CVT-301 for Parkinson's disease: dose and effect size issues

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Oral levodopa plus a dopa-decarboxylase inhibitor (LD-DCI) is the standard of care for Parkinson's disease. However, within 5 years of starting treatment, about 50% of patients develop debilitating off episodes, during which motor and non-motor symptoms reappear. The addition of a dopamine agonist, amine oxidase (flavin-containing) B inhibitor, or catechol-O-methyltransferase inhibitor partly reduces daily duration of off episodes, but some patients remain impaired to a point that justifies the use of complex, aggressive, expensive, and inconvenient device-based therapies. Therefore, safer, cheaper, and more potent and convenient treatments are needed.

The mechanisms generating off episodes induced by levodopa therapy involve a complex interplay between pharmacokinetic and pharmacodynamic factors. This includes erratic gastrointestinal emptying and fluctuations in plasma concentrations below or above a threshold that governs clinical switches from off to on states.[1] A strategy to tackle problems of off episodes is to develop longer acting LD-DCI formulations or more constant methods of delivery than the ones available, to maintain stable concentrations above the threshold to prevent the occurrence of off episodes.[2] Another approach is to administer very rapidly acting agents on demand, as soon as off episodes occur, to exceed the threshold and stop the off state (such as subcutaneous injections of apomorphine).

Pulmonary inhalation of levodopa, bypassing the gastric emptying obstacle, should rapidly bring plasma concentrations above the threshold needed to switch patients to an on state. CVT-301 is a novel levodopa inhalation powder formulation for pulmonary absorption that can be administered with a passive breath-actuated device. Results from a 4-week, phase 2 trial[3] done in 86 patients with Parkinson's disease showed that CVT-301 50 mg decreased patients' disability, as measured by the Unified Parkinson Disease Rating Scale (UPDRS), by 7 units more than did placebo when inhaled during off episodes (p<0·001). CVT-301 also reduced the time spent in an off state by 0·9 h per day compared with placebo (p<0·05).

In *The Lancet Neurology*, Peter A LeWitt and colleagues[4] have now further explored the effects of CVT-301 (60 mg and 84 mg doses) in a 12-week, phase 3 trial in 339 patients with Parkinson's disease.[4] The findings showed that reductions in mean UPDRS score from baseline to 30 min post inhalation were significantly greater with both doses of CVT-301 than with placebo (least-squares mean difference –3 07, 95% CI –5·99 to –0·16; p<0·039 CVT-301 60 mg *vs* placebo; –3·92, –6·84 to –1·00; p<0·0088 CVT-301 84 mg *vs* placebo), supporting some of the initial phase 2 findings with a longer follow-up and in a larger cohort. However, CVT-301 was not better than placebo, or the effect was smaller than anticipated, for several important secondary efficacy outcomes. These results deserve discussion regarding the potential effectiveness of the drug in clinical practice because clinical trials can overestimate efficacy, as a result of their research settings.[5]

Although CVT-301 was superior to placebo in reducing UPDRS scores after 30 min, the difference was minimal at 20 min (p=0·062), despite an expectation of a faster benefit (about 10 min), as reported in previous phase 2 findings. Patients are anxious to switch to an on state as quickly as possible; higher doses than in this trial might be necessary in some patients to provide a faster response.

The reduction in UPDRS scores at 30 min with CVT-301 compared with those of placebo, although significant, was also smaller (–3·9 units) than expected from previous phase 2 results (–7 units). This finding was surprising, knowing the robust effect of levodopa and considering the strong dopaminergic responsiveness of this cohort, illustrated by a mean baseline UPDRS score of about 35 in off and 16 in on states—a 19-unit difference. The authors argue that the patients might have inhaled the drug while not being fully in an off state, which is a possibility. It is also conceivable that the tested doses might not have been high enough to provide a full response in all patients.

Surprisingly, there was no difference between CVT-301 and placebo in reducing the total time that the patients spent in an off state on a daily basis, even in the CVT-301 84 mg group (–0·47 h in CVT-301 84 mg *vs* –0·48 h in placebo). This is a concern because diaries are the most straightforward, validated method to measure the effect of a treatment on off episodes over the day.[6] The minimal clinically significant difference in reducing time spent in the off state is about 1 h per day.[7] Interventions that treat motor fluctuations have consistently achieved this goal.[8] How then could CVT-301 have no effect on

such an outcome? The chances that higher CVT-301 doses than those used in this trial might have exhibited a more robust effect on daily time spent in off state are plausible. Indeed, incomplete responses observed with the trial doses might have been sufficient to partly improve UPDRS scores as rated by the investigators, but insufficient to induce full switches from off to on state, as recorded by patients in their diaries. Perhaps the statistical power of the study was also insufficient, because previous trials that documented the efficacy of other interventions on this endpoint generally enrolled 150–200 patients per group. However, one would have expected at least a trend in favour of CVT-301 in this trial, which was not the case. Intriguingly, CVT-301 50 mg was superior to placebo on daily time spent in an off state in the previously mentioned smaller phase 2 trial[3] (45 patients per group). Another possible reason for this negative result is that patients were not allowed to use CVT-301 before the first morning oral LD-DCI dose. Many patients wake up in an off state and must wait up to 60 min or longer before feeling the beneficial effects of their first oral LD-DCI dose. Therefore, inhaling CVT-301 at such time seems appealing. Unfortunately, CVT-301 does not contain a DCI, and DCIs have short plasma elimination half-lives.[9] Consequently, it is likely that decarboxylation might not be sufficiently blocked in the morning—after a night of LD-DCI withdrawal—to prevent the production of dopamine from CVT-301 at the periphery, which risks reduced efficacy and more gastrointestinal and cardiovascular adverse reactions. Furthermore, as pointed out by the authors, patients did not use CVT-301 during the day as much as they could have done because they inhaled it on average twice per day only, although they had a mean of three or more off episodes per day. This low usage might have also reduced the chances of CVT-301 producing a larger decrease in daily time spent in off state.

Trials also tend to underestimate adverse reactions. Patients with severe dyskinesia were excluded from this study, and only about 40% of participants reported dyskinesia at baseline, although patients with dyskinesia are at greater risk of worsening dyskinesia on dopaminergic supplementation. A longer and larger follow-up is also required before excluding pulmonary safety concerns regarding inhaled levodopa, especially in patients with lung comorbidities.

In summary, the trial by LeWitt and colleagues is a welcome addition, because the principle of inhaling levodopa is appealing and findings provide evidence that CVT-301 improves symptoms of Parkinson's disease. However, the effect sizes recorded in this trial are not as good as anticipated, in terms of speed and amplitude of the acute response and of the effect on daily time spent in an off state. Some patients might require higher doses than 84 mg to fully switch to an on state and this should be investigated, if technically possible with this device. Post-hoc analyses of off-time responders rather than UPDRS responders might facilitate understanding of the specific target population. Moreover, CVT-301 should be compared with apomorphine subcutaneous injections, which significantly improve UPDRS scores by 10–20 units within 20 min after administration.[10–12] Inhaling a drug is more convenient that using a penjet. Inhaled and sublingual apomorphine formulations are also under development for this reason.[13,14]

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Evidence for treatment of spasticity in motor neuron disease

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Motor neuron disease is a relentlessly progressive disease. Expert consensus guidelines have been developed for key care concerns in patients with motor neuron disease, including respiratory management, nutrition, and palliative care.[1] Because there is no cure, symptom control to maintain quality of life is the mainstay of treatment. Spasticity is one of the defining characteristics of primary lateral sclerosis, but occurs to a variable degree in patients with amyotrophic lateral sclerosis.[2] Spasticity, however, is usually not the focus of management in patients with motor neuron disease. Notably, a Cochrane review[3] for treatment of spasticity in motor neuron disease identified only one randomised controlled trial of moderate-intensity, endurance-type exercise versus usual activities in 25 patients with amyotrophic lateral sclerosis. The authors of this Cochrane review concluded that further research was needed.[3] Available antispasticity drugs—ie, baclofen, dantrolene, benzodiazepines, gabapentin, and levetiracetam—have been reported to reduce spasticity in patients with amyotrophic lateral sclerosis,[4] but no controlled studies have been done. Additionally, these medications can be associated with increased muscle weakness or fatigue.

In *The Lancet Neurology*, Nilo Riva and colleagues report the results of a multicentre, randomised, double-blind, placebo-controlled phase 2 trial[5] of the safety and efficacy of nabiximols, a *Cannabis sativa* extract, on spasticity symptoms in patients with motor neuron disease (CANALS). After positive results for, and the subsequent regulatory approval of, cannabinoids for symptomatic treatment of spasticity in patients with multiple sclerosis,[6] Riva and colleagues initiated their proof-of-concept study at four tertiary motor neuron disease centres in Italy. Eligible patients had amyotrophic lateral sclerosis or primary lateral sclerosis. Patients were randomly assigned (1:1) to either a standardised oromucosal spray containing a defined combination of delta-9-tetrahydrocannabinol and cannabidiol (nabiximols) or to placebo for 6 weeks.

The primary endpoint was the change in Modified Ashworth Scale (MAS) scores, assessed at baseline and at the end of treatment. In the nabiximols group the MAS score improved by a mean of 0·11 (SD 0·48), whereas in the placebo group the score deteriorated by a mean of 0·16 (0·47). The difference between groups was significant (adjusted effect estimate –0·32 [95% CI –0·57 to –0·07]; p=0·013). Nabiximols was well tolerated, and no participants withdrew from the blinded phase of the study. Adverse events were mild to moderate and included asthenia, somnolence, vertigo, and nausea. However, substantially more adverse events occurred in the nabiximols group than in the placebo group. With respect to secondary outcomes, significant improvements were noted in scores on the pain numeric rating scale and in participants' global impression of change in the nabiximols group compared with the placebo group. No significant improvements were noted on various other secondary outcome measures, such as the upper motor neuron score and spasms and spasticity numeric rating scales. However, sample size might have been a limitation in this respect.

After 6 weeks of masked treatment, all participants were given the opportunity to enrol in an open-label phase. Two patients did not enter the open-label extension study, and seven withdrew during the open-label phase because of side-effects or disease progression. The mean MAS score of patients who had been assigned to the placebo group improved substantially during the open-label study.

The results of this study are promising, but the trial had several limitations. First, there was a bias towards patients