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

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

Question

"For patients with schizophrenia, how effective is chlorpromazine, versus placebo, for improving patient outcomes?"

Clarification of question using PICO structure

Patients:	Patients with schizophrenia
Intervention:	Chlorpromazine
Comparator:	Placebo
Outcome:	Any patient outcomes

Plain Language Summary

Research evidence suggests that chlorpromazine is an effective treatment in reducing symptoms of schizophrenia and increasing patient functioning. However the studies included were of low quality. Higher quality and more current research trials need to be carried out in order to adequately assess the effectiveness of chlorpromazine.

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

Clinical and research implications

Evidence form one well conducted systematic review suggests that chlorpromazine is an effective treatment for people with schizophrenia, reducing relapse rates and improving global measures of symptoms and functioning. However, it should be noted that the review found that chlorpromazine had no significant effect on measures of behavioural disturbance and was associated with a substantial adverse event profile.

As noted by the authors of the review, its reliability is limited by the quality of the included studies, which was generally low; most studies were published before 1990. Large, high quality trials are needed to adequately assess the effectiveness of chlorpromazine and these should focus on key outcomes such as quality of life, levels of satisfaction, relapse, hospital discharge or admission and number of violent incidents.

What does the evidence say?

Number of included studies/reviews (number of participants)

We identified one systematic review which assessed the effects of chlorpromazine, compared to placebo, in people with schizophrenia.[1] This review assessed a variety of outcomes including relapse, measures of mental state and illness severity, behavioural symptoms, and adverse events.

Main Findings

One Cochrane review, which included 55 randomised, placebo controlled trails of generally low methodological quality and mostly published before 1990, assessed the effectiveness of chlorpromazine for the treatment of schizophrenia. The evidence included in the review suggested that chlorpromazine was associated with small, but statistically significant improvements in relapse rates (RR 0.65 (95% CI: CI 0.47 to 0.90), 3 studies, n=512) and global measures of symptoms and functioning (RR 0.71 (95% CI: CI 0.58 to 0.86), 14 trials, n=1164 participants), particularly in the medium term (9 weeks to 6 months). However, chlorpromazine had no statistically significant effect on measures of behavioural disturbance and was associated with a significant adverse event profile; sedation, movement disorders, Parkinsonism, weight gain, and low blood pressure/dizziness were all significantly increased in patients taking chlorpromazine compared to those on placebo.

Authors Conclusions

The review confirmed the effectiveness and adverse event profile of chlorpromazine as a treatment for schizophrenia. The authors noted that larger, better conducted and reported trials are needed and that these should focus on key outcomes such as quality of life, levels of satisfaction, relapse, hospital discharge or admission and number of violent incidents.

Reliability of conclusions/Strength of evidence

This evidence summary is based on the findings of one well conducted Cochrane review. The review included 55 randomised controlled trials. Although the review provides a good summary of the available evidence, it should be noted that (as stated by the review authors) the methodological quality of the included studies was generally low.

What do guidelines say?

SIGN guidelines states in service users with an acute exacerbation or recurrence of schizophrenia prescribers should consider amisulpride, olanzapine or risperidone as the preferred medications with chlorpromazine and other low-potency first-generation antipsychotics providing suitable alternatives. Consideration should be given to previous response to individual antipsychotic medications and relative adverse effect profiles.

For maintenance treatment, prescribers should consider amisulpride, olanzapine or risperidone as the preferred medications with chlorpromazine and other low-potency first-generation antipsychotics providing suitable alternatives.

Individuals with schizophrenia, which is in remission, should be offered maintenance treatment with antipsychotic medication at low to moderate regular dosing of around 300-400 mg of chlorpromazine, 4-6 mg of risperidone, or their equivalents daily.

NICE guidance says that if prescribing chlorpromazine, warn of its potential to cause skin photosensitivity. Advise using sunscreen if necessary.

Date question received: 29/01/2015
Date searches conducted: 04/03/2015
Date answer completed: 21/12/2015

References

Systematic Reviews

1. Adams, C. E., Awad, G. A., Rathbone, J., Thornley, B., & Soares-Weiser, K. (2014). Chlorpromazine versus placebo for schizophrenia. *Cochrane Database of Systematic Reviews* 2014, Issue 1. Art. No.: CD000284. DOI: 10.1002/14651858.CD000284.pub3.

Guidelines

2. Scottish Intercollegiate Guidelines Network (SIGN). (2013). Management of Schizophrenia (SIGN publication no. 131.)
   Available from URL: http://www.sign.ac.uk/pdf/sign131.pdf

3. National Institute for Health and Clinical Excellence (NICE). (2014). Psychosis and schizophrenia in adults: treatment and management (NICE clinical guideline 178).
   Available from URL: http://www.nice.org.uk/guidance/cg178

Results

Systematic Reviews

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Adams et al. (2012)	May 2012	***Participants*:** The inclusion criteria specified people with schizophrenia and other types of schizophrenia-like psychoses (schizophreniform and schizoaffective disorders) however diagnosed, irrespective of age, sex or severity of illness. Included studies were of adult patients between the ages of 18 and 64 years with a clinical diagnosis of schizophrenia. However, one study did not clearly state the diagnoses but included psychiatric outpatients who were 'schizophrenic and non-schizophrenic', with the majority having schizophrenia; and a second study reported it randomised people with mental illnesses who were 'chronic and intractable 'with motor restlessness, psychomotor agitation, and excitement. ***Intervention*:** Chlorpromazine (any dose or mode of administration – doses in the included studies ranged from 25 mg/day to 2400 mg/day. The mean dose was 574 mg/day (SD 446). ***Comparator*:** Placebo or no treatment.	55 (n=5,499 participants, range 18 to 838)	This review aimed to assess the effects of chlorpromazine compared with placebo, for the treatment of schizophrenia. Chlorpromazine was associated with a reduction in the number of participants experiencing a relapse at six months to two years follow-up (RR 0.65 (95% CI: CI 0.47 to 0.90), 3 studies, n=512). The effect remained at 2 to 5 years follow-up (RR 0.74 (95% CI: 0.51 to 1.09), 2 studies, n-394), but was not statistically significant. Chlorpromazine had no effect on relapse rates in the short to medium term (up t6o 6 months). The results of one study indicated that high dose (>500 mg/d) chlorpromazine may be more effective. Chlorpromazine was also associated with a global improvement in symptoms and functioning (RR 0.71 (95% CI: CI 0.58 to 0.86), 14 trials, n=1164 participants). Sub-group analyses indicated that people who	The objective of the review was clearly stated and appropriate inclusion criteria were defined. The Cochrane Schizophrenia group's trial register was searched for relevant studies. This search was supplemented by screening the bibliographies of included studies and by contact with pharmaceutical companies. The data extraction

		Outcome**:** Primary - Death, relapse, global impression, satisfaction with treatment, violent or aggressive behaviour, leaving the study early. Secondary – Duration of hospital stay, re-admission, severity of illness, general and specific symptoms, positive symptoms (delusions, hallucinations, disordered thinking), negative symptoms (avolition, poor self-care, blunted affect), depression, general behaviour, social functioning, employment status, violent incidents, adverse events. ***Study design*****:** Randomised controlled trials.		were chronically ill were more likely to experience short to medium term global improvement than those with acute (<1 month) illness. Fewer people allocated to chlorpromazine left trials early (RR 0.64 (95% CI: CI 0.53 to 0.78) compared with placebo, 27 studies, n=1831 participants); however, this effect was not apparent in studies of over six months duration. Chlorpromazine was also associated with short to medium term (<6 months follow-up) improvements in mental state, as measured using endpoint Brief Psychiatric Rating Scale (BPRS), WMD -7.70 (95% CI: -14.77 to -0.63), 3 studies, n=79 participants. Chlorpromazine had no statistically significant effect on measures of behavioural disturbance. There were many adverse effects. Chlorpromazine was associated with: sedation (RR 2.79 (95% CI: 2.25 to 3.45), 23 trials, n=1627, participants); acute movement disorders (RR 3.47 (95% CI: 1.50 to 8.03), 5 trials, n=942 participants);	process and the assessment of the methodological quality of included studies included measures to minimise error and bias. However, it was not clear w2hether similar measures were applied to the study selection process. The meta-analysis methods used were broadly appropriate. Sub-group analyses were used to explore possible sources of heterogeneity.

				Parkinsonism (RR 2.11 (95% CI: 1.59 to 2.80), 15 trials, n=1468); lowering of blood pressure with accompanying dizziness (RR 2.38 (95% CI: 1.74 to 3.25), 18 trials, n=1488); weight gain (RR 4.92 (95% CI: 2.32 to 10.43), 5 trials, n=165). Akathisia did not occur more often in the chlorpromazine group than placebo.	

Risk of Bias:

SRs

Author (year)	RISK OF BIAS				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
Adams et al. (2012)	☺	☺	?	☺	☺

☺Low Risk ☹High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	Chlorpromazine	12	2
Primary Studies			
CENTRAL	#1 anadep* or chloractil* or chlorazin* or chlorpromados* or chlorpromazine* or chlorprom-ez-ets* or chromedazine* or cpz* or elmarine* or esmind* or fenactil* or hibanil* or hibernal* or klorazin* or klorproman* or klorpromez* or largactil* or megaphen* or neurazine* or plegomazine* or procalm* or promachel* or promacid* or promapar* or promexin* or promosol* or prozil* or psychozine* or psylactil* or serazone* or sonazine* or thoradex* or thorazine* or tranzine*:ti,ab,kw (Word variations have been searched) 1165 #2 MeSH descriptor: [Chlorpromazine] explode all trees 578 #3 #1 or #2 1165 #4 placebo 159529 #5 #3 and #4 301 #6 2011 or 2012 or 2013 or 2014 or 2015 267479 #7 #5 and #6 114	20	0
MEDLINE	9. MEDLINE; exp SCHIZOPHRENIA/; 86031 results. 10. MEDLINE; CHLORPROMAZINE/; 15451 results. 11. MEDLINE; PLACEBO/; 0 results. 12. MEDLINE; (anadep* OR chloractil* OR chlorazin* OR chlorpromados* OR chlorpromazine* OR chlorprom-ez-ets* OR chromedazine* OR cpz* OR elmarine* OR esmind* OR fenactil* OR hibanil* OR hibernal* OR klorazin* OR klorproman* OR klorpromez* OR largactil* OR megaphen* OR neurazine* OR plegomazine* OR procalm* OR promachel* OR promacid* OR promapar* OR promexin* OR promosol* OR prozil* OR psychozine* OR psylactil* OR serazone* OR sonazine* OR thoradex* OR thorazine* OR tranzine*).ti,ab; 11809 results.	0	0

	13. MEDLINE; 10 OR 12; 19587 results. 14. MEDLINE; 9 AND 13; 2139 results. 15. MEDLINE; 11 AND 14; 0 results. 16. MEDLINE; 15 [Limit to: Publication Year 2011-2015]; 0 results. 17. MEDLINE; SCHIZOPHRENIA AND DISORDERS WITH PSYCHOTIC FEATURES/ OR PSYCHOTIC DISORDERS/; 32565 results. 18. MEDLINE; 13 AND 17; 540 results. 19. MEDLINE; placebo.ti,ab; 162668 results. 20. MEDLINE; 18 AND 19; 15 results. 21. MEDLINE; 20 [Limit to: Publication Year 2011-2015]; 1 results. RCT only 0		
EMBASE	33. EMBASE; exp SCHIZOPHRENIA/; 141750 results. 34. EMBASE; CHLORPROMAZINE/; 36053 results. 35. EMBASE; PLACEBO/; 252907 results. 36. EMBASE; (anadep* OR chloractil* OR chlorazin* OR chlorpromados* OR chlorpromazine* OR chlorprom-ez-ets* OR chromedazine* OR cpz* OR elmarine* OR esmind* OR fenactil* OR hibanil* OR hibernal* OR klorazin* OR klorproman* OR klorpromez* OR largactil* OR megaphen* OR neurazine* OR plegomazine* OR procalm* OR promachel* OR promacid* OR promapar* OR promexin* OR promosol* OR prozil* OR psychozine* OR psylactil* OR serazone* OR sonazine* OR thoradex* OR thorazine* OR tranzine*).ti,ab; 11467 results. 37. EMBASE; 34 OR 36; 38038 results. 38. EMBASE; 33 AND 37; 7330 results. 39. EMBASE; SCHIZOPHRENIA AND DISORDERS WITH PSYCHOTIC FEATURES/ OR PSYCHOTIC DISORDERS/; 66776 results. 40. EMBASE; 37 AND 39; 2660 results. 41. EMBASE; placebo.ti,ab; 207625 results. 42. EMBASE; 40 AND 41; 95 results. 43. EMBASE; 42 [Limit to: Publication Year 2011-2015]; 11 results. 44. EMBASE; random*.ti,ab; 939745 results.	11	0

	45. EMBASE; factorial*.ti,ab; 24204 results. 46. EMBASE; (crossover* OR cross-over*).ti,ab; 71944 results. 47. EMBASE; placebo*.ti,ab; 209029 results. 48. EMBASE; (doubl* ADJ blind*).ti,ab; 147652 results. 49. EMBASE; (singl* ADJ blind*).ti,ab; 15298 results. 50. EMBASE; assign*.ti,ab; 251551 results. 51. EMBASE; allocat*.ti,ab; 89115 results. 52. EMBASE; volunteer*.ti,ab; 183278 results. 53. EMBASE; CROSSOVER PROCEDURE/; 41657 results. 54. EMBASE; DOUBLE BLIND PROCEDURE/; 118089 results. 55. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 361087 results. 56. EMBASE; SINGLE BLIND PROCEDURE/; 19568 results. 57. EMBASE; 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56; 1488307 results. 58. EMBASE; 43 AND 57 [Limit to: Publication Year 2011-2015]; 11 results.		
PsychINFO	1. PsycINFO; exp SCHIZOPHRENIA/; 74568 results. 2. PsycINFO; CHLORPROMAZINE/; 1646 results. 3. PsycINFO; PLACEBO/; 3991 results. 4. PsycINFO; (anadep* OR chloractil* OR chlorazin* OR chlorpromados* OR chlorpromazine* OR chlorprom-ez-ets* OR chromedazine* OR cpz* OR elmarine* OR esmind* OR fenactil* OR hibanil* OR hibernal* OR klorazin* OR klorproman* OR klorpromez* OR largactil* OR megaphen* OR neurazine* OR plegomazine* OR procalm* OR promachel* OR promacid* OR promapar* OR promexin* OR promosol* OR prozil* OR psychozine* OR psylactil* OR serazone* OR sonazine* OR thoradex* OR thorazine* OR tranzine*).ti,ab; 3650 results. 5. PsycINFO; 2 OR 4; 3730 results. 6. PsycINFO; 1 AND 5; 926 results. 7. PsycINFO; 3 AND 6; 8 results. 8. PsycINFO; 7 [Limit to: Publication Year 2011-2015]; 0 results.	0	0

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