SHORT REPORT

# High dose naltrexone for dyskinesias induced by levodopa

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**Abstract**

**Ten patients with Parkinson's disease and levodopa induced dyskinesias (LIDs) took part in this randomised, placebo controlled, double blind, crossover trial to assess the efficacy and tolerability of high dose oral naltrexone for LIDs in Parkinson's disease. Patients received naltrexone (5 mg/kg/day) or placebo for 2.5 weeks with 1 week wash out in between. Dyskinesias and motor function were assessed with a levodopa challenge, unified Parkinson's disease rating scale (UPDRS), the unified dyskinesia rating scale (UDRS), and patient diaries. Eight patients completed the trial. There was a small reduction in LIDs measured by patient diaries with naltrexone (20.5 (SD 24.9)%) compared with placebo (−4.1 (SD 22.6)%), p<0.05, although no difference was found by other subjective or objective measures. Naltrexone was well tolerated and caused no significant differences in UPDRS motor scores or off time. This study suggests that short term therapy with high dose naltrexone (250–350 mg/day) has no or minimal effect on reducing LIDs in Parkinson's disease.**

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Levodopa induced dyskinesias (LIDs) are a considerable challenge in the long term management of Parkinson's disease. Recently, non-dopaminergic pathways have been targeted as a means of controlling dyskinesias without worsening parkinsonism,[1] and promising results with the glutamate antagonist amantadine have been reported.[2 3]

Levodopa induced dyskinesias are thought to be associated with changes in the balance of neurotransmitter systems within the basal ganglia,[4] and it is thought that opioid receptor antagonism may reverse some of these changes and thus lessen dyskinesias.[1] Conflicting results with opiate receptor antagonists for LIDs in Parkinson's disease have been previously published. Acute intravenous administration of naloxone successfully reduced LIDs in two out of three studies[5 6] whereas 100 mg/day naltrexone, an orally active opiate antagonist licensed for use in opiate addiction, was ineffective.[7] However, recent studies with the MPTP lesioned marmoset model of Parkinson's disease demonstrated a marked reduction of LIDs with oral naltrexone at doses of 10 mg/kg/day.[1 8] The aim of this study was to investigate the antidyskinetic effect of higher dose naltrexone (5 mg/kg/day).

## Methods

Ten patients (six men and four women) with idiopathic Parkinson's disease participated in the trial. Their mean age was 62 (range 53–80) years, mean duration of Parkinson's disease, 13.2 (range 8–22) years, and mean duration of levodopa therapy, 11.5 (range 7–17) years. Six patients were taking oral dopamine agonists (mean pergolide equivalent dose 3.2 mg/day), one was on a continuous apomorphine infusion, and two were taking amantadine. All had disabling LIDs and had been receiving a fixed dose of their usual antiparkinsonian medication for a period of at least 1 month before inclusion. Exclusion criteria included patients with moderate to severe hepatic impairment, concurrent use of opioid containing medication or opiate dependency, hypersensitivity to naltrexone, and moderate to severe dementia. All patients gave informed consent to participate and the joint medical ethics committee of the National Hospital for Neurology and Neurosurgery approved the study.

Baseline screening tests, performed between 1 and 2 weeks before the start of the study, included a full medical history and examination, mini mental state examination,[9] an ECG, full blood count, urea, electrolytes, and liver function testing. The trial was double blind, placebo controlled, and crossover in design with 2.5 weeks on each treatment separated by 1 week for washout. Patients were given oral naltrexone (5 mg/kg (to the nearest 50 mg)), in three divided doses, to be taken after meals. The dose was gradually increased from 100 mg by 50 –100 mg increments a day over the 3 to 4 days of each treatment period.

Patients were assessed with levodopa challenges, at baseline, and at the end of each treatment period. The challenges were performed in a standard fashion using the patient's normal maximum dose (range 100–300 mg) required to achieve the on state and assessed after an overnight fast and withdrawal of medication (except naltrexone), using Hoehn and Yahr

ratings and unified Parkinson's disease rating scale (UPDRS) in the off and full on state. Once the on state was achieved, patients were videotaped three times at 20 minute intervals. During each recording, patients were engaged in the following motor and mental tasks, previously shown to elicit dyskinesia[10 11]:

(1) Sitting still for 1 minute at rest
(2) Mental calculation
(3) Drinking from a cup
(4) Putting on and buttoning a coat
(5) Walking.

At the end of the challenge, patients were also videotaped preparing and eating breakfast.

Dyskinesias were assessed blindly by two trained neurologists (AJM and RK) on later review of the videotape, using the modified Goetz 5 point (0–4) severity scale[12] for tasks 3–5 (excluding phenomenological rating) and the modified AIM scale, for task 1 and 2.[11 13] Orofacial and buccolingual, global, and dental ratings were excluded from the AIM scale, giving a maximum score of 24. Both scales were used to rate dyskinesias while preparing and eating breakfast.

Patients were also asked to complete diary cards for five days and the Lang and Fahn unified dyskinesia rating scale (UDRS)[14] before each assessment. The diaries included daily recording of time spent in the on and off states, and an overall daily subjective dyskinesia assessment using a visual analogue scale (VAS). After each treatment phase, patients were also asked about their subjective impression of dyskinesia improvement and adverse effects on a four point scale (0=none, 1=mild, 2=moderate, 3=marked).

Patients were given prerandomised treatment numbers in the order in which they entered the trial, receiving blindly naltrexone (50 mg capsules) or matched placebo first.

For the objective video ratings, mean Goetz and AIM scores were taken for each assessment for each rater and the mean of the two raters' scores was then taken for the final analysis. Results for the two scales were analysed separately.

For the subjective diary ratings of dyskinesia severity and off time, the mean VAS score (measured in cm), and mean off time (as a percentage of the waking day) from the 5 days scored was taken for each patient.

Each patient's percentage reduction in dyskinesia score from baseline was calculated separately for both treatment arms and the means of the percentage reduction for the two treatment arms were compared using Wilcoxon's test.

Interrater reliability was assessed by first correlating the two raters' scores and then assessing the mean difference of each rater's score from the mean of the two raters' scores for each assessment.

## Results

Eight patients completed the trial. One patient dropped out due to adverse effects on day 1 of the first treatment period. Another dropped out before the first treatment phase due to a psychotic episode during baseline assessment. Neither patient was included in the final analysis. The mean dose of naltrexone taken was 306 (range 250—350) mg/day.

The results are summarised in table 1.

Interrater reliability for the blinded objective dyskinesia rating was good for both scales. Pearson's *r* between the two raters' scores for AIMS was 0.86 ($p<0.01$), with a mean difference between scores of 0.6 (SD 0.5). Spearman's *r* for the Goetz scale was 0.67 ($p<0.01$), with a mean difference between raters' scores of 0.3 (SD 0.2).

No change in daily on times or objective UPDRS scores were found between the two treatment periods.

Severe nausea and vomiting led to withdrawal on the first day of naltrexone treatment in one patient. The patient had inadvertently taken 350 mg naltrexone, without titrating up the dose, on an empty stomach. Two further patients reported moderate to severe anorexia during the naltrexone treatment period but were able to continue. Naltrexone was otherwise well tolerated and there were no changes in liver function. There were no adverse events during the placebo phase.

## Discussion

A very mild subjective improvement in dyskinesia occurred with naltrexone (5 mg/kg/day). No improvement was seen with objective measures, and only two patients reported a moderate improvement of dyskinesias with naltrexone, which was not different from placebo. Although the patient numbers were small, this study was designed to investigate a clinically relevant antidyskinetic effect, which has been shown to be possible by careful and detailed analysis of small samples.[3 15]

*Table 1 Effect of high dose naltrexone and placebo on dyskinesia by all measures*

| *Measure* | *Baseline Mean (range/SD)* | *Placebo Mean (range/SD)* | *Naltrexone Mean (range/SD)* | *P- value for difference* |
|---|---|---|---|---|
| Objective dyskinesia ratings: | | | | |
| Mean AIM scores (max 24) | 9.3 (4.8–12.7) | 10.2 (7.25–13.1) | 9.8 (7–14.8) | |
| Mean % reduction Aims scores | | −13.4 (20.1) | −9.4 (22.1) | 0.7 |
| Mean Goetz scores (max 4) | 1.5 (0.8–2.4) | 1.5 (1.0–2.1) | 1.5 (1.0–2.0) | |
| Mean % reduction Goetz scores | | 0.003 (0.002) | 0.007 (0.1) | 0.4 |
| Subjective impression: | | | | |
| Diary scores | 5.5 (3.9–7.7) | 5.51 (3.5–8.3) | 4.4 (2.7–8.4) | |
| Mean % reduction diary scores | | −4.1 (22.5) | 20.5 (24.9) | 0.03 |
| Mean UDRS score | 12.1 (10–16) | 1.7 (1.0) | 0.3 (0.3) | |
| Mean % reduction UDRS scores | | 9.7 (18.7) | 11.2 (16.3) | 0.7 |
| Mean % reduction UPDRS item 32 (dyskinesia severity) | | 9.4 (18.1) | 12.5 (35.4) | 0.7 |
| Mean % reduction UPDRS item 33 (dyskinesia duration) | | 0 (26.7) | 18.7 (37.2) | 0.4 |
| Patient impression (4 point scale) | | 0.3 (0.5) | 0.6 (0.9) | 0.3 |

Results are means (data ranges or SD as appropriate)

Naltrexone may exert a very small antidyskinetic effect, which could only be detected by patient diaries. As these do not have a standardised scale, but work via VASs, based on individual patients' severity ranges, they are potentially more sensitive. However, it seems improbable that an important clinically relevant antidyskinetic effect has been missed.

Several non-dopaminergic drugs, including opioid antagonists, have been reported to have potent antidyskinetic effects in animal models,[1 8 16] and this study illustrates the difficulty in translating these results to clinical practice. A possible explanation for this discrepancy could be the relatively lower dose of naltrexone (5 mg/kg/day) used in our study, compared with 10 mg/kg/day used in the MPTP lesioned marmosets. However, the dosage used was the maximum allowed by our centre's ethics committee, due to concerns about increases in serum transaminases.[17] Doses up to 800 mg/day have, however, been shown to be well tolerated and non-toxic in volunteers and clinical trials in psychiatric disorders, and long term treatment for opiate addiction with 350 mg/day has proved safe.[18]

Naltrexone is active at μ, κ, and δ receptors, and antagonism at κ and δ opioid receptors could potentially reduce LIDs through modulation of the direct and indirect striatopallidal pathways, as previously described. However, naltrexone is preferentially active at μ receptors,[19] and although these have been implicated in LID generation,[8] the selective μ antagonist cyprodime failed to suppress involuntary movements in the rat model of LID.[20] It is therefore possible that naltrexone's activity at δ receptors at the dosage used is inadequate to attenuate dyskinesia.

Although the previous clinical and preclinical studies successfully demonstrating an antidyskinetic effect did so acutely, it is conceivable that resetting of the receptors may require longer treatment periods. Reduction of dyskinesia with apomorphine monotherapy usually takes 3 to 6 months.[21]

Studies with higher doses of naltrexone or for longer treatment periods may therefore be warranted.

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