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 Clozapine augmentation compared to Clozapine alone, for improving patient outcomes?"

Clarification of question using PICO structure

Patients:	Adults with schizophrenia
Intervention:	Clozapine augmentation
Comparator:	Clozapine alone
Outcome:	Any patient outcomes

Plain Language Summary

The studies included in this summary found that clozapine augmentation is more effective the clozapine alone for reducing schizophrenia symptoms. Although there have been a few studies completed in this area, they were all fairly small and so it is hard to generalise the results. More, larger studies should be completed to provide more understanding in this area.

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Clinical and research implications

A total of 36 studies from two systematic reviews and four individual randomised controlled trials suggest that there is some low to moderate quality evidence that clozapine augmentation may be more beneficial than clozapine alone for reducing negative and other symptoms in adults with schizophrenia. However most studies were small and of short duration (8 to 24 weeks) so further research into clozapine augmentation in schizophrenia is needed using larger, multi-centre trials with longer follow-up periods, blinded outcome assessment, and comparing different additional treatments. At present none of the available evidence compared different antipsychotic medications only one alone versus placebo, so there is a lack of evidence to suggest which treatment is most effective.

What does the evidence say?

Number of included studies/reviews (number of participants)

Two systematic reviews (14 studies and 18 studies) and four RCTs (164 participants) provided evidence for this question. One review contained 14 studies (734 participants) and evaluated clozapine augmentation with a range of antipsychotic treatments compared to placebo in adults with schizophrenia (Taylor et al. (2012)). The other review contained seven trials (122 participants) of glutamate agonists and 11 trials (358 participants) of glutamate antagonists compared to placebo (both plus clozapine) in adults with clozapine-resistant schizophrenia (Veerman et al. (2014)).

The four RCTs were all conducted in Italy and used similar methodologies. They were all small, ranging in size from 24 to 60 patients, and made the following comparisons to placebo (plus clozapine) in adult outpatients with schizophrenia and persistent symptoms despite clozapine therapy for at least one year: ziprasidone 80 mg/day for 16 weeks (Muscatello et al. (2014)); duloxetine 60 mg/day for 16 weeks (Mico' et al. (2011)); lamotrigine 25 to 200 mg/day for 24 weeks (Zoccali et al. (2007)); and mirtazapine 30 mg/day for 8 weeks (Zoccali et al. (2004)).

Main Findings

One systematic review found that clozapine augmentation significantly reduced symptom scores compared to placebo (SMD -0.239, 95% CI -0.452 to -0.026) but that this benefit was only seen in studies of more than 10 weeks duration, there was no significant difference between clozapine augmentation and placebo in studies of less than 10 weeks duration (Taylor et al. (2012)).The other systematic review found that glycine augmentation significantly worsened positive symptoms compared to placebo (SMD -0.644, 95% CI -1.117 to -0.171; 3 studies) but had no impact on negative or overall schizophrenic symptoms. Lamotigrine (6 studies) and topiramate (4 studies) had no significant impact on positive, negative or overall symptoms. One small study of memantine (21 patients) found that memantine augmentation) found significant reductions in positive symptoms ($p = 0.002$), negative and overall clinical symptoms (both $p < 0.001$) and cognitive functioning ($p = 0.003$) after 12 weeks (Veerman et al. (2014)).

The trial of ziprasidone augmentation found significant improvements in negative symptoms ($p = 0.006$), general psychopathology ($p = 0.009$), and semantic fluency after 16 weeks of ziprasidone treatment (Muscatello et al. (2014)). The trial of duloxetine augmentation found significant improvements in negative symptoms ($p < 0.0001$), general psychopathology ($p < 0.0001$), total PANSS score ($p < 0.0001$), and depression measured by CDSS ($p < 0.0001$) and BPRS ($p < 0.0001$)

after 16 weeks of duloxetine treatment (Mico' et al. (2011)). The two trials conducted by Zoccali et al. also found similar results with regards to an improvement in negative symptoms. Twenty four weeks of lamotrigine augmentation resulted in significant improvements in negative symptoms ($p < 0.0001$) overall as well as the individual subscales of alogia, avolition/apathy, anhedonia/asociality and attention. Significant improvements were also seen for hallucinations ($p = 0.0002$), bizarre behaviour ($p < 0.0001$), BPRS total score ($p < 0.0001$) and semantic fluency ($p = 0.001$)). After 8 weeks the mirtazapine augmentation group also had a significantly greater reduction in negative symptoms ($p < 0.01$), avolition/apathy ($p < 0.05$), anhedonia/asociality ($p < 0.05$) as well as in total BPRS score ($p < 0.01$) compared to placebo. In all four trials adverse events were mild and transient, mostly gastrointestinal symptoms, drowsiness and weight gain.

Authors Conclusions

The two systematic reviews concluded that: clozapine augmentation with a second antipsychotic was modestly superior to placebo and equally well-tolerated although there was a lack of evidence that longer trials had better outcomes (Taylor et al. (2012)); and that there is no strong evidence at present indicating how patients with clozapine-resistant schizophrenia can be treated. Glutamate antagonists are a promising choice for augmentation, particularly memantine (Veerman et al. (2014)).

The RCTs concluded that: "the augmentation of clozapine with ziprasidone is well tolerated and may be an effective treatment in in patients with schizophrenia who partially respond to clozapine monotherapy. The effect of ziprasidone on negative and cognitive symptoms was encouraging and more research using larger samples is needed to identify the subgroup of patients with refractory schizophrenia with the most favourable risk-benefit ratio of ziprasidone augmentation" (Muscatello et al. (2014)).

"Duloxetine augmentation of clozapine treatment is well tolerated and may be of benefit for patients who are partially responsive to clozapine monotherapy. Further, double-blind, placebo-controlled trials in larger samples are needed to evaluate clozapine augmentation with duloxetine and other antipsychotic drugs" (Mico' et al. (2011)).

"Lamotrigine augmentation of stable clozapine treatment is well tolerated and can be proposed as an effective therapeutic strategy for improving outcomes in patients with treatment-resistant schizophrenia" (Zoccali et al. (2007)).

"Mirtazapine added to clozapine treatment may improve negative symptoms in schizophrenia patients with persistent negative symptoms" (Zoccali et al. (2004)).

Reliability of conclusions/Strength of evidence

The systematic reviews were both considered to be moderate quality. They both had clear inclusion criteria and reasonable literature searches, but one was more restrictive than the other and only included studies with blinded outcome assessment which were published in English so may have missed some relevant studies (Taylor et al. (2012)). Neither gave complete details about whether all stages of the review were conducted in duplicate to minimise error and bias. One did not evaluate study quality but both used appropriate methods of meta-analysis.

Three of the RCTs were moderate quality, they all used appropriate methods of randomisation and allocation concealment and were double-blind with identical placebo controls. However although they all reported about the years of experience of the medical staff assessing the outcomes, they did not say if the outcome assessments were made blind to knowledge about the treatment group. Two included all participants in the analysis but one only included those participants completing the trial. The fourth trial was considered to be low quality as in addition it did not give details of the methods of randomisation and allocation concealment, it also excluded some participants from the analysis.

Overall there were 36 studies providing some low to moderate quality evidence that clozapine augmentation may be more beneficial than clozapine alone for reducing negative and other symptoms in adults with schizophrenia.

What do guidelines say?

The National Institute for Health and Care Excellence guideline, 'Psychosis and schizophrenia in adults: treatment and management' (2014), makes the following recommendations on the use of Clozapine augmentation for people with schizophrenia:

"For people with schizophrenia whose illness has not responded adequately to clozapine at an optimised dose, healthcare professionals should consider recommendation 1.5.7.1 (including measuring therapeutic drug levels) before adding a second antipsychotic to augment treatment with clozapine. An adequate trial of such an augmentation may need to be up to 8–10 weeks. Choose a drug that does not compound the common side effects of clozapine." (pp178)

The Scottish Intercollegiate Guidelines Network guideline, 'Management of schizophrenia' (2013), makes the following recommendations on the topic:

"A systematic review identified six small RCTs (n=252) of clozapine augmentation. Trials were mainly short term with the longest being 12 weeks. Response was defined as a greater than 20% improvement in PANSS or BPRS scores. Augmentation of clozapine with an antipsychotic (aripiprazole, risperidone or sulpiride) improved symptoms particularly in those receiving treatment for longer than ten weeks.

A meta-analysis of double blinded randomised controlled trials of clozapine augmentation identified 10 studies examining augmentation with antipsychotics. In a small study (n=28) of sulpiride augmentation there was a significant effect with respect to BPRS/PANNS (SMD 0.83, 95% CI 0.07 to 1.59). Meta-analysis of augmentation with other antipsychotics resulted in no statistically significant effects. These findings are in agreement with previous reviews, many of which encompassed less rigorous open label studies.

Summary: A trial of clozapine augmentation with a second SGA should be considered for service users whose symptoms have not responded adequately to clozapine alone, despite dose optimisation. Treatment should be continued for a minimum of ten weeks.

Ginkgo
A review and meta-analysis of small studies of ginkgo as an adjunct therapy in chronic schizophrenia identified six studies (n=828).Response to treatment was monitored using standardised negative and total symptom rating scales. Ginkgo produced a statistically significant improvement in total (SMD -

0.5, 95% CI -0.64 to -0.36) and negative symptoms (SMD -0.48, 95% CI -0.63 to -0.34). Despite the positive evidence it is not possible to make a recommendation for ginkgo due to concerns over dose specification and attendant regulatory and safety issues.

Lamotrigine
A meta-analysis identified five RCTs comparing clozapine augmentation with lamotrigine compared with clozapine plus placebo. Trials were one to 24 weeks duration. The primary outcome was a total score for symptoms of psychosis and the secondary outcome measures were scores for positive and negative symptoms of psychosis. Lamotrigine was superior to placebo augmentation in both the primary outcome measure SMD 0.57 (95% CI 0.25 to 0.89) and secondary outcome measures SMD 0.34 (95% CI 0.02 to 0.65) for positive symptoms and SMD 0.43 (95% CI 0.11 to 0.75) for negative symptoms.

Summary: A trial of clozapine augmentation with lamotrigine may be considered for those service users whose symptoms have had an insufficient response to clozapine alone.

Lamotrigine is not licensed for augmentation of clozapine in service users with schizophrenia." (pp20)

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Date searches conducted: 13/02/2015
Date answer completed: 14/11/2016

References

Systematic Reviews/Meta-analyses

Taylor, D. M., Smith, L., Gee, S. H., & Nielsen, J. (2012). Augmentation of clozapine with a second antipsychotic–a meta-analysis. *Acta psychiatrica Scandinavica*, *125*(1), 15-24.

Veerman et al. (2014)- Clozapine augmented with glutamate modulators on refractory schizophrenia: a review and metaanalysis. *Psychopsychiatry, 47(6),* 185-194.

RCTs

Muscatello, M. R. A., Pandolfo, G., Micò, U., Castronuovo, E. L., Abenavoli, E., Scimeca, G., ... & Bruno, A. (2014). Augmentation of clozapine with ziprasidone in refractory schizophrenia: a double-blind, placebo-controlled study. *Journal of clinical psychopharmacology*, *34*(1), 129-133.

Mico', U., Bruno, A., Pandolfo, G., Romeo, V. M., Mallamace, D., D'Arrigo, C., Spina, E., ... & Muscatello, M. R. A. (2011). Duloxetine as adjunctive treatment to clozapine in patients with schizophrenia: a randomized, placebo-controlled trial. *International clinical psychopharmacology*, *26*(6), 303-310.

Zoccali, R., Muscatello, M. R., Bruno, A., Cambria, R., Mico, U., Spina, E., & Meduri, M. (2007). The effect of lamotrigine augmentation of clozapine in a sample of treatment-resistant schizophrenic patients: a double-blind, placebo-controlled study. *Schizophrenia research*, *93*(1), 109-116.

Zoccali, R., Muscatello, M. R., Cedro, C., Neri, P., La Torre, D., Spina, E., ... & Meduri, M. (2004). The effect of mirtazapine augmentation of clozapine in the treatment of negative symptoms of schizophrenia: a double-blind, placebo-controlled study. *International clinical psychopharmacology*, *19*(2), 71-76.

Guidelines

National Institute for Health and Care Excellence (2014). *Psychosis and schizophrenia in adults: treatment and management.* National Institute for Health and Care Excellence Clinical Guidelines 2014, *CG178* http://www.nice.org.uk/guidance/cg178/resources/guidance-psychosis-and-schizophrenia-in-adults-treatment-and-management-pdf

The Scottish Intercollegiate Guidelines Network (2013). *Management of schizophrenia.* The Scottish Intercollegiate Guidelines Network, SIGN 131 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
Taylor et al. (2012)	02/2015	*Participants*: Adults diagnosed with schizophrenia (varying inclusion/criteria across studies) *Intervention*: Augmentation of clozapine with a second antipsychotic medication. *Comparator*: Placebo (13 studies); unclear control (1 study) *Outcome*: Positive and negative symptoms and neurocognitive functioning measured using recognised symptoms scales by blinded assessors, adverse effects, withdrawals *Study design*: Randomised, placebo-controlled trials of at least 6 weeks duration reported in English.	14 (N = 734)	All studies used the Positive and Negative Symptom Scale (PANSS) or the Brief Psychiatric Rating Scale (BPRS) as outcome measures. The treatments under evaluation were: amisulpride (400 mg/day); aripiprazole (5 – 15 mg/day); chlorpromazine (up to 400 mg/day); haloperidol (4 mg/day); pimozide (2 to 8 mg/day); risperidone (3 to 6 mg/day); sertindole (16 mg/day) and sulpiride (up to 60 mg/day). Follow-up ranged from 6 to 24 weeks. Clozapine augmentation significantly reduced symptom scores compared to placebo (standardised mean difference (SMD) = -0.239, 95% CI -0.452 to -0.026; p = 0.028). Sensitivity analyses excluding each study did not alter this conclusion. When analyses were split by study duration, there was no significant difference between treatments in studies of less than 10 weeks duration (SMD -0.103, 95% CI -0.365 to 0.158) but results favoured augmentation in studies of more	Moderate The inclusion criteria were stated but only included studies published in English and with blinded outcome assessment, so some relevant studies may have been excluded. The searches covered a range of databases and efforts to locate unpublished material. No details were given of how many reviewers performed the study selection or data extraction. Some details of study quality were given in the

				than 10 weeks duration (SMD –0.223, 95% CI -0.432 to -0.015). There was no significant difference between groups in the risk of discontinuing treatment for any reason.	study details table but it was not in the methods so the tool used for assessment was unclear. The methods of meta-analysis were appropriate.
Veerman et al. (2014)	02/2015	*Participants*: Adults with clozapine-resistant schizophrenia (varying inclusion/criteria across studies) *Intervention*: Glutamate modulators augmented with clozapine broken down into (i) Glutamate agonists (glycine 30 to 60 g, D-serine (30 mg/kg), D-cycloserine (50 mg), ampakine CX 516 (3600 mg) and sarcosine (2 g), (ii) Glutamate antagonists (lamotrigine (200 to 400 mg), topiramate (200 to 300 mg), memantine (20 mg)). *Comparator*: Placebo plus clozapine *Outcome*: Positive and negative symptoms (SAN, PANSS, BPRS). *Study design*: Randomised, double-blind trials.	18 (N = 122 glutamate agonists, N = 358 glutamate antagonists)	Glutamate agonists (7 studies): There was no evidence that glutamate agonists in combination with clozapine had any effect on schizophrenia symptoms, affective symptoms or cognitive functioning. One short study of 4 weeks duration did show a significant improvement in negative symptoms (p = 0.002) and overall symptoms (p = 0.01) with ampakine CX516. A meta-analysis of three glycine studies found a significant worsening of positive symptoms with glycine augmentation (SMD -0.644 95% CI -1.117 to -0.171, p = 0.008) but no significant differences in negative symptoms (p = 0.77) or overall symptoms (p = 0.50). Glutamate antagonists (11 studies): A meta-analysis of six lamotrigine studies found no significant difference compared to placebo in positive symptoms (p = 0.065), negative symptoms (p = 0.163) or overall symptoms (p = 0.297). A meta-analysis of four	Moderate The inclusion criteria were stated and were not restricted by language or publication year. The searches covered a range of databases Two reviewers independently extracted data but it was not clear if they also selected the studies. There was no assessment of study quality The methods of meta-analysis seemed appropriate but 95% CI were not reported for all the studies.

				topiramate studies also found no significant difference in positive symptoms (p = 0.153), negative symptoms (p = 0.321) or overall symptoms (p = 0.068). One small study of memantine (21 patients) found significant reductions in positive symptoms (p = 0.002), negative and overall clinical symptoms (both p < 0.001) and cognitive functioning (p = 0.003) after 12 weeks.	

RCTs

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Muscatello et al. (2014) Italy	*Participants*: Outpatient adults diagnosed with schizophrenia reporting persistent symptoms despite an adequate trial of clozapine alone. *Intervention*: Ziprasidone 80 mg/day plus clozapine for 16 weeks *Comparator*: Placebo plus clozapine	40 (I = 20, C = 20)	Thirty-three patients (82.5%) completed the study with dropout rates of 20% for ziprasidone and 15% for placebo. The groups were well-balanced at baseline and the mean age was 35 years, 33% were male, and the mean daily clozapine dose was 446 mg. After 16 weeks of treatment the ziprasidone group had significantly greater reductions in negative	Moderate Pre-randomised codes generated by a computer were allocated at registration. This ensured allocation concealment and research personnel were unaware of

	for 16 weeks *Outcome*: The Brief Psychiatric Rating Scale (BPRS); the Calgary Depression Scale for Schizophrenia (CDSS); Positive and negative symptoms (PANSS); Neurocognitive functioning; Adverse effects (including effects on blood chemistry).		symptoms compared to control (mean change -2.7 (SD 3.8) vs. 1.1 (SD 2.1), p = 0.006) and general psychopathology (mean change -5.3 (SD 3.8) vs. -0.7 (SD 2.01), p = 0.009). There was also a significant increase in semantic fluency with ziprasidone (mean change 4.4 (SD 3.5) vs. -0.1 (4.1), p < 0.0001). There were no significant between group differences in positive symptoms, total PANSS score, BPRS score, CDSS score or other neurocognitive tests. The ziprasidone-clozapine combination was generally well-tolerated, adverse events were mostly gastrointestinal symptoms which were mild and reduced or disappeared with further treatment.	assignment during the study. The trial was double-blind and the treatments were dispensed in identical capsules. It was unclear if the psychiatrists performing the assessments were blinded to treatment. All participants were included in the analyses and all outcomes were reported. This was a small study without a sample size calculation.
Mico' et al. (2011) Italy	*Participants*: Outpatients diagnosed with schizophrenia and demonstrating persistent positive and negative symptoms despite an adequate trial of clozapine (monotherapy of 450 to 650 mg/d for at least one year with a stable dose in the previous month). *Intervention*: Duloxetine (60 mg/day) plus clozapine for 16 weeks *Comparator*: Placebo plus clozapine	40 (I = 20, C = 20)	Thirty-three patients (82.5%) completed the study with dropout rates of 20% for duloxetine and 15% for placebo. The groups were well-balanced at baseline and the mean age was 35 years, 60% were male, the mean duration of illness was 6.5 years and the mean daily clozapine dose was 518 mg. After 16 weeks of treatment the duloxetine group had significantly greater reductions in negative symptoms compared to control (mean change -4.4 (SD 3.1) vs. 0.7 (SD 1.9), p < 0.0001), general	Moderate Randomisation used an automated system which also ensured allocation concealment. The trial was double-blind and the treatments were dispensed in identical capsules.

	for 16 weeks *Outcome*: Psychiatric symptoms (PANSS, BPRS, CDSS) and neurocognitive functioning measured with the Wisconsin card-sorting test (WCST), the verbal fluency test and the stroop color-word test.		psychopathology (mean change -10.4 (SD 11.7) vs. 0.3 (SD 2.6), p < 0.0001) and PANSS total score (mean change -15.9 (SD 14.9) vs. 0.8 (SD 3.9), p < 0.0001). The duloxetine group also had significantly greater reductions in depression with the CDSS total score (mean change -3.2 (SD 3.1) vs. 0.1 (SD 1.1), p < 0.0001) and BPRS total score (mean change -8.3 (SD 6.7) vs. -0.2 (2.1), p < 0.0001. There were no significant between group differences for any of the neurocognitive tests. The duloxetine-clozapine combination was generally well-tolerated, adverse events were mostly mild and transient gastrointestinal symptoms.	It was unclear if the clinicians performing the assessments were blinded to treatment. All participants were included in the analyses and all outcomes were reported. This was a small study without a sample size calculation.
Zoccali et al. (2007) Italy	*Participants*: Outpatients diagnosed with schizophrenia and demonstrating persistent positive and negative symptoms despite an adequate trial of clozapine (150 to 650 mg monotherapy for at least 1 year, stable dose for previous month). *Intervention*: Lamotrigine (25mg/ay rising to maximum 200mg/day) plus clozapine for 24 weeks *Comparator*: Placebo plus clozapine for 24 weeks	60 (I = 30, C = 30)	Fifty one patients (85%) completed the study with dropout rates of 13% for lamotrigine and 16% for placebo. The groups were well-balanced at baseline and the mean age was 31.4 years, 55% were male, the mean duration of illness was 9.9 years and the mean daily clozapine dose was 318 mg. After 24 weeks of treatment the lamotrigine group had a significantly greater reduction in the total negative symptoms score compared to placebo (mean 17.9 (SD 16.3) vs. 47.4 (SD 22.9), p < 0.0001), as well as for the individual domains of alogia, avolition/apathy, anhedonia/asociality, and	Moderate Randomisation used an automated system which also ensured allocation concealment. The trial was double-blind and the treatments were dispensed in identical capsules. It was unclear if the clinicians performing the assessments were blinded

	Outcome: Negative and positive symptoms (SAPS and SANS), BPRS, CDSS, neurocognitive functioning, adverse events.		attention. Significant improvements with lamotrigine were also seen for the positive scales of hallucinations (mean 0.2 (SD 0.6) vs. 2.8 (SD 4.2), p =0.0002) and bizarre behaviour (mean 0 (SD 0) vs. 1.0 (SD 1.5), p <0.0001) and the BPRS total score (mean 24.0 (SD 4.4) vs. 31.5 (SD 6.7), p < 0.0001). For neurocognitive tests lamotrigine significantly improved semantic fluency compared to placebo (mean 41.9 (SD 7.3) vs. 33.7 (9.8), but not phonemic fluency or scores on the stroop test or WCST. The duloxetine-clozapine combination was generally well-tolerated, adverse events were mostly mild and transient gastrointestinal symptoms.	to treatment. Nine (15%) patients were excluded from the analyses. All outcomes were reported.
Zoccali et al. (2004) Italy	*Participants*: Outpatients diagnosed with schizophrenia and demonstrating persistent negative symptoms despite an adequate trial of clozapine (150 to 650 mg monotherapy for at least 1 year, stable dose for previous month). *Intervention*: Mirtazapine (30 mg/day) plus clozapine for 8 weeks *Comparator*: Placebo plus clozapine for 8 weeks *Outcome*: Negative and positive	24 (I = 12, C = 12)	Twenty patients (84%) completed the study with dropout rates of 16% in each group. The groups were well-balanced at baseline and the mean age was 32.1 years, 63% were male, the mean duration of illness was 11.6 years and the mean daily clozapine dose was 322.5 mg. After 8 weeks of treatment the mirtazapine group had a significantly greater reduction in the total negative symptoms score compared to placebo (mean 36.1 (SD 4.7) vs. 51 (SD 7.5), p < 0.01) as well as the individual domains of avolition/apathy and anhedonia/asociality (both p < 0.05). The total	High No details were provided about the methods of randomisation and allocation concealment. The trial was double-blind but it was not reported whether the treatments were dispensed in identical capsules. It was unclear if the

	symptoms (SANS and SAPS), depressive symptoms (BPRS), adverse events		BPRS score was also significantly lower with mirtazapine compared to placebo (mean 25.4 (SD 3.2) vs. 44.7 (SD 3.2), $p < 0.01$) but there were no significant differences in depressive symptoms, or positive symptoms as measured by the SAPS. 0.0001). Three patients in the mirtazapine group experienced mild and transient drowsiness and two experienced weight gain.	clinicians performing the assessments were blinded to treatment. Four (16%) patients were excluded from the analyses. All outcomes were reported. This was a very small trial with a short follow-up.

Risk of Bias:

SRs

Author (year)	RISK OF BIAS				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
Taylor et al (2012)	☹	☺	?	?	☺
Veerman et al (2014)	☺	☺	?	☹	☺

RCTs

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Muscatello et al (2014)	☺	☺	☺	?	☺	☺
Mico' et al (2011)	☺	☺	☺	?	☺	☺
Zoccali et al (2007)	☺	☺	☺	?	☹	☺
Zoccali et al (2004)	?	?	☺	?	☹	☺

☺ Low Risk ☹ High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	Schizophrenia		
CDSR	Search Name: Date Run: 13/02/15 14:41:39.215 Description: ID Search Hits #1 clozapine:ti,ab,kw (Word variations have been searched) 999 #2 schizophrenia 10125 #3 "clozapine augment*" 10 #4 #1 and #2 and #3 10	3	
Primary studies			
CENTRAL	Search Name: Date Run: 13/02/15 14:41:39.215 Description: ID Search Hits #1 clozapine:ti,ab,kw (Word variations have been searched) 999 #2 schizophrenia 10125 #3 "clozapine augment*" 10 #4 #1 and #2 and #3 10	6	
PsycINFO	9. PsycINFO; 1 AND 2; 2368 results. 10. PsycINFO; (clozapine adj2 augment*).ti,ab; 115 results.	19	

	11. PsycINFO; 10 [Limit to: (Methodology 0830 Systematic Review or 1200 Meta Analysis or 2000 Treatment Outcome/Clinical Trial)]; 28 results. 16. PsycINFO; 9 AND 10; 89 results. 17. PsycINFO; 16 [Limit to: (Methodology 0830 Systematic Review or 1200 Meta Analysis or 2000 Treatment Outcome/Clinical Trial)]; 19 results.		
Embase	12. EMBASE; 1 AND 2; 13838 results. 13. EMBASE; (clozapine adj2 augment*).ti,ab; 158 results. 14. EMBASE; 12 AND 13; 136 results. 15. EMBASE; 14 [Limit to: (EBM-Evidence Based Medicine Systematic Review) and (Clinical Trials Randomized Controlled Trial)]; 1 results.	1	
Medline	1. MEDLINE; CLOZAPINE/; 6821 results. 2. MEDLINE; exp SCHIZOPHRENIA/; 85920 results. 3. MEDLINE; 1 AND 2; 3248 results. 4. MEDLINE; "clozapine augumentation".ti,ab; 0 results. 5. MEDLINE; "clozapine augmentation".ti,ab; 26 results. 6. MEDLINE; (clozapine adj2 augment*).ti,ab; 121 results. 7. MEDLINE; 3 AND 6; 79 results. 8. MEDLINE; 7 [Limit to: (Publication Types Randomized Controlled Trial or Systematic Reviews)]; 34 results.	34	
Summary	**NA**	**NA**	

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