 15), Lille (n = 10), Avranches (n = 9), Marseilles (n = 8), Saint-Brieuc (n = 8), Rennes (n = 6), Nice (n = 5), Nantes (n = 4), Strasbourg (n = 3), Toulouse (n = 3), Troyes (n = 3), Brest (n = 2), Créteil (n = 2), Metz (n = 2), Paris (Pitié Salpêtrière Hospital: n = 2; Léopold Bellan Hospital: n = 1), Amiens (n = 1), Aulnay sous Bois (n = 1), Fréjus (n = 1), Lyon (n = 1), Nancy (n = 1), Poitiers (n = 1), Quimper (n = 1), and Reims (n = 1). At the time of Duodopa initiation, the mean ± SD age



was 72.7 ± 11 years (with 63% of the population aged over than 70) and the disease duration was 17 ± 6 years (with 44% of the patients having suffered from PD for over 15 years). The male/female ratio was 1.5. The PD was considered to be sporadic in 93% of the patients and familial in the remaining 7%. Before duodenal levodopa infusion, the mean time since the onset of motor complications was 10.4 ± 6.2 years (Fig. 1).

In 98% of the patients, the medication used immediately before duodenal levodopa infusion was oral levodopa (Fig. 2). The mean daily levodopa-equivalent dose was 1176.4 ± 468.62 mg (400–2150),[13] with a

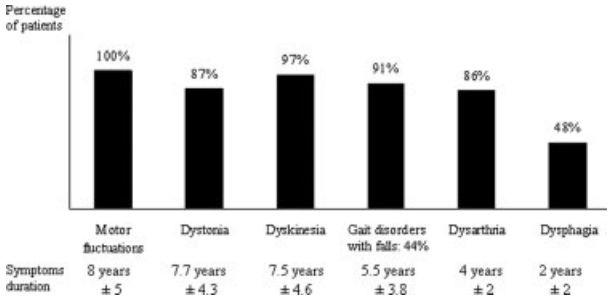


FIG. 1. The motor complications profile including levodopa-related motor complications and axial signs. The percentage of patients and the duration of the symptoms before duodenal levodopa infusion are indicated. Values are means and standard deviations.

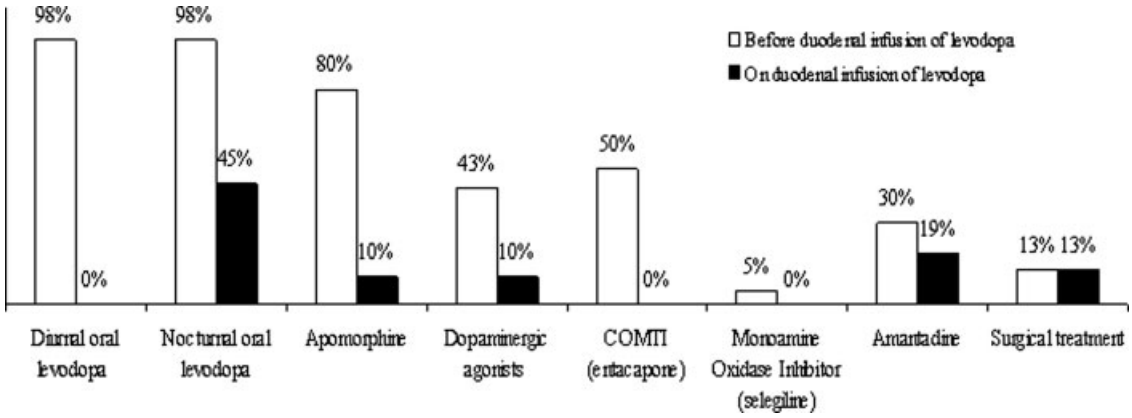


FIG. 2. Therapeutic strategy before and during duodenal levodopa infusion.

mean of 5 carbidopa/levodopa doses daily. Only one patient had been using an apomorphine pump without levodopa. Amantadine was prescribed (after 12.2 ± 6.6 years) for its antidyskinetic properties in 13.1% of the population. Subcutaneous apomorphine injection had been used by 80% of the population, either by pen (16%) or by pump (64%). Thirteen percent of the population had been previously treated neurosurgically, with 10 patients undergoing STN stimulation, one patient undergoing unilateral (left-side) thalamic stimulation because of severe rest tremor of the right hand and one patient having received a bilateral fetal cell transplant in 1993.

Cognitive and behavioral complications were frequent. Visual hallucinations were observed in 65% of the population, including severe, persistent hallucinations with delirium in 42% of the population. Thirty percent was being treated with antipsychotics (clozapine in 90% of these cases). Major depression had been diagnosed and treated in 32% (with administration of a selective serotonin reuptake inhibitor in 90% of these cases, in combination with anxiolytics in 24%). Severe cognitive disorders suggestive of PD dementia were displayed by 50% of the population (based on an MMSE score <24, DSM IV criteria and, in some instances, an additional neuropsychological examination) and was being treated with an anticholinesterase in only 13% (rivastigmine in 83%). The patients with severe cognitive disorders were also assessed with the caregiver.

Medication

The levodopa/carbidopa gel (Duodopa®) was used according to the manufacturer's recommendations (Solvay Pharma, Suresnes, France). The formulation was an aqueous suspension containing the micronized active compounds levodopa (20 mg/mL) and carbidopa (5 mg/mL) in 2.92% methylcellulose.[14] The gel was administered using a portable pump (CADD-Legacy Duodopa; Smiths Medical, Minneapolis, MN) and initially through a nasoduodenal Bengmark tube (Nutricia, Chatel-Saint-Denis, Switzerland) during a 1-week period test. The previous anti-PD drugs were replaced by the calculated equivalent dose of levodopa gel on the first day. If the patient, the caregiver and the neurologist were happy with the result, a percutaneous gastrostomy access tube, with a stomach tube tip (T-port), was fitted at the beginning of the second week. Individual dose optimization was carried out during the 2 weeks of hospitalization.

Study Design and Efficacy and Safety Evaluations

The present retrospective, multicenter study was based on a questionnaire filled out by neurologists after examination of each patient and according to their patients' opinions and medical files. All the data were reported from a single assessment at the last examination [Flowchart; mean time of follow up of 18 ± 8.4 months (12–48)]. An exhaustive list of PD therapeutic strategies was addressed, with a particular focus on the indications, efficacy and safety of apomorphine and neurosurgical treatments. Neurologists were asked to state the indication for duodenal levodopa infusion. Efficacy was assessed for motor fluctuations, dyskinesia, dystonia, pain, gait disorders, dysphagia, dysarthria (all rated by the neurologists on a three-point scale: improvement, no change, worsening), quality of life, autonomy and the clinical global improvement (CGI) (all rated on a five-point scale by the patients: great improvement, moderate improvement, slight improvement, no change, worsening). All adverse events were

TABLE 1. *Efficacy of duodenal levodopa infusion in terms of motor symptoms*

Patients (n = 75)	Improvement	No change	Worsening
Motor fluctuations	96% (n = 72)	2.7% (n = 2)	1.3% (n = 1)
Dyskinesia	94.7% (n = 71)	4% (n = 3)	1.3% (n = 1)
Dystonia	90.7% (n = 68)	8% (n = 6)	1.3% (n = 1)
Pain	74.7% (n = 56)	24% (n = 18)	1.3% (n = 1)
Gait disorders (freezing, festination, postural instability)	61.4% (n = 46)	37.3% (n = 28)	1.3% (n = 1)
Dysphagia	60% (n = 45)	38.7% (n = 29)	1.3% (n = 1)
Dysarthria	34.7% (n = 26)	64% (n = 48)	1.3% (n = 1)

The percentages and the numbers (n) represent the proportion of the population concerned, as assessed by the neurologist on a three-point scale at the last examination.

classified according to their relationship with (1) levodopa treatment, (2) gastrostomy, or (3) technical aspects. Practical, everyday use was also investigated and included the total daily infused dose of levodopa and the involvement of a nurse, a caregiver or the patient for setting up the device in the morning, administering extra doses as required and shutting down the device in the evening. Solvay Pharma's role in the study was restricted to the provision of logistic support (production, mailing, and recovery of the case report forms). All received data were transferred to the authors for analysis.

RESULTS

Therapeutic Strategy (n = 91)

Severe motor complications represented the main indication of duodenal infusion for all patients. In 98% of cases, duodenal levodopa infusion was the last line of therapy because apomorphine pump and/or STN stimulation therapy had failed or were contraindicated. Apomorphine treatment had been discontinued before duodenal levodopa infusion in 69% of the patients due to one or more reasons: lack of efficacy on motor fluctuations (30%), induction or worsening of severe confusion and hallucinations (27%), cutaneous intolerance (15%) or hypotension (9%). Twenty percent of the population was not eligible for apomorphine treatment because of dementia with severe hallucinations (15%) or an a priori decision of inferior efficacy (5%). Finally, 11% of the population decided to switch from apomorphine treatment to duodenal levodopa infusion because of a lack of efficacy (9%) or safety concerns (2%). The patients having undergone neurosurgical treatment (13%) had experienced ineffective motor complication control (6%) or infection or technical problems leading to treatment withdrawal (5%). Eighty-seven percent of the patients were not eligible for STN stimulation at the time of initiation of duodenal levodopa infusion for at least one of the following reasons: PD-associated psychosis (42%), major depression (32%), severe cognitive disorders suggestive of PD dementia (50%), age ≥ 70 years (80%), morphological (mainly camptocormia and axial deformations) or surgical contraindications (9.5%) or refusal (9.5%). Duodenal levodopa infusion was the first-line therapy in the 2% of the population which fulfilled the indication criteria for STN stimulation and apomorphine pump therapy.

Continuous duodenal infusion of levodopa was performed during the daytime in 90% of patients and round the clock in the remaining 10%. The mean daily levodopa-equivalent dose was 1388 ± 654 mg (range: 500–3300) and was higher (by 199 ± 441 mg) than the study population's pre-treatment value (*t* test: $t = -3.2$; $P = 0.002$), due to a dose increase in 66% of the patients and a slight decrease in the remaining 34%. Eighty-five percent of the population used 1 to 3 extra doses per day with a mean dose of each extra dose of 2.7 ± 1.5 mL (54 mg). Dopamine agonists were maintained in only 20% of cases, including 10% with apomorphine injection by pen. Most of the antiparkinsonian treatments were reduced in dose or withdrawn (Fig. 2). The morning set-up involved a nurse in 62% of cases, a caregiver in 32% of cases and the patient alone in 6% of cases. A nurse was less frequently required for stopping the device in the evening (in 50% of cases, compared with the caregiver in 41% of cases and the patient alone in 9% of cases). Extra doses were administered by the patient alone in 32% of cases (a much higher proportion than for set-up and shut-down), by the caregiver in 43% of cases and by a nurse in 25% of cases.

Efficacy of Duodenal Levodopa Infusion

Efficacy was assessed in 75 patients, including 66 patients (73%) having undergone long-term duodenal levodopa infusion and in nine patients who had stopped the therapy after at least 3 months (see Flowchart). Efficacy in terms of motor symptoms is detailed in Table 1. Only one patient reported worsening

TABLE 2. *Efficacy of duodenal levodopa infusion in terms of quality of life, autonomy and clinical global improvement*

Patients (n = 75)	Great improvement	Moderate improvement	Slight improvement	No change	Worsening
Quality of life	48% (n = 36)	41.3% (n = 31)	4% (n = 3)	4% (n = 3)	2.7% (n = 2)
Autonomy	32% (n = 24)	42.7% (n = 32)	16% (n = 12)	5.3% (n = 4)	4% (n = 3)
Clinical global improvement	61.3% (n = 46)	32% (n = 24)	4% (n = 3)	1.3% (n = 1)	1.3% (n = 1)

The percentages and the numbers (n) represent the proportion of the population concerned, as assessed by the patient him/herself and his/her caregiver on a five-point scale at the last examination.

(leading to discontinuation). At the final examination, the average "on levodopa" Hoehn Yahr stage was 3.3 ±1.2, the average "on levodopa" UPDRS motor score was 26.8 ±10 (35 available analyses) and the average MMSE score was 23 ± 4.2. Ninety-two percent of the patients stated an improvement in their quality of life. Improvements in terms of autonomy (90% of cases) and CGI (99% of cases) were also reported (Table 2).

Safety was assessed in all 91 patients. Seven patients (all bedridden) died from pneumonia due to severe dysphagia. One patient suffered cardiac arrest after the gastrostomy, despite the absence of obvious surgical and anesthesia-related anomalies. All adverse events are reported in Table 3. Four patients had a peritoneal reaction qualified as peritonitis. Two cases of severe psychosis were noted. In the 42% of patients who had suffered from severe hallucinations before initiation of duodenal levodopa infusion, none reported a worsening. One or more technical problems were noted in 62.6% (n = 57) of the patients. Technical aspects led to discontinuation in six patients. One elderly, female subject discontinued the treatment after complaining that the pump was too heavy.

DISCUSSION

This report is the first ever exhaustive collection of data on almost all French PD patients having received Duodopa treatment in their natural care environment. The very advanced disease stage of our population was reflected by the long duration of motor complications, the high rate of cognitive and behavioral complications, related with the age and the long disease duration, and the death of seven bedridden patients. Our results demonstrate that in France, duodenal levodopa infusion represents the prime treatment for motor complications after apomorphine pump and STN stimulation has failed or been ruled out in 98% of the population. Conversely, duodenal levodopa infusion was the primary choice in only 2% of the population who met the indication criteria for STN stimulation[15] or apomorphine pump therapy. Our unselected population differed from those in the four previous studies,[9,11,14,16] which reported results for small (n = 7–28) cohorts of selected patients free of dementia, hallucinations or psychiatric disorders (and who thus met the criteria for deep brain stimulation).[9,11,14,16] This could be partly related to the widespread use of STN stimulation and apomorphine pump therapy in France. Moreover, gastrostomy might be considered by some patients as an end-of-life act.

The study was designed to exhaustively assess the characteristics of the population, the main indication and to report the safety concerns. To obtain the maximum of responses from the centers on these criteria, the three- and five-level scales, were chosen, despite

TABLE 3. *Safety of duodenal levodopa infusion in all 91 patients*

Adverse events	Frequency (n = 91)	Adverse events	Frequency (n = 91)	Leading to discontinuation
Related to levodopa treatment	2.2% (n = 2)	Severe psychosis induction within a week of starting treatment	2.2% (n = 2)	2.2% (n = 2)
Related to gastrostomy	18% (n = 18)	Peritonitis	4.3% (n = 4)	No
		Transient, benign, local treated infection	9.8% (n = 9)	1% (n = 1)
		Persistent, benign, local inflammation	2.2% (n = 2)	No
		Transient, benign, local inflammation	3.3% (n = 3)	No
Related to technical aspects and requiring replacement	62.6% (n = 57)	Pump failure	5.5% (n = 5)	No
		Inner tube disconnected responsible for leakage	19.8% (n = 18)	No
		Inner tube pulled out because of severe motor handicap or dementia	17.5% (n = 16)	3.3% (n = 3)
		Inner tube obstructed	16.5% (n = 15)	No
		Inner tube dislocated with secondary migration in the intestine	20.8% (n = 19)	3.3% (n = 3)

Adverse events classified according to their relationship with (1) levodopa treatment, (2) gastrostomy, or (3) technical aspects.

the methodological limitation, to easy rate the efficacy. Patients, caregivers, and neurologists were highly satisfied regarding motor complication control, which represented the main indication. A high proportion of neurologists also reported an improvement in pain and axial signs. Quality of life, autonomy and clinical global status were also frequently improved. Our results agree with other studies reporting reduced motor complications on the UPDRS part II and IV[9,11,14,16] scales and improvements in quality of life on the PDQ39 scale.[11,16]

In contrast to previous reports, we observed an increase in the mean daily levodopa-equivalent dose during duodenal levodopa infusion. Indeed, previous studies have reported either a lack of difference after only 2 or 3 weeks[11,16] or a decreased by an average of 5% after a mean of 3.7 years in 65 patients.[17]

Only two patients reported severe psychosis, leading to treatment discontinuation. Despite the slightly higher daily levodopa-equivalent dose, the patients with severe hallucinations (42%) remained stable and most study patients reported a decrease in dyskinesia. This could be explained by clozapine use in 30% and the less pulsatile administration of levodopa provided by duodenal infusion, since a simple relationship between daily levodopa-equivalent dose and hallucinations has not been found.[18] Transient, local, benign complications related to gastrostomy were noted in 14% of the population. The diagnosis of peritonitis was raised in 4%, based on a combination of pneumoperitonitis and fever; although pneumoperitonitis is normal the day after gastrostomy and fever can be also encountered after gastrostomy. The rapid, full recovery after a second surgery and the continuation of treatment for all but one of the patients argues against severe peritonitis. No deaths were considered to be directly related to gastrostomy. Seven patients developed pneumonia several days after the gastrostomy, raising the question of the risk of gastrotomy in a very elderly, advanced PD population.

Duodenal levodopa infusion still suffers from a high incidence of technical problems, with the inner tube frequently requiring replacement. These complications (notably the inner tubes pulled out or dislocated) may have been further exaggerated by the high degree of motor handicap and the presence of dementia. These factors probably increase the treatment's overall cost and worsen its psychological tolerability. Indeed, these technical problems prompted seven patients to stop the treatment. These aspects need to be improved if duodenal levodopa infusion is to develop further. At present, the use of endoscopic gastrostomy for duodenal infusion avoids the need for general anesthesia but requires an inner tube. In contrast, direct jejunostomy requires brief general anesthesia but has the advantage to avoid inner tube. In our practice, two patients underwent jejunostomy, which eliminated technical complications and had better ergonomics. Previous studies in small samples of selected, less advanced PD patients have reported that (1) adverse events are rare and benign and (2) the occurrence of PD-related psychiatric and cognitive complications led to discontinuation of duodenal levodopa infusion.[9,11,14,16] Our study underlined (1) the higher frequency of adverse events in patients with advanced PD and (2) the risk/benefit ratio in the treatment of severe motor complications seemed to be still favorable in advanced PD. The high degree of nurse involvement in everyday use of duodenal levodopa infusion may be regarded as a limiting economic factor but could easily be reduced by educating the patients and caregivers.

In conclusion, the favorable risk/benefit ratio of duodenal levodopa infusion raises the question of earlier introduction of this technique for motor complication control and (probably) better systemic and local tolerability. However, some technical aspects need to be further improved and jejunostomy should be considered. Because of the retrospective design, our results require confirmation in a large, prospective trial. Further studies comparing the risk/benefit ratio and economic aspects of early introduction of duodenal levodopa infusion (relative to deep brain stimulation and apomorphine pump therapy) are also warranted.

APPENDIX

French DUODOPA Study Group: Agid Y (Department of Neurology, Hôpital La Pitié Salpetrière Paris, France), Al Khedr A (Department of Neurology, CHU Amiens, Centre Nord, France), Annic A (Department of Neurology, EA2683 IFR114 IMPRT, CHU Lille, France), Azulay JP (Department of Neurology, CHU Timone, Marseilles, France), Bakchine S (Department of Neurology, Hôpital de la Maison Blanche, Reims, France), Barroche G (Department of Neurology, Hôpital Central Nancy, France), Bayreuter C (Department of Neurology, Hôpital Pasteur, Nice, France), Benoit T (Department of Neurology, Hôpital Robert Ballanger Aulnay sous Bois, France), Billaud B (Department of Neurology, Hôpital Des Hauts Clos Troyes, France), Bonnefoi B (Department of Neurology, CH du Pays d'Aix, Aix en Provence, France), Bonnet AM (Department of Neurology, Hôpital La Pitié Salpetrière Paris), Borg M (Department of Neurology, Hôpital Pasteur,

Nice, France), Brefel-courbon C (Department of Neurology, Hôpital Purpan, Toulouse, France), Brandel JP (Department of Neurology, Hôpital Leopold Bellan, Paris, France), Broussolle E (Department of Neurology, Hôpital Neuro Pierre Wertheimer, Lyon, France), Busson P (Department of Neurology, CH Avranches, France), Cantiniaux S (Department of Neurology, CHU Timone, Marseilles, France), Césaro P (Department of Neurology, Hôpital H. Mondor, Créteil, France), Corvol JC (Department of Neurology, Hôpital La Pitié Salpetrière Paris), Coustans M (Department of Neurology, CH De Cornouaille, Quimper, France), Damier P (Department of Neurology, Hôpital Guillaume Et Rene Laennec, Nantes, France), Danisi C (Department of Neurology, CH du Pays d'Aix, Aix en Provence, France), Decombe R (Department of Neurology, Hôpital Des Hauts Clos Troyes, France), Defebvre L (Department of Neurology, EA2683 IFR114 IMPRT, CHU Lille, France), Derkinderen P (Department of Neurology, Hôpital Guillaume Et Rene Laennec, Nantes, France), Destée A (Department of Neurology, EA2683 IFR114 IMPRT, CHU Lille, France), Doedemaindreville A (Department of Neurology, Hôpital de la Maison Blanche, Reims, France), Drapier S (Department of Neurology, Hôpital Pontchaillou, Rennes, France), Dupuy D (Department of Neurology, CHU Amiens, Centre Nord, France), Fénelon G (Department of Neurology, Hôpital H. Mondor, Créteil, France), Gayraud D (Department of Neurology, CH du Pays d'Aix, Aix en Provence, France), Gérard P, Godefroy O (Department of Neurology, CHU Amiens, Centre Nord, France), Godet E (Department of Neurology, Hôpital Notre Dame du Bon Secours, Metz, France), Grabli D (Department of Neurology, Hôpital La Pitié Salpetrière Paris), Gros P (Department of Neurology, CH Fréjus, France), Houeto JL (Department of Neurology, CHU La Miletrie, Poitiers, France), Kreisler A (Department of Neurology, EA2683 IFR114 IMPRT, CHU Lille, France), Krystkowiak P (Department of Neurology, EA2683 IFR114 IMPRT, CHU Lille, France, Department of Neurology, CHU Amiens, Centre Nord, France), Lallement F, Madigand F (Department of Neurology, Hôpital Y. le Foll, CH De St Brieuc, France), Mesnage V (Department of Neurology, CHU La Miletrie, Poitiers, France), Moreau C (Department of Neurology, EA2683 IFR114 IMPRT, CHU Lille, France), Nahum-Moscovici L (Department of Neurology, Hôpital Robert Ballanger Aulnay sous Bois, France), Ory-Magnier F (Department of Neurology, Hôpital Purpan, Toulouse, France), Rascol O (Department of Neurology, Hôpital Purpan, Toulouse, France), Remy P (Department of Neurology, Hôpital H. Mondor, Créteil, France), Renié L (Department of Neurology, CH du Pays d'Aix, Aix en Provence, France), Seguy D (Department of Gastroenterology, CHU Lille, France), Senard JM (Department of Neurology, Hôpital Purpan, Toulouse, France), Thobois S (Department of Neurology, Hôpital Neuro Pierre Wertheimer, Lyon, France), Tranchant C (Department of Neurology, Hôpital Civil, Strasbourg, France), Vérin M (Department of Neurology, Hôpital Pontchaillou, Rennes, France), Viallet F (Department of Neurology, CH du Pays d'Aix, Aix en Provence, France), Vidailhet M (Department of Neurology, Hôpital La Pitié Salpetrière Paris), Wagner M (Department of Neurology, Hôpital Notre Dame du Bon Secours, Metz, France), Witjas T (Department of Neurology, CHU Timone, Marseilles, France), Xie J (Department of Neurology, Hôpital Neuro Pierre Wertheimer, Lyon, France), Zagnoli F (Department of Neurology, Hôpital Clermont Tonnerre, Brest, France), Ziegler M (Department of Neurology, Hôpital Leopold Bellan, Paris, France).

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