BEST in Mental Health
BEST.awp.nhs.uk

Best Evidence Summaries of Topics in Mental Healthcare

BEST *in* MH *clinical question-answering service*

Question

In adults with Parkinson's disease, what is the most effective pharmacological intervention in reducing hallucinations?

Clarification of question using *PICO* structure

Patients: Adults with Parkinson's disease
Intervention: Any pharmacological intervention
Comparator: Any other pharmacological intervention or placebo
Outcome: Reduction in hallucinations

Plain language summary

Research suggests that clozapine and pimavanserin may be effective in reducing hallucinations in older adults with Parkinson's disease. However, more rigorous trials are needed to provide further clarification into the most effective pharmacological intervention.

Clinical and research implications

Evidence from two, generally well conducted, systematic reviews and two additional randomised controlled trials suggests that both clozapine and the 5-HT_{2A} receptor modulator pimavanserin may be effective in treating hallucinations and other psychotic symptoms in older adults with Parkinson's disease. The observed effects were not associated with any increase in Parkinsonian symptoms.

No evidence was identified for any other negative modulators of 5-HT_{2A} receptors and there were no studies comparing clozapine and pimavanserin.

The available evidence, from one systematic review and three additional randomised controlled trials suggests that the atypical antipsychotics quetiapine and olanzapine are ineffective in treating psychotic symptoms in people with Parkinson's disease.

Larger, high quality trials are needed to confirm the existing evidence and to assess the effectiveness of other negative modulators of 5-HT_{2A} receptors and atypical antipsychotics. Evidence is particularly lacking about the effectiveness of treatments for psychosis in younger patients with Parkinson's disease.

What does the evidence say?

Number of included studies/reviews (number of participants)

We identified two systematic reviews,[1,2] and five additional randomised controlled trials (RCTs)[3,4,5,6,7] which were considered relevant to this evidence summary. All studies were conducted in people with Parkinson's disease and psychotic symptoms and all reported at least one outcome measure relating to hallucinations, delusions, or general psychotic symptoms. All studies were conducted in older patients (mean age around 70 years). Study durations ranged from 4-12 weeks. One systematic review considered the effectiveness of atypical antipsychotics[1] and the other assessed the effectiveness of negative modulators of 5-HT_{2A} receptors.[2] In addition to the systematic reviews, we identified one placebo-controlled RCT each for clozapine,[3] olanzapine,[5] and quetiapine.[7] There were a further two RCTs comparing clozapine to the atypical antipsychotics quetiapine[4] and ziprasidone.[6]

Main findings

Evidence from two placebo-controlled RCTs included in a systematic review[1] and one additional placebo-controlled RCT[3] suggested that clozapine may be effective in reducing psychotic symptoms (measured by the Brief Psychiatric Rating Scale (BPRS),[1,3] Positive and Negative Syndrome in Schizophrenia Scale (PANSS),[1] and the Scale for Assessment of Positive Symptoms (SAPS).[3] Specifically, hallucinations improved by 1.9 points in the clozapine group, compared to 0.7 points in the placebo group (P=0.002) (BPRS).[3] The results of meta-analyses, reported in the second systematic review,[2] indicated that pimavanserin was associated with an overall reduction in psychotic symptom on the Scale for Assessment of Positive Symptoms (SAPS): WMD -2.26 (95% CI: -3.86 to -0.67), 4 studies (n=502). Reductions in hallucinations (SAPS-hallucinations), WMD -2.15 (95% CI: -3.45 to – 0.86), 2 studies (n=237) and delusions (SAPS-delusions), WMD -1.32 (95% CI: -2.32 to -0.32), 2 studies (n=237), were also observed.[2] No RCT evidence was identified for any other negative modulators of 5-HT_{2A} receptors.[2] Neither clozapine nor pimavanserin were associated with any increase in Parkinsonian symptoms.[1,3,2] One further RCT, comparing clozapine to quetiapine, found

that both hallucination and delusion frequency was reduced by 1.5 points after the second month, compared to baseline (p=0.0015 and p=0.0063, respectively) in the clozapine arm; there were no significant changes in the quetiapine arm.[4]

Two placebo-controlled RCTs, included in a systematic review,[1] and one additional placebo-controlled RCT,[7] found that quetiapine was ineffective in treating the symptoms of psychosis (measured by BPRS,[1,7] Neuropsychiatric Inventory (NPI),[7] and the Baylor PD hallucination scale[7]) in people with Parkinson's disease. One further RCT, comparing clozapine to quetiapine, found no significant changes in hallucination and delusion frequency in the quetiapine arm.[4] Two placebo-controlled RCTs, included in a systematic review,[1] and one additional placebo-controlled RCT,[5] found no significant differences in the severity or frequency of psychosis (BPRS) between the olanzapine and placebo groups. Finally, one very small RCT (n=16, with 14 completers) found no significant differences between the two treatment groups with respect to SAPS hallucinations and delusions scores or BPRS.[6] However, as noted by the authors, the sample size was unlikely to have been large enough to detect statistically significant differences between the treatment groups.[6]

Authors conclusions

Frieling 2007 – The authors stated that, Based on randomised trial evidence which is currently available, only clozapine can be fully recommended for the treatment of dopamimetic psychosis in Parkinson's disease.

Yasue 2016 – The authors stated that pooled RCT results suggest that pimavanserin is beneficial for the treatment of Parkinson's disease psychosis and is well tolerated.

Freidman 1999 – The authors concluded that Clozapine, at daily doses of 50 mg or less, is safe and significantly improves drug-induced psychosis without worsening Parkinsonism.

Merims 2006 – The authors concluded that clozapine and quetiapine are effective for the treatment of psychotic symptoms in Parkinson's disease and that clozapine has greater efficacy in reducing the frequency of hallucinations and delusions, but its use is associated with increased risk of leukopenia.

Nichols 2013 – the authors conclude that their study adds to existing evidence that olanzapine is ineffective in treating medication-induced psychosis in Parkinson disease.

Pintor 2012 – The authors concluded that ziprasidone appears to be at least as effective as clozapine for the treatment of psychotic symptoms in people with Parkinson's disease.

Shotbolt 2009 – The authors stated that, in their small study, quetiapine at doses of up to 150 mg/day failed to significantly improve psychosis compared to placebo.

Reliability of conclusions/Strength of evidence

This evidence summary is based on information from two generally well conducted systematic reviews and five additional, very small RCTs, which were of variable methodological quality. Small sample sizes mean that the findings of individual studies may be unreliable.

What do guidelines say?

NICE guidelines for Parkinson's disease (2006, CG35) makes the following recommendations when treating psychosis;

"All people with PD and psychosis should receive a general medical evaluation and treatment for any precipitating condition.

- Consideration should be given to withdrawing gradually antiparkinsonian medication that might have triggered psychosis in people with PD.

- Mild psychotic symptoms in people with PD may not need to be actively treated if they are well tolerated by the patient and carer.

- Typical antipsychotic drugs (such as phenothiazines and butyrophenones) should not be used in people with PD because they exacerbate the motor features of the condition.

- Atypical antipsychotics may be considered for treatment of psychotic symptoms in people with PD, although the evidence base for their efficacy and safety is limited.

- Clozapine may be used in the treatment of psychotic symptoms in PD, but registration with a mandatory monitoring scheme is required. It is recognised that few specialists caring for people with PD have experience with clozapine." (pp.19)

Date question received: 16/03/16
Date searches conducted: 05/04/16
Date answer completed: 02/05/16

References

Systematic reviews

1. Frieling, H., Hillemacher, T., Ziegenbein, M., Neundörfer, B., & Bleich, S. (2007). Treating dopamimetic psychosis in Parkinson's disease: structured review and meta-analysis. *European neuropsychopharmacology*, *17*(**3**), 165-171.

2. Yasue, I., Matsunaga, S., Kishi, T., Fujita, K., & Iwata, N. (2016). Serotonin 2A Receptor Inverse Agonist as a Treatment for Parkinson's Disease Psychosis: A Systematic Review and Meta-analysis of Serotonin 2A Receptor Negative Modulators. *Journal of Alzheimer's Disease*, (Preprint), 1-8.

Randomised controlled trials

3. Friedman, J., Lannon, M., Comella, C., Factor, S., Kurlan, R., Richard, I., ... & Brown, D. (1999). Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. *New England Journal of Medicine*, *340*(10), 757-763.

4. Merims, D., Balas, M., Peretz, C., Shabtai, H., & Giladi, N. (2006). Rater-blinded, prospective comparison: quetiapine versus clozapine for Parkinson's disease psychosis. *Clinical neuropharmacology*, *29*(6), 331-337.

5. Nichols, M. J., Hartlein, J. M., Eicken, M. G., Racette, B. A., & Black, K. J. (2013). A fixed-dose randomized controlled trial of olanzapine for psychosis in Parkinson disease. *F1000Research*, *2*.

6. Pintor, L., Valldeoriola, F., Baillés, E., Martí, M. J., Muñiz, A., & Tolosa, E. (2012). Ziprasidone versus clozapine in the treatment of psychotic symptoms in Parkinson disease: a randomized open clinical trial. *Clinical neuropharmacology*, *35*(2), 61-66.

7. Shotbolt, P., Samuel, M., Fox, C., & David, A. S. (2009). A randomized controlled trial of quetiapine for psychosis in Parkinson's disease. *Neuropsychiatric disease and treatment*, *5*, 327.

Guidelines

National Institute for Health and Care Excellence (2006) Parkinson's disease in over 20s: diagnosis and management CG35. NICE:London.
https://www.nice.org.uk/guidance/cg35/resources/parkinsons-disease-in-over-20s-diagnosis-and-management-975388237765

Results

Systematic reviews

Author (year)	Search date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Frieling et al. (2007)	8th February 2006	***Participants*:** People with Parkinson's disease and subsequent psychosis due to treatment with dopaminergic drugs. ***Intervention*:** Antipsychotic medication. ***Comparator*:** Other antipsychotic medication or placebo. ***Outcome*:** Clinical response assessed by standardized psychometric scales, worsening of motor function, adverse events, amount of participants leaving the study. ***Study design*:** Randomised controlled trials	n=7 studies (419 participants)	This systematic review aimed to assess the efficacy and safety of atypical antipsychotic drugs for the treatment of dopamimetic psychosis in people with Parkinson's disease. The review included seven small studies, with sample sizes ranging from 31 to 87. There were a total of 149 female participants, 212 males and 58 of unknown sex; the mean age of study participants was 71.4 years. *Clozapine versus placebo:* The review included two placebo controlled trials of clozapine. Both trials reported outcomes at four weeks. One trial (n=54), mean clozapine dose 24.7 mg (range 6.25 to 50 mg), reported that clozapine was associated with a reduction in psychotic symptoms on the Brief Psychiatric Rating Scale (BPRS): WMD −6.70 (95% CI: −7.45 to	The review question was clearly stated and appropriate inclusion criteria were defined. Four bibliographic databases were searched for relevant studies and search terms were reported. No language restrictions were applied. No additional sources were searched. The study selection and data extraction

				−5.95). The second trial (n=60), mean clozapine dose 35.8 mg, (range 12.5 to 50 mg), reported that clozapine was associated with an improvement in psychotic symptoms on the positive sub-score of the Positive and Negative Syndrome in Schizophrenia Scale (PANSS): WMD −4.80 (95% CI: −6.50 to −3.10). Summary estimates for the two studies indicated that clozapine was also associated with improvements in severity (indicated by CGI scores) and improvement in overall symptoms and motor score on the Unified Parkinson's Disease Rating Scale (UPDRS). *Clozapine versus quetiapine:* One study compared clozapine (mean dose 26±12 mg) to quetiapine (mean dose 92±47 mg). Outcomes measured at 12 weeks indicated no significant differences in clinical efficacy between the two treatments. **There were no specific measures of psychotic symptoms.** *Quetiapine versus placebo:* The review included two placebo controlled trials of quetiapine (total n=89) with mean doses of 169.1±46.4 mg and 123.3±63 mg.	processes included measures to minimise error and bias. However, assessment of the methodological quality of included studies was focussed solely on allocation concealment. Appropriate methods of synthesis were used.

				Outcomes measured at 12 weeks indicated no significant differences in clinical efficacy between quetiapine and placebo. Both studies measured BPRS, but no numerical results were reported. *Olanzapine versus placebo:* Two studies (results from the USA and European centres of the same study, reported in one publication, total n=158) compared olanzapine (mean dose 4.2±2.6 mg) to placebo. Outcomes were measured at four weeks. There were no significant differences in psychotic symptoms (BPRS total, positive and negative sub-scores, and hallucinations) between olanzapine and placebo. However, olanzapine was associated with worsening of Parkinsonian symptoms and with greater numbers of participants leaving the study due to adverse events.	
Yasue et al. (2016)	18th August 2015	***Participants*:** People with Parkinson's disease psychosis. ***Intervention*:** Negative modulators of 5-HT_{2A} receptors. ***Comparator*:** Placebo ***Outcome*:** Psychosis symptoms, motor symptoms, discontinuation rate and individual	n=4 studies (680 participants)	This systematic review aimed to assess the effectiveness of negative modulators of 5-HT_{2A} receptors for the treatment of Parkinson's disease psychosis. The review included four placebo controlled trials of pimavanserin; no RCT evidence was	The review question was clearly stated and appropriate inclusion criteria were defined.

		adverse events. ***Study design*:** Randomised placebo-controlled trials		identified for any other negative modulators of 5-HT_{2A} receptors. The mean age of study participants ranged from 69 to 72 years; no information about the numbers of male and female participants was reported. Doses ranged from 10 to 60 mg and included fixed and flexible regimens; two of the four studies compared different doses, however, the meta-analyses used combined data for all doses. The study duration was four weeks in one study and six weeks in all other studies. Two of the include studies used completers only analyses. The results of meta-analyses suggested that pimavanserin was associated with an overall reduction in psychotic symptom on the Scale for Assessment of Positive Symptoms (SAPS): WMD -2.26 (95% CI: -3.86 to -0.67), 4 studies (n=502). Reductions in hallucinations (SAPS-hallucinations), WMD -2.15 (95% CI: -3.45 to – 0.86), 2 studies (n=237) and delusions (SAPS-delusions), WMD -1.32 (95% CI: -2.32 to -0.32), 2 studies (n=237), were also observed. Parkinson's symptoms (UPDRS) and discontinuations due to adverse events were similar between the pimavanserin and placebo groups.	Three bibliographic databases were searched for relevant studies; the search strategy was reported and no language restrictions were applied. Trials registries were screened for additional studies. All stages of the review process included measures to minimise error and bias. The methodological quality of included studies was assessed using the Cochrane risk of bias tool. The analysis methods were broadly

					appropriate, however, combining data for all doss may have resulted in loss of relevant information.

Randomised controlled trials

Author (year)	**Inclusion criteria**	**Number of participants**	**Summary of results**	**Risk of bias**
Friedman et al. (1999)	***Participants*****:** People with idiosyncratic Parkinson's disease and drug-induced psychosis of at least four weeks' duration. Exclusion criteria: history of leukopenia; systemic factors that might contribute to a behavioural disorder; dopamine-blocking drugs within the three months before the study began; neuroleptic drugs administered in depot form within the year before the study; change in antidepressant or anxiolytic drugs within the month before the study; previous clozapine; any illness that would make the use of clozapine potentially hazardous; myocardial infarction during	n=60 (n=30 placebo arm, n=30 clozapine arm)	This trial aimed to assess the efficacy of clozapine for the treatment of drug-induced psychosis in people with Parkinson's disease. All study participants had experienced significant hallucinations or delusions. There were no significant differences, in participant characteristics, duration of Parkinson's disease or symptoms, or the use of anti-Parkinsonian or psychotropic drugs between the treatment and placebo groups at baseline. The mean age of study participants was approximately 71 years, the proportion of males was 57%, and the mean duration of Parkinson's disease was approximately 10.6 years. The mean daily dose of clozapine at the end of the study was 24.7 mg (range 6.25 to 50 mg) and the study duration was four weeks.	Randomisation was stratified by age (<70 years, ≥70 years); no further details of randomisation or allocation concealment were reported. The study was described as

	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; an inability to tolerate the current level of psychosis for one month; dementia severe enough to preclude assessment on the psychiatric-test battery. ***Intervention*:** Clozapine, dose initiated at 6.25mg for ten days, then adjusted as needed. ***Comparator*:** Placebo ***Outcome*:** Parkinsonian symptoms (UPDRS), psychiatric symptoms (BPRS, BPRM-M, CGIS, SAPS, MMSE)		**Hallucinations improved by 1.9 points in the clozapine group, compared to 0.7 points in the placebo group (P=0.002) (BPRS).** Clozapine was also associated with greater improvements than placebo on all other measures of psychosis: change in total BPRS score -9.3±1.5 vs. -2.6±1.3 (p=0.002); change in BPRS-M score -8.6±1.3 vs. -2.5±1.2 (p=0.003); change in CGI score -1.6±0.3 vs. -0.5±0.2 (p<0.001); change in SAPS score -11.8±2.0 vs. -3.8±1.9 (p=0.01). There was no worsening of motor symptoms in either group and clozapine was associated with a statistically significant improvement in tremor. Three patients receiving clozapine and three patients receiving placebo withdrew from the study.	having double-blind evaluation, lasting for four weeks. The analyses used a modified intention-to-treat approach. Results were reported for all specified outcome measures.
Merims et al. (2006)	***Participants***: Patients with advanced Parkinson's disease, treated with levodopa, who had significant psychotic symptoms of recent onset and who required neuroleptic treatment. No exclusion criteria were reported. ***Intervention*:** Clozapine, initiated at 6.25 mg, increased every 2 weeks, initially to 12.5 mg and then 25mg and 50mg. ***Comparator*:** Quetiapine, initiated at	n= 27 (n=14 clozapine arm, n=13 quetiapine arm)	This trial aimed to compare the efficacy and safety of quetiapine and clozapine for the treatment of recent-onset psychotic symptoms in people with Parkinson's disease. There were no significant differences between the two treatment groups at baseline with respect to age, Parkinson's disease duration and symptoms, or duration of psychotic symptoms. The mean age of study participants was approximately 72 years, the mean duration of Parkinson's disease was approximately 8.8 years and the mean duration	No details of the randomisation procedure or allocation concealment were reported. The study was

	25mg, increased every 2 weeks by 25 mg/d to a maximum of 150mg. ***Outcome*:** Psychosis severity (NPI, CGIC).		of psychotic symptoms was approximately 10.2 weeks. The distribution of male and female study participants was not reported. The duration of follow-up was 22 weeks. **Both hallucination and delusion frequency was reduced by 1.5 points after the second month, compared to baseline (p=0.0015 and p=0.0063, respectively). There was no significant reduction in frequency of hallucinations or delusions in the quetiapine group. There were no significant changes in the severity of hallucinations or delusions in either treatment group.** Eleven patients in each treatment group achieved satisfactory control of psychotic symptoms with a mean daily dose of 90.9±47 mg for quetiapine and 13.1±7.0 for clozapine. One patient in the clozapine group developed significant leukopenia and neutropenia, and two others showed decreased leukocyte count. No change in Parkinsonian symptoms was observed in either treatment arm. Only 7 patients from the clozapine arm and 9 from the quetiapine arm completed follow-up.	described as 'rater-blinded', but no details of the blinding of participants or clinicians were reported. Analytic methods were broadly appropriate. Results were reported for all specified outcome measures.
Nichols et al.	***Participants*:** Patients over 30 years of age at the Washington University Movement	n=23 (n=9 placebo	This study aimed to assess the efficacy of olanzapine for the treatment of medication-induced psychosis in people with	Participants were

(2013)	Disorder Centre with idiopathic Parkinson's disorder based on the presence of at least two of three cardinal manifestations of the disease, response to levodopa or a dopamine agonist and absence of historical or examination features suggesting secondary Parkinsonism. Participants were treated with levodopa and were experiencing clinically significant hallucinations or delusions. Exclusion criteria: MMSE score <27; pregnancy; delirium; potentially confounding CNS disorders; antipsychotic use within the last month; olanzapine sensitivity; severity of psychosis that warranted hospitalisation. ***Intervention*:** Olanzapine ***Comparator*:** Placebo ***Outcome*:** Quality of life (PDQ-39), psychopathology (BPRS, MMSE, HDRS, BDI) and sleep.	arm, n=14 intervention arm).	Parkinson's disease. There were no significant differences in age, Parkinsonian symptoms, or psychosis symptoms, between the two treatment groups at baseline. The mean age of study participants was 71 years. No details of the distribution of male and female participants, or the duration of Parkinson's disease or psychosis symptoms were reported. Doses in the intervention arms were reduced to 2.5 mg and 5 mg ant two weeks. One participant (not included in the analysis) continued on 10mg. **There were no significant differences in severity or frequency of psychosis between the two treatment groups.** There were no significant differences in Parkinsonian symptoms, quality of life, or other outcome measures, between the two treatment groups. Participants in the olanzapine group reported a higher frequency of mild adverse events.	randomised 1:1:1 to olanzapine 5 mg, olanzapine 10 mg or placebo. Randomisation was done by the funder (Lilly Research Laboratories). Participants received matched tablets or capsules provided by Lilly Research Laboratories, 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. A modified intention-to-treat analysis was performed. Full numerical results were not reported, however, data files were provided on-

				line.
Pintor et al. (2012)	***Participants*:** Patients with Parkinson's disease according to UK Brain Bank criteria, who had experienced a psychotic episode. Patients were included in psychotic symptoms persisted after dose adjustment of dopaminergic drugs and a minimum 5-day washout of anticholinergics, amantadine, catechol-O-methyltransferase inhibitors, or selegiline. All participants were on fixed doses of levodopa and dopaminergic agonists throughout the trial and follow-up period. Exclusion criteria: neuroleptic treatment in the previous 30 days; anticholinesterasic drugs; history of leukopenia; other serious medical or psychiatric conditions. ***Intervention*:** Clozapine initiated at 12.5 mg/d which could be titrated to a maximum of 100 mg/d. ***Comparator*:** Ziprasidone initiated at 20 mg/d which could be titrated to a maximum of 80 mg/d. ***Outcome*:** Neurologic status (UPDRS, AIMS, Schwab and England Scale), cognitive and psychiatric status (MMSE, BPRS, SAPS and CGIS).	n=16 (n=8 clozapine arm, n=8 ziprasidone arm)	This study aimed to compare the efficacy and safety of ziprasidone and clozapine for the treatment of psychotic symptoms in people with Parkinson's disease. There were no significant differences between the two treatment groups at baseline with respect to age, sex distribution, duration and severity of Parkinson's disease, or severity of psychosis symptoms. The mean age of study participants was approximately 73 years, 38% were male, and the mean duration of Parkinson's disease was approximately 14 years. At the end of the study, the mean daily dose of clozapine was 32.1±12.2 mg and the mean daily dose of ziprasidone was 35.0±19.1 mg. **There were no significant differences between the two treatment groups with respect to SAPS hallucinations and delusions scores or BPRS**, other SAPS sub-scales, MMSE, CGI, or Parkinsonian symptoms (UPDRS,AIMS, Hoehn-Yahr, Schwab and England).	No details of the randomisation procedure were reported. Participants and psychiatrists new the drug and dose administered, but outcome assessors were blind to treatment group. The authors stated that results for the 16 patients enrolled in the study (ITT analysis) were the same as

				those for the 14 completers; only results for the completer analysis were reported.
Shotbolt et al. (2009)	***Participants*:** Patients with idiopathic Parkinson's disease according to UK Brain Bank criteria, with either hallucinations, suspiciousness or delusions of a severity of >3/7 on the BPRS. Symptoms must have been present for over two weeks. Participants' current antiparkinsonian treatment had to be deemed to be optimal by the attending specialist consultants. Exclusion criteria: current treatment with cholinesterase inhibitors; antipsychotics in the preceding two weeks; contraindication to quetiapine; major concomitant medical illness; Lewy body dementia. ***Intervention*:** Quetiapine ***Comparator*:** Placebo ***Outcome*:** Time to dropout due to lack of improvement of psychosis, psychotic symptoms (UPDRS, BPRS, NPI and the Baylor PD hallucination scale).	n=24 (n=13 placebo arm, n=11 quetiapine arm).	This study aimed to assess the efficacy of quetiapine for the treatment of psychosis in Parkinson's disease. Because of the high drop-out rate (only four patients from each group completed the 12-week double-blind phase of the study), outcomes were reported at six weeks. **No significant changes, from baseline to six weeks, were observed for any measure of psychosis (BPRS, Neuropsychiatric Inventory (NPI), and the Baylor PD hallucination scale) in either group.** Quetiapine had no effect on Parkinsonian symptoms (UPDRS score) or time to dropout. The mean daily dose of quetiapine was 72.7±26.1 mg.	No details of the randomisation procedure or allocation concealment were reported. The trial was described as double-blind. Intention-to-treat analyses were performed. Results were reported for

				all specified outcome measures.

Risk of bias

Systematic reviews

Author (year)	RISK OF BIAS				
	Inclusion criteria	Searches	Review process	Quality assessment	Synthesis
Frieling et al. (2007)	☺	☺	☺	☹	☺
Yasue et al. (2016)	☺	☺	☺	☺	?

Randomised controlled trials

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Friedman et al. (1999)	?	?	☺	☺	☺	☺
Merims et al. (2006)	?	?	?	☺	☺	☺
Nichols et al. (2013)	☺	☺	☺	☺	☺	☺
Pintor et al. (2012)	?	☹	☹	☺	☺	☺
Shotbolt et al. (2009)	?	?	☺	☺	☺	☺

☺ Low risk ☹ High risk ? Unclear risk

Search details

Source	Search Strategy	Number of hits	Relevant evidence identified
Guidelines			
NICE	Parkinson	13	
Systematic Reviews			
MEDLINE	1 parkinson*.ab,ti. (85243) 2 (parkinson* adj2 (disorder* or disease* or diagnos*)).ab,ti. (66607) 3 exp Parkinson Disease/ (52010) 4 exp Parkinsonian Disorders/ (63274) 5 1 or 2 or 3 or 4 (95085) 6 exp Psychotic Disorders/ (44888) 7 exp Hallucinations/ (9567) 8 exp Delusions/ (6991) 9 exp Delirium/ (6645) 10 (hallucin* or delus* or delir*).ab,ti. (29782) 11 6 or 7 or 8 or 9 or 10 (76441) 12 exp Antipsychotic Agents/ (110317) 13 exp Central Nervous System Agents/ (1176192) 14 exp Neurotransmitter Agents/ (1214225) 15 exp Antiparkinson Agents/ (37355) 16 exp Dopamine Agonists/ (27553) 17 (antipsycho* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (16665) 18 (central adj2 nerv* adj2 system* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (1836) 19 (neurotransmitter* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (441) 20 (antiparkinson* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (1802) 21 (pharma* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (55497) 22 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (1892042)		

	23 5 and 11 and 22 (1507) 24 – 43 **SYSTEMATIC REVIEW FILTER APPLIED** (935429) 44 23 and 43 (118)		
EMBASE	1 parkinson*.ab,ti. (117595) 2 (parkinson* adj2 (disorder* or disease* or diagnos*)).ab,ti. (93497) 3 exp Parkinson disease/ (112545) 4 exp parkinsonism/ (22910) 5 1 or 2 or 3 or 4 (149690) 6 exp psychosis/ (245022) 7 exp hallucination/ (30143) 8 exp delirium/ (21380) 9 exp delusion/ (24145) 10 (halluc* or delus* or delir*).ab,ti. (46098) 11 6 or 7 or 8 or 9 or 10 (271353) 12 exp central nervous system agents/ (1514767) 13 exp antiparkinson agent/ (111071) 14 exp dopamine receptor stimulating agent/ (181935) 15 (antipsycho* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (24801) 16 (central adj2 nervous* adj2 system* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (2356) 17 (neurotransmitter* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (557) 18 ((antiparkinson* or anti-parkinson*) adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (3694) 19 (pharma* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (80929) 20 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (1636743) 21 5 and 11 and 20 (9306) 22 – 72 **SYSTEMATIC REVIEW FILTER APPLIED** (929)		
PsycINFO/CINAHL	1 parkinson*.ab,ti. (25706) 2 (parkinson* adj2 (disorder* or disease* or diagnos*)).ab,ti. (21589) 3 exp Parkinson's Disease/ (17163) 4 exp Parkinsonism/ (2595) 5 1 or 2 or 3 or 4 (26180) 6 exp Psychosis/ (99638)		

	7 exp HALLUCINATIONS/ (5428) 8 exp DELIRIUM/ (2656) 9 exp DELUSIONS/ (4796) 10 (hallucin* or delus* or delir*).ab,ti. (28294) 11 6 or 7 or 8 or 9 or 10 (119496) 12 exp Drug Therapy/ (125594) 13 exp Dopamine Agonists/ (20107) 14 (antipsycho* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (13111) 15 (central adj2 nervous* adj2 system* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (270) 16 (neurotransmitter* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (117) 17 (antiparkinson* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (777) 18 (pharma* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (12821) 19 12 or 13 or 14 or 15 or 16 or 17 or 18 (155508) 20 5 and 11 and 19 (933) 21 – 30 **SYSTEMATIC REVIEW FILTER APPLIED** (142431) 31 20 and 30 (89)		
Primary Studies			
MEDLINE	1 parkinson*.ab,ti. (85243) 2 (parkinson* adj2 (disorder* or disease* or diagnos*)).ab,ti. (66607) 3 exp Parkinson Disease/ (52010) 4 exp Parkinsonian Disorders/ (63274) 5 1 or 2 or 3 or 4 (95085) 6 exp Psychotic Disorders/ (44888) 7 exp Hallucinations/ (9567) 8 exp Delusions/ (6991) 9 exp Delirium/ (6645) 10 (hallucin* or delus* or delir*).ab,ti. (29782) 11 6 or 7 or 8 or 9 or 10 (76441) 12 exp Antipsychotic Agents/ (110317) 13 exp Central Nervous System Agents/ (1176192) 14 exp Neurotransmitter Agents/ (1214225)		

	15 exp Antiparkinson Agents/ (37355) 16 exp Dopamine Agonists/ (27553) 17 (antipsycho* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (16665) 18 (central adj2 nerv* adj2 system* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (1836) 19 (neurotransmitter* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (441) 20 (antiparkinson* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (1802) 21 (pharma* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (55497) 22 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (1892042) 23 5 and 11 and 22 (1507) 24 - 31 **RCT FILTER APPLIED** (738293) 32 23 and 31 (139)		
EMBASE	1 parkinson*.ab,ti. (117595) 2 (parkinson* adj2 (disorder* or disease* or diagnos*)).ab,ti. (93497) 3 exp Parkinson disease/ (112545) 4 exp parkinsonism/ (22910) 5 1 or 2 or 3 or 4 (149690) 6 exp psychosis/ (245022) 7 exp hallucination/ (30143) 8 exp delirium/ (21380) 9 exp delusion/ (24145) 10 (halluc* or delus* or delir*).ab,ti. (46098) 11 6 or 7 or 8 or 9 or 10 (271353) 12 exp central nervous system agents/ (1514767) 13 exp antiparkinson agent/ (111071) 14 exp dopamine receptor stimulating agent/ (181935) 15 (antipsycho* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (24801) 16 (central adj2 nervous* adj2 system* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (2356) 17 (neurotransmitter* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (557) 18 ((antiparkinson* or anti-parkinson*) adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (3694) 19 (pharma* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (80929) 20 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (1636743)		

	21 5 and 11 and 20 (9306) 22 - 28 **RCT FILTER APPLIED** (916382) 29 21 and 28 (862)		
PsycINFO/CINAHL	1 parkinson*.ab,ti. (25706) 2 (parkinson* adj2 (disorder* or disease* or diagnos*)).ab,ti. (21589) 3 exp Parkinson's Disease/ (17163) 4 exp Parkinsonism/ (2595) 5 1 or 2 or 3 or 4 (26180) 6 exp Psychosis/ (99638) 7 exp HALLUCINATIONS/ (5428) 8 exp DELIRIUM/ (2656) 9 exp DELUSIONS/ (4796) 10 (hallucin* or delus* or delir*).ab,ti. (28294) 11 6 or 7 or 8 or 9 or 10 (119496) 12 exp Drug Therapy/ (125594) 13 exp Dopamine Agonists/ (20107) 14 (antipsycho* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (13111) 15 (central adj2 nervous* adj2 system* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (270) 16 (neurotransmitter* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (117) 17 (antiparkinson* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (777) 18 (pharma* adj2 (agent* or drug* or medic* or treatment*)).ab,ti. (12821) 19 12 or 13 or 14 or 15 or 16 or 17 or 18 (155508) 20 5 and 11 and 19 (933) 21 - 26 **RCT FILTER APPLIED** (174119) 27 20 and 26 (155)		

Disclaimer

BEST in MH answers to clinical questions are for information purposes only. BEST in MH does not make recommendations. Individual health care providers are responsible for assessing the applicability of BEST in MH answers to their clinical practice. BEST in MH is not responsible or liable for, directly or indirectly, any form of damage resulting from the use/misuse of information contained in or implied by these documents. Links to other sites are provided for information purposes only. BEST in MH cannot accept responsibility for the content of linked sites.