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Best Evidence Summaries of Topics in Mental Healthcare

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

Question

For people identified as having experienced a first episode of psychosis (aged 14+), how effective is low dose anti-psychotic medication*, compared with standard dose anti-psychotic medication† in improving any patient outcomes?

Clarification of question using *PICO* structure

Patients:	People identified as having experienced a first episode of psychosis (aged 14+)
Intervention:	Low dose anti-psychotic medication*
Comparator:	Standard dose anti-psychotic medication†
Outcome:	Any patient outcomes

**Refers to any dose less than the defined daily dose by the World Health Organization*
† Refers to the defined daily dose by the World Health Organization

Email: awp.BESTinMH@nhs.net Phone: 0117 378 4232/4233/4335 @BESTinMH

Clinical and research implications

Weak evidence, from two randomised controlled trials included in a systematic review and one additional small randomised controlled trial, suggests that low dose anti-psychotic medication may be at least as effective as standard dose for treating people with first episode psychosis and that lower doses are associated with fewer extrapyramidal symptoms. The limited available evidence was for two specific drugs only, risperidone and haloperidol. Further studies are needed to confirm these effects and to explore the effectiveness of low doses of other antipsychotic medications.

What does the evidence say?

Number of included studies/reviews (number of participants)

We identified one systematic review and one additional randomised controlled trial (RCT) which reported data relevant to this evidence summary. The systematic review aimed to determine risperidone dose response relationships for schizophrenia and schizophrenia-like psychoses and included 11 RCTs.[1] However, only four of the included trials were conducted in people with first episode psychosis and only two of these reported comparisons and outcome data relevant to this evidence summary.[1] The addition RCT compared low dose to standard dose haloperidol in people with first episode psychosis.[2]

Main findings

The summary estimate from the two relevant studies included in the systematic review suggested that there was no difference, between the low (≥2 mg/d to <4 mg/d) and standard (≥4 mg/d to <6 mg/d) dose risperidone groups, in the number of participants experiencing no clinically significant short-term improvement.[1] One study reported data suggesting that low dose risperidone was associated with greater improvements in symptoms, in people with first episode psychosis, than standard dose risperidone (mean difference in endpoint total Positive and Negative Symptom Scale (PANSS) score 12.40 (95% CI: -17.01 to -7.79)).[1] Both studies reported data to suggest that low dose risperidone was associated with a reduction in extrapyramidal symptoms compared to standard dose.[1] The additional RCT found no significant differences in clinical symptoms (PANSS, Clinical Global Impression (CGI), and Calgary Depression Rating Scale) between low (2 mg/d) and standard (8 mg/d) doses of haloperidol, in people with first episode psychosis.[2] This study also found that the severity of extrapyramidal symptoms was significantly lower in the low dose group.[2]

Authors' conclusions

The authors of the systematic review concluded that there is weak evidence suggesting that low doses (≥2 to <4 mg/day) of risperidone may be of value for people in their first episode of illness, and that further research is need in this population.

The authors of the additional RCT concluded that a low dose of haloperidol is at least as effective as, and better tolerated than a high dose of haloperidol for the treatment of first-episode psychosis.

Reliability of conclusions/Strength of evidence

One high quality Cochrane systematic review and one additional RCT, which was generally well conducted but had some reporting weaknesses, found some limited evidence to suggest that low dose antipsychotics may be at least as effective as standard dose for treating people with first episode psychosis and that lower doses are associated with fewer extrapyramidal symptoms.

However, evidence was derived from only three studies and the authors of the additional RCT noted that their study was underpowered to detect differences in treatment effect. In addition, the available evidence relates to only two specific drugs: risperidone and haloperidol.

What do guidelines say?

The Scottish Intercollegiate Guidelines Network guidance, 'Management of Schizophrenia', provides the following advice regarding the effectiveness of low dose antipsychotic medication for people experiencing a first episode of psychosis:

"5.4.4. No meta-analyses or systematic reviews were identified around dose of antipsychotic for people in the first episode of psychosis. A Cochrane review of risperidone dose identified four trials of individuals in the first episode which reflect current dosage regimens. Doses of risperidone below 2 mg daily did not have any clinical effect due to participants leaving the study early, providing weak evidence to support a dosage regimen of 2-4 mg daily. An RCT identified by a meta-analysis compared risperidone with haloperidol and found that a mean risperidone dose of 3.3 mg daily was associated with remission from symptoms in three quarters of participants.

There is evidence that low doses of both [first generation antipsychotic medication] and [second generation antipsychotic medication] are effective in individuals in the first episode of schizophrenia. The biological sensitivity in first episode also relates to tolerability, and lower doses of the chosen medication may reduce the adverse effect burden.

Minimum effective dose of either first- or second-generation antipsychotics should be used in individuals in the first episode of schizophrenia." (p.14-15).

Date question received: 24/03/2015
Date searches conducted: 13/04/2015
Date answer completed: 20/04/2015

References

Systematic reviews

1. Li C, Xia J, Wang J. (2009). Risperidone dose for schizophrenia. *Cochrane Database of Systematic Reviews* 2009, *4*. Art. No.: CD007474. DOI: 10.1002/14651858.CD007474.pub2.

Randomised controlled trials

2. Oosthuizen, P., Emsley, R., Jadri Turner, H., & Keyter, N. (2004). A randomized, controlled comparison of the efficacy and tolerability of low and high doses of haloperidol in the treatment of first-episode psychosis. *The International Journal of Neuropsychopharmacology*, *7*(2), 125-131.

Guidelines

The Scottish Intercollegiate Guidelines Network guidance (2013). Management of Schizophrenia, *The Scottish Intercollegiate Guidelines Network guidance, SIGN 131* (p14-15). Accessed 17th April 2015 http://www.sign.ac.uk/pdf/sign131.pdf

Results

Systematic reviews

Author (year)	Search date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Li et al. (2009).	04/2015	*Participants*: People with schizophrenia and other schizophrenia-type psychoses (schizophreniform and schizoaffective disorders). *Intervention*: Risperidone in oral form (not depot). Doses were separated into: (i) Ultra-low (less than 2mg/day); (ii) Low (2mg/day to just below 4mg/day); Standard-lower (4mg/day to just below 6mg/day); Standard-high ((4mg/day to just below 10mg/day); High (10mg/day and greater). *Comparator*: Comparison between the above dose groups. *Outcomes*: Outcomes taken at: (i) Short-term (up to 12 weeks), (ii) medium-term (13-26 weeks) and (iii) long term (over 26 weeks) *Primary outcomes:* Global state- measured at short term. *Secondary outcomes:* Leaving the studies early;	Total, 11 (n=2498 participants) Four studies (n=327 participants) were conducted in people with first episode psychosis.	This systematic review aimed to determine risperidone dose response relationships for schizophrenia and schizophrenia-like psychoses. Only four of the studies included in this review were conducted in people with a first episode of psychosis. Of these, one study compared ultra-low dose risperidone (<2 mg/d) to low dose risperidone (3 to 4 mg/d), i.e. this study did not include a standard dose comparison. No clinically relevant outcomes were reported for a second study. The two remaining studies, Wei 2006 and Zhang 2004, (n=206) reported data for the primary outcome (number of participants experiencing no	The research question was clearly stated and appropriate inclusion criteria were defined. The Cochrane schizophrenia group trials register was searched for relevant studies, but major bibliographic databases were not searched directly. The bibliographies of identified articles and the website of the FDA were searched for additional studies, and pharmaceutic companies and study authors were also contacted. No restrictions on language or publication status

		Global state (beyond short-term); Relapse; Needing additional medication; Mental state (particularly positive & negative symptoms); Specific symptoms; General functioning; Specific aspects of functioning, such as social or life skills; General behaviour; specific aspects of behaviour; Quality of life/satisfaction with treatment; Cognitive functioning; Service use; Number of patients hospitalised; Time to hospitalisation; Adverse effects; Use of any drugs for adverse effects; Cost of care *Study design*: Randomised controlled trials (RCTs)		clinically important improvement in the short-term (≤12 weeks)). A summary estimate derived from these two studies showed no difference between low dose (≥2 mg/d to <4 mg/d) and standard dose (≥4 mg/d to <6 mg/d) risperidone; RR 1.06 (95% CI: 0.49 to 2.28). One study, Zhang 2004, (n=124), reported data suggesting that low dose risperidone (≥2 mg/d to <4 mg/d) was associated with improved symptoms of schizophrenia compared to standard dose (≥4 mg/d to <6 mg/d); mean difference in endpoint total PANSS score 12.40 (95% CI: -17.01 to -7.79). This effect remained statistically significant for both positive and negative symptom sub-scales. This study also reported that low dose risperidone was associated with reduced rate of extrapyramidal symptoms compared to standard dose; RR 0.44 (95% CI: 0.32 to 0.60). Wei 2006 (n=82) also reported data indicated that low dose risperidone	were reported. The review process included measures to minimise error/bias; two reviewers independently selected studies for inclusion and carried out data extraction and risk of bias assessments. The methodological quality of included studies was assessed using the Cochrane risk of bias tool. Where summary estimates were calculated the methods used were appropriate and heterogeneity was adequately explored.

				(≥2 mg/d to <4 mg/d) was associated with reduced extrapyramidal symptoms compared to standard dose (≥4 mg/d to <6 mg/d); mean endpoint TESS scores 2.19 versus 2.69 (p<0.05).	

Randomised controlled trials

Author (year)	**Inclusion criteria**	**Number of participants**	**Summary of results**	**Risk of bias**
Oosthu-izen et al. (2004)	*Participants*: Inpatients or outpatients aged 16-55 years with a DSM-IV diagnosis of schizophreinform disorder, schizophrenia or schizoaffective disorder, first episode of psychosis, and no more than 4 weeks' exposure to neuroleptic medication in their lifetime. Participants were excluded if also diagnosed with another DSM-IV condition, alcohol or drug dependence, depot antipsychotic treatment, significant medical illness or learning disabilities. *Intervention*: Haloperidol administered orally at low dose (2mg/day). *Comparator*: Haloperidol administered orally higher dose (8mg/day).	n=40	This study aimed to compare the effects of very low dose haloperidol to a standard dose, in people with first episode psychosis. 60% Of study participants were male, and the majority (78%) were white. The mean age of study participants was approximately 28 years, and the mean total PANSS score at baseline was approximately 98. There were no significant differences, in demographic characteristics or symptoms, between the treatment groups at baseline. Both study doses were associated with	No details of the randomisation procedure or allocation concealment were reported. The study was described as double-blind and treatments were appearance matched.

	Outcome: At weekly intervals over the course of six weeks, the following measures were administered: Positive and Negative Symptom Scale (PANSS), Clinical Global Impression (CGI), CGI-CIS, Calgary Depression Rating Scale and (Extrapyramidal Symptom Rating) ESRS. Blood samples for prolactin levels were taken at baseline and endpoint.		significant improvements in symptoms (change from baseline to endpoint in PANSS score). At the end of the study (week 6), there were no statistically significant differences between the groups for PANSS total or for the positive and negative subscales. Similarly there were no significant differences between the groups in mean CGI ratings at week six or depressive symptoms as rated by the Calgary Depression Rating Scale. Ratings on the Parkinsonism section of the EPRS were significantly lower in the 2mg/d group at week six (7.3±8.7) than in the 8 mg/d group (18.6±18.2); this effect reached statistical significance at week two and remained significant at all subsequent time points. Participants in the 8mg/d group had a significant increase in mean prolactin levels from baseline to endpoint (14.1±9.5 ng/mL to 51.4±34.8 ng/mL), whereas those in the 2 mg/d group had only a small, non-significant increase (14.1±10.1 ng/mL to 15.5±8.4 ng/mL).	It was not clear whether outcome assessors were blinded to treatment allocation. Analyses were conducted on an intention-to-treat basis, using last observation carried forward. 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
Li (2009)	☺	☺	☺	☺	☺

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
Oosthuizen (2004)	?	?	☺	?	☺	☺

☺ Low risk ☹ High risk ? Unclear risk

Search details

Source	Search Strategy	Number of hits	Relevant evidence identified
Guidelines			
NICE	Antipsychotic	45	1
Systematic Reviews			
DARE	1 MeSH DESCRIPTOR Schizophrenia EXPLODE ALL TREES 529 Delete 2 MeSH DESCRIPTOR Schizophrenia and Disorders with Psychotic Features EXPLODE ALL TREES 634 Delete 3 MeSH DESCRIPTOR Schizophrenia, Childhood EXPLODE ALL TREES 1 Delete 4 MeSH DESCRIPTOR Schizophrenia, Paranoid EXPLODE ALL TREES 1 Delete 5 MeSH DESCRIPTOR Paranoid Disorders EXPLODE ALL TREES 0 Delete 6 MeSH DESCRIPTOR Psychotic Disorders EXPLODE ALL TREES 158 Delete 7 (schizo* or psychotic* or psychosis or psychoses or hebephreni* or oligophreni*) IN DARE 822 Delete 8 ((First adj3 admission*) OR (first adj3 hospital*) OR (first adj3 episod*) OR (first adj3 breakdown*) OR (initial adj3 admission*) OR (initial adj3 hospital*) OR (initial adj3 episod*) OR (initial adj3 breakdown*) OR (primary adj3 admission*) OR (primary adj3 hospital*) OR (primary adj3 episod*) OR (primary adj3 breakdown*)) IN DARE 215 Delete 9 (Anti?pyschotic* OR Amisulpride OR Aripiprazole OR Asenapine OR Blonanserin OR Chlorpromazine OR Clotiapine OR Clozapine OR Droperidol OR Fluphenazine OR Haloperidol OR Iloperidone OR Levomepromazine OR Loxapine OR Lurasidone OR Mesoridazine OR Molindone OR Mosapramine OR Olanzapine OR Paliperidone OR Perospirone OR Perphenazine OR Pimozide OR Prochlorperazine OR Quetiapine OR Risperidone OR Sertindole OR Sulpiride OR Symbax OR Tetrabenazine OR Thioridazine OR Trifluoperazine OR Ziprasidone OR Zotepine OR Zuclopenthixol) IN DARE 495 Delete 10 MeSH DESCRIPTOR Antipsychotic Agents EXPLODE ALL TREES 705 Delete 11 ((Low-dos*) OR (Low dos*) OR (Small dos*) OR (reduced dos*)) IN DARE 686 Delete 12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 1107 Delete 13 #8 AND #12 40 Delete	4	1

	14 #9 OR #10 956 Delete 15 #11 AND #14 41 Delete 16 #13 AND #15 4 Delete		
Primary Studies			
MEDLINE	18. Medline; PSYCHOSIS/; 0 results. 19. Medline; "first episode".ti,ab; 8402 results. 20. Medline; "early intervention".ti,ab; 10180 results. 21. Medline; 19 OR 20; 18246 results. 22. Medline; 18 AND 21; 0 results. 23. Medline; (first adj3 psychosis).ti,ab; 2351 results. 24. Medline; (early adj3 psychosis).ti,ab; 1233 results. 25. Medline; 22 OR 23 OR 24; 3140 results. 26. Medline; "low dose".ti,ab; 72094 results. 27. Medline; "lower dose".ti,ab; 8058 results. 28. Medline; "standard dose".ti,ab; 5078 results. 29. Medline; DRUG DOSAGES/; 0 results. 30. Medline; 26 OR 27 OR 28 OR 29; 83562 results. 31. Medline; Antipsychotic*.ti,ab; 27816 results. 32. Medline; exp NEUROLEPTIC DRUGS/; 0 results. 33. Medline; 31 OR 32; 27816 results. 34. Medline; 25 AND 30 AND 33; 17 results. 35. Medline; PSYCHOTIC DISORDERS/; 32664 results. 36. Medline; 21 AND 35; 2014 results. 37. Medline; 23 OR 24 OR 36; 3558 results. 38. Medline; exp ANTIPSYCHOTIC AGENTS/; 103826 results. 39. Medline; 31 OR 38; 112321 results. 40. Medline; 30 AND 37 AND 39; 25 results. 43. Medline; randomized.ab; 310208 results. 44. Medline; placebo.ab; 157979 results. 45. Medline; randomly.ab; 224734 results. 46. Medline; trial.ab; 312657 results.	10	1

	47. Medline; groups.ab; 1412283 results. 48. Medline; "randomized controlled trial".pt; 385023 results. 49. Medline; "controlled clinical trial".pt; 88607 results. 50. Medline; 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49; 2050493 results. 51. Medline; 40 AND 50; 10 results.		
EMBASE	39. EMBASE; PSYCHOSIS/; 67094 results. 40. EMBASE; "first episode".ti,ab; 13338 results. 41. EMBASE; "early intervention".ti,ab; 14932 results. 42. EMBASE; 40 OR 41; 27501 results. 43. EMBASE; 39 AND 42; 5271 results. 44. EMBASE; (first adj3 psychosis).ti,ab; 4046 results. 45. EMBASE; (early adj3 psychosis).ti,ab; 2322 results. 46. EMBASE; 43 OR 44 OR 45; 6891 results. 47. EMBASE; "low dose".ti,ab; 94842 results. 48. EMBASE; "lower dose".ti,ab; 10479 results. 49. EMBASE; "standard dose".ti,ab; 7504 results. 50. EMBASE; DRUG DOSAGES/; 0 results. 51. EMBASE; 47 OR 48 OR 49 OR 50; 110322 results. 52. EMBASE; Antipsychotic*.ti,ab; 41086 results. 53. EMBASE; exp NEUROLEPTIC DRUGS/; 0 results. 54. EMBASE; 52 OR 53; 41086 results. 55. EMBASE; 46 AND 51 AND 54; 38 results. 56. EMBASE; PSYCHOSIS/; 67094 results. 57. EMBASE; DRUG DOSAGES/; 0 results. 58. EMBASE; exp NEUROLEPTIC DRUGS/; 0 results. 59. EMBASE; PSYCHOTIC DISORDERS/; 60351 results. 60. EMBASE; exp ANTIPSYCHOTIC AGENTS/; 208806 results. 62. EMBASE; 46 OR 59; 62260 results. 63. EMBASE; 42 AND 59; 4143 results.	9	1

	64. EMBASE; 46 OR 63; 6897 results. 65. EMBASE; 52 OR 60; 214651 results. 66. EMBASE; 51 AND 64 AND 65; 48 results. 67. EMBASE; random*.ti,ab; 955490 results. 68. EMBASE; factorial*.ti,ab; 24641 results. 69. EMBASE; (crossover* OR cross-over*).ti,ab; 72786 results. 70. EMBASE; placebo*.ti,ab; 211184 results. 71. EMBASE; (doubl* ADJ blind*).ti,ab; 148870 results. 72. EMBASE; (singl* ADJ blind*).ti,ab; 15504 results. 73. EMBASE; assign*.ti,ab; 255675 results. 74. EMBASE; allocat*.ti,ab; 90834 results. 75. EMBASE; volunteer*.ti,ab; 185287 results. 76. EMBASE; CROSSOVER PROCEDURE/; 42210 results. 77. EMBASE; DOUBLE BLIND PROCEDURE/; 119287 results. 78. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 366567 results. 79. EMBASE; SINGLE BLIND PROCEDURE/; 19913 results. 80. EMBASE; 67 OR 68 OR 69 OR 70 OR 71 OR 72 OR 73 OR 74 OR 75 OR 76 OR 77 OR 78 OR 79; 1510986 results. 81. EMBASE; 66 AND 80; 9 results.		
PsycINFO	1. PsycInfo; PSYCHOSIS/; 21309 results. 2. PsycInfo; "first episode".ti,ab; 4719 results. 3. PsycInfo; "early intervention".ti,ab; 8880 results. 4. PsycInfo; 2 OR 3; 13224 results. 5. PsycInfo; 1 AND 4; 2284 results. 6. PsycInfo; (first adj3 psychosis).ti,ab; 2492 results. 7. PsycInfo; (early adj3 psychosis).ti,ab; 1513 results. 8. PsycInfo; 5 OR 6 OR 7; 3880 results. 9. PsycInfo; "low dose".ti,ab; 4575 results. 10. PsycInfo; "lower dose".ti,ab; 753 results.	17	0

	11. PsycInfo; "standard dose".ti,ab; 213 results. 12. PsycInfo; DRUG DOSAGES/; 8920 results. 13. PsycInfo; 9 OR 10 OR 11 OR 12; 13362 results. 14. PsycInfo; Antipsychotic*.ti,ab; 22005 results. 15. PsycInfo; exp NEUROLEPTIC DRUGS/; 17638 results. 16. PsycInfo; 14 OR 15; 28270 results. 17. PsycInfo; 8 AND 13 AND 16; 33 results. 18. PsycInfo; random*.ti,ab; 140051 results. 22. PsycInfo; (doubl* ADJ blind*).ti,ab; 19195 results. 23. PsycInfo; (singl* ADJ blind*).ti,ab; 1655 results. 29. PsycInfo; RANDOMIZED CONTROLLED TRIAL/; 640 results. 30. PsycInfo; groups.ti,ab; 384155 results. 31. PsycInfo; exp EXPERIMENTAL DESIGN/; 9675 results. 32. PsycInfo; controlled.ti,ab; 86759 results. 33. PsycInfo; (clinical adj3 study).ti,ab; 11653 results. 34. PsycInfo; trial.ti,ab; 73799 results. 35. PsycInfo; 18 OR 22 OR 23 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34; 592824 results. 36. PsycInfo; 17 AND 35; 17 results.		
CENTRAL	1 MeSH descriptor: [Psychotic Disorders] explode all trees 1565 #2 "first episode" or "early intervention" 3264 #3 #1 and #2 207 #4 "first episode of psychosis" 89 #5 #3 or #4 253 #6 "low dose" 16105 #7 "standard dose" 2066 #8 #6 or #7 17628 #9 #6 and #7 543 #10 #8 or #9 17628 #11 MeSH descriptor: [Antipsychotic Agents] explode all trees 3860 #12 antipsychotic* 6312	4	0

	#13 #11 or #12 6312 #14 #5 and #10 and #13 14 Central only 4		

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