RESEARCH ARTICLE

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

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v1 **First Published:** 09 Jul 2013, **2**:150 (doi: 10.12688/f1000research.2-150.v1)
Latest Published: 09 Jul 2013, **2**:150 (doi: 10.12688/f1000research.2-150.v1)

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 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.

Article Status Summary

Referee Responses

Referees	1	2
v1 published 09 Jul 2013	report 1	report 1

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Latest Comments

No Comments Yet

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How to cite this article: Nichols MJ, Hartlein JM, Eicken MG *et al.* (2013) A fixed-dose randomized controlled trial of olanzapine for psychosis in Parkinson disease [v1; ref status: indexed, http://f1000r.es/1au] *F1000Research* 2013, **2**:150 (doi: 10.12688/f1000research.2-150.v1)

Grant information: This study was funded by Lilly Research Laboratories (Investigator-Initiated Trial F1D-MC-I012).
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: No competing interests were disclosed.

First Published: 09 Jul 2013, **2**:150 (doi: 10.12688/f1000research.2-150.v1)
First Indexed: 22 Aug 2013, **2**:150 (doi: 10.12688/f1000research.2-150.v1)

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[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 incidence of parkinsonism in schizophrenia, have potential advantages for treatment of hallucinations in this sensitive population[1].

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[6–8]. 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[1]. Thus alternative treatments have been eagerly sought.

Quetiapine has become the most commonly prescribed antipsychotic in DIP[9]. 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[10–15], and a head-to-head comparison found clozapine superior to quetiapine[16]. Ziprasidone showed some benefit in open-label experience[17], including in a random-assignment open comparison to clozapine[18]. However, ziprasidone can cause motor side effects in PD and is not generally considered standard therapy for DIP[1,19]. 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[1,19]. Recently, a phase III clinical trial of a serotonin $5HT_{2A}$ inverse agonist, pimavanserin, showed benefit over placebo, but the drug will not be available in the U.S. at least until late 2014[20–22].

Clozapine's antipsychotic efficacy is often attributed to its D_4 receptor antagonism. It is also posited that its robust $5HT_{2A}$ receptor antagonism, especially in relation to its relatively weaker D_2 receptor blockade, actually increases dopamine transmission in prefrontal cortical and nigrostriatal projections[23]. This may account for the cognitive improvement as well as paucity of extrapyramidal adverse events observed in clozapine-treated patients with dopaminomimetic-induced psychosis[23,24]. Olanzapine, therefore, with its ostensibly similar receptor binding profile to clozapine at D_2, D_4, and serotonergic receptors (especially $5HT_{2A}$ and $5HT_{2C}$), and muscarinic sites, provides a theoretically encouraging alternative to clozapine in this fragile population[25].

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[26]. Aarsland and colleagues replicated these findings in a relatively more challenging population of Parkinson disease patients with and without dementia[27]. 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[28–30]. Another small open-label trial and case report series suggested unacceptable Parkinsonian motor deterioration in the context of dubious antipsychotic efficacy[31,32]. Later, two 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)[33,34]. As a result, experts have recommended against the use of olanzapine in PD[1,19].

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[35,36] and the original study protocol are available in the Data Files.

Ethics statement

All patients gave written informed consent to participate in the study, which was approved by the Washington University Human Studies Committee (approval # 97-0366). 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.

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 disorders specialist and diagnosed with idiopathic PD 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, as judged by their treating neurologist or psychiatrist and by the investigator (KJB). 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 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. Exclusion criteria included a Folstein Mini-Mental State Examination (MMSE) score < 22[37], pregnancy, concurrent diagnosis of delirium (unless clearly explained by dopaminomimetics), catatonia or neuroleptic malignant syndrome (NMS)-like syndrome, other confounding central nervous system (CNS) illness or systemic illness with potential CNS effects, antipsychotic use within the last month predating study enrollment (within the past six 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 1:1:1 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 (Indianapolis, IN), who provided the investigator with sealed, sequentially numbered envelopes containing the medication identity for each subject. The envelopes were not opened until after all data were collected and reviewed for accuracy, and after all decisions about statistical analysis were final, so that both investigators and patients were blind to intervention assignment. The randomization was done by Lilly. KJB enrolled subjects and patients were assigned to treatment packages sequentially by enrollment date.

After the first five patients were enrolled, an interim safety analysis was conducted by a reviewer otherwise not involved in the study, in light of reports published since the study initiation that higher olanzapine doses caused intolerable exacerbation of parkinsonism in PD. Though serious adverse events were no more common in the treatment groups than in the placebo group, it was decided at this time that the two active treatment arms would be changed to fixed doses of 2.5mg and 5mg olanzapine, maintained throughout the four weeks of study. New treatment packages were received and the blind was maintained until after data analysis, as above. No other changes to the protocol were made. See Table 1 for a summary of the final study design. The study was planned for 10 subjects in each of three 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.*[26] report.

Subjects received a baseline evaluation that involved a full psychiatric, neurologic, and medical history and examination, CGI (Clinical Global Impression) by MD[38], PDQ-39, a self-rated quality-of-life measure for PD[39], videotaped interview for later BPRS (Brief Psychiatric Rating Scale) rating blind to drug dose and blind to which visit was being rated[40], Schwab-England ADL assessment[41], UPDRS (Unified Parkinson's Disease Rating Scale), section III (motor)[42], MMSE[37], HDRS (Hamilton Depression Rating Scale)[43], BDI (Beck Depression Inventory)[44], and patient/caretaker reported hours and quality of sleep. Repeated measures at the two-week interim visit and the final four-week evaluation included CGI (by MD, patient, and caretaker), videotaped interview for later blinded BPRS, Schwab-England ADL assessment, UPDRS, MMSE, PDQ-39, BDI, sleep questionnaire, and pill counts. All assessments were done at Washington University Medical Center.

Primary efficacy measures were CGI scores and BPRS ratings of psychosis. At each visit, the coordinator interviewed the patient during videotaping using a semi-structured interview designed to facilitate later scoring of psychopathology using the BPRS[40,45,46]. After all subjects had completed participation, the videotaped segments were edited to remove references to date or study visit. Author KJB in consultation with a BPRS expert (John G Csernansky, MD) wrote rules for rating "motor retardation" and other BPRS items potentially influenced by parkinsonism (see Supplementary materials), and trained author MJN in BPRS ratings. Videotaped segments were reviewed in random order by 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[40]. 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)

Table 1. Summary of final study design.

Baseline	Weeks 1–2	2 week visit	Weeks 3–4	4 week visit
Clinical evaluation; randomize	Placebo 2.5mg 5mg	Clinical evaluation; ↑ dopaminometic, if indicated	Placebo 2.5mg 5mg	Clinical evaluation; return to routine clinical care

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

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 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 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 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

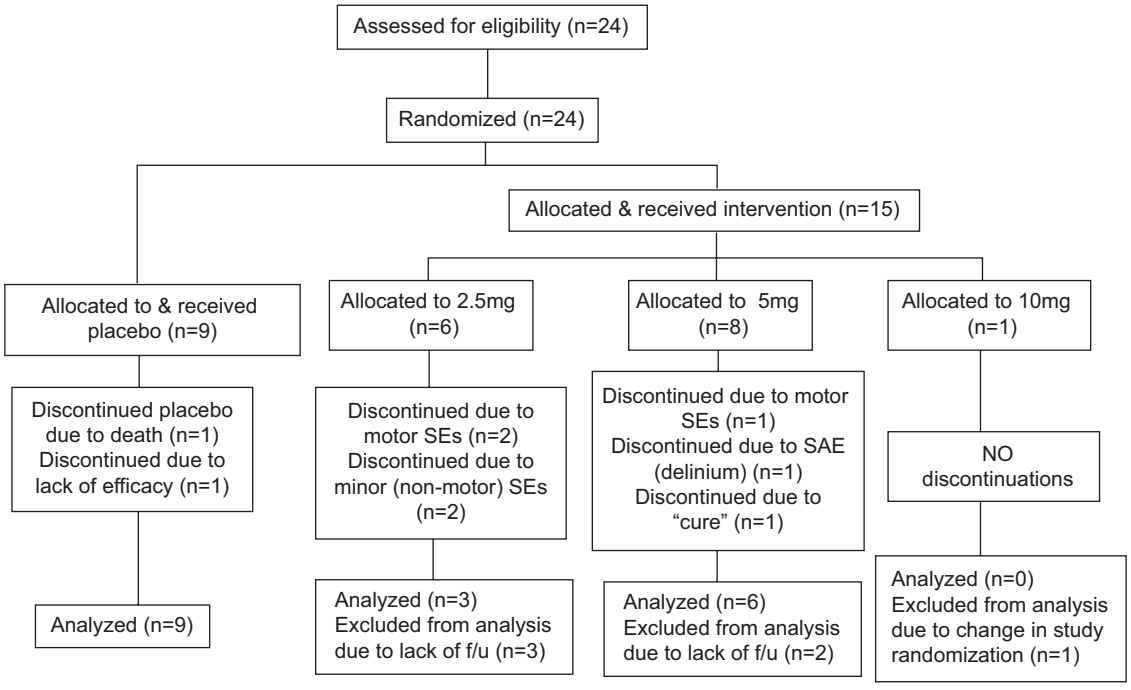

Figure 1. CONSORT flowchart.

Table 2. Patient characteristics at baseline.

		Olanzapine		
Measure	**Placebo (n=9)**	**2.5mg (n=6)**	**5mg (n=8)**	**p value**
Age	71.3 (6.5)	70.7 (8.1)	72.4 (4.8)	0.882
MMSE	26 (2.6)	27 (3.6)	27 (2.7)	0.976
BPRS-T	34.8 (5.9)	34.3 (5.4)	33.4 (3)	0.874
BPRS-P	7.9 (2)	9 (3)	7.8 (2.1)	0.633
UPDRS, motor score	30 (11)	27.5 (13.1)	31 (11.6)	0.855
PDQ-39	53 (25.7)	59 (15.9)	59 (27.3)	0.867
BDI	10.1 (6)	9.8 (6)	12.6 (9.2)	0.738
HAM-D	8.7 (6.1)	5.3 (1.6)	11.6 (7.6)	0.177
CGI	4.1 (0.9)	3.2 (1)	3.9 (0.8)	0.161
INS	4.2 (4)	4 (2.1)	2.6 (2.6)	0.566
HYPINS	1.5 (1)	2.3 (1.9)	2.6 (2.1)	0.446
SEADL	76 (15)	72 (24)	75 (17)	0.918

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.

Table 3. Subject retention and side effects by group.

		Olanzapine			
	Placebo	**2.5mg**	**5mg**	**All**	**p value**
# enrolled	9	6	8	23	
# withdrew	2 (22%)	4 (66%)	3 (38%)	9 (39%)	0.2232
# withdrew for motor SEs	0 (0%)	2 (33%)	1 (12%)	3 (13%)	0.1712
# w/motor SE complaint	1 (11%)	2 (33%)	1 (12%)	4 (17%)	0.4863
# w/any mild SEs	2 (22%)	5 (83%)	2 (25%)	9 (39%)	*0.0356
# w/serious adverse events	1 (11%)	0 (0%)	2 (25%)	3 (13%)	0.3795
# included in 1st epoch	9 (100%)	3 (50%)	5 (63%)	17 (74%)	0.0640
# included in 2nd epoch	7 (78%)	2 (33%)	5 (63%)	14 (61%)	0.2232
# w/dopaminomimetic ↑	1 (11%)	2 (33%)	1 (13%)	4 (17%)	0.4863

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.

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 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, χ^2=12.29, p=0.0021; for study subjects, χ^2=6.94, p=0.0312). However, the videotape rater had no information about side effects.

Negative results from a randomized controlled trial of olanzapine for psychosis in Parkinson disease: data, CONSORT checklist and initial study protocol

5 Data Files

http://dx.doi.org/10.6084/m9.figshare.730446

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).

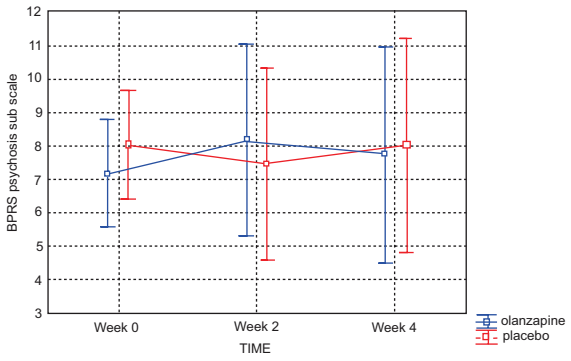

Figure 2. Brief Psychiatric Rating Scale (BPRS) scores across four week study revealed no significant difference between placebo and olanzapine groups among study completers. Current effect: F(2, 24)=0.64064, p=0.53573. Effective hypothesis decomposition. Vertical bars denote 0.95 confidence intervals.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

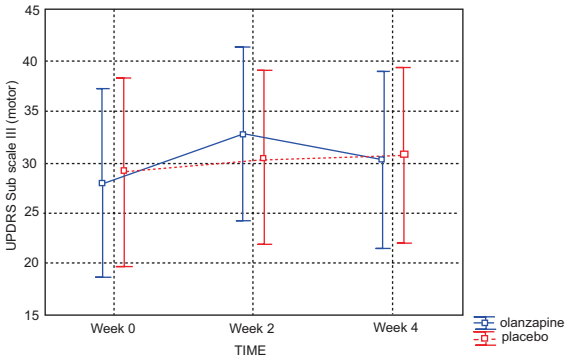

Figure 3. Unified Parkinson's Disease Rating Scale (UPDRS) scores across four week study revealed no significant difference between placebo and olanzapine groups among study completers. Current effect: F(2, 24)=0.50826, p=0.60787. Effective hypothesis decomposition. Vertical bars denote 0.95 confidence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

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.

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[14,33]. In study completers, we did not observe the motoric exacerbation documented in several studies in the literature[28–34], 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[1,19]. 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.

Author contributions

Approximate contributions to this manuscript are as follows. MJN performed 50% of data analysis and 70% of manuscript preparation. JMH performed 50% of data collection. MGAE performed 10% of data analysis. BAR performed 10% of data collection. KJB 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 30% of manuscript preparation. All authors reviewed the manuscript.

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

This study was funded by Lilly Research Laboratories (Investigator-Initiated Trial F1D-MC-I012).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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.

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Current Referee Status:

Referee Responses for Version 1

Eric Molho
Department of Neurology, Albany Medical Center, NY, USA

Approved: 22 August 2013

Referee Report: 22 August 2013
This is a well conceived and rigorously carried out clinical trial addressing an important issue in a difficult to study patient population. Although the data was collected a decade ago, the information is still relevant because remarkably little progress has been made since 2003 in the treatment of PD related psychosis. Dr. Richard's referee response presents the methodological shortcomings and correctly points out resulting limitations in data interpretation. I agree with all of the comments in her review.

In addition, I would like to add the following comments/observations:

In the abstract and introduction, the authors suggest that because olanzapine has a similar receptor binding profile to clozapine, it is a good candidate drug to study in the PD population and they cite Seeman *et al.* 1993. More recent work by Seeman shows that what is unique about clozapine is that it binds D2 receptors "loosely" and that its receptor occupancy is short-lived. Quetiapine has a similar D2 binding profile to clozapine but, olanzapine behaves much more like haloperidol and risperidone in this regard. This may explain the motor worsening that seems to be associated with olanzapine use in PD. (Kapur and Seeman. Am J Psychiatry 2001;158:360-369. Seeman and Tallerico. Am J Psychiatry 1999;156:876-884.)

I disagree with the statement in the introduction that "*Delusions, when they occur, often antedate visual hallucinations....*" The natural history of hallucinations in PD has been looked at in only a few longitudinal studies and the interaction between hallucination and delusions has not been adequately studied but my clinical experience and the bulk of what is presented in the literature suggests that minor hallucinatory phenomena (illusions, passage or presence hallucinations, benign hallucinations with insight) are much more common and occur earlier in PD than delusions. Delusions are generally associated with more severe underlying cognitive impairment, by definition are associated with lost insight and are generally considered to indicate a more advanced stage of disease progression than isolated visual hallucinations. (Fenelon *et al.* Brain 2000;123:733-745).

I would also question the premise that allowing for a dopaminergic medication dose adjustment in the study protocol (to reverse any worsening of PD motor symptoms due to the introduction of low dose olanzapine) might produce study results that are a more appropriate way to evaluate how this drug might work in the clinic. My experience is that this strategy is unsustainable even in the short term in this population. One reason is that each dose increase of dopaminergic medication is prone to reignite symptoms of psychosis and thus lead to a need for higher doses of the antipsychotic, setting up a cycle of overall worsening. Secondly, these patients tend to have more advanced motor symptoms including high risk symptoms such as postural instability and dysphagia. It may be very difficult to continue a drug known to worsen PD motor symptoms after the first fall or choking episode even if one cannot be sure it was a

direct result of the antipsychotic drug.

I would suggest more clearly pointing out that this study cohort had relatively mild cognitive impairment (MMSE >26) which may be quite different than what is encountered in practice. More demented patients may be more susceptible to side effects of atypical neuroleptics including sedation, encephalopathy and motor worsening. More demented patients may also have more severe psychosis which is likely to be less responsive to the low doses used in this and some other clinical trials.

Finally, I suspect that some readers may not have a full grasp of “Type II error”. This should probably be spelled out without jargon in the discussion.

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

Author Response

Kevin J. Black, Washington University in St. Louis, USA
Posted: 22 Aug 2013

Dr. Molho's comments are well thought out and much appreciated.

I agree with the discussion about clozapine pharmacology with reference to higher dissociation rate/decreased binding avidity as a better explanation for clozapine's superior tolerability in PD.

I agree that delusions usually follow hallucinations in this population; my error.

Dr. Molho's comments on mid-protocol antiparkinsonian dose adjustment are reasonable. Nevertheless the rationale described explains the original protocol design, and as he points out, we need more controlled data to definitively answer this and other questions about treatment.

I agree that the mild cognitive impairment in this sample limits the application of the results to a total clinical population of psychosis in PD. However, it can also be seen as a strength of the study, in that psychosis with dementia may conceivably differ in etiology and optimal treatment, so in that respect this sample may be considered more "pure."
Competing Interests: I'm the corresponding author.

Irene Richard
University of Rochester, Rochester, NY, USA

Approved: 11 July 2013

Referee Report: 11 July 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 olanazapine 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 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

Author Response

Kevin J. Black, Washington University in St. Louis, USA
Posted: 11 Jul 2013

I agree with Dr. Richard's comments about the limitations and possible conclusions from this report.
Competing Interests: I'm the corresponding author.