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Abstract

Background: Psychosis is a common and debilitating side effect of long-term dopaminergic treatment of Parkinson disease (PD). While clozapine is an effective treatment, the need for blood monitoring has limited its first-line use. Objective: Since olanzapine shows similar receptor affinity to clozapine, we hypothesized that it may be an effective alternative to clozapine for treatment of drug-induced psychosis (DIP) in PD. Methods: We conducted a four-week, double-blind, placebo-controlled, parallel group, fixed dose trial of olanzapine (0, 2.5mg, or 5mg) in 23 Parkinson’s patients with DIP while allowing for clinically realistic dose adjustments of dopamimetic mid-study. Videotaped Brief Psychiatric Rating Scale (BPRS), rated by blinded observer after study termination, and CGI (Clinical Global Impression) were the primary tests of efficacy; Unified Parkinson’s Disease Rating Scale motor subscale was the primary measure of tolerability. Results: Intention-to-treat analysis found no significant differences among treatment groups in study completion or serious adverse events. However, a disproportionate number of olanzapine vs. placebo subjects reported mild side effects (p<0.04), many citing motor worsening. Fourteen patients completed the study (7 on placebo, 2 on 2.5mg olanzapine, 5 on 5mg olanzapine). In study completers, analysis by repeated measures ANOVA revealed no significant difference between olanzapine and placebo groups in BPRS psychosis reduction (p=0.536), parkinsonism (p=0.608), or any other measured parameters (CGI, MMSE, Beck Depression Inventory, Hamilton Depression score, PDQ-39, Schwab-England ADL assessment, and sleep scores). Conclusion: This study adds to the growing body of evidence that olanzapine is ineffective in treating medication-induced psychosis in Parkinson’s disease.
Key Words

Parkinson disease; psychosis; olanzapine; randomized controlled trial; BPRS; videotape

Introduction

Drug-induced psychosis (DIP) is a significant and disabling complication of long-term treatment of Parkinson disease (PD). This complication affects almost a third of PD patients receiving chronic dopaminergic therapy.\(^1\) Visual hallucinations are the most commonly reported psychotic phenomena in this population, with auditory, tactile, somatic, and olfactory hallucinations being much less common; delusions, when they occur, often antedate visual hallucinations and commonly are paranoid or persecutory in nature.\(^2,3\) In addition to the increased caregiver burden caused by psychosis and its sequelae, hallucinations in the context of chronically treated PD tend to be progressive in nature, resulting in increased propensity for nursing home placement and subsequent higher mortality.\(^4,5\) These sobering associations suggest aggressive management of DIP in this population. However, either dose reduction of antiparkinsonian medications or addition of traditional neuroleptics usually increases parkinsonian motor disabilities. Atypical antipsychotics, with their comparatively lower D2 receptor affinity, have potential theoretical advantages for treatment of hallucinations in this frail and sensitive population.\(^2\)

The only treatment proven with randomized, placebo-controlled studies to reduce DIP is clozapine, an agent that does not worsen motor function.\(^6,7,8\) Despite these favorable data, widespread use of clozapine has been limited secondary to its risk of agranulocytosis and consequent
necessity for frequent blood draws. Structurally similar quetiapine, a dibenzothiazepine, and olanzapine, a dibenzodiazepine, received much attention after their release to the market as possible alternatives to clozapine for DIP given their ease of use and absence of association with blood dyscrasias.

Open label trials with quetiapine suggested some efficacy of this medication in reducing hallucinations with only mild worsening of motor function, insufficient to warrant discontinuation of the neuroleptic.\(^9,10,29\) However, although double-blind, placebo-controlled trials of quetiapine in PD confirmed prior reports of motoric tolerability; at doses up to 200mg/day it was not significantly more effective than placebo in treating psychosis.\(^11,30,38\)

Clozapine’s antipsychotic efficacy is often attributed to its D\(_4\) receptor antagonism. It is also posited that its robust 5-HT\(_{2A}\) receptor antagonism, especially in relation to its relatively weaker D\(_2\) receptor blockade, actually increases dopamine transmission in prefrontal cortical and nigrostriatal projections. This may account for the cognitive improvement as well as paucity of extrapyramidal adverse events observed in clozapine treated patients with dopaminergic-induced psychosis.\(^12,13\) Olanzapine, therefore, with its ostensibly similar receptor binding profile to clozapine at D\(_2\), D\(_4\), serotonergic receptors (especially 5-HT\(_{2A}\) and 5-HT\(_{2C}\)), and muscarinic sites, provides a theoretically encouraging alternative to clozapine in this fragile population.\(^14\)

An initial open study of olanzapine in Parkinson’s disease revealed antipsychotic benefit without motor deterioration when drug dosage was optimized in a slow titration (mean daily dose at end of study was 6.5mg) and dopaminomimetic dose adjustments were allowed.\(^15\) Aarsland and
colleagues replicated these findings in a relatively more challenging population of Parkinson’s disease patients with and without dementia.\textsuperscript{16} Several other small, open-label studies of olanzapine, however, have demonstrated antipsychotic benefit but at the expense of intolerable worsening of gait and bradykinesia, frequently leading to premature termination of the drug.\textsuperscript{17-19} Another small open-label trial and case report series suggested unacceptable Parkinsonian motor deterioration in the context of dubious antipsychotic efficacy.\textsuperscript{20,21} Later, two double-blind placebo-controlled trials revealed equivocal antipsychotic benefit and problematic motor decline in Parkinson’s patients with DIP treated with 2.5-15mg/day olanzapine (mean final doses 4.1-4.6mg/d).\textsuperscript{22,23} As a result, experts have recommended against the use of olanzapine in PD.\textsuperscript{24}

None of these studies, however, were parallel-group fixed-dose trials, and several allowed for neuroleptic dose in the same range as approved for schizophrenia; experience with clozapine suggests that an effective antipsychotic dose in Parkinson’s disease is often an order of magnitude less than that typical for schizophrenia treatment. In addition, the two double-blind placebo-controlled trials did not permit adjustments of subjects’ dopaminomimetics, which might have alleviated motoric side effects. Finally, some of the studies cited were terminated prematurely due to side effects. Given that efficacy has been shown only for clozapine, demonstrating efficacy for an alternative agent would be important, and a fixed low dose of olanzapine (2.5mg/d) may allow reasonably low incidence of side effects. We discuss here the findings of a double-blind, placebo controlled study of fixed, low-dose olanzapine for treatment of DIP in the context of flexible dopaminomimetic dosing. The hypothesis was that olanzapine given in this fashion would effectively reduce DIP in patients with idiopathic Parkinson’s disease without causing intolerable motor worsening.
Methods and Materials

Patient selection. Twenty-four patients were recruited from the Washington University Movement Disorders Center from February 1998 to October 2003. All patients gave written informed consent to participate in the study, which was approved by the Washington University Human Studies Committee. In most cases an appropriate substitute decision maker also provided consent. Patients were examined by a movement disorders specialist and diagnosed with idiopathic Parkinson disease based on presence of at least two of three cardinal manifestations of the disease (rigidity, bradykinesia, rest tremor), response to levodopa or a dopamine agonist, and absence of historical or examination features suggesting secondary parkinsonism. Subjects were treated with levodopa and were experiencing clinically significant hallucinations or delusions. For study entry, patients were required to be treated with the lowest clinically acceptable dose of dopamimetic. Patients treated only with a dopamine agonist were not entered in the study, as it was deemed more clinically appropriate to try a switch to levodopa before adding an antipsychotic. Subjects were required to be over 30 years old and have a caregiver who could provide a reliable report. Exclusion criteria included a MMSE<sup>25</sup> score <22, pregnancy, concurrent diagnosis of delirium (unless clearly explained by dopamimetics), catatonia or NMS-like syndrome, other confounding CNS illness or systemic illness with potential CNS effects, antipsychotic use within the last month predating study enrollment (6 months for depot neuroleptics), history of olanzapine sensitivity, or any expectation of significant medical or surgical intervention within six weeks after enrollment. Subjects were
also excluded if severity of psychosis warranted hospitalization or if, in the investigator’s judgment, psychosis severity would have made randomization to placebo inappropriate.

_Treatment protocol._ Patients were randomized to treatment with placebo or either of two doses of olanzapine. At study initiation, treatment groups consisted of a placebo arm, a 5mg arm, in which patients received this dosage nightly throughout the four weeks of investigation, and a 10mg arm, in which patients received 5mg for the first week and 10mg thereafter. Subjects received matched tablets or capsules provided by Lilly Research Laboratories under investigator-initiated IND #53,556. After the first five patients were enrolled, an interim safety analysis was conducted by a reviewer otherwise not involved in the study. Though serious adverse events were no more common in the treatment groups than in the placebo group, it was decided at this time, in light of reports published since study initiation that higher olanzapine doses caused intolerable exacerbation of parkinsonian symptoms, that the treatment arms would be changed to fixed doses of 2.5mg and 5mg olanzapine, maintained throughout the four weeks of study. No other changes in protocol were made. See Table 1 for summary of final study design. The study was initially planned for 10 subjects in each of 3 dose arms. This would produce 90% power (at alpha = 0.05) to detect a change of the magnitude and variability seen in the Wolters et al (1996) report.¹⁵

Subjects received a baseline evaluation which involved a full psychiatric, neurologic, and medical history and examination, CGI (Clinical Global Impression) by MD,³² PDQ-39 (a self-rated quality-of-life measure for Parkinson’s Disease),³⁶ videotaped interview for later BPRS (Brief Psychiatric Rating Scale) scoring blind to drug dose and blind to which visit was being
rated, Schwab-England ADL assessment, UPDRS (Unified Parkinson’s Disease Rating Scale), MMSE (Folstein Mini-Mental State Examination), HDRS (Hamilton Depression Rating Scale), BDI (Beck Depression Inventory), and patient/caretaker reported sleep hours/quality. Repeated measures at two week interim visit and final four week evaluation included CGI (by MD, patient, and caretaker), videotaped interview for later blinded BPRS, Schwab-England ADL assessment, UPDRS, MMSE, pill counts, PDQ-39, BDI, and sleep questionnaire.

Primary efficacy measures were CGI scores and BPRS ratings of psychosis. At each visit, the coordinator interviewed the patient during videotaping using a semistructured protocol designed to facilitate later scoring of psychopathology using the BPRS. After all subjects had completed participation, the videotaped segments were edited to remove references to date or study visit. The senior author in consultation with a BPRS expert (John G. Csernansky, M.D.) wrote rules for rating “motor retardation” and other BPRS items potentially influenced by parkinsonism, and trained author MJN in BPRS ratings. Videotaped segments were reviewed in random order by author MJN, who was unaware of drug assignment or treatment duration at the time of the visit. BPRS ratings used the anchored BPRS and each item was scored from 1-7. Secondary efficacy measures included the PDQ-39, ADL assessments (Schwab-England and UPDRS), BDI, and sleep log. Primary safety measures were UPDRS motor ratings, sleep logs, and MMSE in addition to clinical review of systems.

Statistical analysis. Prior to unblinding of drug codes, the decision was made to analyze data from weeks 0-2 and weeks 2-4 separately. This a priori decision was made since adjustment of
dopaminetics was allowed at the interim (week 2) visit. Change from 0 to 2 weeks was chosen to be the primary test of efficacy. An intention-to-treat (ITT) analysis was performed on all enrolled subjects. Since some subjects dropped out without any formal follow-up visit, the ITT analysis was limited to between-group comparisons of dropout rate, serious adverse events, and reported worsening of parkinsonism or other side effects judged to be at least mild in severity. Adverse events, side effects, and study withdrawal were compared between groups using the chi-squared test.

For those subjects with data at both time points of an epoch, primary and secondary efficacy measures were tested separately for the two epochs using repeated-measures ANOVA to compare the groups. The decision was made a priori to include any subject in these analyses if that patient had taken at least one week’s worth of drug during an epoch and returned for a follow-up visit. A secondary post-hoc analysis of the data from trial completers was also performed across all three visits using repeated-measures ANOVA.

Results

Baseline characteristics.
A total of 24 patients were enrolled over the six-year span of this study. Though the original study design sought enrollment of 30 patients, the study was terminated early secondary to the growing body of literature questioning the safety of olanzapine in the treatment of DIP as well as the increasing difficulty in enrolling antipsychotic-naive patients.
Only one subject was treated with 10mg. His hallucinations were rated “very much improved” at study end; he required no adjustment in dopamimetic dose mid-study and no side effects were observed. This 10mg subject was not included in statistical analyses. In the remaining 23 subjects, no significant imbalances were present at baseline between placebo and treatment groups on any demographic characteristic or any psychiatric or neurologic measure (Table 2).

Intention-to-treat analyses.

The intention-to-treat analyses did not show significant differences between groups except for report of mild side effects (p<0.04) (Table 3). While spontaneous report of motoric side effects was not statistically significant between groups, a disproportionate number of olanzapine vs. placebo group subjects who withdrew did so secondary to reported motor side effects (0% of placebo withdrawers vs. 21% of olanzapine withdrawers). Nine subjects did not complete the study: two from the placebo group, four from the 2.5mg olanzapine group, and three from the 5mg olanzapine group. In the placebo group, one patient died of myocardial infarction and another withdrew from the study secondary to lack of efficacy. In the 5mg olanzapine group, two reported serious adverse events and a third quit her medication following the first dose, declaring herself “cured.” Of the 5mg subjects who withdrew for serious adverse events, one was hospitalized with delirium three weeks into the study; the other withdrew after day six due to hospitalization with hip fracture and pneumonia, and reported worsening Parkinson’s symptoms prior to dropout. Of the four subjects who dropped out of the 2.5mg olanzapine group, two withdrew due to worsening Parkinsonian symptoms, one secondary to unspecified side effects, and one secondary to “feeling confused.” Only two subjects in the 2.5mg group completed the study, both requiring increases of their levodopa dose at their interim visit. One each in the
placebo and 5mg olanzapine arms also required levodopa adjustment at their two-week assessment. Retention and attrition of study subjects is summarized in Table 3.

To assess adequacy of blinding, both the primary investigator and study subjects were asked on study completion (or drop-out) to guess the identity of administered medication (i.e., olanzapine vs. placebo). Both investigator and patient were much more likely than chance would predict to correctly guess the identity of administered medication (for investigator, \( p=0.0021, \chi^2=12.29 \); for study subjects \( p=0.0312, \chi^2=6.94 \)). However, the videotape rater had no information about side effects.

**Primary planned analyses.**

Analysis of the psychosis subscale of BPRS scores (the more sensitive of our primary efficacy measures) did not reveal a statistically significant difference between groups (drug doses) in severity of psychosis in either the week 0-2 epoch (\( p=0.433 \)) or the week 2-4 epoch (\( p=0.393 \)). Again, *post hoc* analysis in study completers revealed no statistical significance in psychosis reduction between olanzapine (combined groups) and placebo (\( p=0.536 \)), as shown in Figure 1.

Data from the first and second epochs revealed no statistically significant difference in parkinsonian signs across treatment groups, as measured by the UPDRS III (week 0-2 epoch, placebo vs 2.5mg olanzapine group \( p=0.172 \); week 2-4 epoch \( p=0.677 \)). *Post hoc* analysis of UPDRS motor scores comparing olanzapine (combined groups) versus placebo across the duration of study found no significant difference in parkinsonism among study completers (\( p=0.608 \)) [Figure 2].
Analyses were repeated in like fashion for all other psychiatric and neurological parameters (CGI impression, CGI improvement, BPRS total, BDI, MMSE, insomnia score, hypersomnolence score, PDQ-39, and Schwab-England ADL assessment), none of which revealed statistical significance between olanzapine groups and placebo.

Conclusions

Our study failed to reject the null hypothesis. This could be a problem of power; however, larger studies of olanzapine also failed to demonstrate antipsychotic efficacy of this drug in the Parkinson’s population. In study completers, we did not observe the motoric exacerbation documented in several studies in the literature, but perhaps this is a function of our allowance for dopaminergic increase mid-study as well as a selection bias in some analyses for those subjects who best tolerated the medication and therefore completed the study. After all, of the nine subjects who withdrew from the study, a third identified a worsening of their motor disability prior to dropout, all of whom were discovered on unblinding to have been randomized to olanzapine. Therefore the good retrospective accuracy of investigator and patient guesses of study drug identity is not surprising.

The current algorithm for approaching DIP in Parkinson’s disease involves first addressing any potential causes other than anti-parkinsonian agents (i.e., metabolic disturbances, infections, subdural hematoma, drugs); second, eliminating anticholinergics and amantadine, as these can cause psychosis; and third, examining and simplifying any psychotropic medication regimens (as
serotonergic and cholinergic systems together have been implicated in hallucinations). Next, dopamine agonists are switched to levodopa if possible, since at equally effective doses there is a lower incidence of psychosis on levodopa. Once these factors have been taken into account, minimization of dopaminetics is traditionally followed by addition of an antipsychotic. Other treatments, such as ondansetron, acetylcholinesterase inhibitors, and electroconvulsive therapy are supported by limited data in idiopathic Parkinson disease and are generally not viewed as first-line therapy. Our trial supports the increasing body of evidence suggesting that olanzapine is ineffective for relieving dopaminetic-induced psychotic symptoms in Parkinson’s disease and that its use may be associated with intolerable worsening of Parkinson motor disability.

One methodological innovation in this study was the use of videotape to record semi-standardized interviews for later analysis by a rater blind not only to drug assignment but also to time (i.e., week 0, week 2, or week 4). The rationale was to minimize rater expectation of improvement over time that might reduce our power to detect significantly greater improvement in the active treatment groups.

Use of the newer atypical agents quetiapine and ziprasidone for the treatment of DIP in Parkinson’s disease has been encouraging in initial open-label trials. However, as previously noted, double-blind, randomized, placebo-controlled trials of quetiapine for DIP in Parkinson’s disease have failed to demonstrate efficacy. Our trial underscores the importance of rigorous study design for the assessment of drug effectiveness in special populations. If clozapine’s prominence in the clinical management of DIP in Parkinson’s disease
is to be usurped, antipsychotic agents will have to meet the burden of proof of double-blind, randomized, placebo-controlled trials.

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Approximate contributions to this manuscript are as follows. Dr. Nichols performed 50% of data analysis and 75% of manuscript preparation. Ms. Hartlein performed 50% of data collection. Ms. Albin performed 10% of data analysis. Dr. Racette performed 10% of data collection. Dr. Black designed the study, supervised all aspects of the study, takes responsibility for all aspects of the manuscript, and performed 40% of data analysis, 40% of data collection, and 25% of manuscript preparation. All authors reviewed the manuscript.
References


TABLE AND FIGURE LEGENDS

Table 1
Summary of study design

Table 2
Patient characteristics at baseline. Values are mean (SD). MMSE, Folstein mini mental test examination; BPRS-T, Brief Psychiatric Rating Scale total score; BPRS-P, psychosis subscale; UPDRS, unified Parkinson's disease rating scale; PDQ-39, Parkinson's disease quality of life questionnaire; BDI, Beck depression inventory; HAM-D, Hamilton depression rating scale; CGI, clinical global impression; INS, insomnia score; HYP, hypersomnia score; SEADL, Schwab-England ADL assessment.

Table 3
Subject retention and side effects by group, including number requiring dopamimetic increase. Side effects (SEs) were any complaint of drug spontaneously reported by the patient, independent of whether SE intensity was severe enough to prompt withdrawal from the study. Serious adverse events always prompted withdrawal. SE, side effects; ↑, increase; 1st epoch, week 0-2 analysis; 2nd epoch, week 2-4 analysis, *, statistically significant (p<0.05).

Figure 1. BPRS scores across four week study revealed no significant difference between olanzapine and placebo groups among study completers.
Figure 2. UPDRS scores across four week study revealed no significant difference between olanzapine and placebo groups among study completers.
Table 1. Summary of study design.

<table>
<thead>
<tr>
<th>Baseline Evaluation</th>
<th>Weeks 1-2</th>
<th>2 wk visit</th>
<th>Weeks 3-4</th>
<th>4 wk visit</th>
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<tbody>
<tr>
<td>clinical evaluation; clinical placebo</td>
<td>placebo</td>
<td>clinical eval; 2.5 mg</td>
<td>placebo</td>
<td>clinical evaluation; 2.5 mg return to routine</td>
</tr>
<tr>
<td>randomize</td>
<td>5 mg</td>
<td>↑ dopamimetic, if indicated</td>
<td>5 mg</td>
<td>clinical care</td>
</tr>
<tr>
<td>Measure</td>
<td>Placebo (n=9)</td>
<td>2.5 mg (n=6)</td>
<td>5 mg (n=8)</td>
<td>p value</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------------</td>
<td>--------------</td>
<td>------------</td>
<td>---------</td>
</tr>
<tr>
<td>age</td>
<td>71.3 (6.5)</td>
<td>70.7 (8.1)</td>
<td>72.4 (4.8)</td>
<td>0.882</td>
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<tr>
<td>MMSE</td>
<td>26 (2.6)</td>
<td>27 (3.6)</td>
<td>27 (2.7)</td>
<td>0.976</td>
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<tr>
<td>BPRS-T</td>
<td>34.8 (5.9)</td>
<td>34.3 (5.4)</td>
<td>33.4 (3)</td>
<td>0.874</td>
</tr>
<tr>
<td>BPRS-P</td>
<td>7.9 (2)</td>
<td>9 (3)</td>
<td>7.8 (2.1)</td>
<td>0.633</td>
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<td>UPDRS, motor score</td>
<td>30 (11)</td>
<td>27.5 (13.1)</td>
<td>31 (11.6)</td>
<td>0.855</td>
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<td>PDQ-39</td>
<td>53 (25.7)</td>
<td>59 (15.9)</td>
<td>59 (27.3)</td>
<td>0.867</td>
</tr>
<tr>
<td>BDI</td>
<td>10.1 (6)</td>
<td>9.8 (6)</td>
<td>12.6 (9.2)</td>
<td>0.738</td>
</tr>
<tr>
<td>HAM-D</td>
<td>8.7 (6.1)</td>
<td>5.3 (1.6)</td>
<td>11.6 (7.6)</td>
<td>0.177</td>
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<td>CGI</td>
<td>4.1 (0.9)</td>
<td>3.2 (1)</td>
<td>3.9 (0.8)</td>
<td>0.161</td>
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<tr>
<td>INS</td>
<td>4.2 (4)</td>
<td>4 (2.1)</td>
<td>2.6 (2.6)</td>
<td>0.566</td>
</tr>
<tr>
<td>HYP</td>
<td>1.5 (1)</td>
<td>2.3 (1.9)</td>
<td>2.6 (2.1)</td>
<td>0.446</td>
</tr>
<tr>
<td>SEADL</td>
<td>76 (15)</td>
<td>72 (24)</td>
<td>75 (17)</td>
<td>0.918</td>
</tr>
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</table>
Table 3. Subject retention & side effects by group & number requiring dopaminergic increase.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>2.5 mg</th>
<th>5 mg</th>
<th>All</th>
<th>p value</th>
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<tbody>
<tr>
<td># enrolled</td>
<td>9</td>
<td>6</td>
<td>8</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td># withdrew</td>
<td>2 (22%)</td>
<td>4 (66%)</td>
<td>3 (38%)</td>
<td>9 (39%)</td>
<td>0.2232</td>
</tr>
<tr>
<td># withdrew for motoric SEs</td>
<td>0 (0%)</td>
<td>2 (33%)</td>
<td>1 (12%)</td>
<td>3 (13%)</td>
<td>0.1712</td>
</tr>
<tr>
<td># w/ motor SE complaint</td>
<td>1 (11%)</td>
<td>2 (33%)</td>
<td>1 (12%)</td>
<td>4 (17%)</td>
<td>0.4863</td>
</tr>
<tr>
<td># w/ any mild SEs</td>
<td>2 (22%)</td>
<td>5 (83%)</td>
<td>2 (25%)</td>
<td>9 (39%)</td>
<td>*0.0356</td>
</tr>
<tr>
<td># w/ serious adverse events</td>
<td>1 (11%)</td>
<td>0 (0%)</td>
<td>2 (25%)</td>
<td>3 (13%)</td>
<td>0.3795</td>
</tr>
<tr>
<td># included in 1st epoch</td>
<td>9 (100%)</td>
<td>3 (50%)</td>
<td>5 (63%)</td>
<td>17 (74%)</td>
<td>0.064</td>
</tr>
<tr>
<td># included in 2nd epoch</td>
<td>7 (78%)</td>
<td>2 (33%)</td>
<td>5 (63%)</td>
<td>14 (61%)</td>
<td>0.2232</td>
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<tr>
<td># w/ dopaminergic ↑</td>
<td>1 (11%)</td>
<td>2 (33%)</td>
<td>1 (13%)</td>
<td>4 (17%)</td>
<td>0.4863</td>
</tr>
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</table>

Side effects (SEs) were any complaint of drug spontaneously reported by the patient, independent of whether SE intensity was severe enough to prompt withdrawal from study or not. Serious adverse events always prompted withdrawal. 1st epoch refers to week 0-2 analysis; 2nd epoch refers to week 2-4 analysis.

* indicates statistical significance (p<0.05)
Figure 1

Current effect: F(2, 24) = 64.084, p = .000573
Effective hypothes is decomposed
Vertical bars denote 95% confidence intervals
Figure 2
Assessed for eligibility (n=24)

Randomized (n=24)

Allocated & received placebo (n=9)
- Discontinued placebo due to death (n=1)
- Discontinued due to lack of efficacy (n=1)

Allocated & received intervention (n=15)
- Allocated to 2.5mg (n=6)
  - Discontinued due to motor SEs (n=2)
  - D/c due to minor (non-motor) SEs (n=2)
  - Analyzed (n=3)
  - Excluded from analysis due to lack of f/u (n=3)

- Allocated to 5mg (n=8)
  - D/c due to motor SEs (n=1)
  - D/c due to SAE (delirium) (n=1)
  - D/c due to “cure” (n=1)
  - Analyzed (n=6)
  - Excluded from analysis due to lack of f/u (n=2)

- Allocated to 10mg (n=1)
  - No discontinuations

- Analyzed (n=0)
  - Excluded from analysis due to change in study randomization (n=1)