The Timing of Continuous Dopaminergic Stimulation for Optimal Clinical Outcomes

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Abstract

The timing of continuous dopaminergic stimulation (CDS) treatment is an important consideration for achieving optimal motor functioning in Parkinson's disease patients. Delaying treatment with levodopa/carbidopa intestinal gel (LCIG) infusion in patients with severe 'on-off' fluctuations may result in a poorer and slower response, while early initiation of CDS therapy increases the chance of achieving continuous 'on' without dyskinesia. Furthermore, overnight LCIG infusion is indicated when there is severe akinesia overnight, but daytime-only LCIG infusion treatment can lead to a reduction in overnight motor fluctuations after several months.

Keywords

Parkinson's disease, levodopa, continuous dopaminergic stimulation, levodopa/carbidopa intestinal gel infusion, motor fluctuations

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The timing of continuous dopaminergic stimulation (CDS) therapy is an important consideration in achieving the most favourable motor outcomes. According to the official product information in Germany, levodopa/carbidopa intestinal gel (LCIG) infusion should be used for the 'treatment of advanced, levodopa-responsive Parkinson's disease with severe motor fluctuations AND hyper-/dyskinesia when available antiparkinsonian treatment is not satisfying anymore'.[1] In Germany, younger patients without cognitive impairments are more likely to receive deep brain stimulation (DBS), while older patients with cognitive impairments are more likely to receive LCIG infusion therapy. In addition, there is a tendency in Germany for DBS to be performed when there is only 'wearing off' in patients, while LCIG infusion treatment is not initiated before there are more severe motor fluctuations including hyperkinesia. An interesting question is whether this approach to use LCIG treatment later in the course of the disease compared with DBS is optimal. Two patient cases are presented here to illustrate the effects of starting LCIG infusion at different stages of Parkinson's disease (PD), and the effects of daytime-only LCIG infusion on overnight motor fluctuations.

Case Reports

Baseline Motor Performance

Two patient cases are presented and these are referred to as 'Patient 1' and 'Patient 2'. Patient 1 is a man in his early 60s who experienced severe motor fluctuations. Sometimes he only had good motor 'on' for about 20 % of the day and was either 'off' or 'on with severe dyskinesia' for the remainder of the day. He sometimes shifted from 'on' with severe dyskinesia directly to the 'off' phase, and had very difficult nights with severe 'off' phases (see *Table 1A*). Patient 1 had depression, cognitive impairment and slight hallucinations, and was taking the following medications when he first presented at our department: levodopa 200 mg every three hours (six times daily), entacapone 200 mg every three hours (six times daily), amantadine 200 mg twice daily, cabergoline 4 mg once daily and levodopa at request (up to 600 mg a day). Most of the levodopa at request was taken at night to treat severe night-time 'off' phases. He also took mirtazapine 15 mg in the evening and escitalopram 10 mg in the morning for his depression, and quetiapine 25 mg in the evening for his hallucinations.

Patient 2 is a man in his late 60s, and suffered from motor fluctuations, moving between 'off' and 'on' phases, with no dyskinesia (see *Table 2A*). He was taking levodopa 100–150 mg every 2.5 hours, levodopa slow-release 200 mg at night and rotigotine 4 mg (a higher dose was not possible because of orthostatic problems). He could not be treated with entacapone or tolcapone because of severe diarrhoea, and other dopamine agonists were not tolerated because of orthostatic problems. In addition, further increases in levodopa dosage were not tolerated due to severe orthostatic hypotension. Despite his medications, the patient was still experiencing 'off' phases. Furthermore, he had severe night-time cramping that did not respond to levodopa, magnesium or quinine treatment.

Table 1A: Patient 1 – Diary at Baseline before Starting Levodopa/Carbidopa Intestinal Gel Infusion Therapy

Time	Sleep	OFF	ON	ON slight dys	ON severe dys
06:00		X			
06:30			X		
07:00			X		
07:30			X		
08:00		X			
08:30		X			
09:00			X		
09:30				X	
10:00					X
10:30					X
11:00					X
11:30					X
12:00				X	
12:30				X	
13:00					X
13:30					X
14:00				X	
14:30			X		
15:00			X		
15:30			X		
16:00		X			
16:30			X		
17:00		X			
17:30		X			

Time	Sleep	OFF	ON	ON slight dys	ON severe dys
18:00		X			
18:30		X			
19:00		X			
19:30		X			
20:00			X		
20:30		X			
21:00		X			
21:30			X		
22:00			X		
22:30			X		
23:00			X		
23:30		X	200 mg Levodopa		
00:00		X			
00:30	X				
01:00	X				
01:30		X	200 mg Levodopa		
02:00	X				
02:30	X				
03:00	X				
03:30		X	200 mg Levodopa		
04:00		X			
04:30		X			
05:00		X			
05:30		X			

Table 1B: Patient 1 – Diary at Five Days after Starting Levodopa/Carbidopa Intestinal Gel Infusion Therapy

Time	Sleep	OFF	ON	ON slight dys	ON severe dys
06:00					
06:30					
07:00		X			
07:30		X			
08:00				X	
08:30				X	
09:00				X	
09:30				X	
10:00					X
10:30					X
11:00					X
11:30					X
12:00					X
12:30					X
13:00			X		
13:30			X		
14:00		X			
14:30		X			
15:00				X	
15:30				X	
16:00				X	
16:30				X	
17:00			X		
17:30			X		

Time	Sleep	OFF	ON	ON slight dys	ON severe dys
18:00		X			
18:30		X			
19:00			X		
19:30			X		
20:00			X		
20:30			X		
21:00			X		
21:30			X		
22:00		X			
22:30		X			
23:00			X		
23:30			X		
00:00					
00:30					
01:00					
01:30					
02:00					
02:30					
03:00					
03:30					
04:00					
04:30					
05:00					
05:30					

Table 1 is continued on next two pages.

Table 1C: Patient 1 – Diary at One Month after Starting Levodopa/Carbidopa Intestinal Gel Infusion Therapy

Time	Sleep	OFF	ON	ON slight dys	ON severe dys
06:00	X				
06:30		X			
07:00		X			
07:30			X		
08:00				X	
08:30			X		
09:00			X		
09:30				X	
10:00		X			
10:30			X		
11:00			X		
11:30			X		
12:00			X		
12:30			X		
13:00			X		
13:30			X		
14:00			X		
14:30		X			
15:00			X		
15:30			X		
16:00			X		
16:30		X			
17:00		X			
17:30		X			

Time	Sleep	OFF	ON	ON slight dys	ON severe dys
18:00		X			
18:30			X		
19:00			X		
19:30			X		
20:00			X		
20:30			X		
21:00				X	
21:30					X
22:00					X
22:30					X
23:00					X
23:30					X
00:00			X		
00:30		X	200 mg Levodopa		
01:00		X			
01:30		X			
02:00		X	200 mg Levodopa		
02:30	X				
03:00	X				
03:30		X	200 mg Levodopa		
04:00	X				
04:30	X				
05:00	X				
05:30	X				

Table 1D: Patient 1 – Diary at Three Months after Starting Levodopa/Carbidopa Intestinal Gel Infusion Therapy

Time	Sleep	OFF	ON	ON slight dys	ON severe dys
06:00	X				
06:30	X				
07:00		X			
07:30		X			
08:00				X	
08:30				X	
09:00				X	
09:30				X	
10:00				X	
10:30				X	
11:00				X	
11:30				X	
12:00			X		
12:30			X		
13:00			X		
13:30			X		
14:00			X		
14:30			X		
15:00		X			
15:30			X		
16:00			X		
16:30			X		
17:00			X		
17:30			X		

Time	Sleep	OFF	ON	ON slight dys	ON severe dys
18:00			X		
18:30			X		
19:00		X			
19:30		X			
20:00			X		
20:30			X		
21:00				X	
21:30				X	
22:00				X	
22:30			X		
23:00		X			
23:30	X				
00:00	X				
00:30	X				
01:00		X	200 mg Levodopa		
01:30		X			
02:00		X			
02:30		X			
03:00		X	200 mg Levodopa		
03:30			X		
04:00			X		
04:30			X		
05:00		X			
05:30		X			

Table 1E: Patient 1 – Diary at Six Months after Starting Levodopa/Carbidopa Intestinal Gel Infusion Therapy

Time	Sleep	OFF	ON	ON slight dys	ON severe dys
06:00	X				
06:30	X				
07:00	X				
07:30	X				
08:00	X				
08:30			X		
09:00			X		
09:30			X		
10:00			X		
10:30			X		
11:00			X		
11:30			X		
12:00			X		
12:30			X		
13:00			X		
13:30			X		
14:00			X		
14:30			X		
15:00			X		
15:30				X	
16:00				X	
16:30				X	
17:00				X	
17:30				X	

Time	Sleep	OFF	ON	ON slight dys	ON severe dys
18:00			X		
18:30		X			
19:00				X	
19:30				X	
20:00				X	
20:30				X	
21:00				X	
21:30				X	
22:00				X	
22:30					X
23:00					X
23:30					X
00:00					X
00:30					X
01:00					X
01:30	X		No Levodopa		
02:00	X		required overnight		
02:30	X				
03:00	X				
03:30	X				
04:00	X				
04:30	X				
05:00	X				
05:30	X				

Table 1A–E: Patient 1 received levodopa/carbidopa intestinal gel (LCIG) infusion from 06:30 until 22:30 and additional levodopa tablets at night as requested. At five days after starting therapy (Table 1B), night-time fluctuations were not assessed as this was during hospital stay. Six months after, night-time levodopa was no longer required. Dys = dyskinesia.

Early versus Delayed Initiation of Levodopa/Carbidopa Intestinal Gel Infusion Treatment

LCIG infusion therapy was considered as a treatment option for these two patients. Patient 1 was also considered for DBS, but there was a higher risk of side effects due to his cognitive impairments and depression. Thus, after discussion of his treatment options, the patient decided to go for LCIG treatment. Patient 2 was primarily considered for DBS but he refused brain operation and was therefore offered LCIG infusion.

The issue was, would LCIG infusion treatment be meaningful for these patients, and if it was, should it be started immediately or delayed? For example, was the treatment suitable for Patient 2, who had a fluctuating syndrome with no hyperkinesia? Patient 1 was 15 years into his disease, with already several years of dyskinesia, while Patient 2 was eight years into his disease with only 'on-off' phenomenon, when they first came to our clinic. In the end, both started LCIG infusion treatment within six months of their first visit to our clinic. Their motor performance over time is presented below.

Motor Performance of Patient 1 Over Time

Five days after having started LCIG infusion treatment via nasojejunal tubing, Patient 1's motor function did not improve significantly (see *Table 1B*). However, he already felt better and decided to go for percutaneous endoscopic gastrostomy surgery. At discharge from hospital, his effective LCIG morning dose – i.e., after filling of percutaneous endoscopic jejunostomy tubing – was 10 ml. His LCIG infusion was at a continuous rate of 6.8 ml/h, with an extra dose of 4 ml. The patient was advised to only take extra doses when absolutely required, and over the coming months he was very restrictive in this respect and only applied a maximum of one extra dose per day, even though the severity of frequent 'off' phases would have necessitated more. After one month, there was increased time spent in the 'on' phase and less severe hyperkinesias in the morning (see *Table 1C*). However, the fluctuations were still severe in the afternoon, and there remained many 'off' phases during the night. After three months, 'on' phases increased, but there were still profound motor fluctuations (see *Table 1D*). Furthermore, the nights remained difficult. Only after six months of LCIG infusion treatment did the patient report a substantial change: he experienced 'on' with slight or no dyskinesia for most of the morning and afternoon (see *Table 1E*). The nights improved and the patient did not experience severe night-time akinesia anymore. He was able to go to the bathroom at night, which had not been possible before due to akinesia, and during most nights he was able to sleep continuously without waking up due to severe 'off' phases. This situation has now remained stable for more than 2.5 years after initiation of LCIG infusion treatment.

Motor Performance of Patient 2 Over Time

In contrast, after only five days of treatment with LCIG infusion, Patient 2 was in the 'on' phase continuously, with no hyperkinesias (see *Table 2B*). At discharge from hospital, his effective morning dose was 4 ml, the continuous rate was 3.8 ml/h and he did not require any extra doses. A good response to LCIG treatment was maintained at one month, with only 30 minutes of 'off' time a day (see *Table 2C*). This situation has now been stable for more than one year after the start of LCIG infusion treatment. The patient has a maximum of two hours of 'off' periods during the day, but these are much less severe than before LCIG treatment and do not require an extra LCIG dose.

Table 2A: Patient 2 – Diary at Baseline before Starting Levodopa/Carbidopa Intestinal Gel Infusion Therapy

Time	Sleep	OFF	ON	ON slight dys	ON severe dys
06:00		X			
06:30	X				
07:00		X			
07:30		X			
08:00	X				
08:30		X			
09:00		X			
09:30		X			
10:00			X		
10:30			X		
11:00			X		
11:30			X		
12:00			X		
12:30			X		
13:00			X		
13:30			X		
14:00		X			
14:30		X			
15:00		X			
15:30			X		
16:00			X		
16:30			X		
17:00		X			
17:30	X				
18:00		X			
18:30			X		
19:00			X		
19:30		X			
20:00		X			
20:30			X		
21:00			X		
21:30			X		
22:00		X			
22:30		X			
23:00		X			
23:30		X			
00:00	X				
00:30	X				
01:00	X				
01:30	X				
02:00	X				
02:30	X				
03:00	X				
03:30	X				
04:00		X			
04:30	X				
05:00	X				
05:30		X			

Table 2B: Patient 2 – Diary at Five Days after Starting Levodopa/Carbidopa Intestinal Gel Infusion Therapy

Time	Sleep	OFF	ON	ON slight dys	ON severe dys
06:00					
06:30					
07:00		X			
07:30		X			
08:00			X		
08:30			X		
09:00			X		
09:30			X		
10:00			X		
10:30			X		
11:00			X		
11:30			X		
12:00			X		
12:30			X		
13:00			X		
13:30			X		
14:00			X		
14:30			X		
15:00			X		
15:30			X		
16:00			X		
16:30			X		
17:00			X		
17:30			X		
18:00			X		
18:30		X			
19:00			X		
19:30			X		
20:00			X		
20:30			X		
21:00			X		
21:30			X		
22:00			X		
22:30					
23:00					
23:30					
00:00					
00:30					
01:00					
01:30					
02:00					
02:30					
03:00					
03:30					
04:00					
04:30					
05:00					
05:30					

Table 2 is continued on the next page.

Table 2C: Patient 2 – Diary at One Month after Starting Levodopa/Carbidopa Intestinal Gel Infusion Therapy

Time	Sleep	OFF	ON	ON slight dys	ON severe dys
06:00		X			
06:30			X		
07:00			X		
07:30			X		
08:00			X		
08:30			X		
09:00			X		
09:30			X		
10:00			X		
10:30			X		
11:00			X		
11:30			X		
12:00			X		
12:30			X		
13:00			X		
13:30			X		
14:00			X		
14:30			X		
15:00			X		
15:30			X		
16:00			X		
16:30			X		
17:00			X		
17:30			X		

Time	Sleep	OFF	ON	ON slight dys	ON severe dys
18:00			X		
18:30			X		
19:00			X		
19:30			X		
20:00			X		
20:30			X		
21:00			X		
21:30			X		
22:00	X				
22:30	X				
23:00	X				
23:30	X				
00:00	X				
00:30	X				
01:00	X				
01:30	X				
02:00	X				
02:30	X				
03:00	X				
03:30	X				
04:00	X				
04:30	X				
05:00	X				
05:30	X				

Table 2A–C: At five days after starting therapy (Table 2B), night-time fluctuations were not assessed as this was during hospital stay. Dys = dyskinesia.

Conclusion

These cases show that titration of LCIG infusion is straightforward when motor fluctuations are not very severe, as in Patient 2. In addition, early initiation of LCIG infusion therapy, before the development of severe motor fluctuations, may induce a motor state of continuous 'on' without dyskinesia. In the case of Patient 2, this continuous 'on' has now been sustained for more than one year after initiation of treatment.

This suggests that early initiation of LCIG infusion treatment may optimally re-open the therapeutic window. This theory is supported by data in animal models of PD, which show that CDS achieved by transplantation of dopamine neurons[2,3] or intracerebral gene therapy[4,5] improves motor function, reduces the severity of pre-existing levodopa-induced dyskinesias and prevents the development of levodopa-induced dyskinesia.

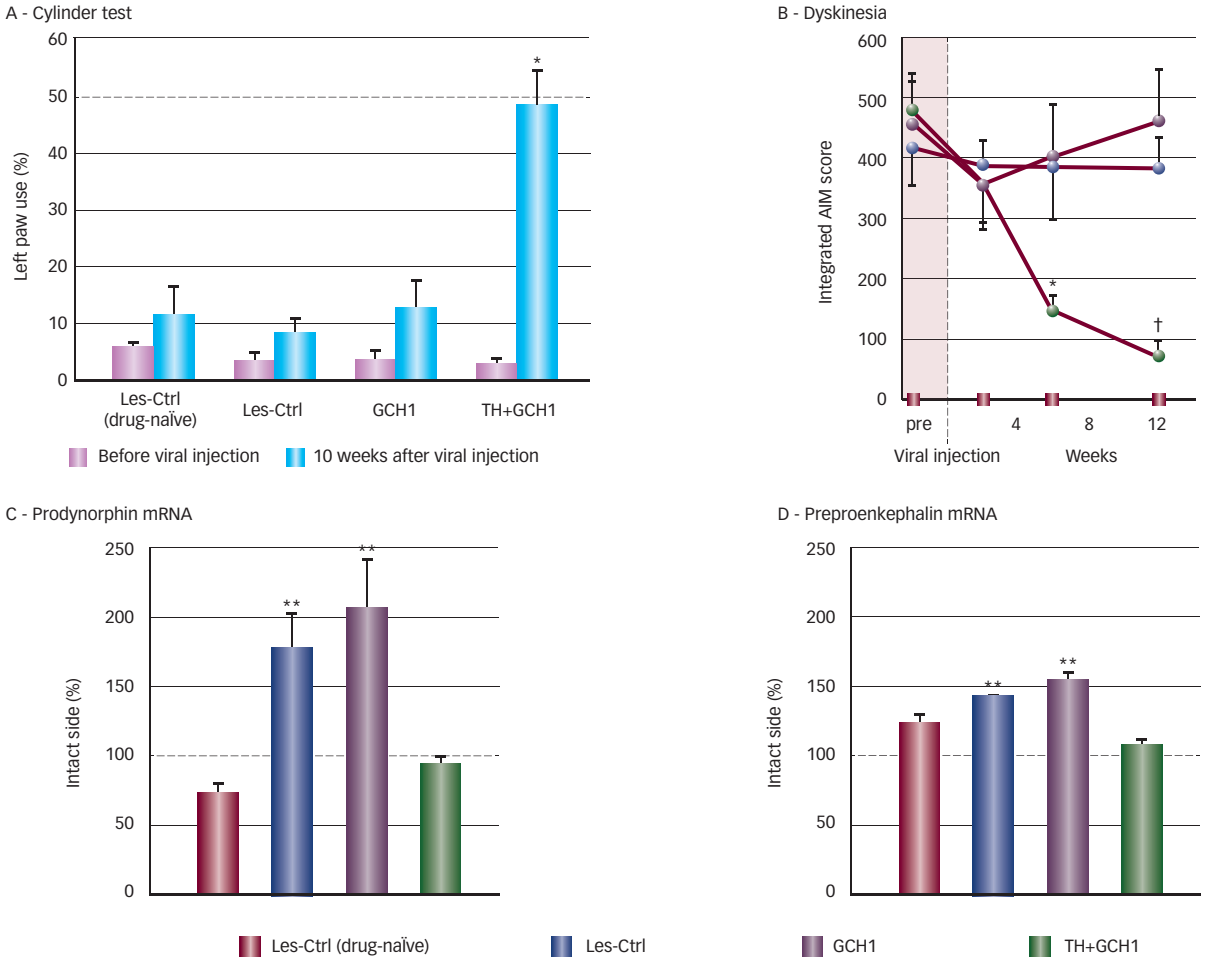
Levodopa/Carbidopa Intestinal Gel Infusion Treatment and Night-time Akinesia

At baseline, Patient 1 took 600 mg levodopa overnight (a 200 mg dose at 23:30, 01:30 and 03:30) for his severe night-time akinesia (see *Table 1A*). The medication reduced the severity of the night-time 'off' phases, but they were still present and sleep was severely disturbed by them. The official product guidelines in Germany state that LCIG infusion treatment may be continued overnight only if there is a medical reason.[1] Patient 1 was prescribed LCIG infusion therapy from 06:30 to 22:30 at an infusion rate of 6.8 ml/h. Due to the night-time 'off' phases and the need for oral levodopa boluses throughout the night, he could potentially benefit from 24-hour LCIG infusion. After one month of LCIG infusion treatment, the patient continued to have many 'off' phases and very disturbed sleep at night, requiring him to take 600 mg levodopa (200 mg at 00:30, 02:00 and 03:30 – see *Table 1C*). The possibility to perform 24-hour LCIG infusion was discussed with the patient, but he decided to continue with daytime treatment only. After three months, sleep remained very disturbed, but the patient reported that 'off' phases felt a little less severe and he needed 'only' 400 mg levodopa overnight (200 mg at 01:00 and 03:00 – see *Table 1D*). After six months, overnight levodopa was no longer required and the patient was able to sleep through the night (see *Table 1E*). At the same time, his daytime motor fluctuations were largely eliminated. He has not needed overnight levodopa up to now, after more than 2.5 years of LCIG infusion treatment.

Although continuation of LCIG infusion treatment overnight is indicated when there is severe akinesia at night, we have observed in Patient 1 and in two other patients that, several months after starting daytime-only LCIG infusion treatment, overnight motor fluctuations subsided. This suggests that there is plasticity in the brain that requires some months to fully develop and that treatment may thus take some months to exert its full effect.

It has been shown in an animal model of PD that CDS by intracerebral gene therapy normalises mRNA expression of critical genes in the brain in parallel with improving motor behaviours and dyskinesia (see *Figure 1*).[4] The study used animals with the equivalent of late-stage PD that were having severe motor fluctuations – i.e., comparable to Patient 1 – and the full motor effect and reduction of dyskinesia in these animals were not seen until three months into treatment.

Figure 1: Behavioural and Molecular Changes after Gene Therapy in the Rat Parkinson's Disease Model



*A: Spontaneous forelimb use in rats evaluated by the cylinder test before and 10 weeks after viral vector injection. Rats were placed in a glass cylinder and spontaneous explorations were measured by paw contacts to the cylinder wall. Rats with unilateral 6-hydroxydopamine lesions usually do not use their bad paw, which is shown by reduced left paw use. Rats were given daily injections of levodopa (Les-Ctrl) or vehicle (Les-Ctrl [drug-naïve]) for 22 days. Among the rats given levodopa injections, some received viral vectors encoding dopamine-synthesising enzymes, either GTP cyclohydrolase 1 (GCH1) only or GCH1 plus tyrosine hydroxylase (TH). Data show left (i.e., impaired) paw use as a percentage of the total paw contacts with the wall of the cylinder. The dashed line at 50 % represents symmetric paw use displayed by normal rats. Before viral vector injection, all groups showed a strong bias in paw use. The group that received the combined TH + GCH1 gene transfer showed complete recovery in left paw use at 10 weeks. * Significant difference from all other groups (p<0.0001). B: Time course of levodopa-induced dyskinesia measured as integrated abnormal involuntary movement (AIM) score after transduction with viral vectors encoding for GCH1 and TH. The dashed line represents the time point of viral vector injection. After six weeks, dyskinesia is reduced, but this effect is not fully developed before 12 weeks after viral vector injection. * Significantly different from levodopa-treated sham controls and rAAV-GCH1 control vector-injected animals; † not different from drug-naïve lesion animals [one-way ANOVAs [6 weeks: F(3,32) = 7.41, p=0.0008; 12 weeks: F(3,32) = 17.57, p<0.0001], followed by Tukey's HSD post hoc analysis]. C and D: The expression of prodynorphin (C) and preproenkephalin (D) messenger RNA (mRNA) in the striatum is significantly increased in dyskinetic animals (Les-Ctrl group). After treatment with viral vectors encoding for GCH1 and TH, both mRNA expressions are normalised. ** Significantly different from the drug-naïve control group and the rAAV-TH + rAAV-GCH1 vector group [one-way ANOVAs [prodynorphin: F(3,32) = 8.97, p=0.001; preproenkephalin: F(3,32) = 20.98, p<0.0001]; followed by Tukey's HSD post hoc analysis]. Source: Modified from T Carlsson, C Winkler, C Burger, N Muzyczka, RJ Mandel, A Cenci, A Björklund, D Kirik, Reversal of dyskinesias in an animal model of Parkinson's disease by continuous l-DOPA delivery using rAAV vectors,* Brain*, 2005, 128, 3, 559–69,[4] by permission of Oxford University Press.*

This plasticity in the brain, as seen in the animal model, may be the correlate to the motor improvement seen in our patients.

Overall Conclusion

The patient cases presented in this article illustrate the importance of the timing of CDS treatment in achieving optimal motor improvement. Earlier initiation of CDS treatment by LCIG infusion, before the development of severe motor fluctuations including dyskinesia, may induce good motor effects within a short period of time after initiation of treatment, and at the same time improves the likelihood of achieving continuous 'on' with no dyskinesia. With late initiation of LCIG treatment, patients will also show great benefit, including improvement of motor function and reduction of fluctuations, but this process may take longer compared with early initiation of LCIG treatment. Furthermore, achieving a state of continuous 'on' either with or without dyskinesia may be the maximum effect that can be expected. In addition, although overnight LCIG infusion is indicated when there is severe night-time akinesia, daytime-only LCIG infusion treatment can lead to reduced overnight motor fluctuations after several months in some patients. As demonstrated in animal studies, CDS therapy may bring about changes in the brain that correlate with improvements in motor function. Further research into this brain plasticity may help to further enhance CDS treatment of PD patients. ■

1. Duodopa® product information, Abbott Products GmbH, Hannover, Germany, January 2011.
2. García J, Carlsson T, Döbrössy M, et al., Impact of dopamine to serotonin cell ratio in transplants on behavioral recovery and L-DOPA-induced dyskinesia, *Neurobiol Dis,* 2011;43:576–87.
3. Lee CS, Cenci MA, Schulzer M, Björklund A, Embryonic ventral mesencephalic grafts improve levodopa-induced dyskinesia in a rat model of Parkinson's disease, *Brain,* 2000;123:1365–79.
4. Carlsson T, Winkler C, Burger C, et al., Reversal of dyskinesias in an animal model of Parkinson's disease by continuous L-DOPA delivery using rAAV vectors, *Brain,* 2005;128:559–69.
5. Björklund T, Carlsson T, Cederfjäll EA, et al., Optimized adeno-associated viral vector-mediated striatal DOPA delivery restores sensorimotor function and prevents dyskinesias in a model of advanced Parkinson's disease, *Brain,* 2010;133:496–511.