A Human Factors Study of the DopaFuse® Delivery System

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Objective

SynAgile has developed the DopaFuse Delivery System to noninvasively and continuously administer oral LD/CD into the mouths of patients with Parkinson's Disease (PD). The system is intended to reduce fluctuation in plasma levodopa levels and the associated motor symptoms. The objective of this study is to test whether the System can be used safely by the intended users in the a planned Phase 2 clinical trial.

Background

DopaFuse is the first of a new class of drug delivery devices that reside in the mouth and that non-invasively and continuously deliver drugs to patients at a constant rate for absorption via the gastro-intestinal and/or buccal routes. The System consists of a reusable custom dental retainer, its case, and a pre-filled, single-use drug Container, shown in Figures 1-3.

Fig. 1: Retainer

Fig. 2: Drug Container

Fig. 3: Case

Multiple clinical studies have demonstrated that continuous administration of a short-acting dopaminergic agent such as levodopa is associated with reduced motor complications in comparison to intermittent dosing with the same agent[1-11]. Continuous intra-intestinal infusion of levodopa has been shown to reduce motor "off" time and increase"on" time with no increase in dyskinesia in comparison to optimized treatment with standard doses of oral levodopa therapy[10, 12, 13]. However, intestinal infusion is cumbersome and is associated with frequent and potentially serious adverse events related to the surgical procedure,the tubing and the pump.

SynAgile conducted a single proof-of-concept study in 2015 to test the hypothesis that continuous oral delivery of LD/CD results in improved LD pharmacokinetics and reduced Off time. The study found significantly less variability in plasma LD concentration and reduced Off with continuous versus intermittent oral levodopa delivery.[14] Based on the positive results of the study, the DopaFuse Delivery System is being developed to provide the benefits of continuous LD/CD delivery with fewer complications than existing treatments for advanced PD.

Methods

This formative human factors study was conducted on five patient-participant pairs. Each pair consisted of one patient with advanced PD along with their adult caregiver. Pairs attended a single training session followed by a one-hour decay period before testing. Testing was conducted with the patient participant alone, with the caregiver participant alone, and the patient-caregiver pair together.

During each session, the participant was asked to set up the system for use, simulate use on a manikin, and store the System. Participants were tested on their ability to conduct the critical task of inserting the drug container properly into the retainer, as as well as a number of non-critical tasks. The critical task was evaluated by two study assessments; one was conducted by observing participants' performance, while the second was presented as a knowledge task question. Success was defined as ability to complete the tasks safely without requiring further help.

Aside from the critical task, 12 performance tasks required in the Instructions for Use were also tested. Tasks tested include opening the packaging, removing the drug container from the retainer inserting and removing the retainer to and from the manikin's mouth, pausing the system when not in use (e.g. mealtimes), and storing the system after use.

References

1. Olanow CW, Obeso JA, Stocchi F. Continuous dopamine receptor stimulation in the treatment of Parkinson's Disease: Scientific rationale and clinical implications. Lancet Neurology 2006;5:677-687.
2. Chase TN, Baronti F, Fabbrini G, et al. Rationale for continuous dopaminomimetic therapy of Parkinson's disease. Neurology 1989; 39(Suppl 2):7-10; discussion, 19.
3. Olanow CW, Schapira AH, Rascol O. Continuous dopamine receptor stimulation in early Parkinson's disease. Trends Neurosci 2000;23(10 Suppl):S117-S126.
4. Bibbiani F, Costantini LC, Patel R, et al. Continuous dopaminergic stimulation reduces risk of motor complications in parkinsonian primates. Exp Neurol 2005;192:73-78.
5. Stockwell KA1, Scheller D, Rose S, et al. Continuous administration of rotigotine to MPTP-treated common marmosets enhances anti-parkinsonian activity and reduces dyskinesia induction. Exp Neurol 2009;219:533-542.
6. Stocchi F, Ruggieri S, Vacca L, Olanow CW. Prospective randomized trial of lisuride infusion versus oral levodopa in patients with Parkinson's disease. Brain 2002;125:2058-2066.
7. Kurlan R, Rubin AJ, Miller C, et al.. Duodenal delivery of levodopa for on-off fluctuations in parkinsonism: preliminary observations. Ann Neurol 1986;20: 262-265.
8. Sage JI, Trooskin S, Sonsalla PK, et al. Long-term duodenal infusion of levodopa for motor fluctuations in parkinsonism. Ann Neurol 1988;24:87-89.
9. Bredberg E, Nilsson D, Johansson K, et al. Intraduodenal infusion of a water-based levodopa dispersion for optimisation of the therapeutic effect in severe Parkinson's disease. Eur J Clin Pharmacol 1993;45:117-122.
10. Kurth MC, Tetrud JW, Tanner CM, et al. Double-blind, placebo-controlled, crossover study of duodenal infusion of levodopa/carbidopa in Parkinson's disease patients with 'on-off' fluctuations. Neurology 1993;43:1698-1703.
11. Nyholm D, Askmark H, Gomes-Trolin C, et al. Optimizing levodopa pharmacokinetics: intestinal infusion versus oral sustained-release tablets. Clin Neuropharmacol 2003;26:156-163.
12. Nyholm D, Nilsson Remahl AI, Dizdar N, et al. Duodenal levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson disease. Neurology 2005;64:216-223.
13. Olanow CW, Kieburtz K, Odin P, et al. Double-Blind, Double-Dummy Study of Continuous Intrajejunal Delivery of Levodopa/Carbidopa Intestinal Gel in Advanced Parkinson's Disease. Lancet Neurol 2014; 13: 141-149.
14. Olanow CW, Torti M, Kieburtz K et al. Continuous oral administration of levodopa in Parkinson's patients with motor fluctuations – a pharmacokinetics, safety, and efficacy study. Mov Disord.2019 Mar;34(3):425-429.

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Results

All participant pairs were able to conduct the critical task of inserting the drug container into the retainer, although one pair took longer than expected. Figure 4 shows the instructions for conducting the critical task, extracted from the Instructions for Use (IFUs) used during the study. One patient participant did not continue the study after the instruction portion of the study.

Table 1: Critical Task Performance

Participant	Success Rate
Patient (n=4)	3/4 (75%)
Caregiver (n=5)	5/5 (100%)
Pair (n=4)	4/4 (100%)

Table 2: Non-Critical Task Performance

Participant	Success Rate
Patient (n=4)	39/48 tasks (81%)
Caregiver (n=5)	54/60 tasks (90%)
Pair (n=4)	45/48 tasks (94%)

Table 3: Knowledge Test Performance

Participant	Success Rate
Patient (n=4)	10/12 questions (83%)
Caregiver (n=5)	14/15 questions (93%)
Pair (n=4)	10/12 questions (83%)

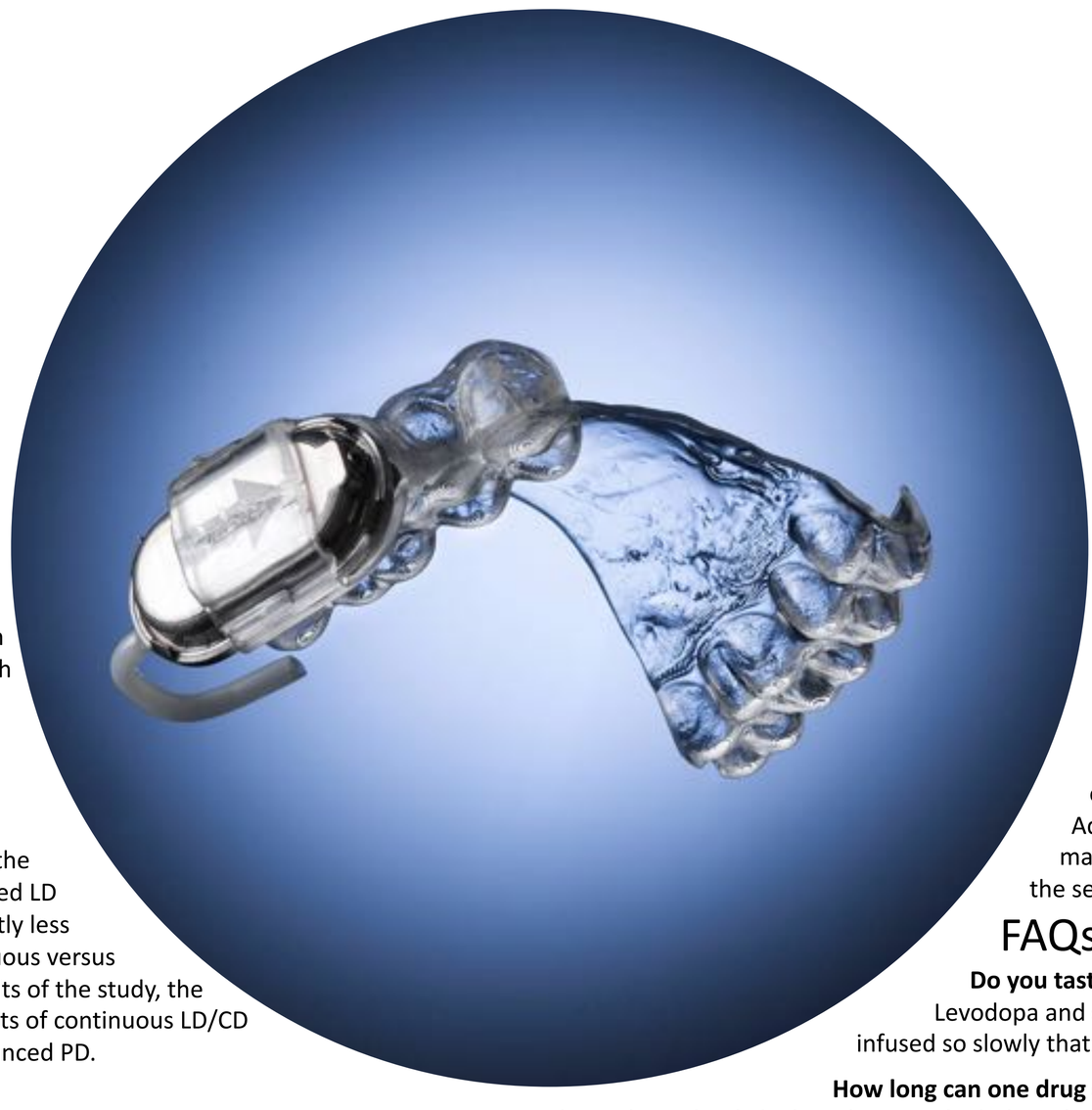


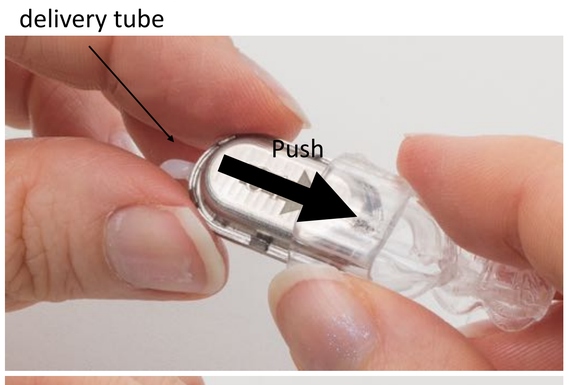
Fig. 4: Instructions for Use Extract

Insert the Drug Container

- Insert the drug container into the retainer pocket. Do not push or pull on the delivery tube.

Inserting the Drug Container

Do not hold by the delivery tube



- Push the container all the way in until it can not be pushed any further
- There should not be any gap between the end of the container and the pocket
- DO NOTE USE if the drug container does not fit snugly in the retainer pocket
- DO NOT HOLD by the delivery tube

Conclusions

This study suggests that patients with advanced PD and their caregivers will be able to safely use the DopaFuse Delivery System in the upcoming Phase 2 clinical trial. Some patients were able to use the system independently, with others requiring assistance from a caregiver.

Human trials on the DopaFuse Delivery System are expected to begin in early 2020. The Instructions for Use have been updated to incorporate the feedback from the participants. It is expected that success rates can be further improved with expanded educational tools such as training videos and a helpline. Additionally, using the system in a patient's own mouth may be easier than on a manikin, as the patient would have the sensorial feedback from feeling it in their mouth.

FAQs

Do you taste the drug?
Levodopa and carbidopa have no taste. Most other drugs would be infused so slowly that the user would not be able to perceive any taste.

How long can one drug container last?
It depends on the daily drug dose. For high dose drugs such as levodopa, the drug container should be changed 2-3 times per day. For low dose drugs, one drug container could last up to several weeks.

Can patients sleep with DopaFuse?
DopaFuse is designed to be safe for both daytime and nighttime use.

Is the DopaFuse system comfortable?
The DopaFuse system is similar to an ordinary retainer. Retainers are custom made for each patient. Patients will go through a fitting and adjustment with their dentist to ensure comfort.

Can patients eat or drink with DopaFuse?
DopaFuse should be removed for eating. Patients may drink liquids and swallow pills while wearing DopaFuse. Sugary drinks should be avoided while wearing the System.

How do you maintain the System?
The retainer should be cleaned daily with a toothbrush and toothpaste. The case should be cleaned daily with water and a soft cloth.

Is the System visible to others?
The system is designed to be invisible to others. Figure 5 shows a volunteer inserting and wearing the system.

Fig. 5: Wearing the DopaFuse Delivery System