Best Evidence Summaries of Topics in Mental Healthcare

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

Question

In adults with psychosis, how effective is Paliperidone in managing psychosis and reducing psychotic symptoms?

Clarification of question using PICO structure (PICTRO for diagnostic questions)

Patients: Adults with psychosis.
Intervention: Paliperidone.
Comparator: Any other pharmacological intervention.
Outcome: Reduction in psychotic symptoms.

Clinical and research implications

The studies included in this evidence summary indicate no clear differences between the effectiveness of oral paliperidone and other psychotropic medications (risperidone, olanzapine and quetiapine) in reducing psychotic symptoms in patients with schizophrenia. Evidence from two RCTs included in a systematic review also indicated no significant difference between the effectiveness of palperidone palmitate injection and long-acting risperidone injection in reducing psychotic symptoms in patients with schizophrenia. There was some evidence, from one RCT, that paliperidone may be more effective than quetiapine in reducing psychotic symptoms in the very short term (2 weeks) in patients with schizophrenia, who are experiencing acute exacerbations. A systematic review of adverse effects indicated that the adverse effects most frequently experienced by patients treated with paliperidone are extra-pyramidal symptoms, headache, insomnia, somnolence, tachycardia and weight gain.

Further research is needed to fully elucidate the comparative effectiveness of paliperidone and other anti-psychotic medications in reducing psychotic symptoms in adults. In particular a wider range of comparisons is needed and studies should include patients with psychotic symptoms arising from conditions other than schizophrenia (e.g. bipolar disorder).

What does the evidence say?

Number of included studies/reviews (number of participants)

We identified two systematic reviews[2,3] and two additional RCTs,[4,5] which fully met the inclusion criteria for this evidence summary. One additional systematic review, which did not strictly meet inclusion criteria because it did not compare paliperidone with another pharmacological antipsychotic treatment, was included for additional information; this review used data from 15 randomised, placebo-controlled trials, mainly conducted in adults with schizophrenia, to assess the adverse event profile of paliperidone.[1] The two remaining systematic reviews assessed the effectiveness of oral paliperidone[2] and paliperidone palmitate injections,[3] in adults with schizophrenia. Both reviews included both placebo-controlled RCTs and RCTs with an active antipsychotic comparator.[2,3] One RCT compared extended release paliperidone with quetiapine in patients with schizophrenia who were experiencing acute exacerbation.[4] The second RCT compared extended release paliperidone with continuation of risperidone in patients with schizophrenia who were receiving a stable dose of risperidone prior to the study.[5]

Main Findings

One systematic review reported data on the short term (< 12 weeks) effectiveness of oral paliperidone compared with various other antipsychotic medications.[2] This review found no statistically significant difference in risk of recurrence of psychotic symptoms or total positive and negative syndrome scale (PANSS) score between paliperidone and olanzapine (3 studies, n = 715).[2] The same review also found no significant difference in risk of recurrence of psychotic symptoms between paliperidone and risperidone (1 study, n = 113), or between paliperidone and quetiapine (1 study, n = 317).[2] However, a significant improvement in mean change in PANSS score was observed for paliperidone treatment compared with quetiapine (mean difference -4.60 (95% CI: -5.02 to -4.18), based on 1 study (n = 317).[2] The second systematic review assessed the effectiveness of paliperidone palmitate injections.[3] Only 2 of the 7 RCTs included in this review had an active antipsychotic comparator (n = 1,969); both of these studies compared flexibly dosed, gluteal administration of palperidone palmitate with flexibly dosed, long-acting, gluteal injection of risperidone.[3] Data from these two studies indicated no statistically significant differences, in risk of recurrence of psychotic symptoms, total PANSS score, or the severity scale of the clinical global impressions score (CGI-S), between the two treatment groups.[3] The systematic review of the adverse event profile of paliperidone found that the adverse events with the highest incidence were extra-pyramidal symptoms (23%), headache (14%), insomnia (11%), somnolence (9%), tachycardia (9%) and weight gain (8%).[1] The RCT, which compared extended release paliperidone with quetiapine in patients with schizophrenia, who were experiencing acute exacerbation, (n = 319 for this comparison) found significantly greater improvements in total PANSS score (between group least squares mean difference in change -6.7 ± 1.6, $p < 0.001$), CGI-S (between group least squares mean difference in change -0.3 ± 0.1, $p = 0.002$) and the change scale of CGI (between group least squares mean difference in change scores -0.4 ± 0.1, $p = 0.002$) for the extended release paliperidone group after two weeks of mono-therapy; however, these differences were not continued after a four week extension phase where additional therapies were allowed.[4] The second RCT, which compared extended release paliperidone with continuation of risperidone in patients with schizophrenia, who were receiving a stable dose of risperidone prior to the study, found no statistically significant difference in mean change in total PANSS score, or in the positive, negative or general psychopathology sub-scores, between the two treatments.[5]

Authors Conclusions

One systematic review concluded that, in patients with schizophrenia, flexibly dosed oral paliperidone had comparable efficacy to other psychotropics (data were for respiridone, olanzapine and quetiapine).[2] A second systematic review concluded that, in patients with schizophrenia, paliperidone palmitate appeared to have comparable short-term efficacy and tolerability to long-acting risperidone injections.[3] A systematic review of the adverse event profile of paliperidone concluded that paliperidone treatment was associated with a 50% reduction in treatment emergent psychosis in schizophrenic patients, compared with placebo, however the reduction of a psychotic event was approximately equal to the occurrence of an adverse event with paliperidone.[1] One RCT concluded that treatment with extended release paliperidone improved symptoms earlier and to a greater degree than quetiapine release in patients with recently exacerbated schizophrenia requiring hospitalization, with no unexpected tolerability findings.[4] A second RCT concluded that switching from risperidone to extended release paliperidone may lead to additional cognitive and social functional improvements; this study did not draw any conclusions with respect to changes in psychotic symptoms.[5]

Reliability of conclusions/Strength of evidence

One high quality Cochrane systematic review found no substantive differences in the effectiveness of oral paliperidone and other psychotropics (risperidone, olanzapine, and quetiapine) in reducing psychotic symptoms in patients with schizophrenia; there was some evidence, from one included RCT, suggesting a greater improvement in PANSS score for patients treated with paliperidone than for those treated with quetiapine.[2] These data were supported by one additional, small, poor quality RCT, which also found no significant difference in PANSS score between paliperidone and risperidone.[5] A second RCT, of resonable methodological quality, suggested that paliperidone may be associated with greater improvements in psychotic symptoms than quetiapine, in the very short term (2 weeks), in patients with schizophrenia, who were experiencing acute exacerbations.[4] A second, high quality Cochrane systematic review included two RCTs which indicated no significant differences in psychotic symptoms between patients with schizophrenia who were treated with palperidone palmitate injection compared with those who were treated with long-acting injection of risperidone.[3]

What do guidelines say?

NICE (2010) pp.229

"Zotepine is associated with lowest costs and highest benefits (QALYs) and consequently dominates all other treatment options. It can be seen that paliperidone and olanzapine dominate all drugs except zotepine; therefore, if zotepine is not an option for the treatment of people with schizophrenia that is in remission, then the decision (solely in terms of cost-effectiveness) would have to be made between paliperidone and olanzapine."

The above recommendation from NICE guidelines is based solely on cost-effectiveness analyses and is not contradicted by the data included in this evidence summary, which indicate no clear differences in clinical effectiveness.

Date question received: 12.04.13
Date searches conducted: 15.04.2013
Date answer completed: 29.04.2013

References;

Guidelines

National Institute for Health and Care Excellence (2010) Schizophrenia. Core interventions in the treatmenr and management of schizophrenia in adults in primary and secondary care (updated edition). CG82. London: National Institute for Health and Care Excellence. http://www.nice.org.uk/nicemedia/live/11786/43607/43607.pdf

SRs

1. Harrington, C.A. and English, C. (2010) Tolerability of paliperidone: a meta-analysis of randomized, controlled trials. *International Clinical Psychopharmacology* 25 (**6**)

2. Nussbaum, A.M. and Stroup, T.S. (2008) Oral paliperidone for schizophrenia. *Cochrane Database of Systematic Reviews* 2.

3. Nussbaum, A.M. and Stroup, T.S. (2012) Paliperidone palmitate for schizophrenia. *Cochrane Database of Systematic Reviews* 6.

RCTs

4. Canuso, C.M., Dirks, B., Carothers, J., Kosik-Gonzalez, C., Bossie, C.A., Zhu, Y., Damaraju, C.V., Kalali, A.H. and Mahmoud, R. (2009) Randomized, Double-Blind, Placebo-Controlled Study of Paliperidone Extended-Release and Quetiapine in Inpatients With Recently Exacerbated Schizophrenia. *American Journal of Psychiatry 166* pp. 691–701

5. Kim, S.W., Chung, Y.C., Lee, Y.H., Lee, J.H., Kim, S.Y., Bae, K.Y., Kim, J.M., Shin, I.S. and Yoon, J.S. (2012) Paliperidone ER versus risperidone for neurocognitive function in patients with schizophrenia: a randomized, open-label, controlled trial. *International Clinical Psychopharmacology 27* (**5**)

Results

Systematic Reviews

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Harrington and English (2010)	03/10/2010	*Patients:* RCTs in adults were included if they reported population sizes and incidence of adverse events in both the intervention and placebo arms. *Intervention:* Oral paliperidone. *Comparator:* Placebo *Outcome:* Treatment emergent adverse events (TEAEs).	15 (n = 3,779)	The aim of this review was to assess the adverse effect profile of the atypical antipsychotic, paliperidone. The review does not match the PICOS criteria for this evidence summary since it did not compare paliperidone with another pharmacological antipsychotic treatment and did not include psychotic symptoms as an outcome. However, a summary is included for additional information. Fifteen RCTs, with a total of 3,779 (range 42 to 1,318) participants were included in the review. Most studies were conducted with acute schizophrenic populations, two were for prevention in chronic schizophrenia and two were for schizoaffective disease. One study included only older adults. Two unpublished studies examined treatment of Bipolar I disorder. No further details of study participants were reported. Paliperidone doses ranged from 1.5 to 15mg per day and study durations ranged from 2 to 6 weeks (12 of the 15 studies were	The research question was clearly reported and appropriate inclusion criteria were defined. Two bibliographic databases were searched and un-published trial data were sought. However, the restriction to English language publications may have resulted in omission of relevant data. No measures to minimise error and bias in the review

				conducted over 6 weeks). Most studies required pre-study discontinuation of all medications. A variety of concomitant medications were allowed for treatment of adverse effects. Antidepressants were usually not discontinued if dosing was stable and long term (>3 months). Adverse events with the highest incidence in the paliperidone population were: any treatment-emergent adverse event (68%); extra-pyramidal symptoms (23%); headache (14%); insomnia (11%); somnolence (9%); tachycardia (9%); weight gain (8%). The risk difference, or AR, for an adverse event is defined as incidence in the treatment group minus incidence in the placebo group. The most highly drug-related adverse events were: extra-pyramidal symptoms (AR=10); any treatment-emergent adverse event (AR=6); tachycardia (AR=4); weight gain at least 7% of baseline (AR=4). Adverse events which occurred only in the paliperidone group were hypersalivation (3), dysarthria (2), and sexual dysfunction (1). The review also reported a meta-analysis of treatment benefit (reduction in emergent	process (e.g. study selection/data extraction by two reviewers, or a checking process) were reported. No assessment of the methodological quality of included studies was reported. The meta-analytic methods described were broadly appropriate.

				psychotic events) for patients with schizophrenia, which showed a recuction of approximately 50% associated with paliperidone treatment (RR 0.50 (95% CI: 0.34 to 0.72)), 5 studies (n = 1,203).	
Nussbaum and Stroup (2008)	12/2006 updated 11/2008	*Patients:* People diagnosed with schizophrenia or schizophrenia-like illnesses, diagnosed by any criteria, irrespective of age or gender. *Intervention:* Paliperidone (trade name Invega), of any dose, by either oral or intramuscular administration, either alone or as an adjunct or augmenting agent. *Comparator:* Placebo, alternative psychotropic agent, of any dose or route of administration, either alone or as an adjunct or augmenting agent, or other methods of treatment. *Outcome:* Primary outcomes; global state, relapse (recurrence of psychotic symptoms), no clinically important change in global state (as defined by individual studies), discontinuation of treatment or leaving the study early. (Secondary outcomes can be found on page 4 of the research article). Authors grouped outcomes by duration of treatment into short term (up to 12 weeks), medium term (13 to 26 weeks), and long term (over 26 weeks).	8 (n = 2,567)	This review aimed to compare effects of oral paliperidone with any other treatment for people with schizophrenia and schizophrenia-like illnesses. Eight RCTs, with a total of 2,567 (range 42 to 630) participants were included in the review. All study participants had a diagnosis of schizophrenia. Most studies were conducted in adults (>18 years); mean age, where reported, ranged from 33 to 42 years and between 52% and 68% of participants were male. One study included only older adults (>65 years); mean age 70 years and 27% of participants were male. Study settings were mainly 'hospital followed by out-patients'; one study was conducted solely in a hospital setting. All studies assessed the effectiveness of oral paliperidone; doses ranged from 3 to 15 mg per day. Comparators varied between studies and included risperidone (4 mg per day), olanzapine (10 mg per day), quetiapine (mean dose 690.1 mg per day), and placebo.	A clear research question was reported and inclusion criteria were described. The stated aim of the review was to assess the effectiveness of oral paliperidone, but studies of intramuscular injection were also eligible for inclusion; all included studies were of oral paliperidone. Studies were identified by searching the Cochrane Schizophrena Group's Specialised

				Most studies were conducted over six weeks; durations ranged from 14 days to 6 weeks + a 29 week open label phase. The review assessed a large number of outcome measures; summarised below are those data which directly rate to the PICOS criteria for this evidence summary (i.e. comparison of psychotic symptoms in paliperidone versus another pharmacological antipsychoric treatment). Paliperidone (any dose or flexible doses) versus olanzapine (10 mg/day), short term (≤ 12 weeks): There was no statistically significant difference in the risk of relapse (recurrence of psychotic symptoms) between the two treatment groups, based on 3 studies (n = 1,327); this remained the case for increasing doses of paliperidone. There was no significant difference in mean change in positive and negative syndrome scale (PANSS) score between the two treatments, based on 3 studies (n = 715). Paliperidone (any dose or flexible doses) versus risperidone (fixed dose), short term (≤ 12 weeks): There was no statistically significant	Register, supplemented by reference screening and contact with study authors and pharmaceutical companies. The review process (study selection, data extraction and assessment of the methodological quality of included studies) was done, independently, by two reviewers, to minimise the potential for error and/or bias. The methodological quality of included studies was assessed according to methods described in the Cochrane Handbook.

				difference in the risk of relapse (recurrence of psychotic symptoms) between the two treatment groups, based on 1 study (n = 113). Paliperidone (any dose or flexible doses) versus quetiapine (flexible dose), short term (≤ 12 weeks): There was no statistically significant difference in the risk of relapse (recurrence of psychotic symptoms) between the two treatment groups, based on 1 study (n = 317). The same study indicated a significant improvement in mean change in PANSS score associated with paliperidone treatment (mean difference -4.60 (95% CI: -5.02 to -4.18). The majority of included studies were judged to be at high risk of bias with respect to selective outcome reporting and blinding was not reported in most studies.	Appropriate meta-analytic methods were used.
Nussbaum and Stroup (2012)	11/2009	*Patients:* People diagnosed with schizophrenia or schizophrenia-like illnesses, diagnosed by any criteria, irrespective of age or gender. *Intervention:* Paliperidone palmitate (any dose, deltoid or gluteal administration, alone or as an adjunct or augmenting agent). *Comparator:* Placebo, alternative psychotropic agent (any dose or route of administration,	7 (n = 4,184)	This review aimed to compare the effects of paliperidone palmitate with any other treatment for people with schizophrenia and schizophrenia-like illnesses. Five RCTs, with a total of 4,184 (range 247 to 1,220) participants were included in the	The research question was clearly reported and appropriate inclusion criteria were defined.

		alone or as an adjunct or augmenting agent), or other methods of treatment. *Outcome:* Primary outcomes; global state, discontinuation of treatment or leaving the study early. (Secondary outcomes can be found on page 7 of the research article). Authors grouped outcomes by duration of treatment into short-term (up to 12 weeks), medium-term (13 to 26 weeks), and long-term (over 26 weeks).		review. However, only two studies (n = 1,969) compared paliperidone palmitate with an alternative antipsychotic and hence were relevant to this evidence summary. Both studies were conducted in participants with a DSM-IV diagnosis of schizophrenia. The mean ages of study participants were 40.7 and 39.2 years and approximately 58% of all participants were male. Both studies were conducted in out-patient settings with hospitalisation at the investigators' discretion. Study durations were 53 weeks and 13 weeks. Both studies compared flexibly dosed, gluteal administration of palperidone palmitate with flexibly dosed, long-acting injection of risperidone (gluteal administration. The mean doses of palperidone palmitate were 73.3 ± 21.9 mg and 104.5 ± 30.5 mg, and the mean doses of risperidone were 35.3 ± 10.3 mg and 31.7 ± 9.3 mg. The review assessed a large number of outcome measures; summarised below are those data which directly rate to the PICOS criteria for this evidence summary (i.e.	Studies were identified by searching the Cochrane Schizophrena Group's Specialised Register, supplemented by reference screening and contact with study authors, the FDA and pharmaceutical companies. The review process (study selection, data extraction and assessment of the methodological quality of included studies) was done, independently, by two reviewers, to minimise the potential for error and/or bias. The methodological quality of included

				comparison of psychotic symptoms in paliperidone palmitate versus another pharmacological antipsychoric treatment). Paliperidone palmitate (any dose or flexible doses) versus risperidone (long-acting injection): There was no statistically significant difference in the risk of relapse (recurrence of psychotic symptoms) between the two treatment groups, based on 2 studies (n = 1,961). There was no significant difference in mean change in PANSS score between the two treatments, based on 2 studies (n = 1,335). There was no significant difference in mean change in clinical global impression (severity) (CGI-S) score between the two treatments, based on 2 studies (n = 1,587). One study was rated as high risk of bias for incomplete outcome data and the other was rated as high risk of bias for incomplete outcome data and selective reporting. All other specific criteria were rated as low risk of bias; both studies were rated as unclear for un-specified other sources of bias.	studies was assessed according to methods described in the Cochrane Handbook. Appropriate meta-analytic methods were used.

RCTs

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Canuso et al. (2009)	*Patients:* Patients were 18 to 65 years of age and had a diagnosis of schizophrenia (paranoid, disorganized, or un-differentiated types) according to DSM-IV criteria and confirmed by the Mini-International Neuropsychiatric Interview–Plus Version. The trial was conducted in inpatient settings in India, Russia, the Ukraine, and the United States. Exclusion criteria were a DSM-IV axis I diagnosis (except for schizophrenia and substance abuse); an axis II diagnosis of mental retardation or borderline personality disorder; acute psychotic symptoms explained by substance use or medical illness; evidence for imminent risk of self-harm; a history of treatment resistance; treatment with quetiapine, paliperidone extended-release, or risperidone for 7 or more days prior to assessment for study entry; sensitivity to paliperidone extended-release, risperidone, or quetiapine; depot antipsychotic treatment within one cycle before baseline; and ECT within 3 months of entry. *Intervention:* At baseline (day 0), participants discontinued all	n = 394 (paliperidone extended-release, n = 160, quetiapine, n = 159, placebo, n = 80)	This study aimed to compare the short-term efficacy and safety of paliperidone extended-release and quetiapine in hospitalised patients with a recent exacerbation. The study comprised a two week, randomised, double-blind, mono-therapy phase, followed by a four week additive-therapy phase. Participants had been experiencing an acute exacerbation for > 4 days and < 4 weeks and had symptom scores ≥4 (at least moderate) on at least two of the PANSS items of hostility, excitement, tension, uncooperativeness, and poor impulse control, and a total combined score ≥17 for these items. Patients had a score ≥5 (at least markedly ill) on the CGI-S scale and were hospitalised or required hospitalisation; all participants were hospitalised for a minimum of 10 days. There were no apparent differences in participant demographic characteristics or distribution of schizophrenia sub types between the three groups. Use of other psychotropic medications was prohibited during the monotherapy phase of the study, except for: injectable lorazepam, amobarbital sodium, or midazolam as needed for severe agitation or restlessness; zaleplon, zopiclone, or zolpidem for insomnia; and benztropine mesylate or equivalent treatments for movement disorders. During the additive-therapy phase, any psychotropic medication, including antipsychotics, was permitted, except for	Randomization was stratified by site in blocks of five, and assignments were made using an interactive voice response system. Allocation concealment was not described. All medication, including placebo, was presented as identical capsules. It was not clear whether outcome assessors were blind to treatment groups. Efficacy analyses were conducted on an intention-to-treat basis. Results were reported for all specified outcome measures.

	psychotropic medications. Paliperidone extended-release was initiated at 6 mg (days 1–3) and increased to 9 mg at day 4, with an optional increase to 12 mg at day 8. *Comparator:* Quetiapine or placebo. Quetiapine was initiated at 50 mg (day 1) and increased to 100 mg on day 2, 200 mg on day 3, 400 mg on day 4 and 600 mg on day 5, with an optional increase to 800 mg on day 8. *Outcome:* Efficacy was assessed by the PANSS, the severity and change scores of the Clinical Global Impressions scale (CGI-S and CGI-C, respectively) and a composite response measure (a PANSS total score reduction ≥30% and a CGI-C score of 1 or 2 [very much or much improved]).		risperidone, additional paliperidone extended-release, quetiapine, lithium, herbal medications with psycotropic effects and drugs that prolong the QTc interval. Completion rates for the mono-therapy phase were similar for the paliperidone extended-release (87.5%), quetiapine (84.9%), and placebo (82.5%) groups. At the end of the study (mono-therapy phase plus additive-therapy phase), the discontinuation rate was lower for paliperidone extended-release (21.5%) than for quetiapine (33.3%), p=0.036) and placebo (36.3%), p=0.032; it was similar for quetiapine and placebo. Mono-therapy phase: At the end of the 2 week mono-therapy phase, participants in the paliperidone extended-release group showed significantly greater improvement in PANSS scores than those in the quetiapine group (between group least squares mean difference in change -6.7 ± 1.6, $p < 0.001$); this difference was apparent from week 5 onwards. Participants in the paliperidone extended-release group also showed significantly greater improvements in CGI-S (between group least squares mean difference in change -0.3 ± 0.1, p = 0.002) and CGI-C (between group least squares mean difference in change scores -0.4 ± 0.1, p = 0.002) than those in the quetiapine group. Similar proportions of participants achieved a composite response (40.1% in the paliperidone extended-release group and 31.2% in the quetiapine group. Additive-therapy phase: No statistically significant differences between the paliperidone extended-release and the quetiapine group persisted at the end of the additive therapy phase.	

Hough et al. (2011)	**EXCLUDED – Does not report psychotic symptoms as an outcome measure**			
Kim et al. (2012)	*Patients:* In-patients and out-patients in Korea, aged 18–59 years who met the DMS-IV diagnostic criteria for schizophrenia and were receiving risperidone mono-therapy. Participants were required to be symptomatically stable, and have been receiving a stable dose of risperidone for a minimum of 2 weeks before enrollment. Exclusion criteria were acute psychotic symptoms (including severe behavioural disturbance, severe and unstable physical illnesses), or a diagnosis of mental retardation. *Intervention:* Paliperidone switch group, Risperidone was tapered off during the first 2 weeks of the study, while paliperidone was titrated simultaneously. It was recommended that paliperidone be prescribed once daily in the morning, and the dose of paliperidone was adjusted according to the clinical judgment of each research psychiatrist, in the range of 3–12 mg/day. *Comparator:* Risperidone-continuation group, in which they continued to receive risperidone. *Outcome:* Primary outcome - Computerized neurocognitive function test battery	n = 58 (paliperidone extended release, n = 32, risperidone, n = 26)	This study aimed to determine the effectiveness of paliperidone extended release on cognitive function in patients with schizophrenia in comparison with risperidone; secondary outcomes, relevant to this evidence summary, included the PANSS scale. The study was a 12-week, randomised, parallel-group, open-label, flexible-dose design. The mean age of study participants was 34.1 ± 8.3 years and 65.5% were male. The mean duration of illness was 9.1 ± 6.2 years. There were no significant differences between the two groups in terms of gender, age, years of education, duration of illness, or pre-study dose of Risperidone. The mean dose of trial medication at the last observation was 4.9 ± 2.8 mg/day for risperidone and 9.0 ± 2.7 mg/day for paliperidone. Five (19.2%) patients in the risperidone group and three (9.4%) patients in the paliperidone group did not complete the study; there was no significant difference in drop-outs between the two groups. There was no statistically significant difference in mean change in total PANSS score, or in the positive, negative, or general psychopathology sub-scores, between the two treatments.	Randomisation used computerized random number generator and was stratified by site; because of a “technical error”, two patients randomised to continue riperidone received paiparidone. Allocation concealment was not described. The study was open-label. Study participants were analysed according to the treatment received and one patient appeared to be missing from each group. Results were reported for all specified outcome measures.

	attention span and vigilance was measured using the Digit Span Test. Verbal memory (Rey auditory verbal learning test), Psychomotor speed and the degree of motor coordination (Finger Tapping Test Trail Making Test), global cognitive (mini-mental status examination) letter and category fluency, for verbal fluency, working memory, and cognitive speed (Controlled Oral Word Association Test). Secondary outcomes can be found on page 268 of the research article and included the PANSS scale.			

Risk of Bias: SRs

Author (year)	Risk of Bias				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
Harrington 2010	☺	☹	?	☹	☺
Nussbaum 2008	☺	☺	☺	☺	☺
Nussbaum 2012	☺	☺	☺	☺	☺

RCTs

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Canuso 2010	☺	?	☺	?	☺	☺
Hough 2011	**EXCLUDED – Does not report psychotic symptoms as an outcome measure**					
Kim 2012	☹	?	☹	☹	☹	☺

☺ Low Risk ☹ High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	Paliperidone	20	1
DARE	1 (paliperidone OR invega) IN DARE 12 2 (psychosis OR psychotic* OR schizo*) IN DARE 692 3 MeSH DESCRIPTOR Affective Disorders, Psychotic EXPLODE ALL TREES 129 4 MeSH DESCRIPTOR Psychotic Disorders EXPLODE ALL TREES 117 5 MeSH DESCRIPTOR Schizophrenia and Disorders with Psychotic Features EXPLODE ALL TREES 445 6 MeSH DESCRIPTOR Psychotic Disorders EXPLODE ALL TREES 117 7 MeSH DESCRIPTOR Psychotic Disorders EXPLODE ALL TREES 117 8 MeSH DESCRIPTOR Schizophrenia EXPLODE ALL TREES 372 9 MeSH DESCRIPTOR Schizophrenic Psychology EXPLODE ALL TREES 76 10 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 998 11 #1 AND #10 12	12	3
Primary studies			
CENTRAL	Paliperidone	56	
PsycINFO	1. PsycINFO; Paliperidone.ti,ab; 200 results. 2. PsycINFO; exp PSYCHOSIS/; 86457 results. 3. PsycINFO; (psychosis OR psychotic).ti,ab; 47038 results. 4. PsycINFO; exp SCHIZOPHRENIA/; 68163 results. 5. PsycINFO; schizo*.ti,ab; 94812 results. 6. PsycINFO; 2 OR 3 OR 4 OR 5; 129233 results. 7. PsycINFO; 1 AND 6; 152 results. 8. PsycINFO; "learning disab*".ti,ab; 18526 results. 9. PsycINFO; "learning difficult*".ti,ab; 3043 results. 10. PsycINFO; LEARNING DISABILITIES/; 18479 results. 11. PsycINFO; "intellectual disabilities".ti,ab; 3823 results.	152	

	12. PsycINFO; 8 OR 9 OR 10 OR 11; 27654 results. 13. PsycINFO; 7 AND 12; 0 results.		
Embase	14. EMBASE; Paliperidone.ti,ab; 708 results. 15. EMBASE; exp PSYCHOSIS/; 195412 results. 16. EMBASE; (psychosis OR psychotic).ti,ab; 51169 results. 17. EMBASE; exp SCHIZOPHRENIA/; 127352 results. 18. EMBASE; schizo*.ti,ab; 120989 results. 19. EMBASE; 15 OR 16 OR 17 OR 18; 228224 results. 20. EMBASE; 14 AND 19; 579 results. 21. EMBASE; "learning disab*".ti,ab; 8111 results. 22. EMBASE; "learning difficult*".ti,ab; 2187 results. 24. EMBASE; "intellectual disabilities".ti,ab; 2683 results. 27. EMBASE; INTELLECTUAL IMPAIRMENT/; 7773 results. 28. EMBASE; LEARNING DISORDER/; 20271 results. 29. EMBASE; 21 OR 22 OR 24 OR 27 OR 28; 30712 results. 30. EMBASE; 20 AND 29; 1 results. 31. EMBASE; 20 [Limit to: (Clinical Trials Clinical Trial or Randomized Controlled Trial or Controlled Clinical Trial or Multicenter Study or Phase 1 Clinical Trial or Phase 2 Clinical Trial or Phase 3 Clinical Trial or Phase 4 Clinical Trial)]; 157 results. 32. EMBASE; PALIPERIDONE/; 1536 results. 33. EMBASE; 14 OR 32; 1610 results. 34. EMBASE; 19 AND 33; 1189 results. 35. EMBASE; 29 AND 34; 6 results. 36. EMBASE; 34 [Limit to: (Clinical Trials Clinical Trial or Randomized Controlled Trial or Controlled Clinical Trial or Multicenter Study or Phase 1 Clinical Trial or Phase 2 Clinical Trial or Phase 3 Clinical Trial or Phase 4 Clinical Trial)]; 291 results.	290	
Medline	38. MEDLINE; Paliperidone.ti,ab; 331 results. 39. MEDLINE; exp PSYCHOSIS/; 36419 results. 40. MEDLINE; (psychosis OR psychotic).ti,ab; 37519 results. 41. MEDLINE; exp SCHIZOPHRENIA/; 80721 results. 42. MEDLINE; schizo*.ti,ab; 98211 results. 43. MEDLINE; 39 OR 40 OR 41 OR 42; 154668 results.	229	

	44. MEDLINE; 38 AND 43; 229 results.		
Summary	**NA**	**NA**	

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