A fixed-dose randomized controlled trial of olanzapine for psychosis in Parkinson disease

Michelle J Nichols, Washington University School of Medicine in St. Louis
Johanna M Hartlein, Washington University School of Medicine in St. Louis
Meredith GA Eicken, Washington University School of Medicine in St. Louis
Brad A Racette, Washington University School of Medicine in St. Louis
Kevin J Black, Washington University School of Medicine

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RESEARCH ARTICLE

A fixed-dose randomized controlled trial of olanzapine for psychosis in Parkinson disease [v1; ref status: approved 1, http://f1000r.es/1au]

Michelle J Nichols¹,², Johanna M Hartlein¹,³, Meredith GA Eicken⁴,⁵, Brad A Racette³, Kevin J Black¹,³,⁶,⁷

¹Department of Psychiatry, Washington University School of Medicine, St. Louis MO, 63110, USA
²Current affiliation: UT Southwestern Medical Center, Dallas TX, 75390, USA
³Department of Neurology, Washington University School of Medicine, St. Louis MO, 63110, USA
⁴Department of Biology, Washington University, St. Louis MO, 63110, USA
⁵Current affiliation: Massachusetts General Hospital, Boston MA, 02114-2622, USA
⁶Department of Radiology, Washington University School of Medicine, St. Louis MO, 63110, USA
⁷Department of Anatomy & Neurobiology, Washington University School of Medicine, St. Louis MO, 63110, USA

Abstract

Background: Psychiatry 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 might be an effective alternative to clozapine for treatment of drug-induced psychosis (DIP) in PD, and that lower doses than usual might make it tolerable.

Methods: In 1998-2003 we conducted a four-week, double-blind, placebo-controlled, parallel group, fixed-dose trial of olanzapine (0, 2.5mg, or 5mg) in 23 PD patients with DIP while allowing for clinically realistic dose adjustments of dopaminomimetic mid-study. The primary outcome measures were Brief Psychiatric Rating Scale (BPRS) ratings scored from videotaped interviews after study termination by an observer blinded to dose assignment and to interview timing, and CGI (Clinical Global Impression). The Unified Parkinson’s Disease Rating Scale motor subscale (UPDRS) 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 (seven on placebo, two on 2.5mg olanzapine, five 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, PDQ39, Schwab-England ADL assessment, and sleep...
scores).

**Conclusion:** This study adds to other evidence that olanzapine is ineffective in treating medication-induced psychosis in Parkinson disease.

**Corresponding author(s):** Kevin J Black (kevin@wustl.edu)

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Introduction

Drug-induced psychosis (DIP) is a significant and disabling complication of long-term treatment of Parkinson disease (PD), affecting a large minority of PD patients receiving chronic dopaminergic therapy. 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. 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. 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 incidence of parkinsonism in schizophrenia, have potential advantages for treatment of hallucinations in this sensitive population.

Until recently, the only treatment proven with randomized, placebo-controlled studies to reduce DIP has been clozapine, an agent that does not worsen motor function. Despite these favorable data, use of clozapine has been limited secondary to its rare but potentially serious risk of agranulocytosis and the consequent necessity for frequent blood draws. Thus alternative treatments have been eagerly sought.

Quetiapine has become the most commonly prescribed antipsychotic in DIP. Although double-blind, placebo-controlled trials of quetiapine in PD confirmed it is well tolerated in terms of motor side effects, it has not proven significantly more effective than placebo in treating psychosis, and a head-to-head comparison found clozapine superior to quetiapine. Ziprasidone showed some benefit in open-label experience, including in a random-assignment open comparison to clozapine. However, ziprasidone can cause motor side effects in PD and is not generally considered standard therapy for DIP. Other treatments, such as ondansetron, acetylcholinesterase inhibitors, and electroconvulsive therapy are supported by limited data in idiopathic Parkinson disease but are generally not viewed as first-line therapy. Recently, a phase III clinical trial of a serotonin 5HT2A inverse agonist, pimavanserin, showed benefit over placebo, but the drug will not be available in the U.S. at least until late 2014.

Clozapine’s antipsychotic efficacy is often attributed to its D4 receptor antagonism. It is also posited that its robust 5HT2A receptor antagonism, especially in relation to its relatively weaker D2 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 dopaminomimetic-induced psychosis. Olanzapine, therefore, with its ostensibly similar receptor binding profile to clozapine at D2, D4, and serotonergic receptors (especially 5HT2A and 5HT2C), and muscarinic sites, provides a theoretically encouraging alternative to clozapine in this fragile population.

An initial open study of olanzapine in Parkinson 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. Aarsland and colleagues replicated these findings in a relatively more challenging population of Parkinson disease patients with and without dementia. 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. A double-blind placebo-controlled trials revealed equivocal antipsychotic benefit and problematic motor decline in PD patients with DIP treated with 2.5–15mg/day olanzapine (mean final doses 4.1–4.6mg/day). As a result, experts have recommended against the use of olanzapine in PD.

None of these studies, however, were parallel-group fixed-dose trials, and some allowed for neuroleptic dose in the same range as approved for schizophrenia; experience with clozapine suggests that an effective antipsychotic dose in PD 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 the only marketed drug for which efficacy has been shown is clozapine, demonstrating efficacy for an alternative agent would be important, and a fixed low dose of olanzapine (2.5mg/day) may allow a reasonably low incidence of side effects if dopaminomimetic dose adjustments are allowed. 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 reduce DIP in patients with idiopathic PD significantly more than would a placebo, without causing intolerable motor worsening.

Methods and materials

The completed CONSORT checklist and the original study protocol are available in the Data Files.
The envelopes were not opened sequentially numbered envelopes containing the medi-
5mg for the first week and 10mg thereafter. Subjects received of investigation, and a 10mg arm, in which patients received this dosage nightly throughout the four weeks ment groups consisted of a placebo arm, a 5mg arm, in which either of two doses of olanzapine. At study initiation, treat-

Patients were randomized 1:1:1 to treatment with placebo or adding an antipsychotic. Exclusion criteria included a Folstein Mini-Mental State Examination (MMSE) score < 22, pregnancy, concurrent diagnosis of delirium (unless clearly explained by dopaminomimetics), catatonia or neuroleptic ma-

Subjects were required to be over 30 years old and have a caregiver who could provide a reliable report. At study entry, patients were required to be treated with the lowest clinically acceptable dose of dopaminomimetic. Patients treated only with a dopa-

Sweden. In this study, which was approved by the Washington University Hu-

All patients gave written informed consent to participate in the study, which was approved by the Washington University Hu-

Ethics statement
All patients gave written informed consent to participate in the study, which was approved by the Washington University Hu-

Treatment protocol
Patients were randomized 1:1:1 to treatment with placebo or either of two doses of olanzapine. At study initiation, treat-

Primary efficacy measures were CGI scores and BPRS ratings of psychosis. At each visit, the coordinator interviewed the pa-

Patient selection
Twenty-four patients were recruited from the Washington University Movement Disorders Center from February 1998 to October 2003. Patients were examined by a movement dis-

Subjects received a baseline evaluation that involved a full psychiatric, neurologic, and medical history and examina-

After the first five patients were enrolled, an interim safety analy-

Subjects were treated with levodopa and were experiencing clinically sign-

Exclusion criteria included a Folstein Mini-Mental State Examination (MMSE) score < 22, pregnancy, concurrent diagnosis of delirium (unless clearly explained by dopaminomimetics), catatonia or neuroleptic ma-

Primary efficacy measures were CGI scores and BPRS ratings of psychosis. At each visit, the coordinator interviewed the pa-

In most cases an appropriate surrogate decision maker also consented. FDA approval was through IND # 53,556. This trial concluded in 2003, so it is exempt from the current ICMJE requirement of prospectively registering clinical trials.

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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 dopaminomimetics 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. However, since some subjects dropped out without completing outcome measures at a 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. Statistical computations used STATISTICA 7.1 (StatSoft, Inc., Tulsa, OK) or Excel (Microsoft, Redmond, WA).

Results
Baseline characteristics
A total of 24 patients were enrolled (see Figure 1). Though the original study design sought enrollment of 30 patients, the

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**Table 1. Summary of final study design.**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Weeks 1–2</th>
<th>2 week visit</th>
<th>Weeks 3–4</th>
<th>4 week visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical evaluation; randomize</td>
<td>Placebo 2.5mg</td>
<td>Clinical evaluation; ↑ dopaminomimetic, if indicated</td>
<td>Placebo 2.5mg</td>
<td>Clinical evaluation; return to routine clinical care</td>
</tr>
</tbody>
</table>

This table summarizes the study design and timing of assessments and interventions for the last 19 subjects enrolled in the study. ↑ dopaminomimetic: dose increase allowed for antiparkinsonian medication, if parkinsonism had worsened since starting the study. See Methods and Figure 1 for further details.

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**Figure 1. CONSORT flowchart.**
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 (one other was randomized to the 10mg group, but was treated only for one week, so received only 5mg doses). His hallucinations were rated “very much improved” at the study end; he required no adjustment in dopaminomimetic 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 incidence of mild side effects (p<0.04) (Table 3). While spontaneous report of motor 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 withdrawals vs. 21% of olanzapine withdrawals). 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 discontinued 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 PD 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 and Figure 1.

To assess adequacy of blinding, both the primary investigator and study subjects were asked on study completion (or dropout) to guess the identity of administered medication (i.e., olanzapine vs. placebo). Both investigator and patient were much more likely than chance to correctly guess the identity of administered medication (for investigator, χ²=12.29, p=0.0021; for study subjects, χ²=6.94, p=0.0312). However, the videotape rater had no information about side effects.

**Table 2. Patient characteristics at baseline.**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Placebo (n=9)</th>
<th>2.5mg (n=6)</th>
<th>5mg (n=8)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<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>
</tr>
<tr>
<td>MMSE</td>
<td>26 (2.8)</td>
<td>27 (3.6)</td>
<td>27 (2.7)</td>
<td>0.976</td>
</tr>
<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>
</tr>
<tr>
<td>UPDRS, motor score</td>
<td>30 (11)</td>
<td>27.5 (13.1)</td>
<td>31 (11.6)</td>
<td>0.855</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>CGI</td>
<td>4.1 (0.9)</td>
<td>3.2 (1)</td>
<td>3.9 (0.8)</td>
<td>0.161</td>
</tr>
<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>HYPINS</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>
</tbody>
</table>

Values are given as 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.

**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 2.

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 3).

Analyses were repeated in like fashion for all other psychiatric and neurological parameters (CGI impression, CGI improve-
Table 3. Subject retention and side effects by group.

<table>
<thead>
<tr>
<th></th>
<th>Olanzapine</th>
<th>Placebo 2.5mg</th>
<th>5mg</th>
<th>All</th>
<th>p value</th>
</tr>
</thead>
<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 motor 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 compliant</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>0.0640</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>
</tr>
<tr>
<td># w/dopaminomimetic ↑</td>
<td>1 (11%)</td>
<td>2 (33%)</td>
<td>1 (13%)</td>
<td>4 (17%)</td>
<td>0.4863</td>
</tr>
</tbody>
</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 the study. Serious adverse events always prompted withdrawal. SE: side effects; ↑, increase; 1st epoch, week 0–2 analysis; 2nd epoch, week 2–4 analysis, *, p<0.05.

Figure 2. Brief Psychiatric Rating Scale (BPRS) scores across four week study revealed no significant difference between placebo and olanzapine groups among study completers. Current effect: F(2, 24)=0.64064, p=0.53573. Effective hypothesis decomposition. Vertical bars denote 0.95 confidence intervals. Olanzapine-blue; placebo-red.

Figure 3. Unified Parkinson’s Disease Rating Scale (UPDRS) scores across four week study revealed no significant difference between placebo and olanzapine groups among study completers. Current effect: F(2, 24)=0.50826, p=0.60787. Effective hypothesis decomposition. Vertical bars denote 0.95 confidence intervals. Olanzapine-blue; placebo-red.

Discussion
The study failed to reject the null hypothesis. This could be a Type II error, but larger studies of olanzapine also failed to demonstrate antipsychotic efficacy of this drug in the PD 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 dopaminomimetic 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 subjects enrolled are relatively typical of PD patients with psychotic symptoms with a few exceptions. Subjects with urgent need for treatment were not enrolled for ethical reasons. Although mild dementia was allowed, this sample had relatively high cognitive functioning, with a mean MMSE score > 26 (Table 2). Finally, at this center, some of the patients are referred for subspecialty movement disorders consultation, though a large fraction of the patients are not referred and are typical of PD patients treated in the community. With these caveats, the results appear to be generally applicable to patients with PD and psychosis.

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. It also reduced the likelihood of rater unblinding.

This trial supports other evidence suggesting that olanzapine is ineffective for relieving dopaminomimetic-induced psychotic symptoms in Parkinson disease and that it may cause intolerable worsening of motor disability. This trial also underscores the importance of rigorous study design for the assessment of drug effectiveness in special populations, as we and others have not replicated the early, positive open-label experience reported for olanzapine in this population. If clozapine’s prominence in the clinical management of DIP in PD is to be usurped, antipsychotic agents will have to meet the burden of proof of double-blind, randomized, placebo-controlled trials.

Competing interests
This study was funded by Lilly Research Laboratories (Investigator-Initiated Trial F1D-MC-I012). When this manuscript was submitted for publication (June 2013), KJB was a site investigator on a study of pimavanserin for psychosis in PD funded by Acadia Pharmaceuticals. Neither company influenced the design of the study, the data analysis, the decision to publish, or the manuscript.

Grant information
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Acknowledgements
Joel S. Perlmutter, M.D., gave valuable advice on study design and was instrumental in patient referral. Special thanks to Colleen Taylor, Jonathan Koller, Maria Chushak, Tamara Hershey, Ph.D., and John G. Csernansky, M.D., for their assistance with this project.

Supplementary materials

Guidelines for rating selected BPRS items in a treatment study of psychosis in Parkinson disease.

1. Emotional withdrawal = interpersonal relatedness during interview.
2. Tension:
   a. Ignore: rest tremors, postural tremors, chorea, athetosis, dystonia.
   b. Include: tardive dyskinesia and akathisia.
3. Depressive mood rating does not consider “pure apathy” (i.e., apathy w/o other depressive signs or symptoms), but apathy can contribute to the total judgment of depressive mood if other signs or symptoms are present.
4. Hallucinatory behavior:
   a. 2 = illusions and “shadow in the corner of the eye”.
   b. 3 = e.g., colors on the wall.
   c. 4 = definitively abnormal sensory perceptions.
5. Motor retardation: Speed of movement, not amplitude (also, depressive retardation is not substantially helped by external cues; if slowed movement is substantially helped by external cues, then it may be more parsimoniously attributed to PD).
6. Unusual thought content: Ratings ≥ 5 require action on delusion.
7. Blunted affect: Rate according to scale, considering emotional variance, regardless of amplitude; remember that flat/blunted affect is not equivalent to depressed affect.
8. Disorientation: Off by one day of week = 3.
   Motor hyperactivity: Limit rating to pressured speech and voluntary movement; festination does not count.

Kevin J Black MD consulted with John G Csernansky MD to write these additional rules for scoring BPRS items potentially influenced by motor signs in Parkinson disease patients.
References

22. ACADIA announces expedited path to NDA filing for pimavanserin following meeting with FDA. Business Wire, 2013.
The study (completed in 2003) was well designed, albeit with a relatively small sample size, and intended to answer an important and clinically relevant question. After reviewing the manuscript I would agree that it probably does support the notion that olanzapine may cause intolerable worsening of motor disability but I do not think that one can draw any conclusions regarding efficacy or lack thereof based on this study.

One element of the trial design (i.e. permitting changes in dopaminergic medications) may have created some challenges when interpreting the data. The investigators speculated that olanzapine may be better tolerated if adjustments in dopaminergic medications were allowed (and therefore permitted dopaminergic medication adjustment at the 2 week visit). While this may be true, it could also increase the chances that dopaminergic drug induced psychosis could worsen (if dopaminergic medication were increased in an effort to improve motor worsening). This could potentially be a "set up" for decreased efficacy (if dopaminergic medications were changed more frequently in active vs. placebo). It is noted that medications were adjusted in one of the placebos, two of the 2.5 mg active and one of the 5 mg active. The authors note that there was an apriori decision to analyze data from weeks 0-2 and 2-4 separately. Change from 0-2 weeks was chosen to be the primary test of efficacy, apparently in order to limit the confound of changes in dopaminergic medications allowed at week two. However, one could question if 2 weeks is long enough to demonstrate efficacy.

In addition, a series of unplanned events contributed to challenges with data interpretation. These events included a change in design after study initiation, lower than expected enrollment and high dropout rate.

The change in study design was a decrease in study drug dosage after enrollment of 5 subjects ("in light of reports published since study initiation that higher olanzapine doses cause intolerable exacerbation of parkinsonism in PD"). This resulted in one subject being excluded from analyses (see below) and perhaps, decreased the chance of demonstrating study drug efficacy (if higher dosages were required).

Only 24 (of an anticipated 30) subjects were enrolled and 9 withdrew (39%) which is a fairly high dropout rate. One of the 24 subjects was not included in the analyses because he was the only one to receive the initially planned dosage of 10 mg.

While spontaneous reports of motor side effects were not statistically significant between groups, a disproportionate number of olanzapine vs. placebo who withdrew did so due to motor side effects. This finding does suggest that olanzapine may be associated with worsening motor function. However this may not be true for every patient, as exemplified by the one subject who was the only one to receive the initially planned dosage of 10 mg. He had no worsening of motor function (and an improvement in psychosis).
I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

**Competing Interests:** No competing interests were disclosed.

1 Comment

**Kevin J. Black**, Washington University in St. Louis, USA  
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I agree with Dr. Richard's comments about the limitations and possible conclusions from this report.