BEST in Mental Health
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Best Evidence Summaries of Topics in Mental Healthcare

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

Question

"In adults with Parkinson's disease and psychosis, how effective are anti-psychotics, compared to treatment as usual, for treating psychotic symptoms? Which is the most effective and is the most tolerable?"

Clarification of question using PICO structure

Patients:	Adults with Parkinson's disease and psychosis
Intervention:	Anti-psychotics
Comparator:	Treatment as usual
Outcome:	Tolerance and the reduction of reducing psychotic symptoms.

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Clinical and research implications

No definite clinical implications can be made from the available evidence. There are very few methodologically robust head-to-head studies, so that it is not possible to determine which anti-psychotic is most effective. Several treatments were compared with placebo (olanzapine, clozapine, quetiapine, and pimavanserin); only two treatments reported significant findings. Clozapine showed significant improvement for *some* outcomes (mean scores on the CGI, and the positive subscore of PANSS), but somnolence was more frequent with treatment. A well-conducted study demonstrated that primavanserin significantly reduced psychotic symptoms in patients with moderate to severe Parkinson's disease. Although this treatment was well-tolerated, there was an increase in discontinuation in the treatment group compared with placebo. One RCT with a very small sample size compared risperidone with clozapine and found no significant differences in outcomes between the groups. Two open-label RCTs compared clozapine with quetiapine, but there were no differences between groups for any of the behavioural and motor function parameters evaluated, although in one of the studies, patients treated with clozapine experienced significantly fewer delusions. Studies of clozapine reported adverse effects including neutropenia and leukopenia. These findings are generally consistent with the systematic review results.

It is clear from the authors of the included studies that further research into new treatment alternatives for psychosis in PD is warranted. It has been suggested that RCTs are needed to evaluate newer atypical antipsychotics (i.e. zipasidone or aripiprazole) and other treatment strategies (e.g. rivastigmine or orondansetron). A well-conducted RCT also suggested that pimavanserin may be a viable alternative for the treatment of psychosis in Parkinson's disease, but further research is needed.

What does the evidence say?

Number of included studies/reviews (number of participants)

One systematic review (SR) (Frieling et al. 2007), and eight randomised controlled trials (RCTs) met the inclusion criteria for this BEST summary (Breier et al. 2002; Cummings et al. 2014; Ellis et al. 2000; Pollak et al. 2004; Merims et al. 2006; Morgante et al. 2004; Rabey et al. 2007; Shotbolt et al. 2000). Some of these RCTs were also included in the SR, and these have been noted below.

Main Findings

The aim of the SR was to evaluate which neuroleptic drugs were effective in treating drug-induced pyschosis (DIP) in Parkinson's disease (Frieling et al. 2007). This review included 7 RCTs: two compared low-dose *clozapine vs. placebo* and results from pooled analyses revealed that severity (Clinical Global Impression [CGI]) and motor functioning were significantly improved with treatment, although there was no difference between groups in Mini Mental State Examination (MMSE) scores. One trial that compared *clozapine vs. quetiapine* found no difference between groups the groups for clinical efficacy (CGI; BPRS), motor functioning (Unified Parkinson's Disease Rating Scale [UPDRS]; Abnormal Involuntary Movement Scale [AIMS]), and adverse events. Two 12-week trials compared *quetiapine vs. placebo*, and both reported no significant difference in efficacy or safety between groups. Two further studies compared *olanzapine vs. placebo*. No significant difference between groups was found for clinical efficacy using the CGI score and Brief Psychiatric Rating Scale (BPRS)

total scores – and also MMSE. Treatment with olanzapine lead to a significant worsening of Parkinson symptoms (UPDRS total, motor score and activities of daily living [ADL]).

Olanzapine vs. placebo

As presented in the above SR, Breier et al. (2002) reported on two studies (one conducted in the USA [n=83] and one conducted in Europe [n=77]) that compared olanzapine (up to 15 mg/day) with placebo. In both studies, no significant treatment-group difference for any outcome measure were found after 4 weeks of treatment: BPRS total – and positive/negative; BPRS hallucinations; CGI-S psychosis; NPI total; NPI hallucinations; NPI delusions; MMSE).

Clozapine vs. placebo

One RCT (not included in the above SR), compared clozapine (mean 35.8 mg/day) with placebo in 60 patients with PD (Pollak et al. 2004). After 4 weeks, mean scores on the CGI, and the positive subscore of PANSS significantly improved with clozapine compared with placebo. There was no significant difference between groups for MMSE, total UPDRS, or motor UPDRS scores. The authors also reported that somnolence was more frequent in the clozapine treatment group.

Risperidone vs. clozapine

We identified a RCT (excluded from the SR above) that compared the efficacy and safety of risperidone (mean 1.2 mg/day) with clozapine (mean 62.5 mg/day) for the treatment of psychosis in Parkinson's disease (Ellis et al. 2000). This study, however, included only 10 participants. The authors reported no significant differences between treatments in BPRS psychosis score, BPRS total score, or UPDRS motor score. The authors noted that one patient treated with clozapine developed neutropenia.

Clozapine vs. quetiapine

Two open-label RCTs compared clozapine with quetiapine. One of these was included in the SR above (Morgante et al. 2004), but the other was not (Merims et al. 2006). The first compared clozapine (mean 26 mg/day) vs. quetiapine (mean 91 mg/day) in 45 patients, but no significant differences were found between groups in any of the behavioural and motor function parameters evaluated (BPRS, Clinical CGI-S, UPDRS III, AIMS) after 12 weeks. Side effects were found to be mild in both groups. The other RCT evaluated clozapine (mean 13.1 mg/day) vs. quetiapine (mean 90.9 mg/day) in 27 patients with PD (Merims et al. 2006). After 22 weeks, clozapine and quetiapine were found to be equally effectives in improving psychotic symptoms over time (CGIC), although patients treated with clozapine experienced significantly fewer delusions (p=0.011), but not significantly fewer hallucinations (p=0.097). Neither treatment showed improvements in hallucination or delusion severity. One patient treated with clozapine developed significant leukopenia, and two others stopped treatment due to lower leukocyte counts.

Quetiapine vs. placebo

Two RCTs (not included in the above SR) evaluated the effectiveness of quetiapine compared to placebo for psychosis in Parkinson's disease (Rabey et al. 2007; Shotbolt et al. 2009). The mean dose of quetapine was 119 mg/day in the trial by Rabey et al. (2007) and 'up to 150 mg/day' in the trial by Shotbolt et al. (2009). The trial by Rabey included 58 patients who were treated for 12 weeks. The authors reported no significant differences between groups for all parameters evaluated (motor UPDRS, total BPRS, MMSE, the Hamilton Rating Scale for Depression (HAM-D), the Epworth Sleepiness Score (ESS), and the CGI-S). Seven of the patients in this trial reported hypersomnolence,

and 2 of them stopped treatment due to this. In the 12 week trial by Shotbolt et al. (2009), 24 patients were randomised, but as the trial suffered from a high drop-out rate, data were only reported at six weeks. The authors reported that no significant changes were found for any of the outcomes (BPRS, NPI, Baylor PD hallucination scale, and UPDRS) in either group.

Pimavanserin vs. placebo
Another RCT evaluated the effectiveness of pimavanserin compared with placebo in 199 people with Parkinson's disease (Cummings et al. 2014). After six weeks of treatment, the authors reported significant reductions in psychotic symptoms in patients with moderate to severe Parkinson's disease. They also reported that primavanserin was well tolerated, although there was an increase in discontinuation in the treatment group compared with placebo.

Authors Conclusions
The authors of the systematic review concluded that only clozapine can be fully recommended for the treatment of DIP in Parkinson's disease, and that olanzapine should not be used in this indication (Frieling et al. 2007). The authors noted in their discussion, however, that clozapine treatment is associated with a rare, but potentially life-threatening occurrence of agranulocytosis.

Breier et al. (2002) concluded that their findings did not demonstrate superior efficacy of olanzapine over placebo.

Pollak et al. (2004) concluded that clozapine at a mean dose lower than 50 mg/day improves drug induced psychosis in PD without significant worsening of motor function, and that the effect wears off once the treatment stops.

Ellis et al. (2000) concluded that risperidone may be a reasonable alternative to clozapine in the treatment of psychosis in patients with PD. The authors noted, however, that risperidone may worsen extrapyramidal symptoms more than clozapine and must be used with caution.

Both Morgante et al. (2004) and Merims et al. (2006) concluded that clozapine and quetiapine were effective atypical neuroleptics for the treatment of psychotic symptoms in PD. Merims et al. (2006) also concluded that clozapine had greater efficacy in reducing delusion frequency, but a high risk of leukopenia.

Rabey et al. (2007) concluded that quetiapine was effective compared with placebo, but that the high drop-out rate probably influenced the study results. Shotbolt et al. (2009) concluded that quetiapine did not have a significant impact on time to drop-out. Due to methodological problems, the authors also concluded that the trial did not answer the question of whether quetiapine is an effective treatment for PD psychosis.

Cummings et al. (2014) concluded that pimavanserin may benefit patients with Parkinson's disease psychosis for whom few other treatment options exist.

Reliability of conclusions/Strength of evidence

Shotbolt et al. (2009), Ellis et al. (2000), and Merims et al. (2006) all had very small sample sizes and a high risk of bias so that any results presented from these studies are unlikely to be reliable. Morgante et al. (2004) also had a high risk of bias. While the SR was well-conducted, the studies included in the review appear not to be methodologically robust.

Breier et al. (2002) had an unclear risk of bias as full details of their study methodology were not reported.

The RCTs by Cummings et al. (2014), Pollak et al. (2004), and Rabey et al. (2007) had a low risk of bias in terms of methods of randomisation, and blinding, however, the latter two studies had relatively small sample sizes. The trial by Cummings et al. (2014) was the most methodologically robust and the results of this trial are likely to be reliable.

What do guidelines say?

NICE guidelines for Parkinson's disease (2006, CG35) makes the following recommendations regarding the treatment of 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 anti-parkinsonian 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.21)

SIGN guidelines (2010, CG113) for Parkinson's disease makes the following recommendations regarding the treatment of psychosis:

"Before considering use of antipsychotic medications, other treatable causes of psychosis should be excluded.

Patients with psychosis in Parkinson's disease should be considered for treatment with low-dose clozapine and undergo weekly monitoring for the first 18 weeks of treatment followed by fortnightly monitoring for the first year and then monthly thereafter. Where weekly monitoring of blood is not possible on a consistent basis, low-dose quetiapine should be considered as an alternative antipsychotic for the treatment of patients with psychosis in Parkinson's disease." (pp.33)

Date question received: 10/03/2014
Date searches conducted: 10/03/2014
Date answer completed: 01/04/2014

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Systematic reviews

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Randomised controlled trials

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Morgante, L., Epifanio, A., Spina, E., Zappia, M., Rosa, A.E., Marconi, R., Basile, G., Raimondo, G.D., Spina, P.L. and Quattrone, A. (2004) Quetiapine and Clozapine in Parkinsonian Patients With Dopaminergic Psychosis. *Clinical Neuropharmacology 27* **(4)** pp. 153-156.

Pollak, P., Tison, F., Rascol, O., Destee, A., Pere, J.J., Senard, L.M., Durif, f. and Bourdeix, I. (2004) Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up. *Journal of Neurology, Neurosurgery and Psychiatry 75* **(5)** pp.689-695.

Rabey, J.M., Prokhorov, T., Miniovitz, A., Dobronevsky, E. and Klein, C. (2007) Effect of Quetiapine in Psychotic Parkinson's Disease Patients: A Double-Blind Labeled Study of 3 Months' Duration. Movement Disorders 22 (3) pp.313-318.

Shotbolt, P., Samuel, M., Fox, C. and David, A.S. (2009) A randomized controlled trial of quetiapine for psychosis in Parkinson's disease. *Neuropsychiatric Disease and Treatment 5* **(1)** pp.327-332.

Guidelines

National Institute for Health and Care Excellence (2006) Parkinson's disease. Diagnosis and management in primary and secondary care. CG35. London: National Institute for Health and Care Excellence. **http://www.nice.org.uk/nicemedia/live/10984/30088/30088.pdf**

Scottish Intercollegiate Guidelines Network (2010) Diagnosis and pharmacological management of Parkinson's disease. A national Clinical Guideline. CG113. Edinburgh: Scottish Intercollegiate Guidelines Network. http://www.sign.ac.uk/pdf/sign113.pdf

Results

Systematic Reviews

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Frieling et al. (2007)	08/02/ 2006	P: Adults with Parkinson's disease suffering from drug-induced psychosis under dopamimetic treatment. I: Atypical antipsychotic drugs. C: Any other atypical antipsychotic drug or placebo. O: (1) amount of participants leaving the study early; (2) clinical response assessed by standardized psychometric scales; (3) worsening of motor function assessed by standardized rating scales; (4) adverse events.	7 RCTs	Of the seven studies included in the review, one was considered to have a low risk of bias, and the others were considered to have a moderate risk of bias. **Clozapine vs. placebo:** Two 4-week trials compared clozapine (mean 35.8 mg and 24.7 mg) vs. placebo. Patients in the treatment group improved significantly in the severity (as assessed using the CGI) compared to placebo: WMD -1.1 (95% CI -1.24 to -0.97), and in psychotic symptoms: data not pooled. In addition, UPDRS total and motor scores significantly improved with treatment (WMD -2.39 (95% CI -3.58 to -1.20) and (WMD – 1.74 (95% CI -2.57 to -0.92) respectively (no heterogeneity was observed between the studies for these comparsions). There was no significant difference between groups in the change of MMSE scores or leaving the study early. **Clozapine (mean 26 mg) vs. quetiapine (mean 91 mg)**: One 12-week trial with 40	Low

				patients reported no significant difference between the two groups for clinical efficacy (CGI; BPRS) and motor functioning (UPDRS; AIMS). There was also no significant difference between groups in the frequency of adverse events. **Quetiapine vs. placebo:** Two 12-week trials compared quetiapine mean 169.1 mg and mean 123.3 mg) vs. placebo. Both reported no significant difference in efficacy or safety between groups. **Olanzapine vs. placebo:** Two 4-week trials compared olanzapine (mean 4.1 mg and mean 4.2 mg) vs. placebo. Significantly more patients in the olanzapine treatment group left the study early due to adverse events compared with placebo group: RR 7.18 (95% CI 1.76 to 29.24). No significant difference between groups was found for clinical efficacy using the CGI score and BPRS total scores – and also MMSE. Treatment with olanzapine lead to a significant worsening of Parkinson symptoms (UPDRS total, motor score and ADL: SMD 0.59 (95% CI 0.40 to 0.78).	

Randomised controlled trials

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Breier et al. (2002)	P: Patients with idiopathic Parkinson's disease experiencing treatment-associated psychosis as defined by DSM-IV who have been responsive to dopamimetics for motor symptoms, experienced hallucinations, delusion or both in the 2-week period before entry. I: Olanzapine, initiated at 2.5 mg/day with 2.4mg/day increases allowed every 3 or 4 days up to the maximum dose of 15 mg/day. C: Placebo O: Primary outcome: Antipsychotic efficacy (positive symptoms cluster subscore BPRS); secondary outcomes: BPRS total and negative symptom cluster scores, and CGI-S for psychosis and NPI total and individual item subscore.	N = 160 (n=90 Olanzapine, n=70 Placebo)	Results were presented for a study conducted in the US (n=83), and a study conducted in Europe (n=77) (both used the same study methodology). After 4 weeks, olanzapine (mean 4.2 mg/day in the US study and mean 4.1 mg/day in the European study) did not significantly differ from placebo for any outcome measures evaluated: BPRS total – positive/negative; BPRS hallucinations; CGI-S psychosis; NPI total; NPI hallucinations; NPI delusions; MMSE). The authors noted that assessments of some motor functions were worse with olanzapine (UPDRS total and Motor and ADL scales) – although not significantly different from placebo. In the US study, participants in the olanzapine group showed that patients in the olanzapine group had significantly higher reported incidences of three COSTART terms, extrapyramidal syndrome (Olz, 24.4%; Pbo, 2.4%; p = .003), hallucinations (Olz, 24.4%; Pbo, 4.8%; p = .013), and increased salivation (Olz, 22.0%; Pbo, 4.8%; p = .026). In the European study, olanzapine treatment was not associated with a significantly higher incidence of any adverse event, relative to placebo.	Unclear
Cummings et al. (2014)	P: Adults (aged ≥40 years) with Parkinson's disease psychosis according to established diagnostic criteria consistent with UK Brain	N=199 (n=90 placebo, n=95	SAPS-SD scores at day 43 showed a significant improvement in psychosis in favour of pimavanserin: least square treatment change -3.06 (95% CI -4.91 to -1.20), p=0.0014.	Low

	Bank criteria lasting as least 1 year and psychotic symptoms that developed after Parkinson's disease diagnosis that were present for at least 1 month. MMSE score of ≥21 and no delirium. Conducted in USA and Canada. I: Pimavanserin 40 mg/day. C: Matched placebo. O: Primary outcome; Antipsychotic benefit (SAPS-PD) from baseline to day 43. Secondary outcomes; change by day 3 nm CGI-S and CGI-I scale scores, caregiver burden (CBS), sleep hygiene (SCOPA-NS, SCOPA-DS), Parkinson's disease rating (UPDRS II and III).	pimavanserin included in the analysis)	Pimavanserin also showed a significant benefit compared with placebo for the full 20 item SAPS-hallucinations plus delusions (H+D) scale (-3.37 (95% CI -5.40 to -1.35), p=0.0012), and on the separate hallucinations (-2.08 (95% CI -3.46 to –0.71), p=0.0032), and delusions (-1.16 (95% CI -2.22 to –0.10), p=0.0325) domains. Compared with placebo, patients in the pimavanserin group had greater improvements in investigator-assessed measures of antipsychotic benefit, including CGI-S (-0.58 (95% CI -0.92 to –0.25), p=0.0007) and CGI-I (-0.67 (95% CI -1.06 to –0.27), p=0.0011). There was no evidence of treatment-related impairment of motor function in either group. There were small non-significant improvements in motor performance in participants in both groups in terms of UPDRS II and III composite score (–1·69 in the pimavanserin group vs –1·40 in the placebo group; 95% CI –2·14 to 2·72) and individual UPDRS II scores (−0·88 vs −0·52; −0·66 to 1·24) and UPDRS III scores (−0·86 vs −0·80; −2·22 to 0·60). Eleven (11%) participants in the pimavanserin group and four (4%) patients in the placebo group had a serious adverse event. Ten patients in the pimavanserin group discontinued because of an adverse event compared with two in the placebo group. Six discontinuations in the pimavanserin group were for psychosis. Three deaths occurred (one in the placebo group from sudden cardiac death and two in the pimavanserin group from sepsis and septic shock); all were regarded as unrelated to the study drug.	

Ellis et al. (2000)	P: Men and women with a clinical diagnosis of idiopathic Parkinson's disease. All participants had levodopa-exacerbated psychosis not satisfactorily managed by levodopa dose reduction. Excluded if any other major concurrent illnesses were present. I: Risperidone, initiated at 0.5 mg/day and increased by 0.5 mg/day every week for 1 week until symptomatic improvement was achieved or intolerable side effects emerged. C: Clozapine, 12.5 mg at bedtime, gradually increased by 12.5 to 25mg every week for 1 month until symptomatic improvement was achieved or intolerable side effects emerged. O: Primary outcome measure; psychosis (BPRS). Secondary outcome; Parkinson's symptoms (motor section of UPDRS and quantitative electrophysiological test of tremor).	N=10 (n=5 risperidone, n=5 clozapine).	After 3 months, there was no significant difference between groups in the BPRS psychosis score, BPRS total score, or UPDRS motor score. In addition, there was no change in tremor frequency or amplitude in either treatment group. Three participants withdrew from the study due to adverse events (2 taking clozapine and 1 taking risperidone); two of these patients (1 in each group) experienced increased rigidity and incontinence of urine. The other patient developed neutropenia.	High (small sample size)
Merims et al. (2006)	P: Adults with advanced Parkinson's disease treated with levodopa, who experienced recent-onset, significant psychotic symptoms which required neuroleptic treatment. Mean age 71.8 years. I: Quetiapine, initiating 25 mg/day.	N=27 (n=14 clozapine, n=13 quetiapine)	After 22 weeks, there was no significant difference between treatment groups in clinical improvement (as assessed by the CGIC) and hallucination frequency (NPI scores); both groups showed significant improvements over time. There was a significant difference in reducing delusion frequency (NPI scores) in favour of clozapine (p=0.05). There were no significant changes in hallucination or delusion severity over	High (small sample size)

	Increased every 2 weeks by 25 mg/day to a maximum of 150 mg. C: Clozapine, initiating on 6.25 mg/day. Increased every 2 weeks by 12.5 mg/day and then to 25 mg, 50 mg. O: Clinical improvement (CGIC, NPI) delusions, hallucinations, adverse effects.		time in both treatment groups. In the clozapine group, I patient developed significant leukopenia and neutropenia, and 2 others had decreased leukocyte count. Sleepiness and fatigue were common adverse events in both groups.	
Morgante et al. (2004)	P: Adults with idiopathic Parkinson's disease and psychosis induced by antiparkinsonian drugs. A history of L-dopa or L-dopa plus dopamine agonist drug-induced psychosis of at least 3 weeks before study entry and a baseline score of ≥3 on hallucinations or delusions content of BPRS. I: Quetiapine, initiated on 6.25 mg/day tirated up to a maximum of 50 mg/day C: Clozapine, initiated on 25 mg/day tirated up to a maximum of 200 mg/day O: Severity of psychosis (BPRS, CGI-S), Parkinson symptoms (UPDRS III, AIMS).	N= 45 (n=20 Quetiapine, n=20 Clozapine)	After 12 weeks, there was no significant difference between treatment groups for BPRS total, BPRS 5-items, CGI-S, UPDRS III or AIMS. The authors stated that side effects were mild in both groups.	High
Pollak et al. (2004)	P: Adults suffering from idiopathic Parkinson's disease experiencing drug induced psychosis of at least 2 weeks duration. All had failed to respond to standard therapeutic management. Psychotic symptom score ≥4 for with hallucinations or delusions of the subscore on PANSS and >3.	N=60 (n=32 clozapine, n= 28 placebo).	This trial consisted of a 4 week randomised phase followed by a 12 week clozapine open period, plus a one month period after drug discontinuation. After the 4 week randomised phase, the mean scores on the CGI improved by 1.8 (SD 1.5) for the clozapine group compared with 0.6 (SD 1.1) for the placebo group (p = 0.001). The mean positive subscore of PANSS improved by 5.6 (SD	High

	I: Clozapine C:Placebo O: Psychiatric symptoms (CGI, PANSS).		3.9) for the clozapine group compared with 0.8 (SD 2.8) for the placebo group; $p < 0.0001$). There was no significant difference between groups for MMSE, total UPDRS, or motor UPDRS scores. Serious adverse events were reported in 4/32 patients in the clozapine group, and in 7/28 patients in the placebo group. Adverse events leading to withdrawal in the clozapine group included a patient with neutropenia and one with fracture. In the placebo group one patient withdrew due to syncope and one due to hypotension. Somnolence was more frequent in the clozapine treatment group, and Parkinson's also worsened in this group. There were 2 cases of transient cases of neutropenia with clozapine, but no agranulocytosis.	
Rabey et al. (2007)	P: Patients with Parkinson's disease (according to UK Parkinson's Society Brain Bank criteria) and psychosis, defined as the presence of severe visual or auditory hallucinations and/or delusions which significantly affect quality of life). I: Quetiapine, initiated at 12.5 mg/day, increased every 2-3 days as required, until symptoms cleared or side effects limited treatment. C: Placebo O: Primary outcomes; Change in psychotic symptoms (BPRS and CGIS). Secondary outcome; motor symptoms of Parkinson's disease (UPDRS), cognitive functioning	N=58 (n=30 Quetiapine, n=28 placebo).	After 12 weeks of treatment, there were no significant differences between groups for all parameters evaluated (motor UPDRS, BPRS, MMSE, the Hamilton Rating Scale for Depression (HAM-D), the Epworth Sleepiness Score (ESS), and the CGI-S). Somnolence was reported in 7 patients in the quetiapine group (2 of which stopped treatment due to somnolence) compared with 2 in the placebo group; symptomatic orthostatic hypotension occurred in 1 patient in the treatment group and headache in 1 patient also occurred in the treatment group.	Low

	(MMSE), mood (HAM-D) and daily somnolence (ESS).			
Shotbolt et al. (2009)	P: Patients with Parkinson's disease (according to UK Parkinson's Society Brain Bank criteria) and suffered from either hallucinations, suspiciousness, or delusions of a severity of >3/7 on BPRS. These symptoms must have been present for over 2 weeks. I: Quetipaine initiated at 25 mg/day for one week, 25 mg bd for week 2, 50 mg bd for week 3 with an optional increase to 50 mg am, 100 mg nocte if clinically indicated. C: Placebo O: Primary outcomes: Time to dropout (survival analysis) secondary outcomes; improvement in psychotic symptoms (UPDRS, BPRS, NPI and Baylor PD hallucination scale).	N=24 (n=11 quetiapine, n=13 placebo).	The mean dose of quetiapine was 72.7 mg. Due to small numbers and high drop-out rate, the authors stated that secondary measures were only analysed at 6 weeks: No significant differences were observed for any of the outcomes (BPRS, NPI, Baylor PD hallucination scale, and UPDRS) in either group. Three patients on quetiapine dropped out due to adverse events (drowsiness) and 3 patients also dropped out of the placebo group.	High (small sample size with a high drop-out [8 patients completed 12 weeks treatment])

Risk of Bias

Systematic reviews

Author (year)	Risk of Bias				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
Frieling et al. (2007)	☺	☺	☺	☺	☺

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
Breier et al. (2002)	?	?	☺	?	☺	?
Cummings et al. (2014)	☺	☺	☺	☺	☺	?
Ellis et al. (2000)	?	?	☺	☹	☹	?
Merims et al. (2006)	?	?	Open-label	☺	☹	?
Morgante et al. (2004)	?	?	Open-label	☺	☹	?
Pollak et al. (2004)	☺	☺	☺	?	☺	?
Rabey et al. (2007)	☺	☺	☺	?	☺	?
Shotbolt et al. (2009)	?	?	☺	?	☹	?

☺ Low Risk ☹ High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	Parkinson's disease AND psychosis	17	2
DARE	(neurolept* OR antipsychotic*) IN DARE 561 Delete 2 (Amisulpride* OR Chormethiazole* OR Clomethiazole* OR Distraneurin* OR Chlorpromazin* OR Aminazine* OR Chlorazine* OR Chlordelazine* OR Contomin* OR Fenactil* OR Largactil* OR Propaphenin* OR Thorazine* OR (Flupenthixol adj2 decanoate*) OR Emergil* OR Fluanxol* OR Flupentixol* OR alphaFlupenthixol* OR cisFlupenthixol*) IN DARE 123 Delete 3 (Fluphenazin* OR (Fluphenazine adj2 decanoate*) OR Flufenazin* OR (Fluphenazine adj2 Hydrochloride*) OR Lyogen* OR Prolixin* OR Haloperidol* OR Haldol* OR Levomepromazin* OR Levomeprazin* OR Levopromazine* OR Tisercin* OR Tizercine* OR Tizertsin* OR Methotrimeprazine* OR Loxapine* OR Loxapinsuccinate* OR Oxilapine* OR Cloxazepine* OR (Loxapine adj2 Monohydrochloride*)) IN DARE 192 Delete 4 ((Loxipine adj2 Maleate*) OR (Loxipine adj2 Succinate*) OR Loxitane* OR Asendin* OR Desmethylloxapine* OR Amoxapine* OR Olanzapine* OR Perphenazine* OR Chlorpiprazine* OR Perfenazine* OR Trilafonor* OR Pimozide* OR Prothipendyl* OR Quetiapine* OR Fumarate* OR Risperidone* OR Risperidal* OR Sulpiride* OR Dogmatil* OR Eglonyl* OR Sulperide* OR Thioridazine* OR Meleril* OR Mellaril* OR Melleril* OR Melleryl* OR Sonapax* OR (Thioridazine adj2 Hydrochloride*) OR Tiaprid* OR Tiapridal* OR (Trifluoperazine adj2 Hydrochloride*) OR Trifluoroperazine* OR Triftazin* OR Stelazine* OR Trifluperazine*) IN DARE 318 Delete 5 ((Tripfluoperazine adj2 hydrochloride*) OR Cisordinol* OR Zuclopenthixol* OR Clopenthixol*) IN DARE 22 Delete 6 MeSH DESCRIPTOR Antipsychotic Agents EXPLODE ALL TREES 555 Delete 7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 900 Delete 8 (parkinson*) IN DARE 273 Delete 9 MeSH DESCRIPTOR Parkinson Disease EXPLODE ALL TREES 206 Delete 10 MeSH DESCRIPTOR Parkinsonian Disorders EXPLODE ALL TREES 216 Delete	37	1

	11 #8 OR #9 OR #10 369 Delete 12 #7 AND #11		
Primary studies			
CENTRAL	earch Hits #1 MeSH descriptor: [Psychotic Disorders] explode all trees 1464 #2 MeSH descriptor: [Schizophrenia and Disorders with Psychotic Features] explode all trees 5549 #3 #1 or #2 5549 #4 MeSH descriptor: [Parkinson Disease] explode all trees 2147 #5 #3 and #4 44 #6 MeSH descriptor: [Antipsychotic Agents] explode all trees 3653 #7 neuroleptics 965 #8 clozapine 1196 #9 #6 or #7 or #8 4871 #10 #5 and #9 22 Central only 20	20	
PsycINFO	1. PsycINFO; exp PSYCHOSIS/; 90403 results. 2. PsycINFO; PARKINSON'S DISEASE/; 13517 results. 3. PsycINFO; 1 AND 2; 410 results. 4. PsycINFO; exp NEUROLEPTIC DRUGS/; 24896 results. 5. PsycINFO; antipsychotic*.ti,ab; 20339 results. 6. PsycINFO; clozapine.ti,ab; 6154 results. 7. PsycINFO; 4 OR 5 OR 6; 32202 results. 8. PsycINFO; ("parkinson's disease" adj3 psychosis).ti,ab; 118 results. 9. PsycINFO; 3 OR 8; 438 results. 10. PsycINFO; 7 AND 9; 185 results. 11. PsycINFO; CLINICAL TRIALS/; 7349 results. 12. PsycINFO; random*.ti,ab; 126950 results. 13. PsycINFO; groups.ti,ab; 361016 results.	53	

	14. PsycINFO; (double adj3 blind).ti,ab; 17657 results. 15. PsycINFO; (single adj3 blind).ti,ab; 1381 results. 16. PsycINFO; EXPERIMENTAL DESIGN/; 8959 results. 17. PsycINFO; controlled.ti,ab; 79049 results. 18. PsycINFO; (clinical adj3 study).ti,ab; 7768 results. 19. PsycINFO; trial.ti,ab; 66889 results. 20. PsycINFO; "treatment outcome clinical trial".md; 26186 results. 21. PsycINFO; 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20; 558256 results. 22. PsycINFO; 10 AND 21; 53 results.		
Embase	1. EMBASE; exp PSYCHOSIS/; 201249 results. 2. EMBASE; PARKINSON DISEASE/ OR PARKINSON DISEASE, SECONDARY/; 89661 results. 3. EMBASE; ("parkinson* disease" adj3 psychosis).ti,ab; 295 results. 4. EMBASE; antipsychotic.ti,ab; 27692 results. 5. EMBASE; NEUROLEPTIC AGENT/ OR exp ATYPICAL ANTIPSYCHOTIC AGENT/; 104487 results. 6. EMBASE; clozapine.ti,ab; 11046 results. 7. EMBASE; 1 AND 2; 6773 results. 8. EMBASE; 3 OR 7; 6806 results. 9. EMBASE; 4 OR 5 OR 6; 110045 results. 10. EMBASE; 8 AND 9; 2127 results. 11. EMBASE; random*.ti,ab; 848203 results. 12. EMBASE; factorial*.ti,ab; 22143 results. 13. EMBASE; (crossover* OR cross-over*).ti,ab; 66790 results. 14. EMBASE; placebo*.ti,ab; 192048 results. 15. EMBASE; (doubl* ADJ blind*).ti,ab; 137240 results. 16. EMBASE; (singl* ADJ blind*).ti,ab; 13808 results. 17. EMBASE; assign*.ti,ab; 230037 results. 18. EMBASE; allocat*.ti,ab; 80028 results. 19. EMBASE; volunteer*.ti,ab; 170847 results. 20. EMBASE; CROSSOVER PROCEDURE/; 38055 results.	226	

	21. EMBASE; DOUBLE BLIND PROCEDURE/; 111871 results. 22. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 336876 results. 23. EMBASE; SINGLE BLIND PROCEDURE/; 17910 results. 24. EMBASE; 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23; 1359316 results. 25. EMBASE; 10 AND 24; 226 results.		
Medline	1. MEDLINE; SCHIZOPHRENIA/ OR exp PSYCHOTIC DISORDERS/; 109365 results. 2. MEDLINE; PARKINSON DISEASE/ OR PARKINSON DISEASE, SECONDARY/; 50068 results. 3. MEDLINE; ("parkinson's disease" adj3 psychosis).ti,ab; 179 results. 4. MEDLINE; 1 AND 2; 1231 results. 5. MEDLINE; 3 OR 4; 1293 results. 6. MEDLINE; ANTIPSYCHOTIC AGENTS/; 40770 results. 7. MEDLINE; neuroleptic*.ti,ab; 18144 results. 8. MEDLINE; clozapine.ti,ab; 8773 results. 9. MEDLINE; 6 OR 7; 50342 results. 10. MEDLINE; 5 AND 9; 499 results. 11. MEDLINE; "randomized controlled trial".pt; 366903 results. 12. MEDLINE; "controlled clinical trial".pt; 87837 results. 13. MEDLINE; randomized.ab; 286777 results. 14. MEDLINE; placebo.ab; 151417 results. 15. MEDLINE; "drug therapy".fs; 1674296 results. 16. MEDLINE; randomly.ab; 208083 results. 17. MEDLINE; trial.ab; 297029 results. 18. MEDLINE; groups.ab; 1328420 results. 19. MEDLINE; 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18; 3280118 results. 20. MEDLINE; 10 AND 19; 453 results.	453	
Summary	**NA**	**NA**	

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