D.3.4 Psychotic symptoms (hallucinations and delusions)

Bibliographic reference	**Fernandez,H.H., Okun,M.S., Rodriguez,R.L., Malaty,I.A., Romrell,J., Sun,A., Wu,S.S., Pillarisetty,S., Nyathappa,A., Eisenschenk,S., 20100128, Quetiapine improves visual hallucinations in Parkinson disease but not through normalization of sleep architecture: results from a double-blind clinical-polysomnography study, International Journal of Neuroscience, 119, 2196-2205, 2009**
Country/ies where the study was carried out	US
Study type	Pilot, double-blind, placebo-controlled parallel-group study
Aim of the study	To confirm quetiapine's efficacy in improving visual hallucinations (VH), and to determine whether the mechanism was due to its effect on rapid eye movement (REM) sleep architecture.
Study dates	Study dates: Not reported Study duration: ~6.5 - 14 weeks
Source of funding	AstraZeneca Pharmaceuticals LP
Sample size	In total n =16; Quetiapine n = 8, Placebo n = 8 Randomised in a 1:1 drug to placebo ratio
Inclusion criteria	Patients were included if they: • Had been diagnosed with idiopathic PD • Experienced consistent and persistent (i.e., greater than one month), predominantly nocturnal VH • Were on stable doses of PD medications
Exclusion criteria	Patients were excluded if they: • Had been diagnosed with having "brittle" PD • Required constant medication adjustments • With a previous "non-response" to any antipsychotic drug • With threatening psychosis or delusions that make it difficult to justify participation in a place-controlled study • Had significant cognitive impairment that prevented accurate assessment of drug efficacy or understanding or informed consent • Were taking clonazepam or other sleeping agents that could interfere with sleep architecture • Had known central sleep disorders
Interventions	Quetiapine: 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, or 150 mg once a day at bedtime

<table>
<tr><th>Bibliographic reference</th><td>Fernandez,H.H., Okun,M.S., Rodriguez,R.L., Malaty,I.A., Romrell,J., Sun,A., Wu,S.S., Pillarisetty,S., Nyathappa,A., Eisenschenk,S., 20100128, Quetiapine improves visual hallucinations in Parkinson disease but not through normalization of sleep architecture: results from a double-blind clinical-polysomnography study, International Journal of Neuroscience, 119, 2196-2205, 2009</td></tr>
<tr><td>Details</td><td>Quetiapine (or matching placebo) was initiated at dose 25 mg at bedtime. The dose was increased every 3 to 7 days by 25 mg until a final dose of 150 mg at bedtime of quetiapine was reached or a complete resolution of nocturnal hallucinations was experienced, whichever was achieved first. Patients also received a phone call twice per week during the titration phase to monitor for efficacy, tolerance, and side effects. Patients needed to be on their final, stable dose for at least one month prior to obtaining the repeat polysomnogram. One month after the repeat polysomnography, all subjects returned for their final visit.

All PD medications were kept stable throughout the study.

There were no differences in baseline characteristics between the treatment arms except that the placebo group had a longer stage REM (74.7 min vs 40.1 min; p<0.001) at baseline:
<table>
<tr><td>Variable</td><td>Overall (n=16)</td><td>Active arm (n=8</td><td>Placebo arm (n=8)</td><td>p-value</td></tr>
<tr><td>Age</td><td>68 (8.04)</td><td>64.6 (7.48)</td><td>71.5 (7.46)</td><td>.087</td></tr>
<tr><td>Stage REMa</td><td>56.2 (26.4)</td><td>40.1 (17.7</td><td>74.6 (22.8)</td><td>.006</td></tr>
<tr><td>BPRS Total</td><td>30.8 (8.25)</td><td>31.2 (9.43)</td><td>30.2 (7.49)</td><td>.818</td></tr>
<tr><td>BPRS item No. 12</td><td>3.25 (1.1)</td><td>3.5 (1.06)</td><td>3.3 (0.92)</td><td>.334</td></tr>
<tr><td>UPDRS motor</td><td>33.6 (10.58)</td><td>31.6 (9.72)</td><td>35.8 (11.83)</td><td>.460</td></tr>
</table>
[a]Measured in minutes.</td></tr>
<tr><td>Primary outcome measures</td><td>Changes in REM architecture, as demonstrated via polysomnography.</td></tr>
<tr><td>Secondary outcomes measures</td><td>• CGIS
• BPRS
• UPDRS motor</td></tr>
<tr><td>Results</td><td></td></tr>
<tr><td>BPRS Hallucination</td><td>
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>-1.32</td><td>1.13</td><td>8</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td>Fernandez,H.H., Okun,M.S., Rodriguez,R.L., Malaty,I.A., Romrell,J., Sun,A., Wu,S.S., Pillarisetty,S., Nyathappa,A., Eisenschenk,S., 20100128, Quetiapine improves visual hallucinations in Parkinson disease but not through normalization of sleep architecture: results from a double-blind clinical-polysomnography study, International Journal of Neuroscience, 119, 2196-2205, 2009</td></tr>
<tr><td></td><td><table><tr><td>Control</td><td>-0.04</td><td>0.82</td><td>8</td></tr></table></td></tr>
<tr><td>UPDRS Motor</td><td><table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-5.74</td><td>6.84</td><td>8</td></tr><tr><td>Control</td><td>2.83</td><td>7.46</td><td>8</td></tr></table></td></tr>
<tr><td>Mortality</td><td><table><tr><td></td><td>Deaths</td><td>Total</td></tr><tr><td>Experimental</td><td>0</td><td>8</td></tr><tr><td>Control</td><td>0</td><td>8</td></tr></table></td></tr>
<tr><td>Number of dropouts due to adverse events</td><td><table><tr><td></td><td>Events</td><td>Total</td></tr><tr><td>Experimental</td><td>4</td><td>8</td></tr><tr><td>Control</td><td>1</td><td>8</td></tr></table></td></tr>
<tr><td>Results</td><td>Average quetiapine dose was 58.3 mg/day (range: 25-100 mg/day).

The worsening of Parkinsonism was noted to be mild in all cases, and no patients discontinued quetiapine because of Parkinsonism. However, 4 patients randomised to the quetiapine arm eventually dropped out: two due to the lack of efficacy in controlling the hallucinations, one was due to drowsiness, and one was lost to the follow-up.

<table><tr><td>Adverse event</td><td>Quetiapine</td><td>Placebo</td></tr><tr><td>Bronchitis</td><td>0</td><td>1</td></tr><tr><td>Confusion</td><td>1</td><td>1</td></tr><tr><td>Drowsiness</td><td>3</td><td>1</td></tr><tr><td>Dry mouth</td><td>0</td><td>1</td></tr></table></td></tr>
</table>

Bibliographic reference	Fernandez,H.H., Okun,M.S., Rodriguez,R.L., Malaty,I.A., Romrell,J., Sun,A., Wu,S.S., Pillarisetty,S., Nyathappa,A., Eisenschenk,S., 20100128, Quetiapine improves visual hallucinations in Parkinson disease but not through normalization of sleep architecture: results from a double-blind clinical-polysomnography study, International Journal of Neuroscience, 119, 2196-2205, 2009
	<table><tr><td>Dizziness/Syncope</td><td>0</td><td>4</td></tr><tr><td>Depression</td><td>0</td><td>1</td></tr><tr><td>Decreased appetite</td><td>0</td><td>1</td></tr><tr><td>Increased appetite</td><td>1</td><td>0</td></tr><tr><td>Loss of balance/increased</td><td>3</td><td>0</td></tr><tr><td>Nightmares</td><td>1</td><td>0</td></tr><tr><td>Sore throat</td><td>0</td><td>1</td></tr></table> Data extracted for BPRS hallucination and UPDRS motor are the mean change scores from baseline to end point.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? UNCLEAR 2. Was there adequate concealment of allocation? UNCLEAR 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? UNCLEAR* 6. Were the individuals administering care kept blind to treatment allocation? UNCLEAR* 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? NO. Dropout rate >20% 8. Did the study have an appropriate length of follow up? UNCLEAR (6.5 - 14 wks) 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? UNCLEAR 11. Were investigators kept blind to participant's exposure to the intervention? UNCLEAR* 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR* *Level of blinding unclear - no details beyond description of study as "randomized, double-blind, placebo-controlled trial".

Bibliographic reference	Fernandez,H.H., Okun,M.S., Rodriguez,R.L., Malaty,I.A., Romrell,J., Sun,A., Wu,S.S., Pillarisetty,S., Nyathappa,A., Eisenschenk,S., 20100128, Quetiapine improves visual hallucinations in Parkinson disease but not through normalization of sleep architecture: results from a double-blind clinical-polysomnography study, International Journal of Neuroscience, 119, 2196-2205, 2009
	Overall there is likely high risk of bias.

Bibliographic reference	Ondo,W.G., Tintner,R., Voung,K.D., Lai,D., Ringholz,G., 20051019, Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease, Movement Disorders, 20, 958-963, 2005
Country/ies where the study was carried out	US
Study type	Randomised, double-blind, placebo-controlled, parallel study
Aim of the study	To test the effectiveness of quetiapine in PD-associated hallucinations.
Study dates	Study dates: Not reported Study duration: 12 weeks
Source of funding	AstraZeneca Pharmaceuticals
Sample size	In total n= 31; Quetiapine n= 21; Placebo n= 10 Randomised in a 2:1 drug to placebo ratio
Inclusion criteria	Patients were included if they: • Were between 30 - 80 years of age with subjectively problematic visual hallucinations while taking dopaminergic medications
Exclusion criteria	Patients were excluded if they had: • A Mini-Mental State Examination score of <21 • Previous treatment for hallucinations within the past 30 days • Current use of any dopamine antagonist for any reason • The presence of a psychiatric diagnosis not believed to be directly related to their PD
Interventions	Quetiapine: 50 mg or 100 mg twice daily (in the afternoon and at night)
Details	Drug or placebo was titrated up to 50 mg twice daily (in the afternoon and at night). After 3 weeks participants returned for a safety visit and UPDRS testing. They were then further titrated to 100 mg twice daily of quetiapine over 3 weeks, but were allowed to reduce to the dose if adverse events were problematic. Six weeks after this titration period, they returned for assessment.

Bibliographic reference	**Ondo,W.G., Tintner,R., Voung,K.D., Lai,D., Ringholz,G., 20051019, Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease, Movement Disorders, 20, 958-963, 2005**
	There were no demographic or baseline differences between subjects randomised to drug vs. placebo, except that the drug group had a higher initial score on the Goetz Dyskinesia Rating scale ($p < 0.05$):

Variable	Quetiapine n=21	Placebo n= 10
Age (yr)	74 ± 7	71 ± 5
Duration of PD (yr)	12 ± 7	9 ± 4
Fluctuating	12/19	9/12
UPDRS (Part II)	34.2 ± 7.9	30.7 ± 11.9
UPDRS (Motor)	34 ± 8	31 ± 12
Goetz dyskinesia	2.0 ± 3.3	5.6 ± 5.2
MMSE	26.1 ± 2.5	27 ± 2.9
Initial BPRS	11 ± 5	11 ± 5

Primary outcome measures	• Baylor PD Hallucination Questionnaire • UPDRS Motor • UPDRS Part II (in fluctuators only as a mean of their on and off scores) All primary outcome measures were display graphically only. Hence, no data could therefore be extracted.
Secondary outcomes measures	• BPRS Total • BPRS Hallucination • Goetz Dyskinesia rating Scale • HAM-D • Adverse events All secondary outcome measures apart from adverse events/ dropouts were displayed graphically only. Hence no data could be extracted.

<table>
<tr><th>Bibliographic reference</th><th>Ondo,W.G., Tintner,R., Voung,K.D., Lai,D., Ringholz,G., 20051019, Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease, Movement Disorders, 20, 958-963, 2005</th></tr>
<tr><td>Results</td><td></td></tr>
<tr><td>Mortality</td><td><table><tr><td></td><td>Deaths</td><td>Total</td></tr><tr><td>Experimental</td><td>0</td><td>21</td></tr><tr><td>Control</td><td>2</td><td>10</td></tr></table></td></tr>
<tr><td>Number of dropouts due to adverse events</td><td><table><tr><td></td><td>Events</td><td>Total</td></tr><tr><td>Experimental</td><td>0</td><td>21</td></tr><tr><td>Control</td><td>0</td><td>10</td></tr></table></td></tr>
<tr><td>Results</td><td>The final daily dose of active drug in completers was 200 mg (n=11), 150 mg (n= 2), 100 mg (n= 3), and 75 mg (n=1). All placebos were on the daily equivalent of 200mg.

Of 31 recruited subjects, 26 completed the study.

The medication was generally well tolerated. No patients dropped out secondary to a related AE, which included sedation (n=9; 43%) and subjective worsening in PD (n= 4; 19%). One other AE was reported by 10 different subjects while on drug, but none was believed to be serious.
Sedation was reported in 4 (40%) of placebo subjects and a single different AE was reported in all 10 subjects.

Of those randomly assigned to drug, 2 dropped out due to serious unrelated illness, and 2 dropped out due to lack of effect and poor compliance. On placebo, 2 patients dropped out due to unrelated serious illness, both resulting in deaths.

Although no primary or secondary data apart from adverse events, dropouts and mortality were extracted for analysis due to results being presented graphically, the author did report that none of those outcomes reached statistical significance in comparison to placebo. Quetiapine at doses up to 200 mg/day therefore failed to significantly improve hallucinations compared to placebo.</td></tr>
</table>

Bibliographic reference	Ondo,W.G., Tintner,R., Voung,K.D., Lai,D., Ringholz,G., 20051019, Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease, Movement Disorders, 20, 958-963, 2005
	The medication was generally well tolerated. No patients on drug dropped out secondary to a related AE, which included sedation (n=9; 43%) and subjective worsening in PD 9n=4; 19%). One other AE was reported by 10 different subjects while on drug, but none was believed to be serious. Sedation was reported by 4 (40%) of placebo subjects, and a single different AE was reported in all 10 subjects.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? UNCLEAR 2. Was there adequate concealment of allocation? UNCLEAR 3. Were the groups comparable at baseline for all major confounding/prognostic factors? NO (drug group had a significantly higher initial score on the Goetz Dyskinesia Rating Scale) 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? UNCLEAR* 6. Were the individuals administering care kept blind to treatment allocation? UNCLEAR* 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES (number of dropouts similar across but >20%) 8. Did the study have an appropriate length of follow up? YES (12 wks) 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? UNCLEAR 11. Were investigators kept blind to participant's exposure to the intervention? UNCLEAR* 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR* *Level of blinding unclear - no details beyond description of study as "randomized, double-blind, placebo-controlled trial". Overall there is likely high risk of bias.

Bibliographic reference	Nichols,M.J., Hartlein,J.M., Eicken,M.G., Racette,B.A., Black,K.J., 20140314, A fixed-dose randomized controlled trial of olanzapine for psychosis in Parkinson disease, F1000Research, 2, 150-, 2013
Country/ies where the study was carried out	US
Study type	Randomised, double-blind, placebo-controlled, parallel group study

Bibliographic reference	Nichols,M.J., Hartlein,J.M., Eicken,M.G., Racette,B.A., Black,K.J., 20140314, A fixed-dose randomized controlled trial of olanzapine for psychosis in Parkinson disease, F1000Research, 2, 150-, 2013
Aim of the study	To discuss the findings of a double-blind, placebo-controlled study of fixed, low-dose olanzapine for treatment of drug-induced psychosis (DIP) in the context of flexible dopaminomimetic dosing.
Study dates	Study dates: February 1998 - October 2003 Study duration: 4 weeks
Source of funding	Lilly Research Laboratories (Investigator-Initiated Trial F1D-MC-I012)
Sample size	In total n=23; Placebo n=9; Olanzapine 2.5 mg n=6; Olanzapine 5 mg n=8; Olanzapine 10 mg n=1. Randomised in a 1:1:1 to treatment with placebo or either of two doses (2.5 mg or 5 mg) of olanzapine. The one subject treated with 10 mg of olanzapine was excluded from analysis due to change in study randomisation.
Inclusion criteria	Patients were included if they: • Have been diagnosed with idiopathic PD • Have been treated with levodopa and were experiencing clinically significant hallucinations or delusions • >30 years old • Have a caregiver who could provide a reliable report • Were treated with the lowest clinically acceptable dose of dopaminomimetic at study entry
Exclusion criteria	Patients were excluded if they: • Were treated only with a dopamine agonist • Have a Folstein Mini-mental State Examination (MMSE) score < 22 • Were pregnant • Have concurrent diagnosis of delirium (unless clearly explained by dopaminomimetics) • Have catatonia or neuroleptic malignant syndrome (NMS)-like syndrome • Have other confounding central nervous system (CNS) illness or systematic illness with potential CNS effects • Used antipsychotic within the last month predating study enrolment (within the past six months for depot neuroleptics) • Have a history of olanzapine sensitivity • Have any expectation of significant medical or surgical intervention within six weeks after enrolment • Have psychosis warranted hospitalisation or if in the investigator's judgement, psychosis severity would have made randomisation to placebo inappropriate
Interventions	Olanzapine: 2.5 mg or 5mg once a day (night-time)

<table>
<tr><th>Bibliographic reference</th><th>Nichols,M.J., Hartlein,J.M., Eicken,M.G., Racette,B.A., Black,K.J., 20140314, A fixed-dose randomized controlled trial of olanzapine for psychosis in Parkinson disease, F1000Research, 2, 150-, 2013</th></tr>
<tr><td>Details</td><td>All assessments were done at baseline, and on weeks 2 and 4 of treatment (end of trial).
No significant differences were present at baseline between placebo and treatment groups on any demographic characteristic or any psychiatric or neurologic measure:
Olanzapine
<table>
<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>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 (2.6)</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>SEADL</td><td>76 (15)</td><td>72 (24)</td><td>75 (17)</td><td>0.918</td></tr>
</table></td></tr>
<tr><td>Primary outcome measures</td><td>• Clinical Global Impression (CGI) scores
• BPRS ratings of psychosis scored from videotaped interviews after study termination by an observer blinded to dose signment and to interview timing
• UPDRS motor ratings
• MMSE</td></tr>
<tr><td>Secondary outcomes measures</td><td>• PDQ-39
• ADL assessments
• BDI</td></tr>
<tr><td>Results</td><td></td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Nichols,M.J., Hartlein,J.M., Eicken,M.G., Racette,B.A., Black,K.J., 20140314, A fixed-dose randomized controlled trial of olanzapine for psychosis in Parkinson disease, F1000Research, 2, 150-, 2013</th></tr>
<tr><td>BPRS Psychosis</td><td>
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>7.75</td><td>4.97</td><td>9</td></tr>
<tr><td>Control</td><td>8.00</td><td>4.90</td><td>9</td></tr>
</table>
</td></tr>
<tr><td>UPDRS Motor</td><td>
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>30.30</td><td>13.39</td><td>9</td></tr>
<tr><td>Control</td><td>31.00</td><td>13.09</td><td>9</td></tr>
</table>
</td></tr>
<tr><td>Mortality</td><td>
<table>
<tr><td></td><td>Deaths</td><td>Total</td></tr>
<tr><td>Experimental</td><td>0</td><td>14</td></tr>
<tr><td>Control</td><td>1</td><td>9</td></tr>
</table>
</td></tr>
<tr><td>Number of dropouts due to adverse events</td><td>
<table>
<tr><td></td><td>Events</td><td>Total</td></tr>
<tr><td>Experimental</td><td>7</td><td>14</td></tr>
<tr><td>Control</td><td>0</td><td>9</td></tr>
</table>
</td></tr>
<tr><td>Results</td><td>Data extracted for BPRS psychosis and UPDRS motor are the mean endpoint scores.

<table>
<tr><td>Subject retention and side effects</td><td>Placebo</td><td>Olanzapine 2.5 mg</td><td>Olanzapine 5 mg</td><td>All</td><td>p-value</td></tr>
<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</td><td>4</td><td>3</td><td>9</td><td>0.2232</td></tr>
<tr><td># withdrew for motor SEs</td><td>0</td><td>2</td><td>1</td><td>3</td><td>0.1712</td></tr>
<tr><td># w/motor SE complaint</td><td>1</td><td>2</td><td>1</td><td>4</td><td>0.4863</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Nichols,M.J., Hartlein,J.M., Eicken,M.G., Racette,B.A., Black,K.J., 20140314, A fixed-dose randomized controlled trial of olanzapine for psychosis in Parkinson disease, F1000Research, 2, 150-, 2013
	<table><tr><td># w/any mild SEs</td><td>2</td><td>5</td><td>2</td><td>9</td><td>0.0356</td></tr><tr><td># w/serious adverse events</td><td>1</td><td>0</td><td>2</td><td>3</td><td>0.3795</td></tr><tr><td># w/dopaminomimetic ↑</td><td>1</td><td>2</td><td>1</td><td>4</td><td>0.4863</td></tr></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. The extracted data for mortality and number of dropouts due to AEs for the experimental group are the total number of events combined from the two treatment groups (2.5 mg and 5 mg).
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? YES 2. Was there adequate concealment of allocation? YES 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? YES 6. Were the individuals administering care kept blind to treatment allocation? YES 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? NO and number of dropouts >20% 8. Did the study have an appropriate length of follow up? UNCLEAR (4 wks) 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? UNCLEAR 11. Were investigators kept blind to participant's exposure to the intervention? YES 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR Overall there is likely high risk of bias.

Bibliographic reference	Shotbolt,P., Samuel,M., Fox,C., David,A.S., 20110426, A randomized controlled trial of quetiapine for psychosis in Parkinson's disease, Neuropsychiatric Disease & Treatment, 5, 327-332, 2009
Country/ies where the study was carried out	UK
Study type	Randomised, double-blind, placebo-controlled study
Aim of the study	To provide further evidence on the efficacy of quetiapine in the management of PD psychosis
Study dates	Study dates: not reported Study duration: 12 weeks
Source of funding	Parkinson's Disease Society and Medication provided by AstraZeneca UK Ltd
Sample size	In total n=24; Quetiapine n=11; Placebo n=13
Inclusion criteria	Patients were included if: • Diagnosed with idiopathic PD • Suffered from either hallucinations, suspiciousness or unusual though content (delusions) of a severity >3/7, on the Brief Psychiatric Rating Scale (BPRS). Symptoms must have been present for over 2 weeks • They have a reliable caregiver • They have the ability to assent to treatment • Current antiparkinsonian treatment deemed to be optimal by the attending specialist consultants • Their communication ability were sufficient to enable main assessments
Exclusion criteria	Patients were excluded if: • They were under current treatment with cholinesterase inhibitors • They were on antipsychotic medication currently or in the preceding two weeks • There were any contraindication to quetiapine, important drug interactions, major concomitant medical illness, stroke or transient ischemic attack in the six months preceding assessment • They had uncontrolled diabetes or hypertension, uncontrolled atrial fibrillation or other cardiac arrhythmia • They had past drug/alcohol dependence • They have possible delirium • There has been a change in medication over the preceding two weeks (three weeks if cabergoline) • They had dementia with Lewy bodies
Interventions	Quetiapine: 25 mg, 50 mg, 100 mg or 150 mg once or twice a day.

<table>
<tr><th>Bibliographic reference</th><th>Shotbolt,P., Samuel,M., Fox,C., David,A.S., 20110426, A randomized controlled trial of quetiapine for psychosis in Parkinson's disease, Neuropsychiatric Disease & Treatment, 5, 327-332, 2009</th></tr>
<tr><td>Details</td><td>The starting dose was 25 mg for week 1, 25 mg twice a day for week 2, 50 mg twice a day for week 3, with an optional further increase to 50 mg in the morning and 100 mg in the evening if clinically indicated. Clinicians were free to increase or maintain dose of trial medication and placebo up to the beginning of the 6th week (after which it could be reduced if considered necessary due to side effects).
Assessments were performed at 0, 2, 6, and 12 weeks.

Baseline data:
<table>
<tr><td>Variable</td><td>Quetiapine n=11</td><td>Placebo n=13</td></tr>
<tr><td>Age (yr)</td><td>74 ± 8</td><td>70 ± 8</td></tr>
<tr><td>PD duration (yr)</td><td>8 ± 4</td><td>9 ± 5</td></tr>
<tr><td>MMSE</td><td>24.6 ± 3.6</td><td>20.8 ± 5.7</td></tr>
<tr><td>UPDRS total</td><td>59.1 ± 21.0</td><td>59.3 ± 26.5</td></tr>
<tr><td>UPDRS motor</td><td>31.2 ± 14.4</td><td>29.0 ± 16.8</td></tr>
<tr><td>NPI</td><td>15.4 ± 7.4</td><td>21.5 ± 11.3</td></tr>
<tr><td>BPRS</td><td>39.2 ± 8.4</td><td>41.5 ± 6.5</td></tr>
<tr><td>Baylor PD hallucination</td><td>11.6 ± 2.7</td><td>11.9 ± 5.3</td></tr>
</table></td></tr>
<tr><td>Primary outcome measures</td><td>Time remaining in the trial.</td></tr>
<tr><td>Secondary outcomes measures</td><td>• Unified Parkinson's Disease Rating Scale (UPDRS)
• BPRS
• Neuropsychiatric Inventory (NPI)
• Baylor PD hallucination scale</td></tr>
<tr><td>Results</td><td></td></tr>
<tr><td>UPDRS Motor</td><td>
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>28.20</td><td>12.30</td><td>11</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Shotbolt,P., Samuel,M., Fox,C., David,A.S., 20110426, A randomized controlled trial of quetiapine for psychosis in Parkinson's disease, Neuropsychiatric Disease & Treatment, 5, 327-332, 2009
	Control 30.10 10.40 13
Baylor PD Hallucination	<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>8.30</td><td>2.90</td><td>11</td></tr><tr><td>Control</td><td>9.40</td><td>4.90</td><td>13</td></tr></table>
Mortality	<table><tr><td></td><td>Deaths</td><td>Total</td></tr><tr><td>Experimental</td><td>0</td><td>11</td></tr><tr><td>Control</td><td>0</td><td>13</td></tr></table>
Number of dropouts due to adverse events	<table><tr><td></td><td>Events</td><td>Total</td></tr><tr><td>Experimental</td><td>3</td><td>11</td></tr><tr><td>Control</td><td>3</td><td>13</td></tr></table>
Results	Thirteen patients completed six weeks in the double-blind part of the study (four quetiapine patients and nine placebos). Only eight patients completed the 12 week double-blind (four from each group). The mean dose in the quetiapine group was 72.7 ± 26.1 mg; in the placebo group it was 96.2 ± 32 mg. Primary outcome: time remaining in the trial. Patients on quetiapine dropped out faster than patients on placebo. The log rank test was used to compare the survival distributions; they were not found to be significantly different (p=0.68). Quetiapine therefore did not have a significant effect on time to dropout. Secondary outcomes measures were analysed at six weeks due to the small numbers and high dropout rates. The data extracted are the follow-up results at 6 weeks. With regards to tolerability, three patients on quetiapine dropped out due to related adverse events (drowsiness). Three patients on placebo also dropped out due to related adverse events (two drowsiness, one confusion). Data extracted for Baylor PD Hallucination and UPDRS motor are the mean endpoint scores.

Bibliographic reference	**Shotbolt,P., Samuel,M., Fox,C., David,A.S., 20110426, A randomized controlled trial of quetiapine for psychosis in Parkinson's disease, Neuropsychiatric Disease & Treatment, 5, 327-332, 2009**
Overall Risk of Bias	Has an appropriate method of randomisation been used? UNCLEAR 1. Was there adequate concealment of allocation? UNCLEAR 2. Were the groups comparable at baseline for all major confounding/prognostic factors? UNCLEAR 3. Did the comparison groups receive the same care apart from interventions studied? YES 4. Were participants receiving care kept blind to treatment allocation? UNCLEAR* 5. Were the individuals administering care kept blind to treatment allocation? UNCLEAR* 6. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? NO 7. Did the study have an appropriate length of follow up? UNCLEAR (12 wks trial but due to large no. of dropouts, data were only analysed at 6 wks) 8. Did the study use a precise definition of outcome? YES 9. Was a valid and reliable method used to determine that outcome? NO 10. Were investigators kept blind to participant's exposure to the intervention? UNCLEAR* 11. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR* *Level of blinding unclear - no details beyond description of study as "randomized, double-blind, placebo-controlled trial". Overall there is likely high risk of bias.

Bibliographic reference	**Ondo,W.G., Levy,J.K., Vuong,K.D., Hunter,C., Jankovic,J., Olanzapine treatment for dopaminergic-induced hallucinations, Movement disorders, 17, 1031-1035, 2002**
Country/ies where the study was carried out	US
Study type	Randomised, double-blind, placebo-controlled, parallel study
Aim of the study	To determine the effect of low dose olanzapine on hallucinations, motor performance, cognition, and mood in PD patients experiencing hallucinations.
Study dates	Study dates: not reported Study duration: 9 weeks

<table>
<tr><th>Bibliographic reference</th><th>Ondo,W.G., Levy,J.K., Vuong,K.D., Hunter,C., Jankovic,J., Olanzapine treatment for dopaminergic-induced hallucinations, Movement disorders, 17, 1031-1035, 2002</th></tr>
<tr><td>Source of funding</td><td>Eli-Lilly Corporation and National Parkinson's Foundation</td></tr>
<tr><td>Sample size</td><td>In total n= 30; Olanzapine n= 18; Placebo n= 12
Randomised in a 2:1 drug to placebo ratio</td></tr>
<tr><td>Inclusion criteria</td><td>Patients were included if they:
• Had been diagnosed with PD
• Had drug-induced hallucinations
• Had a Mini-Mental Status Examination (MMSE) scores ≥20/30</td></tr>
<tr><td>Exclusion criteria</td><td>Not reported</td></tr>
<tr><td>Interventions</td><td>Olanzapine: 2.5 mg 5 mg or 7.5 mg once a day at night-time.</td></tr>
<tr><td>Details</td><td>Both fluctuating and nonfluctuating patients were included. All patients started at 2.5 mg of olanzapine or placebo as a single night-time dose. At 3 weeks, all participants returned for a complete UPDRS and a hallucination survey. On the basis of clinical judgment it was decided whether or not to increase the drug, or placebo, to 5 mg. Patients were contacted by phone after 3 more weeks. At that time, it was again decided whether to increase, decrease or maintain the same dose. The medication was kept at a constant dose for the last 3 weeks of the study. Patients then returned for a complete evaluation identical to that of the baseline visit, which included an extensive battery of neuropsychological tests, the UPDRS, and assessments of on and off time in fluctuating patients.

There were no significant differences in baseline demographics (age, duration of PD, Hoehn and Yahr), hallucination severity, or MMSE between the two groups. The means of these variables of the 30 patients are described in the table below:
<table>
<tr><td>Variable</td><td>Olanzapine n= 18</td><td>Placebo n= 12</td></tr>
<tr><td>Age (yr)</td><td colspan="2">71 ± 7.1</td></tr>
<tr><td>Mean off Hoehn and Yahr</td><td colspan="2">3.2 ± 0.5</td></tr>
<tr><td>Duration of PD (yrs)</td><td colspan="2">9.6 ± 5.1</td></tr>
<tr><td>MMSE</td><td colspan="2">26.8 ± 3.3</td></tr>
</table>
</td></tr>
<tr><td>Primary outcome measures</td><td>• An extensive battery of neuropsychological tests (including MMSE, HAM-D and others)
• UPDRS Total (while on medications)
• UPDRS Part II (in fluctuating patients to represent the averages of on and off scores)</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Ondo,W.G., Levy,J.K., Vuong,K.D., Hunter,C., Jankovic,J., Olanzapine treatment for dopaminergic-induced hallucinations, Movement disorders, 17, 1031-1035, 2002</th></tr>
<tr><td>Secondary outcomes measures</td><td>Not reported.</td></tr>
<tr><td>Results</td><td></td></tr>
<tr><td>Structured interview for hallucinations in PD</td><td><table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>9.50</td><td>6.80</td><td>16</td></tr><tr><td>Control</td><td>11.10</td><td>4.70</td><td>11</td></tr></table></td></tr>
<tr><td>Mortality</td><td><table><tr><td></td><td>Deaths</td><td>Total</td></tr><tr><td>Experimental</td><td>0</td><td>18</td></tr><tr><td>Control</td><td>0</td><td>12</td></tr></table></td></tr>
<tr><td>Number of dropouts due to adverse events</td><td><table><tr><td></td><td>Events</td><td>Total</td></tr><tr><td>Experimental</td><td>0</td><td>18</td></tr><tr><td>Control</td><td>0</td><td>12</td></tr></table></td></tr>
<tr><td>Results</td><td>16 patients on olanzapine (mean dose, 4.6 mg/night) and 11 on placebo completed the study.

The final mean dose of olanzapine was 4.6 ± 2.2 mg, whereas the mean dose of placebo was the equivalent of 6.6 ± 2.0 mg.

A total of three patients discontinued before completion of the study. One patient randomly assigned to drug dropped out before taking any study medication. One patient in the drug and one in the placebo group dropped out after 3 weeks and 6 weeks, respectively, due to lack of improvement.

Subjective AEs on olanzapine included worsening movement (n=6), worse posture (n=3), dysarthria (n=2), edema (n=2), drooling (n=2), weight gain, dry mouth, nausea, insomnia, sedation, perspiration, and agitation.

AE on placebo included insomnia, sedation, leg cramps, light headedness, weakness, and tremor in one each.</td></tr>
</table>

Bibliographic reference	Ondo,W.G., Levy,J.K., Vuong,K.D., Hunter,C., Jankovic,J., Olanzapine treatment for dopaminergic-induced hallucinations, Movement disorders, 17, 1031-1035, 2002
	Data extracted for structured interview for hallucinations in PD are the mean endpoint score at the final visit.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? YES 2. Was there adequate concealment of allocation? UNCLEAR 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? UNCLEAR* 6. Were the individuals administering care kept blind to treatment allocation? UNCLEAR* 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES and <20 % dropout rate. 8. Did the study have an appropriate length of follow up? YES (9 wks) 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? UNCLEAR 11. Were investigators kept blind to participant's exposure to the intervention? UNCLEAR* 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR* *Level of blinding unclear - no details beyond description of study as "randomized, double-blind, placebo-controlled trial". Overall there is likely high risk of bias.

Bibliographic reference	Pollak,P., Tison,F., Rascol,O., Destee,A., Pere,J.J., Senard,J.M., Durif,F., Bourdeix,I., Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up, J.Neurol.Neurosurg.Psychiatry., 75, 689-695, 2004
Country/ies where the study was carried out	France
Study type	Prospective, randomised, double-blind, placebo-controlled study
Aim of the study	To assess the efficacy and tolerability of clozapine in drug-induced psychosis in Parkinson's disease
Study dates	Study dates: January 1996 and October 1997 Study duration: 4 weeks double-blind, followed by a 12-week clozapine open period, plus a one month period after drug withdrawal.

Bibliographic reference	**Pollak,P., Tison,F., Rascol,O., Destee,A., Pere,J.J., Senard,J.M., Durif,F., Bourdeix,I., Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up, J.Neurol.Neurosurg.Psychiatry., 75, 689-695, 2004**
Source of funding	Novartis Pharma France
Sample size	In total n=60; Clozapine n=32; Placebo n=28 Randomised in a 1:1 drug to placebo ratio
Inclusion criteria	Inclusion criteria were: • Idiopathic PD clinical diagnosis • PD patients experiencing a drug induced psychosis of at least two weeks' duration • Psychotic symptoms score ≥ 4 for at least one of the items P1 (hallucinations) or P3 (delusions) of the positive subscore of the "positive and negative syndrome scale" (PANSS). • >3 on the "clinical global impression scale" (CGI)
Exclusion criteria	Exclusion criteria were: • A history of medical conditions or drug treatment that might put them at special risk or bias the assessment of their clinical or mental status • Patients likely to require continuous treatment with drugs that can lower the white blood cell count, and those previously treated with clozapine • Women of childbearing potential who were not practising a medically approved form of birth control
Interventions	Clozapine: A starting dose of 6.25 mg, followed, if necessary, by progressive dose increases (maximum of three 12.5 mg steps each week) up to a maximum daily dose of 50 mg, which could not be reached within less than 10 days.
Details	This study consists of 4 periods. The first was a period of screening. The second period of four weeks (day 0 to day 28) involved clozapine dose titration according to the intervention schedule. The doses of antiparkinsonian drugs remained unchanged. The dose of clozapine could be reduced if adverse effects occurred by steps of 12.5 mg. All patients who completed period II and those experiencing no improvements after two weeks of treatment entered a 12 week unblinded open label period, where they all received clozapine. At the end of period III, patients demonstrating mental normalisation were subjected to clozapine withdrawal within one week and to a further three week follow up period (period IV). Only results from period II are of interests to this RQ. Baseline characteristics: Variable | Clozapine n=32 | Placebo n=28

<table>
<tr><th>Bibliographic reference</th><td colspan="3">Pollak,P., Tison,F., Rascol,O., Destee,A., Pere,J.J., Senard,J.M., Durif,F., Bourdeix,I., Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up, J.Neurol.Neurosurg.Psychiatry., 75, 689-695, 2004</td></tr>
<tr><td></td><td colspan="3"><table>
<tr><td>Age (yr)</td><td>71.2 (7.4)</td><td>72.8 (8.2)</td></tr>
<tr><td>Duration of PD (yrs)</td><td>12.1 (5.7)</td><td>11.3 (5.4)</td></tr>
<tr><td>Hoehn and Yahr stage</td><td>3.3 (0.9)</td><td>3.1 (1.4)</td></tr>
<tr><td>UPDRS total</td><td>52.6 (21.1)</td><td>52.7 (19.8)</td></tr>
<tr><td>UPDRS motor</td><td>31.5 (14.2)</td><td>31.4 (13.2)</td></tr>
<tr><td>Positive PANSS</td><td>17.8 (4.7)</td><td>15.3 (5.0)</td></tr>
<tr><td>CGI</td><td>5.1 (0.8)</td><td>4.9 (0.9)</td></tr>
<tr><td>MMSE</td><td>26.1 (3.0)</td><td>24.1 (2.8)</td></tr>
</table></td></tr>
<tr><td>Primary outcome measures</td><td colspan="3">CGI</td></tr>
<tr><td>Secondary outcomes measures</td><td colspan="3">• PANSS
• UPDRS
• MMSE</td></tr>
<tr><td>Results</td><td colspan="3"></td></tr>
<tr><td>UPDRS Motor</td><td colspan="3"><table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>-3.50</td><td>7.70</td><td>32</td></tr>
<tr><td>Control</td><td>-3.00</td><td>8.10</td><td>28</td></tr>
</table></td></tr>
<tr><td>Positive PANSS</td><td colspan="3"><table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>-5.60</td><td>3.90</td><td>32</td></tr>
<tr><td>Control</td><td>-0.80</td><td>2.80</td><td>28</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Pollak,P., Tison,F., Rascol,O., Destee,A., Pere,J.J., Senard,J.M., Durif,F., Bourdeix,I., Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up, J.Neurol.Neurosurg.Psychiatry., 75, 689-695, 2004</th></tr>
<tr><td>Mortality</td><td>
<table>
<tr><td></td><td>Deaths</td><td>Total</td></tr>
<tr><td>Experimental</td><td>0</td><td>32</td></tr>
<tr><td>Control</td><td>0</td><td>28</td></tr>
</table>
</td></tr>
<tr><td>Number of dropouts due to adverse events</td><td>
<table>
<tr><td></td><td>Events</td><td>Total</td></tr>
<tr><td>Experimental</td><td>2</td><td>32</td></tr>
<tr><td>Control</td><td>2</td><td>28</td></tr>
</table>
</td></tr>
<tr><td>Results</td><td>By the end of period II, patients were receiving a mean dose of 35.8 (range 12.5-50) mg/day of clozapine or 41.7 (range 6-50) mg/day of placebo.
Serious adverse events were reported in 4 of the 32 patients in the clozapine group and in 7 of the 28 patients in the placebo group during period II.

Table below summarises AEs occurring with a frequency >10% during period II:
<table>
<tr><td>Adverse events</td><td>Clozapine (n=32)</td><td>Placebo (n=28)</td></tr>
<tr><td>Worsening of PD</td><td>7 (21.8%)</td><td>1 (4%)</td></tr>
<tr><td>Sialorrhoea</td><td>3 (9%)</td><td>0</td></tr>
<tr><td>Confusion</td><td>0</td><td>2 (7%)</td></tr>
<tr><td>Somnolence</td><td>17 (53%)</td><td>5 (18%)</td></tr>
<tr><td>Nausea/vomiting</td><td>0</td><td>4 (15%)</td></tr>
<tr><td>Constipation</td><td>1 (3%)</td><td>1 (4%)</td></tr>
<tr><td>Postural hypotension</td><td>6 (19%)</td><td>4 (14%)</td></tr>
<tr><td>Respiratory infection</td><td>5 (16%)</td><td>3 (11%)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Pollak,P., Tison,F., Rascol,O., Destee,A., Pere,J.J., Senard,J.M., Durif,F., Bourdeix,I., Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up, J.Neurol.Neurosurg.Psychiatry., 75, 689-695, 2004**
	<table><tr><td>General condition aggravated</td><td>0</td><td>3 (11%)</td></tr><tr><td>Syncope/malaise</td><td>0</td><td>4 (15%)</td></tr></table> Withdrawals because of adverse events occurred in 4 patients, 2 from each group. The events leading to withdrawal were one neutropenia and one fracture in the clozapine group, and one hypotension and one syncope in the placebo group. Data extracted for UPDRS motor and Positive PANSS are the mean change scores from baseline to end point.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? YES 2. Was there adequate concealment of allocation? UNCLEAR 3. Were the groups comparable at baseline for all major confounding/prognostic factors? NO (MMSE score in clozapine group was higher) 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? UNCLEAR* 6. Were the individuals administering care kept blind to treatment allocation? UNCLEAR* 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES and >20 % dropout rate. 8. Did the study have an appropriate length of follow up? UNCLEAR (4 wks) 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? UNCLEAR 11. Were investigators kept blind to participant’s exposure to the intervention? UNCLEAR* 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR* *Level of blinding unclear - no details beyond description of study as "randomized, double-blind, placebo-controlled trial". Overall there is likely high risk of bias.

Bibliographic reference	**Morgante,L., Epifanio,A., Spina,E., Zappia,M., Di Rosa,A.E., Marconi,R., Basile,G., Di,Raimondo G., La,Spina P., Quattrone,A., Quetiapine and clozapine in parkinsonian patients with dopaminergic psychosis, Clin Neuropharmacol, 27, 153-156, 2004**
Country/ies where the study was carried out	Italy
Study type	Randomised, open-label, blinded-rater, parallel group study
Aim of the study	To investigate the efficacy and safety of quetiapine vs. clozapine in parkinsonian patients with dopaminergic psychosis
Study dates	Study dates: Not reported Study duration: 12 weeks
Source of funding	Not reported
Sample size	In total n=45; Clozapine n=23; Quetiapine n=22
Inclusion criteria	Patients were included if they had: • A diagnosis of idiopathic PD • A documented history of L-dopa or L-dopa plus dopamine agonist drug-induced psychosis of at least 4 weeks before study entry • A baseline score of ≥3 on the items hallucinations or unusual thought content (or delusions) of the BPRS
Exclusion criteria	Patients were excluded if they had: • A history of leukopenia, dementia (MMSE score <24) or any primary psychiatric illness including schizophrenia, psychotic depression, or bipolar disorder • A history of epilepsy • Presence of any underlying intermittent diseases causing psychosis • Presence of cardiovascular diseases or symptomatic orthostatic hypotension • Use of antipsychotic agents in the past 6 months
Interventions	Clozapine: Initial dose of 6.25 mg/day, administered orally once or twice daily. This dose was then titrated up to a maximum of 50 mg/day, according to the individual clinical response and tolerability. Quetiapine: Initial dose of 25 mg/day, administered orally once or twice daily. This dose was then titrated up to a maximum of 200 mg/day, according to the individual clinical response and tolerability.
Details	During the study, the dosage of antiparkinsonian drugs was kept constant. All patients were assessed at baseline and after 2, 4, 8, and 12 weeks. Baseline characteristics:

Bibliographic reference	**Morgante,L., Epifanio,A., Spina,E., Zappia,M., Di Rosa,A.E., Marconi,R., Basile,G., Di,Raimondo G., La,Spina P., Quattrone,A., Quetiapine and clozapine in parkinsonian patients with dopaminergic psychosis, Clin Neuropharmacol, 27, 153-156, 2004**

Variable	Clozapine n=20	Quetiapine n=20
Age (yr)	69 ± 10.7	70 ± 10.1
Duration of illness (months)	115 ± 45	100.5 ± 45
BPRS total	37.4 ± 5.4	37.1 ± 6.1
BPRS (5 items)	16.4 ± 2.6	15.5 ± 3.4
CGIS	3.8 ± 0.8	3.6 ± 0.7
UPDRS motor	58 ± 9.4	53 ± 11

Primary outcome measures

- BPRS
- CGIS
- UPDRS motor
- AIMS

Results

BPRS Psychosis

	Mean	SD	Total
Experimental	8.50	2.00	20
Control	8.40	1.50	20

UPDRS Motor

	Mean	SD	Total
Experimental	56.70	9.20	20
Control	54.00	11.00	20

Mortality

	Deaths	Total
Experimental	0	23

Bibliographic reference	Morgante,L., Epifanio,A., Spina,E., Zappia,M., Di Rosa,A.E., Marconi,R., Basile,G., Di,Raimondo G., La,Spina P., Quattrone,A., Quetiapine and clozapine in parkinsonian patients with dopaminergic psychosis, Clin Neuropharmacol, 27, 153-156, 2004
	Control | 0 | 22
Number of dropouts due to adverse events	| Events | Total Experimental | 3 | 23 Control | 2 | 22
Results	The experimental group represent the Clozapine group and the control group represent the Quetiapine group. Forty patients, 20 on clozapine and 20 on quetiapine, completed the study and were included in the clinical analysis. In the clozapine group, the final mean dose was 26 ± 12 mg/d, while in the quetiapine group, the final mean dose was 91 ± 47 mg/d. Side effects were mild in both groups. Subjective adverse side effects included worsening movement (n=3), sedation (n=1), and dizziness (n=1) in the quetiapine group and drooling (n=1), weight gain (n=1), and sedation (n=1) in the clozapine group. The BPRS psychosis data is the cluster subscores of the items hallucinations, suspiciousness, unusual thought content, hostility, and conceptual disorganisation. Data extracted for BPRS psychosis (five items) and UPDRS motor are the mean endpoint scores at 12 weeks.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? UNCLEAR 2. Was there adequate concealment of allocation? NO 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? NO 6. Were the individuals administering care kept blind to treatment allocation? NO 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES and <20% dropout rate 8. Did the study have an appropriate length of follow up? YES (12 wks) 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? UNCLEAR

Bibliographic reference	**Morgante,L., Epifanio,A., Spina,E., Zappia,M., Di Rosa,A.E., Marconi,R., Basile,G., Di,Raimondo G., La,Spina P., Quattrone,A., Quetiapine and clozapine in parkinsonian patients with dopaminergic psychosis, Clin Neuropharmacol, 27, 153-156, 2004**
	11. Were investigators kept blind to participant's exposure to the intervention? YES 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR Overall there is likely high risk of bias.

Bibliographic reference	**Friedman J, Lannon M, Cornelia C, Factor S, Kurlan R, Richard I et al. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. New England Journal of Medicine 1999;340:757-63.**
Country/ies where the study was carried out	Not reported
Study type	Randomised, double-blinded, placebo-controlled study
Aim of the study	To determine whether clozapine, administered at low doses, is an effective treatment for drug-induced psychosis in patients with Parkinson's disease and to determine its effect on motor function in such patients.
Study dates	Study dates: April 1995 - October 1996 Study duration: 4 weeks
Source of funding	Orphan Drug Division of the Food and Drug Administration and Parkinson Study Group
Sample size	In total n=60 (9 to 12 patients per site (6 sites in total)); Clozapine n=30; Placebo n=30
Inclusion criteria	Patients were included if: • They were diagnosed with idiopathic PD • They had documented history of psychosis of at least 4 weeks' duration before enrolment • They had a reliable caregiver who could accurately report the patient's daily level of function, accompany the patient to each visit and administer the study drug
Exclusion criteria	Criteria for exclusion were: • A history of leukopenia • The presence of any systemic factor that might contribute to a behavioural disorder • Therapy with any dopamine-blocking drug within the three months before this study began • Therapy with neuroleptic drugs administered in depot form within the year before the study

<table>
<tr><th>Bibliographic reference</th><th>Friedman J, Lannon M, Cornelia C, Factor S, Kurlan R, Richard I et al. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. New England Journal of Medicine 1999;340:757-63.</th></tr>
<tr><td></td><td>

A change in antidepressants or anxiolytic drugs within the month before the study
Previous therapy with clozapine for the treatment of psychosis
The presence of symptomatic orthostatic hypotension, uncontrolled seizures, uncontrolled angina, the acquired immunodeficiency syndrome or another illness that would make the use of clozapine potentially hazardous, or narrow-angle glaucoma
Myocardial infarction during the three months before the study
Treatment with chemotherapeutic drugs that lower white-cell counts
An inability to tolerate a fixed dose of antiparkinsonian drugs for one month
The presence of dementia severe enough to preclude assessment on the psychiatric-test battery
Women of childbearing potential who were not using reliable forms of contraception

</td></tr>
<tr><td>Interventions</td><td>Clozapine: 6.25 mg, 12.5 mg, 18.75 mg, 25 mg, 37.5 mg, or 50 mg daily</td></tr>
<tr><td>Details</td><td>All daily doses started at 6.25 mg and could be raised one level depending on the patient's clinical response; if the patient's daily dose had been increased from the initial 6.25 mg level, it could also be lowered one level. The dosage reached at the beginning of the final week was the maximal dose, it could not be increase further but could be decreased, if necessary, because of side effects. Thus, at the final assessment, when all base-line measures were repeated, the patient had been receiving a stable dose or declining dose of study medicine for at least seven days.
There were some significant imbalances at baseline between the groups in the intention-to-treat analysis (the patients receiving clozapine had slightly less severe psychosis than those receiving placebo), but not between the groups in the analysis based on the treatment the patient actually received:
<table>
<tr><th>Variable</th><th>Placebo n=30</th><th>Clozapine n=30</th><th>p value</th></tr>
<tr><td>Age (yr)</td><td>71.9 ± 8.1</td><td>70.8 ± 8.6</td><td>0.62</td></tr>
<tr><td>Duration of Parkinson's disease (yr)</td><td>10.4 ± 7.5</td><td>10.8 ± 6.1</td><td>0.84</td></tr>
<tr><td>Hoehn-Yahr stage of disease</td><td>2.8 ± 0.8</td><td>2.6 ± 0.9</td><td>0.33</td></tr>
<tr><td>UPDRS Motor</td><td>37.1 ± 13</td><td>32.8 ± 11.3</td><td>0.19</td></tr>
<tr><td>UPDRS Total</td><td>61.3 ± 20.3</td><td>52.0 ± 17.3</td><td>0.07</td></tr>
<tr><td>MMSE</td><td>21.7 ± 5.2</td><td>23.8 ± 4.8</td><td>0.11</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Friedman J, Lannon M, Cornelia C, Factor S, Kurlan R, Richard I et al. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. New England Journal of Medicine 1999;340:757-63.</th></tr>
<tr><td></td><td>
<table>
<tr><td>BPRS</td><td>35.0 ± 10.7</td><td>33.1 ± 9.9</td><td>0.47</td></tr>
<tr><td>CGIS</td><td>4.4 ± 1.0</td><td>4.4 ± 0.8</td><td>0.89</td></tr>
</table>
There were no significant differences in the use of antiparkinsonian or psychotropic drugs between the two groups. All 60 patients were taking levodopa.
</td></tr>
<tr><td>Primary outcome measures</td><td>• CGIS for psychosis
• UPDRS</td></tr>
<tr><td>Secondary outcomes measures</td><td>Not reported.</td></tr>
<tr><td>Results</td><td></td></tr>
<tr><td>UPDRS Motor</td><td>
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>-3.60</td><td>9.50</td><td>25</td></tr>
<tr><td>Control</td><td>-1.80</td><td>6.00</td><td>25</td></tr>
</table>
</td></tr>
<tr><td>SAPS</td><td>SAPS
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>-11.80</td><td>10.39</td><td>27</td></tr>
<tr><td>Control</td><td>-3.80</td><td>9.87</td><td>27</td></tr>
</table>
</td></tr>
<tr><td>Mortality</td><td>
<table>
<tr><td></td><td>Deaths</td><td>Total</td></tr>
<tr><td>Experimental</td><td>0</td><td>30</td></tr>
<tr><td>Control</td><td>0</td><td>30</td></tr>
</table>
</td></tr>
<tr><td>Number of dropouts due to adverse events</td><td>
<table>
<tr><td></td><td>Events</td><td>Total</td></tr>
<tr><td>Experimental</td><td>3</td><td>30</td></tr>
<tr><td>Control</td><td>3</td><td>30</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Friedman J, Lannon M, Cornelia C, Factor S, Kurlan R, Richard I et al. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. New England Journal of Medicine 1999;340:757-63.**
Results	Fifty-four patients completed the trial. The mean daily dose of clozapine prescribed at the end of the study was 24.7 mg (range 6.25 to 50). The mean daily dose of placebo was equivalent to 35.2 mg (range 6.25 to 50). Three patients receiving placebo and three receiving clozapine withdrew from the study. The psychiatric condition of two of the three patients receiving placebo worsened. One patient required psychiatric hospitalization, and the other discarded her medications, declaring herself "cured". The third patient was hospitalized for pneumonia. Of the three patients in the clozapine group who withdrew from the study, one discontinued the drug because of leukopenia, one because of myocardial infarction, and one because of sedation. Data extracted for UPDRS motor and SAPS are the mean change scores from baseline to end point.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? UNCLEAR 2. Was there adequate concealment of allocation? UNCLEAR 3. Were the groups comparable at baseline for all major confounding/prognostic factors? NO (some significant imbalances in psychosis at baseline between the groups) 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? UNCLEAR* 6. Were the individuals administering care kept blind to treatment allocation? UNCLEAR* 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES and <20% dropout rate. 8. Did the study have an appropriate length of follow up? UNCLEAR (4 weeks) 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? UNCLEAR 11. Were investigators kept blind to participant's exposure to the intervention? UNCLEAR* 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR* *Level of blinding unclear - no details beyond description of study as "randomized, double-blind, placebo-controlled trial". Overall there is likely high risk of bias.

Bibliographic reference	Breier,A., Sutton,V.K., Feldman,P.D., Kadam,D.L., Ferchland,I., Wright,P., Friedman,J.H., Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease (European Study Results), Biological Psychiatry.52 (5) (pp 438-445), 2002.Date of Publication: 01 Sep 2002., 438-445, 2002
Country/ies where the study was carried out	Europe
Study type	Randomised, double-blind, placebo-controlled trials (2 multi-centre trials)
Aim of the study	To report the findings from two placebo-controlled, double-blind studies of the use of olanzapine for control of dopamimetic psychosis when added to a fixed dose of dopamimetic agent
Study dates	Study date: Not reported Study duration: 4 weeks
Source of funding	Eli Lilly and Company
Sample size	77 in the European study; Olanzapine n = 49, Placebo n = 28
Inclusion criteria	Patients were included if they: • Had a diagnosis of idiopathic PD • Had been responsive to dopamimetics for motor symptoms • Experienced hallucinations, delusions, or both in the 2-week period before entry (Visit 1) • Had an individual Hallucinations or Delusions item score of ≥2 on the Neuropsychiatric Inventory (NPI; Cummings et al 1994) at both study entry (Visit 1) and randomisation (Visit 2). • Had a full-time (7 days/week) caregiver who was familiar with the patient's medical history and accompanied the patient to all office visits. • Were on stable doses of PD medications, defined as the lowest level of anti-PD medications required to control motor symptoms in the judgement of the investigator and consisting of L-DOPA, L-DOPA with decarboxylase inhibitor, dopamimergic receptor agonist therapy, or a combination of these, for at least 1 week immediately before study entry.
Exclusion criteria	Patients were excluded if they had: • Any prior treatment with olanzapine, treatment with clozapine or risperidone within 3 months before Visit 1 • Treatment with any other antipsychotic within 1 month before Visit 1 • Any other concomitant medication that had central nervous system activity
Interventions	Olanzapine: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg or 15 mg once a day.
Details	Enrolled patients were assigned by random allocation to a 4-week, double-blind treatment with either olanzapine or placebo. Doses of dopamimetic therapy were held constant throughout the study. Olanzapine was initiated at 2.5 mg/day (one tablet), with 2.5mg/day increases allowed every 3 to 4 days up to the maximum dose of 15 mg/day (6 tablets), according to the clinical

Bibliographic reference	**Breier,A., Sutton,V.K., Feldman,P.D., Kadam,D.L., Ferchland,I., Wright,P., Friedman,J.H., Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease (European Study Results), Biological Psychiatry.52 (5) (pp 438-445), 2002.Date of Publication: 01 Sep 2002., 438-445, 2002**
	response of psychotic symptoms. Dosage decreases could occur at any time by any number of decrements. Patients who were unable to tolerate the lowest dose of olanzapine were released from the study. Baseline demographic and clinical data did not differ between treatment groups.

European study

Variable	Olanzapine n= 49	Placebo n= 28	p-value
Age: years (SD)	70.9 (6.3)	70.5 (8.2)	
Age at onset: years (SD)	60.8 (8.0)	55.4 (16.1)	
Hoehn and Yahr staging: No.			0.703
Stage 1	0 (0.0)	0 (0.0)	-
Stage 1.5	1 (2.0)	0 (0.0)	-
Stage 2	6 (12.2)	3 (10.7)	-
Stage 2.5	5 (10.2)	4 (14.3)	-
Stage 3	24 (49.0)	10 (35.7)	-
Stage 4	13 (26.5)	11 (39.3)	-
Dementia: No. (%)			0.623
Demented	17 (34.7)	8 (28.6)	-
Nondemented	32 (65.3)	20 (71.4)	-

Primary outcome measures	Positive symptom cluster subscore of the Brief Psychiatric Rating Scale (BPRS; Guy 1976), comprising the sum score of the item scores for Conceptual Disorganization, Suspiciousness, Hallucinatory Behavior, and Unusual Thought Content.
Secondary outcomes measures	• BPRS total and negative symptom cluster scores • Clinical Global Impressions - Severity (CGI-S; Guy 1976) score for psychosis

Bibliographic reference	**Breier,A., Sutton,V.K., Feldman,P.D., Kadam,D.L., Ferchland,I., Wright,P., Friedman,J.H., Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease (European Study Results), Biological Psychiatry.52 (5) (pp 438-445), 2002.Date of Publication: 01 Sep 2002., 438-445, 2002**
	• NPI total score and individual item subscores. A subgroup analysis was also performed to examine efficacy scores among patients characterised at baseline as demented (MMSE score < 4) vs. those without dementia (MMSE ≥ 24).
Results	
BPRS Positive	
BPRS Hallucination	
UPDRS Motor	
NPI Delusions	
NPI hallucination	

	Mean	SD	Total
Experimental	-2.30	4.10	49
Control	-2.90	3.40	28

	Mean	SD	Total
Experimental	-1.00	1.50	49
Control	-1.40	1.50	28

	Mean	SD	Total
Experimental	2.70	6.00	49
Control	-0.30	5.00	28

	Mean	SD	Total
Experimental	-1.10	3.40	49
Control	-2.00	2.60	28

	Mean	SD	Total
Experimental	-2.70	3.30	49
Control	-2.70	3.60	28

Bibliographic reference	**Breier,A., Sutton,V.K., Feldman,P.D., Kadam,D.L., Ferchland,I., Wright,P., Friedman,J.H., Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease (European Study Results), Biological Psychiatry.52 (5) (pp 438-445), 2002.Date of Publication: 01 Sep 2002., 438-445, 2002**
Number of dropouts due to adverse events	<table><tr><td></td><td>Events</td><td>Total</td></tr><tr><td>Experimental</td><td>8</td><td>49</td></tr><tr><td>Control</td><td>1</td><td>28</td></tr></table>
Results	Data extracted for all BPRS subscales and UPDRS motor scale are the mean change scores from baseline to end point. <table><tr><td>Completion Rates</td><td colspan="2">European Study</td></tr><tr><td></td><td>%</td><td>p value vs. Placebo</td></tr><tr><td colspan="3">Completion rates (4 weeks):</td></tr><tr><td>Olanzapine</td><td>75.5</td><td rowspan="2">0.386</td></tr><tr><td>Placebo</td><td>85.7</td></tr><tr><td colspan="3">Discontinued due to adverse event:</td></tr><tr><td>Olanzapine</td><td>16.3</td><td rowspan="2">0.144</td></tr><tr><td>Placebo</td><td>3.6</td></tr></table> Treatment-related adverse events not reported.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? UNCLEAR 2. Was there adequate concealment of allocation? UNCLEAR 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? UNCLEAR* 6. Were the individuals administering care kept blind to treatment allocation? UNCLEAR* 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES but dropout rate >20%

Bibliographic reference	Breier,A., Sutton,V.K., Feldman,P.D., Kadam,D.L., Ferchland,I., Wright,P., Friedman,J.H., Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease (European Study Results), Biological Psychiatry.52 (5) (pp 438-445), 2002.Date of Publication: 01 Sep 2002., 438-445, 2002
	8. Did the study have an appropriate length of follow up? UNCLEAR (4 wks) 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? UNCLEAR 11. Were investigators kept blind to participant's exposure to the intervention? UNCLEAR* 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR* 13. *Level of blinding unclear - no details beyond description of study as "randomized, double-blind, placebo-controlled trial". 14. Overall there is likely high risk of bias.

Bibliographic reference	Breier,A., Sutton,V.K., Feldman,P.D., Kadam,D.L., Ferchland,I., Wright,P., Friedman,J.H., Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease (USA Study Results), Biological Psychiatry.52 (5) (pp 438-445), 2002.Date of Publication: 01 Sep 2002., 438-445, 2002
Country/ies where the study was carried out	US
Study type	Randomised, double-blind, placebo-controlled trials (2 multi-centre trials)
Aim of the study	To report the findings from two placebo-controlled, double-blind studies of the use of olanzapine for control of dopamimetic psychosis when added to a fixed dose of dopamimetic agent
Study dates	Study date: Not reported Study duration: 4 weeks
Source of funding	Eli Lilly and Company
Sample size	83 in the US study; Olanzapine n = 41, Placebo n= 42 Randomised in a 1:1 drug to placebo ratio
Inclusion criteria	Patients were included if they: • Had a diagnosis of idiopathic PD • Had been responsive to dopamimetics for motor symptoms

<table>
<tr><th>Bibliographic reference</th><th>Breier,A., Sutton,V.K., Feldman,P.D., Kadam,D.L., Ferchland,I., Wright,P., Friedman,J.H., Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease (USA Study Results), Biological Psychiatry.52 (5) (pp 438-445), 2002.Date of Publication: 01 Sep 2002., 438-445, 2002</th></tr>
<tr><td></td><td>• Experienced hallucinations, delusions, or both in the 2-week period before entry (Visit 1)
• Had an individual Hallucinations or Delusions item score of ≥2 on the Neuropsychiatric Inventory (NPI; Cummings et al 1994) at both study entry (Visit 1) and randomisation (Visit 2).
• Had a full-time (7 days/week) caregiver who was familiar with the patient's medical history and accompanied the patient to all office visits.
• Were on stable doses of PD medications, defined as the lowest level of anti-PD medications required to control motor symptoms in the judgement of the investigator and consisting of L-DOPA, L-DOPA with decarboxylase inhibitor, dopamimergic receptor agonist therapy, or a combination of these, for at least 1 week immediately before study entry.</td></tr>
<tr><td>Exclusion criteria</td><td>Patients were excluded if they had:
• Any prior treatment with olanzapine, treatment with clozapine or risperidone within 3 months before Visit 1
• Treatment with any other antipsychotic within 1 month before Visit 1
• Any other concomitant medication that had central nervous system activity</td></tr>
<tr><td>Interventions</td><td>Olanzapine: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg or 15 mg once a day.</td></tr>
<tr><td>Details</td><td>Enrolled patients were assigned by random allocation to a 4-week, double-blind treatment with either olanzapine or placebo. Doses of dopamimetic therapy were held constant throughout the study. Olanzapine was initiated at 2.5 mg/day (one tablet), with 2.5mg/day increases allowed every 3 to 4 days up to the maximum dose of 15 mg/day (6 tablets), according to the clinical response of psychotic symptoms. Dosage decreases could occur at any time by any number of decrements. Patients who were unable to tolerate the lowest dose of olanzapine were released from the study.

Baseline demographic and clinical data did not differ between treatment groups in either study and were roughly equivalent between the two studies, although there was a trend toward younger age onset of PD among placebo patients in the European study (55.4(16.1) vs 61.1(10.3) years).
<table>
<tr><th rowspan="2">Variable</th><th colspan="3">United States Study</th></tr>
<tr><th>Olanzapine</th><th>Placebo</th><th>p-value</th></tr>
<tr><td>Age: years (SD)</td><td>73.5 (8.7)</td><td>71.7 (6.8)</td><td>.419</td></tr>
<tr><td>Age at onset: years (SD)</td><td>60.6 (14.1)</td><td>61.1 (10.3)</td><td>.705</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Breier,A., Sutton,V.K., Feldman,P.D., Kadam,D.L., Ferchland,I., Wright,P., Friedman,J.H., Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease (USA Study Results), Biological Psychiatry.52 (5) (pp 438-445), 2002.Date of Publication: 01 Sep 2002., 438-445, 2002**

Hoehn and Yahr staging: No. (%)			0.843
Stage 1	1 (2.4)	0 (0.0)	-
Stage 1.5	0 (0.0)	1 (2.4)	-
Stage 2	8 (19.5)	8 (19.0)	-
Stage 2.5	3 (7.3)	1 (2.4)	-
Stage 3	19 (46.3)	20 (47.6)	-
Stage 4	10 (24.4)	12 (28.6)	-
Dementia: No. (%)			0.266
Demented	19 (46.3)	14 (33.3)	-
Nondemented	22 (53.7)	28 (66.7)	-

Primary outcome measures

Positive symptom cluster subscore of the Brief Psychiatric Rating Scale (BPRS; Guy 1976), comprising the sum score of the item scores for Conceptual Disorganization, Suspiciousness, Hallucinatory Behaviour, and Unusual Thought Content.

Secondary outcomes measures

- BPRS total and negative symptom cluster scores
- Clinical Global Impressions - Severity (CGI-S; Guy 1976) score for psychosis
- NPI total score and individual item subscores.

A subgroup analysis was also performed to examine efficacy scores among patients characterised at baseline as demented (MMSE score < 4) vs. those without dementia (MMSE ≥ 24).

Results

BPRS Positive

	Mean	SD	Total
Experimental	-1.70	3.50	41
Control	-1.60	3.90	42

<table>
<tr><th>Bibliographic reference</th><th>Breier,A., Sutton,V.K., Feldman,P.D., Kadam,D.L., Ferchland,I., Wright,P., Friedman,J.H., Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease (USA Study Results), Biological Psychiatry.52 (5) (pp 438-445), 2002.Date of Publication: 01 Sep 2002., 438-445, 2002</th></tr>
<tr><td>BPRS Hallucination</td><td>
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>-0.70</td><td>1.60</td><td>41</td></tr>
<tr><td>Control</td><td>-0.90</td><td>1.40</td><td>42</td></tr>
</table>
</td></tr>
<tr><td>UPDRS Motor</td><td>
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>2.60</td><td>6.00</td><td>41</td></tr>
<tr><td>Control</td><td>-0.20</td><td>4.30</td><td>42</td></tr>
</table>
</td></tr>
<tr><td>NPI Delusions</td><td>
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>-0.70</td><td>3.30</td><td>41</td></tr>
<tr><td>Control</td><td>-1.70</td><td>3.90</td><td>42</td></tr>
</table>
</td></tr>
<tr><td>NPI hallucination</td><td>
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>-2.10</td><td>4.30</td><td>41</td></tr>
<tr><td>Control</td><td>-2.50</td><td>2.70</td><td>42</td></tr>
</table>
</td></tr>
<tr><td>Number of dropouts due to adverse events</td><td>
<table>
<tr><td></td><td>Events</td><td>Total</td></tr>
<tr><td>Experimental</td><td>10</td><td>41</td></tr>
<tr><td>Control</td><td>1</td><td>42</td></tr>
</table>
</td></tr>
<tr><td>Results</td><td>Data extracted for all BPRS subscales and UPDRS motor scale are the mean change scores from baseline to end point.

<table>
<tr><td rowspan="2">Completion Rates and Adverse Events</td><td colspan="2">United States Study</td></tr>
<tr><td>%</td><td>p value vs. Placebo</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Breier,A., Sutton,V.K., Feldman,P.D., Kadam,D.L., Ferchland,I., Wright,P., Friedman,J.H., Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease (USA Study Results), Biological Psychiatry.52 (5) (pp 438-445), 2002.Date of Publication: 01 Sep 2002., 438-445, 2002
	Completion rates (4 weeks): Olanzapine 61 Placebo 83.3 0.029 Discontinued due to adverse event: Olanzapine 24.4 Placebo 2.4 0.003 Treatment-emergent adverse events - Extrapyramidal syndrome: Olanzapine 24.4 Placebo 2.4 0.003 - Hallucinations: Olanzapine 24.4 Placebo 4.8 0.013 - Increased salivation: Olanzapine 22 Placebo 4.8 0.026
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? UNCLEAR 2. Was there adequate concealment of allocation? UNCLEAR 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? UNCLEAR* 6. Were the individuals administering care kept blind to treatment allocation? UNCLEAR*

Bibliographic reference	Breier,A., Sutton,V.K., Feldman,P.D., Kadam,D.L., Ferchland,I., Wright,P., Friedman,J.H., Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease (USA Study Results), Biological Psychiatry.52 (5) (pp 438-445), 2002.Date of Publication: 01 Sep 2002., 438-445, 2002
	7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES but dropout rate >20% 8. Did the study have an appropriate length of follow up? UNCLEAR (4 weeks) 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? UNCLEAR 11. Were investigators kept blind to participant's exposure to the intervention? UNCLEAR* 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR* *Level of blinding unclear - no details beyond description of study as "randomized, double-blind, placebo-controlled trial". Overall there is likely high risk of bias.

Bibliographic reference	Rabey, J.M., Prokhorov, T., Miniovitz, A., Dobronevsky E., Klein, C., Effect of quetiapine in psychotic Parkinson's disease patients: A double-blind labelled study of 3 months' duration, Movement Disorders Vol. 22, No. 3, 2007, pp. 313-318
Country/ies where the study was carried out	Israel
Study type	Double-blind, placebo-controlled randomised study
Aim of the study	To evaluate the efficacy of quetiapine in PD patients with psychosis
Study dates	Study dates: Not reported Study duration: 3 months
Source of funding	AstraZenica Pharmaceutical Company

<table>
<tr><th>Bibliographic reference</th><th>Rabey, J.M., Prokhorov, T., Miniovitz, A., Dobronevsky E., Klein, C., Effect of quetiapine in psychotic Parkinson's disease patients: A double-blind labelled study of 3 months' duration, Movement Disorders Vol. 22, No. 3, 2007, pp. 313-318</th></tr>
<tr><td>Sampe size</td><td>Total: 58
Quetiapine: 30 (14 Non-demented)
Placebo: 28 (15 Non-demented)</td></tr>
<tr><td>Inclusion criteria</td><td>PD patients with psychosis (defined as the presence of severe visual or auditory hallucinations and/or delusions, which significantly affected the patient's quality life.</td></tr>
<tr><td>Exclusion criteria</td><td>PD patients with:
- A history of psychosis that began within 2 years of the commencement of the motor symptoms
- Fluctuating cognition
- A previous history of schizophrenia, psychotic depression, or bipolar disorder before PD was diagnosed and/or the presence of pyramidal, cerebellar, or eye movement disorders.</td></tr>
<tr><td>Intervention</td><td>Quetiapine started at a single daily dose of 12.5 mg at bedtime and was increased every 2 to 3 days as required in divided daily doses. The titration period was flexible, from a few days up to 4 weeks. The dose was increased until symptoms cleared or side effects limited treatment.</td></tr>
<tr><td>Details</td><td>Baseline characteristics:
<table>
<tr><td>Characteristic</td><td>Quetiapine (n=30) (Mean(SD))</td><td>Placebo (n=28) (Mean(SD))</td></tr>
<tr><td>Age (yr)</td><td>75.5(8.1)</td><td>74.5(8.7)</td></tr>
<tr><td>Duration of disease (yr)</td><td>10.5(6.4)</td><td>10.6(6.4)</td></tr>
<tr><td>Total UPDRS</td><td>64.9(17.8)</td><td>69.2(23.0)</td></tr>
<tr><td>Motor UPDRS (on)</td><td>37.0(9.6)</td><td>39.5(13.1)</td></tr>
<tr><td>BPRS</td><td>34.2(5.0)</td><td>36.0(8.8)</td></tr>
<tr><td>Levodopa daily dose (mg)</td><td>594.6(312.9)</td><td>766.1(442.5)</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Rabey, J.M., Prokhorov, T., Miniovitz, A., Dobronevsky E., Klein, C., Effect of quetiapine in psychotic Parkinson's disease patients: A double-blind labelled study of 3 months' duration, Movement Disorders Vol. 22, No. 3, 2007, pp. 313-318</th></tr>
<tr><td></td><td></td></tr>
<tr><td>Primary outcome measures</td><td>BPRS and CGIS</td></tr>
<tr><td>Secondary outcome measures</td><td>UPDRS III, MMSE, HAM-D and ESS</td></tr>
<tr><td>Results</td><td>Only results reported separately for non-demented people with PD were of relevance and included.

BPRS at follow-up:
<table>
<tr><td>Outcome</td><td colspan="2">Quetiapine (n=14) (Mean(SD))</td><td colspan="2">Placebo (n=15) (Mean(SD))</td></tr>
<tr><td></td><td>Baseline</td><td>Follow-up</td><td>Baseline</td><td>Follow-up</td></tr>
<tr><td>BPRS</td><td>35.0 (7.1)</td><td>30.8 (6.0)</td><td>29.8 (4.6)</td><td>25.3 (2.9)</td></tr>
</table></td></tr>
<tr><td>Overall risk of bias</td><td>1. Has an appropriate method of randomisation been used? YES
2. Was there adequate concealment of allocation? UNCLEAR
3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES but levodopa dosage was higher in the placebo group.
4. Did the comparison groups receive the same care apart from interventions studied? YES
5. Were participants receiving care kept blind to treatment allocation? UNCLEAR*
6. Were the individuals administering care kept blind to treatment allocation? UNCLEAR*
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES but dropout rate >20%
8. Did the study have an appropriate length of follow up? UNCLEAR (12 weeks)
9. Did the study use a precise definition of outcome? YES
10. Was a valid and reliable method used to determine that outcome? YES</td></tr>
</table>

Bibliographic reference	**Rabey, J.M., Prokhorov, T., Miniovitz, A., Dobronevsky E., Klein, C., Effect of quetiapine in psychotic Parkinson's disease patients: A double-blind labelled study of 3 months' duration, Movement Disorders Vol. 22, No. 3, 2007, pp. 313-318**
	11. Were investigators kept blind to participant's exposure to the intervention? UNCLEAR* 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR* *Level of blinding unclear - no details beyond description of study as "randomized, double-blind, placebo-controlled trial". Overall there is likely high risk of bias.