

## SHORT REPORT

# Low dose quetiapine for drug induced dyskinesias in Parkinson's disease: a double blind cross over study

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**Objective:** Drug induced dyskinesias remain a challenging problem in the long term management of Parkinson's disease (PD). We have assessed the effect of quetiapine on dyskinesias in a double blind placebo controlled cross over study.

**Methods:** Nine patients with PD were enrolled and received 25 mg of quetiapine or placebo at night for two weeks in prerandomised order, with one week of wash out between treatment periods. Assessments were made using on-off diaries, self assessment of dyskinesias, and L-dopa challenges at baseline and after each treatment period. Videotapes were rated blindly by two raters using modified Abnormal Involuntary Movement Scale and Goetz scores. Patients subsequently went on open label quetiapine at 50 mg/day, for a mean duration of 30 days, and completed the same self assessment forms.

**Results:** During the double blind phase, no significant change in dyskinesias was found on either 25 mg of quetiapine or placebo. Duration of off states and Unified PD Rating Scale motor scores also remained unchanged. Moderate tiredness and daytime sleepiness occurred in two patients on quetiapine. One patient dropped out early for unrelated reasons. Eight patients completed the open label phase. On 50 mg/day of quetiapine, a slight reduction in dyskinesias occurred on some scales. Reduction in dyskinesia severity on visual analogue scales was by 50.1%. Off time was not significantly increased. This improvement was not strongly reflected in patients' overall impression of treatment effect. Drowsiness and daytime sleep episodes led to discontinuation in four patients, after completion of the study, and two additional patients stopped treatment after the study because of lack of effect.

**Conclusion:** Our study failed to demonstrate an antidyskinetic effect of low dose (25 mg) quetiapine. The absence of an increase in parkinsonism combined with a possible antidyskinetic effect on higher doses warrants further investigation.

Drug induced dyskinesias complicate long term management of Parkinson's disease (PD) in 30–80% of patients.<sup>1</sup> Dopamine receptors of the D1 and D2 subtypes<sup>2</sup> and the manner in which they are stimulated remain central features of the current concept of dyskinesia formation.<sup>3</sup> Early attempts to control dyskinesias by dopamine receptor blocking agents<sup>4–5</sup> using traditional neuroleptics showed no practical benefit because of severe concurrent worsening of parkinsonism.

Newer antipsychotic drugs cause fewer extrapyramidal side effects in psychosis associated with PD.<sup>6–14</sup> Clozapine<sup>15–17</sup> and olanzapine<sup>18</sup> have been shown to improve dyskinesias at low doses. However, clozapine may induce agranulocytosis,

whereas olanzapine has been shown to aggravate parkinsonism even at very small doses. Quetiapine is an atypical neuroleptic with close pharmacological resemblance to clozapine but without known haematological side effects. We have investigated low dose quetiapine as a potential antidyskinetic drug in PD.

## PATIENTS AND METHODS

Patients with PD and disabling dyskinesias who had been on stable antiparkinsonian treatment for at least one month were enrolled. Exclusion criteria included hepatic impairment, low white cell count, prolonged Q-T interval on electrocardiogram, history of ventricular dysrhythmias, and dementia. The trial was placebo controlled, double blind and cross over in design with two weeks on each treatment separated by one week for wash out. Patients' ongoing medication remained unchanged.

The sequence of drug and matching placebo was determined by a prerandomised number according to the order of patients' entry into the study. The study was approved by the Joint Ethics Committee of University College London/University College London Hospitals, and patients gave informed consent.

L-dopa challenges were performed at baseline and at the end of each treatment period, in a standardised fashion, and in a full off state either after drug omission from midnight, or in three patients with dyskinesias predominantly in the afternoon, in a complete end of dose off following a fixed afternoon dosage. The mean L-dopa dose used in the challenges was 265.6 mg. Videotape recordings were performed when patients had reached their full on state and were repeated 20 min and 40 min later. Patients performed tasks known to increase dyskinesias: sitting still for 1 min, performing mental calculations, putting on and buttoning a coat, picking up and drinking from a cup of water, walking, and, after the third recording, preparing food and eating.

Videotapes were rated independently by two blinded raters, using modified versions of the Goetz scale<sup>19</sup> for tasks 3–5 (excluding phenomenological rating) and the Abnormal Involuntary Movements Scale (AIMS)<sup>20</sup> for tasks 1, 2, 6, and 7 (excluding facial muscles and global rating; maximum score = 24).

For the last three days of each treatment period, patients recorded on and off states half hourly and completed visual analogue scales (VAS) for dyskinesias hourly. Unified PD Rating Scale (UPDRS) items 32 and 33 for dyskinesia duration and severity in the previous week, and the Dyskinesia Subjective Rating Scale for impact on activities of daily living were also used.<sup>21</sup> Patients were instructed on

**Abbreviations:** AIMS, Abnormal Involuntary Movements Scale; PD, Parkinson's disease; UPDRS, Unified PD Rating Scale; VAS, visual analogue scale

how to complete these forms, and the ability to distinguish clearly among their own motor states was a requirement for enrolment. Parkinsonism was measured by off time in patients' diaries and by maximum and minimum UPDRS motor scores during challenges.

Following the double blind trial, patients went on open label quetiapine (25 mg) for one week, followed by an increase to 50 mg (25 mg twice/day). Patients completed self assessment scales as before and remained on stable antiparkinsonian treatment.

The trial was powered to detect a 25% difference between AIMS scores on treatment and placebo, considered a clinically relevant change based on previous publications<sup>18</sup> and clinical judgment. Power calculation showed that eight patients completing both treatment arms were required for 80% power at the 5% significance level.

For analysis, the video raters' scores were combined. Interrater reliability was assessed by weighted  $\kappa$  analysis. Means/medians were compared using Wilcoxon's signed ranks test or paired samples *t* test, as appropriate. Percentage changes were calculated for each patient, taking the reading at follow up as a percentage of the initial score.

## RESULTS

Nine patients were enrolled in the study. One patient dropped out because of worsening of psoriasis before starting the study medication. Five men and three women completed the trial. Mean age was 66.5 (range 54–73) years, mean disease duration 13.4 (range 9–38) years, and mean daily L-dopa dose 743.5 mg. Interrater reliability for video rating was satisfactory: weighted total  $\kappa = 0.50$  ( $p < 0.0001$ ) for AIMS and 0.38 ( $p = 0.0002$ ) for Goetz scores. No significant changes in dyskinesias or parkinsonism were found (table 1). No carry over effects were detected.

During the double blind phase, one patient each reported mild dizziness and mild tiredness on placebo, while two patients reported moderate tiredness and increased daytime sleep episodes on quetiapine. No clinically relevant changes in haematological and biochemical parameters occurred.

All eight patients who had completed the cross over trial continued with the open label part of the study. Mean duration was 30 days (range 2–11 weeks). Changes from baseline were Lang & Fahn scale:  $-7.1\%$  ( $p = 0.61$ ); UPDRS

item 32:  $-16.9\%$  ( $p = 0.58$ ); UPDRS item 33:  $-20\%$  ( $p = 0.26$ ); dyskinesia duration and severity (cm in patients' diaries):  $-50.1\%$  ( $p = 0.012$ ); dyskinesia duration (percentage of waking day):  $-7.8\%$  ( $p = 0.32$ ). Mean daily off time was increased by  $6.9\%$  ( $p = 0.58$ ). Five patients felt dyskinesias were better and three felt they were unchanged. Seven patients reported moderate to severe drowsiness and tiredness, and increased daytime sleep episodes occurred in four. Time spent asleep per 24 hr increased by  $9.9\%$  ( $p = 0.35$ ). After the trial, four patients decided to discontinue treatment because of adverse effects and two because of lack of effect.

## DISCUSSION

Our double blind study failed to demonstrate a selective antidyskinetic effect of low dose (25 mg) quetiapine. During the open label phase, 50 mg/day did lead to a small improvement, but this was reflected to only a mild to moderate degree in the patients' overall assessment of treatment effect, and it is likely that this part of the trial may have been affected by the recognised drawbacks of all uncontrolled studies. Moreover, this possible benefit was frequently outweighed by adverse effects, in particular drowsiness and increased daytime sleep episodes.

Comparable doses of clozapine have been shown to considerably improve dyskinesias, but all published studies of clozapine for dyskinesias have been open label. Although L-dopa challenges showed significant dyskinesia reduction on AIMS when rated blindly in two of these studies,<sup>15, 16</sup> these results need to be confirmed in controlled trials. Possible explanations for differences in antidyskinetic properties include more transient D2 receptor occupancy in quetiapine,<sup>22</sup> whereas hypotheses in clozapine have also included non-striatal mechanisms, such as changes in N-methyl-D-aspartate receptor expression<sup>23</sup> or limbic dopamine receptor occupancy.<sup>24</sup> In contrast, olanzapine shows higher D2 type receptor affinity than quetiapine.<sup>22</sup> In view of its transient receptor binding, more frequent administration of quetiapine may be required for an antidyskinetic effect. Night time administration was chosen in our study to avoid daytime sedation, which had occurred on 25 mg/day clozapine.<sup>17</sup>

The choice of a dose of 25 mg quetiapine was based on previous findings with other atypical neuroleptics, where an antidyskinetic effect had been shown at dosages within<sup>15–17</sup> or

**Table 1** Measures of dyskinesias and parkinsonism on 25 mg quetiapine and placebo

Measures	Baseline mean (SD)	Placebo mean (SD)	% change	Quetiapine mean (SD)	% change	p Value for difference drug/placebo (two tailed)
Video ratings						
AIMS score	8.36 (2.83)	8.41 (2.92)	+1.0	8.02 (3.2)	-2.9	0.21
Goetz score	1.57 (0.5)	1.52 (0.47)	-8.0	1.49 (0.52)	-5.3	0.85
Lang & Fahn scale (score)	14	13.5		13.5		0.92
UPDRS item 32 (score)	1.6	1.8		1.5		0.48
UPDRS item 33 (score)	1.9	1.6		1.9		0.16
VAS three days						
Severity (cm/day)	37.2	22.7	-36.6	22.4	-38.8	0.89
Duration (% of waking day)	63.2	60.7	-4.2	49.4	-10.1	0.67
L-dopa challenges						
UPDRS part 3 "off"	37.8 (5.47)	38.1 (6.15)	+0.8	33.8 (8.97)	-10.6	0.17
UPDRS part 3 "on"	18.1 (10.64)	14.9 (6.62)	-17.7	15.6 (5.78)	-13.8	0.50
Diary 3 days						
Off duration (hours/day)	3.3 (1.89)	3.3 (1.83)		2.7 (1.83)		0.44

AIM, Abnormal Involuntary Movement Scale; UPDRS, Unified Parkinson's disease rating scale.

Per cent changes are the mean of person specific percentage changes, calculated in relation to person specific baseline measurements.

below<sup>18</sup> the range usually required for the management of psychosis. With olanzapine, a mean dose of 3.6 mg/day had led to significant dyskinesia reduction in a double blind study,<sup>18</sup> although significant worsening of parkinsonism occurred on doses as small as 1.25 mg. Most studies investigating clozapine for dyskinesias<sup>15–16</sup> used mean doses of 30–50 mg/day. All found dyskinesia reduction without motor worsening, but dose limiting sedation and orthostatic hypotension occurred frequently.

Although the number of patients included in our study was small, sample size had been based on published studies with a similar cross over design. Such studies had been shown to be sufficiently powered to demonstrate statistically and clinically significant changes in dyskinesias.<sup>18–25</sup> It could be argued that a small effect might have been detected with a larger number of patients. However, it seems unlikely that such a small improvement would be of clinical relevance. It is also possible that moderate mean dyskinesia scores at baseline may have caused a floor effect, although patient characteristics were similar in studies that had detected significant changes in dyskinesias.<sup>18–25</sup>

Measures of parkinsonism in our trial are in keeping with existing evidence for a favourable risk profile of quetiapine with respect to extrapyramidal side effects. Open label studies in psychosis associated with PD have either shown no<sup>9–12</sup> or infrequent<sup>13</sup> aggravation of parkinsonism, although a recent report found motor worsening at some point during quetiapine exposure in 32% of patients.<sup>14</sup> The effect of quetiapine on motor function in PD has yet to be demonstrated in a randomised, controlled fashion. The sample size in our study was not based on the detection of motor changes. However, our double blind trial did not reveal any trends suggesting worsening on quetiapine.

In summary, our study provides no support for a useful role of quetiapine at 25 mg/day as a selective antidyskinetic agent in PD. However, in view of the lack of a demonstrable worsening of parkinsonism, further controlled trials using 50 mg/day appear merited.

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