TECHNICAL COMMENTARY

Treatments for medication resistance

NeuRA Discover. Conquer. Cure.

SCHIZOPHRENIA LIBRARY

Introduction

Antipsychotic medications provide symptom respite and improvement in quality of life for many people with schizophrenia. However, for a subset of people with schizophrenia, antipsychotic medications do not provide adequate relief from symptoms. Treatment-resistant schizophrenia has many definitions that vary depending on the individual study, but a broad definition includes those patients whose symptoms have not responded to antipsychotic medications, or only partially responded.

Here we summarise the evidence describing the efficacy of antipsychotic medications and other non-antipsychotic therapies for improving symptom severity in people with treatment-resistant schizophrenia.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, which describes a preferred way to present a meta-analysis[1]. Reviews rated as having less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found 10 systematic reviews that met inclusion criteria[3-12].

- Moderate to high quality evidence finds a general pattern of superiority of clozapine, olanzapine or risperidone over other antipsychotics for improving symptoms in people with treatment-resistant schizophrenia.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Treatments for medication resistance

- For people with inadequate response to clozapine, moderate to high quality evidence finds augmenting clozapine with other second-generation antipsychotics may improve negative and depressive symptoms, but not necessarily positive symptoms. Adjunctive sulpiride and adjunctive ziprasidone were particularly effective for negative symptoms, and adjunctive aripiprazole and adjunctive ziprasidone were particularly effective for depressive symptoms.
- Moderate to low quality evidence finds improved total symptoms with clozapine augmentation of antidepressants fluoxetine, paroxetine and duloxetine. Adding topiramate, sodium valproate or lithium to clozapine may also improve total symptoms, while adding memantine may improve negative symptoms.
- Moderate to low quality evidence finds around half of people not responding to clozapine responded to adjunctive ECT.
- High quality evidence finds better clozapine response in younger patients and in those diagnosed with paranoid schizophrenia. Moderate to low quality evidence suggests patients with lower PANSS negative scores at baseline also have a better response to clozapine. There were no relationships between response to clozapine and gender, smoking, weight, years of education, marital status, age at onset, age at first hospitalisation, number of hospitalisations, duration of illness, length of stay during hospitalisations, baseline total scores on the BPRS, CGI, and the PANSS, or on PANSS baseline positive scores.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Barber S, Olotu U, Corsi M, Cipriani A

Clozapine combined with different antipsychotic drugs for treatment resistant schizophrenia

Cochrane Database of Systematic Reviews 2017; Issue 3. Art. No.: CD006324

View review abstract online

Comparison	**Clozapine plus any antipsychotic for treatment-resistant schizophrenia.**
Summary of evidence	**Low quality evidence (very small samples) is unable to determine any differences between various clozapine augmentations for treatment resistant schizophrenia.**

Symptoms

Measured by clinical response or PANSS

Clozapine plus amisulpride vs. clozapine plus quetiapine

A significant effect of better clinical response with clozapine + amisulpride;

1 RCT, N = 50, MD = -4.00, 95%CI -5.86 to -2.14, $p = 0.000025$

A significant effect of better SAPS (positive symptoms) scores with clozapine + amisulpride;

1 RCT, N = 50, MD = -6.90, 95%CI -12.82 to -0.92, $p = 0.022$

A significant effect of better SANS (negative symptoms) scores with clozapine + amisulpride;

1 RCT, N = 50, MD = -5.20, 95%CI -7.14 to -3.26, $p < 0.00001$

There were no differences in leaving the study early.

Clozapine plus ziprasidone vs. clozapine plus quetiapine

A significant effect of better clinical response with clozapine + ziprasidone;

1 RCT, N = 63, MD = 0.54, 95%CI 0.35 to 0.81, $p = 0.0032$

A significant effect of better global state with clozapine + ziprasidone;

1 RCT, N = 60, MD = -0.70, 95%CI -1.18 to -0.22, $p = 0.0044$

A significant effect of better PANSS total scores with clozapine + ziprasidone;

1 RCT, N = 60, MD = -12.30, 95%CI -22.43 to -2.17, $p = 0.017$

A significant effect of better PANSS positive scores with clozapine + ziprasidone;

1 RCT, N = 60, MD = -3.10, 95%CI -5.52 to -0.68, $p = 0.012$

There were no significant differences in PANSS negative scores or leaving the study early.

Clozapine plus risperidone vs. clozapine plus sulpiride *A significant effect of better PANSS positive scores with risperidone + clozapine;* 1 RCT, N = 60, MD = -2.55, 95%CI -4.64 to -0.46, *p* = 0.02 There were no differences on PANSS total or PANSS negative. Clozapine plus risperidone vs. clozapine plus ziprasidone 1 RCT, N = 24: no differences in clinical response, PANSS positive, PANSS negative, global state or leaving the study early. Clozapine plus aripiprazole vs. clozapine plus haloperidol 1 RCT, N = 106: no differences in clinical response or leaving the study early.	
Risks	There were no significant differences between groups.
Consistency in results‡	Not applicable (1 RCT).
Precision in results§	Imprecise or unable to assess MDs.
Directness of results‖	Direct

Bartoli F, Crocamo C, Di Brita C, Esposito G, Tabacchi TI, Verrengia E, Clerici M, Carra G

Adjunctive second-generation antipsychotics for specific symptom domains of schizophrenia resistant to clozapine: A meta-analysis

Journal of Psychiatric Research 2019; 108: 24-33

View review abstract online

Comparison	**Clozapine plus second-generation antipsychotics vs. clozapine plus placebo.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests augmenting clozapine with second-generation antipsychotics can improve negative and depressive symptoms, but not positive symptoms compared to adjunctive placebo. Adjunctive sulpiride and ziprasidone were particularly effective for negative symptoms, and adjunctive aripiprazole and ziprasidone were particularly effective for depressive symptoms.**
Symptoms	

Significant, small to medium-sized improvements with adjunctive antipsychotics in; Negative symptoms: 12 RCTs, N = 726, SMD = -0.38, 95%CI -0.65 to -0.11, p = 0.005, I^2 = 63%, p = 0.002 Subgroup analysis of individual antipsychotics showed this effect was significant only for sulpiride and ziprasidone, and not for aripiprazole, risperidone, amisulpride or sertindole. Depressive symptoms: 8 RCTs, N = 361, SMD = -0.35, 95%CI -0.58 to -0.12, p = 0.003, I^2 = 5%, p = 0.393 Subgroup analysis of individual antipsychotics showed this effect was significant only for aripiprazole and ziprasidone, and not for sulpiride, risperidone or amisulpride. *There were no significant differences in;* Positive symptoms: 11 RCTs, N = 658, SMD = -0.21, 95%CI -0.51 to 0.09, p = 0.170, I^2 = 68%, p = 0.001 Subgroup analysis of individual antipsychotics showed this effect was not significant for any individual antipsychotic (aripiprazole, risperidone, sertindole, sulpiride, or ziprasidone).

Risks	There were no significant differences in discontinuation rates.
Consistency in results	Inconsistent
Precision in results	Precise
Directness	Direct for antipsychotic class and for individual medications.

Jones R, MacCabe JH, Price MJ, Xiangxin L, Upthegrove R

Effect of age on the relative efficacy of clozapine in schizophrenia

Acta Psychiatrica Scandinavica 2020; 24: doi: 10.1111/acps.13156

View review abstract online

Comparison	**Clozapine vs. other antipsychotics.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, inconsistent, precise, indirect) suggests greater improvement in symptoms with clozapine than other antipsychotics, with no moderating effect of age.**
Symptoms	

A small, significant effect showed clozapine was significantly more effective than other antipsychotics for improving symptoms; 34 studies, N not reported, SMD = -0.207, 95%CI -0.33 to -0.06, $p < 0.05$, $I^2 = 65\%$, $p < 0.0001$ There was no moderating effect of age or duration of illness.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness	Indirect; mixed control conditions.

Lally J, Tully J, Robertson D, Stubbs B, Gaughran F, MacCabe JH

Augmentation of clozapine with electroconvulsive therapy in treatment resistant schizophrenia: A systematic review and meta-analysis

Schizophrenia Research 2016; 171: 215-24

View review abstract online

Comparison	**Clozapine plus electroconvulsive therapy (ECT).** **The mean number of ECT treatments = 11.3.**
Summary of evidence	**Moderate to low quality evidence (small sample, inconsistent, appears imprecise, direct) suggests around half of people not responding to clozapine responded to adjunctive ECT.**
Symptoms	
Around half of people given adjunctive ECT responded to treatment; Total symptoms (PANSS/BPRS/CGI): 5 trials, N = 71, response = 54%, 95%CI 21.8 to 83.6%, $I^2 = 69\%$	
Risks	14% reported adverse events.
Consistency in results	Inconsistent
Precision in results	Appears imprecise.
Directness	Direct

Mizuno Y, McCutcheon RA, Brugger SP, Howes OD

Heterogeneity and efficacy of antipsychotic treatment for schizophrenia with or without treatment resistance: a meta-analysis

Neuropsychopharmacology 2020; 45: 622-31

View review abstract online

Comparison	**Clozapine vs. other antipsychotics.**
Summary of evidence	**Moderate quality evidence (large samples, some inconsistency, precise, indirect) suggests showed clozapine was superior to other antipsychotics in improving symptoms in both treatment-resistant and non-treatment-resistant patients.**
Symptoms	
Small effects showed clozapine was superior to other antipsychotics in improving total symptoms; Treatment-resistance: 10 studies, N = 822, g = 0.34, 95%CI 0.13 to 0.56, $p < 0.05$, $I^2 = 35\%$ Non-treatment-resistance: 29 studies, N = 2,566, g = 0.20, 95%CI 0.08 to 0.32, $p < 0.05$, $I^2 = 43\%$ Clozapine was superior in improving positive symptoms, but not negative symptoms.	
Consistency in results	Some inconsistency
Precision in results	Precise
Directness	Indirect; mixed control conditions

Okhuijsen-Pfeifer C, Sterk AY, Horn IM, Terstappen J, Kahn RS, Luykx JJ

Demographic and clinical features as predictors of clozapine response in patients with schizophrenia spectrum disorders: a systematic review and meta-analysis

Neuroscience and biobehavioral reviews 2020; 111: 246-52

View review abstract online

Comparison	**Factors associated with response to clozapine.**

Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) finds better clozapine response in younger patients and in those diagnosed with paranoid schizophrenia. Lower quality evidence (small samples, inconsistent, imprecise) suggests patients with lower PANSS negative scores at baseline also have a better response to clozapine.** **There were no relationships between response and gender, smoking, weight, years of education, marital status, age at onset, age at first hospitalisation, number of hospitalisations, duration of illness, length of stay during hospitalisations, BPRS baseline total score, CGI baseline total score, PANSS baseline total score, and PANSS baseline positive score.**
Symptoms	
34 studies, N = 9,386 *Factors significantly associated with better clozapine response were;* Younger age: N = 1,247, g = 0.142, 95%CI 0.021 to 0.263, p = 0.022, I^2 = 10% Paranoid schizophrenia: N = 424, g = 0.259, 95%CI 0.006 to 0.513, p = 0.045, I^2 = 0% Lower PANSS negative score: N = 133, g = 0.719, 95%CI 0.036 to 1.401, I^2 = 67% There were no moderating effects of gender, smoking, weight, years of education, marital status, age at onset, age at first hospitalisation, number of hospitalisations, duration of illness, length of stay during hospitalisations, BPRS baseline total score, CGI baseline total score, PANSS baseline total score, and PANSS baseline positive score.	
Consistency in results	Inconsistent for PANSS negative only.
Precision in results	Imprecise for PANSS negative only.
Directness	Direct

Samara MT, Dold M, Gianatsi M, Nikolakopoulou A, Helfer B, Salanti G, Leucht S

Efficacy, Acceptability, and Tolerability of Antipsychotics in Treatment-Resistant Schizophrenia. A Network Meta-analysis

JAMA Psychiatry 2016; 73(3): 199-210

View review abstract online

Comparison	**Antipsychotics vs. placebo.**

Summary of evidence	**Moderate to high quality evidence (large sample, consistent, precise, some indirectness) suggests a general pattern of superiority for olanzapine, clozapine and risperidone over other antipsychotics, with small effect sizes and few significant differences between antipsychotics in general.**
Overall symptoms	
This review included 40 RCTs, N = 5,172 *Olanzapine was significantly more effective than;* Quetiapine: *g* = -0.29, 95%CI -0.56 to -0.02, *p* < 0.05 Haloperidol: *g* = -0.29, 95%CI -0.44 to 0.13, *p* < 0.05 Sertindole: *g* = -0.46, 95%CI -0.80 to -0.06, *p* < 0.05 *Clozapine was significantly more effective than;* Haloperidol: *g* = -0.22, 95%CI -0.38 to -0.07, *p* < 0.05 Sertindole: *g* = -0.40, 95%CI -0.74 to -0.04, *p* < 0.05 *Risperidone was significantly more effective than;* Sertindole: *g* = -0.32, 95%CI -0.63 to -0.01, *p* < 0.05 There were no other significant differences between aripiprazole, clozapine, chlorpromazine, fluphenazine, haloperidol, olanzapine, perphenazine, quetiapine, risperidone, sertindole, thiothixene, or ziprasidone.	
Positive symptoms	
Risperidone was significantly more efficacious than quetiapine; SMD = -0.43, 95%CI -0.81 to -0.09, *p* < 0.05 *Clozapine was significantly more efficacious than quetiapine;* SMD = -0.40, 95%CI -0.75 to -0.09, *p* < 0.05 *Olanzapine was significantly more efficacious than quetiapine;* SMD = -0.33, 95%CI -0.67 to -0.01, *p* < 0.05 *Risperidone was significantly more efficacious than haloperidol;* SMD = -0.29, 95%CI -0.54 to -0.07, *p* < 0.05 *Clozapine was significantly more efficacious than haloperidol;* SMD = -0.27, 95%CI -0.46 to -0.09, *p* < 0.05	
Negative symptoms	

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Olanzapine was significantly more efficacious than clozapine; SMD = -0.14, 95%CI -0.30 to -0.01, $p < 0.05$ *Olanzapine was significantly more efficacious than risperidone;* SMD = -0.24, 95%CI -0.44 to -0.02, $p < 0.05$ *Olanzapine was significantly more efficacious than haloperidol;* SMD = -0.24, 95%CI -0.40 to -0.04, $p < 0.05$ *Olanzapine was significantly more efficacious than chlorpromazine;* SMD = -0.26, 95%CI -0.51 to -0.02, $p < 0.05$ *Olanzapine was significantly more efficacious than sertindole;* SMD = -0.44, 95%CI -0.81 to -0.08, $p < 0.05$ *Ziprasidone was significantly more efficacious than chlorpromazine;* SMD = -0.26, 95%CI -0.53 to -0.04, $p < 0.05$ *Ziprasidone was significantly more efficacious than sertindole;* SMD = -0.44, 95%CI -0.88 to -0.01, $p < 0.05$	
Response to treatment	
Risperidone was significantly more effective than haloperidol; OR = 2.27, 95%CI 1.11 to 4.73, $p < 0.05$ *Clozapine was significantly more effective than haloperidol;* OR = 2.09, 95%CI 1.26 to 3.82, $p < 0.05$ *Olanzapine was significantly more effective than haloperidol;* OR = 2.00, 95%CI 1.16 to 3.76, $p < 0.05$	
All cause treatment discontinuation	
Olanzapine was significantly more effective than haloperidol; OR = 0.56, 95%CI 0.33 to 0.87, $p < 0.05$ *Olanzapine was significantly more effective than fluphenazine;* OR = 0.24, 95%CI 0.03 to 0.87, $p < 0.05$	
Risks	*Weight gain* Risperidone and haloperidol resulted in less weight gain than clozapine and olanzapine. Ziprasidone and quetiapine resulted in less weight gain than olanzapine. *Extrapyramidal side-effects*

	Clozapine resulted in less antiparkinson medication than risperidone and haloperidol. Ziprasidone, olanzapine and quetiapine resulted in less antiparkinson medication than haloperidol. Fluphenazine resulted in less antiparkinson medication than clozapine. *Sedation* Clozapine resulted in more sedation than ziprasidone, olanzapine quetiapine and risperidone.
Consistency in results	Consistent direct and indirect results after excluding 5 studies.
Precision in results	Precise
Directness	Network analysis; direct and indirect

Siskind D, McCartney L, Goldschlager R, Kisely S

Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis

The British Journal of Psychiatry 2016; 209, 385–392

View review abstract online

Comparison	**Clozapine vs. first generation antipsychotics (chlorpromazine and haloperidol) or second-generation antipsychotics (olanzapine, risperidone, quetiapine and ziprasidone).**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests a small effect of greater improvement in overall symptoms with clozapine, particularly in the short term (< 3 months) and particularly when compared to olanzapine, haloperidol or chlorpromazine.**

Symptoms

A significant, small effect of greater improvement in overall symptoms with clozapine;

24 studies, N = 1,858, SMD = -0.29, 95%CI -0.49 to -0.09, $p < 0.005$

Subgroup analysis found this effect was significant only in the short-term (<3 months) and not the long-term (>3 months). However, it was significant at all time points for positive symptoms, but in the short-term only for negative symptoms.

Studies that were restricted to in-patients, those with higher doses, and those not receiving pharmaceutical company funding showed better effects of clozapine in both the short and long term.

There were no differences in results according to first- or second-generation control conditions. For individual control medications, clozapine was superior to olanzapine, haloperidol and chlorpromazine in the short term. There was no difference compared to risperidone in the short or long term, nor compared to olanzapine in the long term.	
Risks	Participants taking clozapine reported more hypersalivation, tachycardia, seizures, fever, dizziness, sedation, constipation, nausea, and vomiting. There were lower rates of insomnia and dry mouth with clozapine, and no differences in hypotension, headache or weight gain.
Consistency in results	Inconsistent in the short-term.
Precision in results	Precise
Directness	Direct

Siskind DJ, Lee M, Ravindran A, Zhang Q, Ma E, Motamarri B, Kisely S

Augmentation strategies for clozapine refractory schizophrenia: A systematic review and meta-analysis

Australian & New Zealand Journal of Psychiatry 2018; 52(8): 751-767

View review abstract online

Comparison 1	**Clozapine plus antipsychotics vs. clozapine plus placebo.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests a medium-sized effect of greater improvement in overall symptoms with adjunctive aripiprazole, particularly for negative symptoms. Lower quality evidence (small sample) finds a large effect of improved overall symptoms with adjunctive penfluridol.**
Symptoms	
A significant, medium-sized effect of improved total symptoms with adjunctive aripiprazole; 5 studies, N = 486, SMD = -0.57, 95%CI -1.02 to -0.13, $p < 0.05$, $I^2 = 82\%$ *A significant, large effect of improved total symptoms with adjunctive penfluridol;* 1 study, N = 83, SMD = -0.90, 95%CI -1.35 to -0.44, $p < 0.05$ There were no significant benefits of other adjunctive antipsychotics (risperidone, sulpride,	

sertindole, pimozide, haloperidol and olanzapine). Subgroup analyses found no significant benefits of any adjunctive antipsychotic for positive symptoms, but there were significant benefits of adjunctive aripiprazole and adjunctive olanzapine for improving negative symptoms. The results were no longer significant for any of the psychosis outcomes when analyses were restricted to higher quality studies and those that used rating scales to define clozapine resistance.	
Risks	There was more restlessness and less sedation with aripiprazole, with no differences in dizziness, drooling, constipation, tachycardia, abnormal liver function tests, weight gain, hyperprolactinaemia, abnormal electrocardiography, dry mouth, insomnia or headache.
Consistency in results	Inconsistent for aripiprazole.
Precision in results	Precise
Directness	Direct
Comparison 2	**Clozapine plus antidepressants vs. clozapine plus placebo.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, unable to assess consistency, some imprecision, direct) suggests large effects of improved total symptoms with adjunctive fluoxetine, paroxetine and duloxetine.**
Symptoms	
Significant, large effects of improved total symptoms with adjunctive antidepressants; Fluoxetine: 5 studies, N = 296, SMD = -0.73, 95%CI -0.97 to -0.50, $p < 0.05$, I^2 not reported Paroxetine: 1 study, N = 66, SMD = -0.97, 95%CI -1.48 to -0.45, $p < 0.05$ Duloxetine: 1 study, N = 33, SMD = -1.23, 95%CI -1.98 to -0.48, $p < 0.05$ There was no significant benefit of mirtazepine. Subgroup analysis found similar results for negative symptoms, but for positive symptoms, only fluoxetine and paroxetine were significant. The results were no longer significant for positive and negative symptom outcomes when analyses were restricted to higher quality studies.	
Risks	Not reported
Consistency in results	Unable to assess; no measure of consistency is reported, or N/A.
Precision in results	Precise for fluoxetine only.
Directness	Direct

Comparison 3	**Clozapine plus antiepileptics/mood stabilizers vs. clozapine plus placebo.**
Summary of evidence	**Moderate to low quality evidence (small samples, unable to assess consistency, imprecise, direct) suggests large effects of improved total symptoms with adjunctive sodium valproate and lithium.**
Symptoms	
Significant, large effects of improved total symptoms with adjunctive mood stabilizers; Sodium valproate: 2 studies, N = 118, SMD = -2.36, 95%CI -3.96 to -0.75, $p < 0.05$, I^2 not reported Lithium: 1 study, N = 59, SMD = -2.13, 95%CI -2.78 to -1.49, $p < 0.05$ There were no significant benefits of topiramate or lamotrigine. Subgroup analysis found similar results for positive symptoms, with also a benefit of topiramate. Only topiramate was significant for negative symptoms.	
Risks	Not reported
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Imprecise
Directness	Direct
Comparison 4	**Clozapine plus glutamatergic agents vs. clozapine plus placebo.**
Summary of evidence	**Moderate to low quality evidence (small sample, unable to assess consistency, precise, direct) suggests a medium-sized effect of improved negative symptoms with adjunctive memantine.**
Symptoms	
Significant, medium-sized effect of improved negative symptoms with adjunctive memantine; 3 studies, N = 134, SMD = -0.56, 95%CI -0.94 to -0.20, $p < 0.05$, I^2 not reported There were no other significant effects of memantine, glycine or sarcosine.	
Risks	Not reported
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Precise

Directness	Direct
Comparison 5	**Clozapine plus other agents vs. clozapine plus placebo.**
Summary of evidence	**Low quality evidence (very small samples, imprecise, direct) is unsure of the effects of adjunctive minocycline, gingko or ECT.**
Symptoms	
Significant, medium to large effects of improved symptoms with adjunctive; Minocycline for negative symptoms: 1 study, N = 50, SMD = -0.58, 95%CI -1.15 to -0.01, $p < 0.05$ Gingko for total symptoms: 1 study, N = 38, SMD = -2.35, 95%CI -3.20 to -1.50, $p < 0.05$ Gingko for negative symptoms: 1 study, N = 42, SMD = -1.10, 95%CI -1.75 to -0.44, $p < 0.05$ ECT for total symptoms: 1 study, N = 39, SMD = -2.45, 95%CI -3.30 to -1.60, $p < 0.05$ There were no other significant effects of minocycline, ECT or TMS.	
Risks	Not reported
Consistency in results	N/A; all 1 study
Precision in results	Imprecise
Directness	Direct

Zheng W, Xiang YT, Yang XH, Xiang YQ, de Leon J

Clozapine Augmentation With Antiepileptic Drugs for Treatment-Resistant Schizophrenia: A Meta-Analysis of Randomized Controlled Trials

Journal of Clinical Psychiatry 2017; 78(5): e498-e505

View review abstract online

Comparison	**Clozapine plus antiepileptics vs. clozapine monotherapy.** **Mean treatment duration = 12.1 weeks.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) finds adjunctive antiepileptics, particularly topiramate and sodium valproate, were associated with a large improvement in total symptoms.**

Symptoms	
Significant, large effect of greater improvement in total symptoms with adjunctive antiepileptics (topiramate, lamotrigine, sodium valproate and magnesium valproate); Total symptoms (PANSS/BPRS): 19 RCTs, N = 944, SMD = -0.82, 95%CI -1.14 to -0.50, p < 0.00001, I^2 = 81% Subgroup analyses of individual agents showed the effect was significant for topiramate and sodium valproate, but not for magnesium valproate or lamotrigine (after removal of outlier).	
Risks	Topiramate was associated with more all-cause discontinuations.
Consistency in results	Inconsistent
Precision in results	Precise
Directness	Direct

Explanation of acronyms

BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impression, CI = confidence interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MD = mean difference effect size, N = number of participants, OR = odds ratio, p = statistical probability of obtaining that result (p < 0.05 generally regarded as significant), PANSS = Positive and Negative Syndrome Scale, RCT = randomised controlled trial, RR = relative risk, SAPS = Scale for the Assessment of Psychotic Symptoms, SMD = standardised mean difference effect size, vs. = versus

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[13].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[13].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[14]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[13];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[15].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C, which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Samara MT, Dold M, Gianatsi M, et al. (2016): Efficacy, acceptability, and tolerability of antipsychotics in treatment-resistant schizophrenia: A network meta-analysis. *JAMA Psychiatry* 73: 199-210.
4. Barber S, Olotu U, Corsi M, Cipriani A (2017): Clozapine combined with different antipsychotic drugs for treatment-resistant schizophrenia. *Cochrane Database of Systematic Reviews* 3: CD006324.
5. Bartoli F, Crocamo C, Di Brita C, Esposito G, Tabacchi TI, Verrengia E*, et al.* (2019): Adjunctive second-generation antipsychotics for specific symptom domains of schizophrenia resistant to clozapine: A meta-analysis. *Journal of Psychiatric Research* 108: 24-33.
6. Lally J, Tully J, Robertson D, Stubbs B, Gaughran F, MacCabe JH (2016): Augmentation of clozapine with electroconvulsive therapy in treatment resistant schizophrenia: A systematic review and meta-analysis. *Schizophrenia Research* 171: 215-24.
7. Siskind D, McCartney L, Goldschlager R, Kisely S (2016): Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: Systematic review and meta-analysis. *British Journal of Psychiatry* 209: 385-92.
8. Siskind DJ, Lee M, Ravindran A, Zhang Q, Ma E, Motamarri B*, et al.* (2018): Augmentation strategies for clozapine refractory schizophrenia: A systematic review and meta-analysis. *Australian and New Zealand Journal of Psychiatry* 52: 751-67.
9. Zheng W, Xiang YT, Yang XH, Xiang YQ, de Leon J (2017): Clozapine Augmentation With Antiepileptic Drugs for Treatment-Resistant Schizophrenia: A Meta-Analysis of Randomized Controlled Trials. *Journal of Clinical Psychiatry* 78: e498-e505.
10. Jones R, MacCabe JH, Price MJ, Xiangxin L, Upthegrove R (2020): Effect of age on the relative efficacy of clozapine in schizophrenia. *Acta Psychiatrica Scandinavica* 24: doi: 10.1111/acps.13156.
11. Mizuno Y, McCutcheon RA, Brugger SP, Howes OD (2019): Heterogeneity and efficacy of antipsychotic treatment for schizophrenia with or without treatment resistance: a meta-analysis. *Neuropsychopharmacology* 45: 622-31.
12. Okhuijsen-Pfeifer C, Sterk AY, Horn IM, Terstappen J, Kahn RS, Luykx JJ (2020): Demographic and clinical features as predictors of clozapine response in patients with schizophrenia spectrum disorders: a systematic review and meta-analysis. *Neuroscience and biobehavioral reviews* 111: 246-52.
13. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
14. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
15. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*