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

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

Question

In adults with treatment resistant schizophrenia (with or without mild learning disabilities), how effective are antipsychotic combinations, compared to any other intervention, in improving patient outcomes?

Clarification of question using *PICO* structure

Population: *Adults with treatment resistant schizophrenia (with or without mild learning difficulties)*
Intervention: *Combinations of antipsychotic medication*
Comparator: *Any or no intervention*
Outcome: *Improvement in psychotic symptoms*

Plain language summary

Research evidence suggests that combining antipsychotic medications may have some benefit to those with treatment resistant schizophrenia; however this evidence available is weak with no clear indication as to which combinations are most effective. More rigorous controlled studies need to be carried out before any definite conclusions or recommendations can be made. No studies were identified looking at combination antipsychotics for patients with treatment resistant schizophrenia and a learning disability.

Clinical and research implications

No definite clinical implications may be made based on the evidence included in this BEST summary. There is weak evidence to suggest that various combined treatments *may* show some improved outcomes in patients with clozapine-resistant schizophrenia compared with placebo, but there is no strong evidence to suggest which combination strategies are superior to others. There is consensus among all of the included reviews/studies that more high quality randomised controlled trials, with adequate sample sizes, are needed before firms recommendations can be made about clozapine augmentation strategies. One of the review authors also suggested that these trials should also measure global outcomes such as 'healthy days', 'social functioning', 'satisfaction with treatment', 'ability to live and work in the community', and compliance.

What does the evidence say?

Number of included studies/reviews (number of participants)

Two Cochrane systematic reviews (SRs) (Cipriani et al. 2009; Wang et al. 2010), and three randomised controlled trials (RCTs) (Barbui et al. 2011; Josiassen et al. 2014; Muscatello et al. 2011) met the inclusion criteria for this BEST summary.

Main findings

One SR aimed to assess the efficacy and tolerability of different clozapine combination strategies with antipsychotics in people with treatment resistant schizophrenia (Cipriani et al. 2009). This review included 3 studies, but the authors of the SR stated that they did not find any data from RCTs with sufficient methodological rigour to address their review question.

Another SR included 4 RCTs that compared clozapine plus sulpiride versus clozapine plus placebo for people with schizophrenia (Wang et al. 2010). The authors found that adding sulpride to clozapine may help with mental state, but the data were weak.

An RCT by Barbui et al. (2011) evaluated the effectiveness of combined clozapine and aripiprazole compared with clozapine and haloperidol in 106 inpatients or outpatients with treatment-resistant schizophrenia. The authors reported no difference between the groups in the proportion of patients who discontinued treatment within 3 months (the primary outcome), or in overall symptoms (measured using the BPRS total score), but clozapine and aripiprazole was associated with significantly better patient perception of adverse events.

A double-blind RCT by Muscatello et al. (2011) compared clozapine plus aripiprazole versus clozapine plus placebo in 40 patients with treatment-resistant schizophrenia. After 24 weeks of treatment, clozapine plus aripiprazole resulted in significantly reduced positive symptoms (measured using the SAPS total score), the bizarre behaviour domain of the SAPS, and the alogia domain of the SANS. The authors also found an improvement in overall symptoms (measured using the BPRS total score) compared with placebo, but using a Bonferonni correction value of $p<0.002$, the authors did not report this finding as statistically significant. There were no significant differences between the groups for affective symptomology (as measured using CDSS total score).

The double-blind RCT by Josiassen et al. (2014) examined clozapine augmented with risperidone compared with clozapine plus placebo in 40 inpatients or outpatients with schizophrenia, refractory to clozapine monotherapy. After 12 weeks of treatment, the authors observed a significant result in favour of clozapine plus risperidone for two main outcomes: mean BPRS total scores, and negative symptoms scores on the SANS. Adverse events were similar between the groups with the exception of absolute neutrophil counts, which were significantly higher in those augmented with risperidone.

Author's conclusions

Cipriani et al. (2009) concluded that due to methodological limitations of the included studies, the SR was not able to show if any particular combination strategy was superior to others.

Wang et al. (2010) concluded that sulpiride plus clozapine 'is probably' more effective than clozapine alone, but much more robust data are needed.

Barbui et al. (2011) concluded that "augmentation of clozapine with aripiprazole offers no benefit with regard to treatment withdrawal and overall symptoms in schizophrenia as compared with augmentation with haloperidol. However, the advance in the perception of adverse effects with aripiprazole treatment may be meaningful for patients. This finding needs to be confirmed by the analysis of the 12-month data and needs also to be replicated by additional randomised trials and high-quality observational studies."

Muscatello et al. (2011) concluded that augmentation of clozapine with aripiprazole was well-tolerated and may confer some benefit 'to patients who are partially responsive to clozapine monotherapy', but that further well-conducted RCTs are needed.

Josiassen et al. (2014) concluded that augmentation of clozapine with risperidone shows improvements in in overall symptoms and positive and negative symptoms of schizophrenia, but definitive conclusions cannot be made without further studies with larger sample sizes.

Reliability of conclusions/Strength of evidence

The SRs by Cipriani et al. (2009) and Wang et al. (2010) were well-conducted, and the authors' cautious conclusions reflect the study data.

Barbui et al. (2011) was well-conducted, although the authors did not reach their target sample size. As such, the authors' appropriately concluded that their results need to be confirmed. The reliability of the trial by Josiassen et al. (2014) is unclear, and given that the study included only 40 participants, it is uncertain whether this study was sufficiently powered. As such, these authors' cautious conclusions are also appropriate. The RCT by Muscatello et al. (2011) is limited to a small sample size, and that the authors did not use intention-to-treat analysis, so that the reliability or their results are uncertain.

What do guidelines say?

The Scottish Intercollegiate Guidelines Network (SIGN) recommends that a trial of clozapine augmentation with a second SGA (Second Generation Antipsychotic) 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.

"5.7.2 Clozapine augmentation with another antipsychotic: 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.112 These findings are in agreement with previous reviews, many of which encompassed less rigorous open label studies"

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References

Systematic reviews

1. Cipriani, A., Boso, M., & Barbui, C. (2009). Clozapine combined with different antipsychotic drugs for treatment resistant schizophrenia. The Cochrane Library.

2. Wang, J., Omori, I. M., Fenton, M., & Soares, B. G. (2010). Sulpiride augmentation for schizophrenia. The Cochrane Library.

Randomised controlled trials

3. Barbui, C., Accordini, S., Nose, M., Stroup, S., Purgato, M., Girlanda, F., & CHAT (Clozapine Haloperidol Aripiprazole Trial) Study Group. (2011). Aripiprazole versus haloperidol in combination with clozapine for treatment-resistant schizophrenia in routine clinical care: a randomized, controlled trial. Journal of clinical psychopharmacology, 31(3), 266-273.

4. Josiassen, R. C., Joseph, A., Kohegyi, E., Stokes, S., Dadvand, M., Paing, W. W., & Shaughnessy, R. A. (2014). Clozapine augmented with risperidone in the treatment of schizophrenia: a randomized, double-blind, placebo-controlled trial. American Journal of Psychiatry

5. Muscatello, M. R. A., Bruno, A., Pandolfo, G., Micò, U., Scimeca, G., Di Nardo, F., & Zoccali, R. A. (2011). Effect of aripiprazole augmentation of clozapine in schizophrenia: a double-blind, placebo-controlled study. Schizophrenia research, 127(1), 93-99.

Guidelines

Scottish Intercollegiate Guidelines Network (2013). *Management of Schizophrenia.* A national Clinical Guideline (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
Cipriani et. al. 2009	Nov 2008	***Participants*:** In patients and outpatients 18 years and over with a formal diagnosis of Schizophrenia ***Intervention*:** Clozapine plus another antipsychotic drug: - **Amisulpride**: clozapine mean dose 536.95 mg/day and amisulpride mean dose 437.03 mg/day - **Risperidone:** clozapine mean dose 406.8 mg/day and risperidone mean dose 3.82 mg/day. (Doses not specified for study 2) ***Comparator*:** Clozapine plus a different other antipsychotic drug: - **Quetiapine:** clozapine mean dose 550 mg/day and quetiapine mean dose 595.65 mg/day - **Sulpiride:** Doses not specified - **Ziprasidone:** clozapine mean dose 361.4 mg/day and ziprasidone mean dose 134	3 studies (N=140)	**Clozapine + risperidone vs. clozapine + sulpiride** (Kong 2001) The response rate (defined as 'important results') was higher in the risperidone group than in the sulpiride group (n=60, 1 RCT, RR 2.33 CI 1.29 to 4.23, p=0.005). At the endpoint, the mean Positive and Negative Symptoms Scale (PANSS) total score was 55.42 (SD 10.11) in the risperidone group and 57.70 (SD 10.15) in the sulpiride group (n=60, 1 RCT, MD -2.28 CI -7.41 to 2.85, p=0.38). At the endpoint, the mean PANSS positive score was 11.56 (SD 4.11) in the risperidone group and 14.11 (SD4.16) in the sulpiride group (n=60, 1RCT, MD-2.55 CI -4.64 to -0.46, p=0.02). At the endpoint, the mean PANSS negative score was 22.06 (SD 6.26) in the risperidone group and 22.60 (SD3.95) in the sulpiride group (n=60, 1 RCT, MD -0.54, CI-3.19 to 2.11, p=0.69). Adverse	Low

		mg/day ***Outcome*:** Clinical response to combined medication treatment: - Positive and Negative Syndrome Scale (PANSS) - Scale for the Assessment of Negative Symptoms (SANS), - Hamilton Depression Scale (HAMD) ***Study design*:** Randomised controlled trials		events: Three patients reported granulocytopenia in the sulpiride group, but the number in the risperidone group is unclear. Hypersalivation was reported by one patient in the risperidone group and three patients in the sulpiride group (n=60, 1 RCT, RR 0.33 CI 0.04 to 3.03, p=0.33). Weight gain was reported by tw opatients in the risperidone group and five patients in the sulpiride group (n=60, 1 RCT, RR 0.40, CI 0.08 to 1.90, p=0.25). In risperidone group, four patients reported agitation, four patients reported akathisia and two rigidity; in the sulpiride group, five patients reported tachycardia and six blood pressure variations. The respective numbers in the other group are not clear. **Clozapine + risperidone vs. clozapine + ziprasidone** (Zink 2008) By the end of the trial (six weeks), a treatment response (20% reduction on the PANSS) was achieved by nine out of twelve patients randomised in the ziprasidone group compared with ten out of twelve patients allocated to risperidone (n=24, 1 RCT, RR 0.90 CI 0.60 to 1.36, p=0.62). The PANSS positive subscore decreased by 20%	

				in eleven patients randomised to ziprasidone and in nine patients randomised to risperidone (n=24, 1 RCT, RR 1.22 CI 0.85 to 1.77, p=0.29). Adverse events: By the end of the study, the ziprasidone group experienced an improvement from 2.4 to1.1 (P= 0.013), whereas EPS scores in the risperidone group did not significantly change (P = 0.184). However, data were not clear. **Clozapine + amisulpride vs. clozapine + quetiapine** (Genc 2007) No reliable outcome data were reported (as stated by the review authors).	
Wang et. al. 2010	July 2009	***Participants*:** People with Schizophrenia and other schizophrenia –like psychosis. ***Intervention*:** Sulipride in combination with Clozapine ***Comparator*:** - Placebo (Or no intervention) in combination with Clozapine - Clozapine monotherapy: - Sulipride monotherapy:	3 studies included (N=221)	**Clozapine + sulipride vs. any antipsychotic drug** In the short-term (up to 12 weeks), the number of people who had not improved was lower in the sulpiride augmentation group compared with those allocated to clozapine alone (n= 193, 3 RCT, RR 0.58 CI 0.3 to 1.09), but the result was not statistically significant (p=0.09). Long-term data showed no significant difference between these groups for global state (’clinical and social lack of recovery’) (n=70, 1 RCT, RR 0.67 CI 0.42 to 1.08) or relapse	Low

		***Outcome*:** Global state: Measured by clinical improvement. Adverse effects: Treatment Emergent Signs and Symptoms (TESS) Mental State: Brief Psychiatric Rating Scale (BPRS), Scale for the Assessment of Negative Symptoms (SANS), and Scale for the Assessment of Positive Symptoms (SAPS). ***Study design*:** Randomised Controlled Trials		(n=70, 1 RCT, RR 0.85 CI 0.5 to 1.3) (Wang 1994). The short-term BPRS data indicated that the number of participants showing 'no clinically important improvement' was less in the sulpiride + clozapine group than in the placebo + clozapine group (n=28, 1 RCT, RR 0.55 CI 0.32 to 0.92, P=0.02) (Shiloh 1997). The short term endpoint BPRS scores of Zhu (1999) favoured sulpiride augmentation of clozapine (n=59, WMD -3.4 CI-6.84 to -0.04, P=0.05). The short- term data of average endpoint SAPS plus SANS scores in Wang 1994 were skewed, and its WMD was unclear. The short term average change in endpoint scores of SAPS plus SANS from Wang 1994 showed that the general symptom improvement was greater in the sulpiride + clozapine group than in the clozapine alone group (n=70, WMD -1.74 CI -3.0 to -0.47, P=0.007). The skewed data of short-term BPRS change in Shiloh 1997 favoured sulpiride augmentation too (P<0.05) (Analysis 1.12). Long-term data (3 year) were available only in one trial (Wang 1994).	

				Average change in the endpoint SAPS plus SANS scores favoured sulpiride augmentation of clozapine compared with clozapine alone (n=70, WMD -3.47 CI -4.90 to -2.04, Z=4.76, P<0.00001). Regarding negative symptoms, the short-term endpoint data of SANS (Xu 2006) indicated that sulpiride + clozapine was more effective on negative symptoms than clozapine alone (n=64, WMD -6.9 CI-10.87 to-2.93, P=0.0007). There was a greater change in endpoint SANS scores in sulpiride + clozapine group than in the control group (P<0.05) was reported in the trial by Shiloh (1997). Regarding positive symptoms, the short term average change in endpoint SAPS scores from Shiloh (1997) showed a greater improvement with sulpiride augmentation than in the control group (P<0.05), but the data are skewed. People allocated to sulpiride + clozapine had more movement disorders (n=70, 1 RCT, RR 48.24 CI 3.05 to 762.56) and an increase in serum prolactin (skewed data, 1 RCT), but	

				less incidence of hypersalivation (n=162, 3 RCTs, RR 0.49 CI 0.29 to 0.83) and less weight gain (n=64, 1 RCT, RR 0.30 CI 0.09 to 0.99). The augmentation of clozapine by sulpiride also caused less appetite loss (n= 70, 1 RCT, RR 0.09 CI 0.01 to 0.70, NNT 4 CI 4 to 12, P=0.02) and less abdominal distension (n=70, 1 RCT, RR 0.10 CI 0.01 to 0.78, P=0.03).	

Randomised controlled trials

Author (year)	**Inclusion criteria**	**Number of participants**	**Summary of results**	**Risk of bias**
Barbui et al. (2011)	***Participants*:** Inpatients and outpatients with a formal diagnosis of schizophrenia currently undergoing Clozapine medication treatment. ***Intervention*:** Clozapine combined with Aripiprazole ***Comparator*:** Clozapine combined with Haloperidol ***Outcome*:**	N=106 (53 in each treatment group)	There was no difference between the treatment groups in the proportion of patients who discontinued treatment within 3 months (the primary outcome): clozapine + aripiprazole (13.2%) vs. clozapine + haloperidol (15.1%), p=0.78. Severity of illness, as measured using the BPRS total score, was similar between the two groups (3 month change scores were clozapine + aripiprazole (-5.9) vs. clozapine + haloperidol (-4.4), p=0.52). Burden of adverse events, as measured by a 3-month decrease of the LUNSERS total score, was significantly better	Low (patients were not blinded, but it is unlikely that the primary outcome measurement was influenced by lack of blinding [as discussed on

	Withdrawal from allocated treatment within 3 months. Withdrawal categorised as the following: (a) clozapine was continued and the allocated treatment stopped, (b) clozapine was stopped and the allocated treatment continued, (c) both clozapine and the allocated treatment were stopped, and (d) other antipsychotic drugs were added on a regular basis to the allocated combination treatment.		in the clozapine + aripiprazole group (-7.4) compared with the clozapine + haloperidol group (-2.0), p=0.006, after adjusting for the baseline value.	p. 271])
Josiassen et al. 2014	***Participants*:** In/outpatients aged between 20 and 65 years with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder, unresponsive or partially unresponsive to clozapine monotherapy. ***Intervention*:** Clozapine combined with Risperidone over a 12 week period: Risperidone started at 1 mg/day, titrated up to 6 mg/day on day 22 ***Comparator*:** Clozapine combined with Placebo over a 12 week period.	N=40 (20 in each treatment group)	After 12 weeks, a treatment response (20% greater reduction in BPRS total score) was achieved in 35% of patients in the clozapine + risperidone group compared with 10% of patients in the clozapine + placebo group ($p<0.01$). Score reductions were similar between the groups up to week 6, but increased in the risperidone group from week 6 to 12. Negative symptoms (SANS scores) significantly decreased at 12 weeks with clozapine + risperidone treatment compared with control ($p<0.04$) (data presented in graphs only). There were very few differences between the groups for adverse events: absolute neutrophil counts were significantly higher in the clozapine + risperidone compared with control (no values reported).	Unclear (and small sample size)

	***Outcome*:** Patient psychopathology: Brief Psychiatric Rating Scale (BPRS) and Scale for the Assessment of Negative Symptoms (SANS).			
Muscatello et al. (2011)	***Participants*:** Outpatients aged 25 – 38 years old with a formal diagnosis of schizophrenia ***Intervention*:** Clozapine combined with aripiprozole over a 24 week period. Initial dose was 10mg per day until week 12, and then increased to 15mg per day until week 24. ***Comparator*:** Clozapine combined with placebo over a 24 week period. Those assigned to this group took the same number of capsules as those assigned to aripiprazole. ***Outcome*:** The following rating scales were used: - Brief Psychiatric Rating Scale (BPRS) - Scale for the Assessment of Negative Symptoms (SANS) - Scale for the Assessment of Positive Symptoms (SAPS)	N=40 (20 in each treatment group) (31 included in the analysis)	At 24 weeks, there were significant differences between the groups such that SAPS 'bizarre behaviour' and total scores were higher in the placebo group ($p<0.001$ for both). SANS 'alogia' was also significantly higher in the placebo group ($p=0.002$). There were no significant differences between the groups on CDSS total score. The authors reported no difference in the SANS total scores or BPRS total scores using a significance value of $p<0.002$ (using a Bonferroni correction). Clozapine plus aripiprazole was generally well-tolerated; common side effects were restlessness (36%), insomnia (21%), and nausea (7%). (significant differences between the treatment groups were not reported)	High

	- Calgary Depression Scale for Schizophrenia (CDSS)			

Risk of bias

Systematic reviews

Author (year)	RISK OF BIAS				
	Inclusion criteria	Searches	Review process	Quality assessment	Synthesis
Cipriani et al. (2009)	☺	☺	☺	☺	☺
Wang et al. (2010)	☺	☺	☺	☺	☺

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
Barbui et al. (2011)	☺	☺	☹	☺	☺	?
Josiassen et al. (2014)	?	?	☺	☺	☺	?
Muscatello et al. (2011)	☺	☺	☺	☺	☹	?

☺Low risk ☹High risk ? Unclear risk

Search details

Source	Search Strategy		Number of hits	Relevant evidence identified
Guidelines				
NICE/SIGN	Treatment resistant schizophrenia		17	1
Systematic Reviews & Primary Studies				
MEDLINE	1 exp Schizophrenia/	91547	83	
	2 exp Psychotic Disorders/	41214		
	3 (treatment adj resistant).ab,ti.	5523		
	4 (treatment-resistant adj (schizophrenia or psychosis)).ab,ti.	557		
	5 2 and 3	168		
	6 1 and 3	745		
	7 4 or 5 or 6	960		
	8 exp Antipsychotic Agents/	107882		
	9 exp Pharmaceutical Preparations/	660317		
	10 ((drug or pharmac* or medicin*) adj3 (therp* or intervention or treatment)).ab,ti.	81839		
	11 8 or 9 or 10	834857		
	12 combination.ab,ti.	615506		
	13 11 and 12	47491		
	14 7 and 13	83		

EMBASE	1 exp Schizophrenia/ 150701 2 exp Psychotic Disorders/ 229458 3 (treatment adj resistant).ab,ti. 8254 4 (treatment-resistant adj (schizophrenia or psychosis)).ab,ti. 850 5 2 and 3 1769 6 1 and 3 1494 7 4 or 5 or 6 1790 8 exp Antipsychotic Agents/ 216169 9 exp Pharmaceutical Preparations/ 2206645 10 ((drug or pharmac* or medicin*) adj3 (therp* or intervention or treatment)).ab,ti. 112260 11 8 or 9 or 10 2471355 12 combination.ab,ti. 751370 13 11 and 12 105131 14 7 and 13 192	192	
PsycINFO/CINAHL	1 exp Schizophrenia/ 61767 2 (treatment adj resistant).ab,ti. 3829 3 (treatment-resistant adj (schizophrenia or psychosis)).ab,ti. 590 4 ((drug or pharmac* or medicin*) adj3 (therp* or intervention or treatment)).ab,ti. 20705 5 combination.ab,ti. 53950	96	

	696	exp Neuroleptic Drugs/ or exp Drugs/	220542	
	7	(antipsychotic adj (drug* or medication or therap or treatment or intervention)).ab,ti.	8884	
	8	4 or 6 or 7	235466	
	9	5 and 8	10910	
	10	exp Psychosis/	77323	
	11	psychotic disorder.ab,ti.	2201	
	12	1 or 10 or 11	78002	
	13	2 and 12	949	
	14	3 or 13	1003	
	15	9 and 14	96	

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