TECHNICAL COMMENTARY

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Antipsychotic polypharmacy

Introduction

Antipsychotic combination treatment, also called polypharmacy, has been utilised in clinical practice for patients who are unresponsive or partially responsive to antipsychotic monotherapies. This topic covers antipsychotic combinations; for adjunctive treatments other than antipsychotics, please see the adjunctive treatments topics.

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 11 reviews that met our inclusion criteria[3-13].

- Moderate to high quality evidence finds a medium-sized improvement in overall symptoms, and a small improvement in clinical response, with antipsychotic polypharmacy vs. monotherapy. There is also less study discontinuation for any reason with antipsychotic polypharmacy. However, studies assessing rates of relapse after switching from polypharmacy to monotherapies found no differences in relapse rates and more study discontinuation with polypharmacy.
- Moderate quality evidence finds antipsychotic polypharmacy is most often associated with the use of first-generation antipsychotics and with inpatient status and

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is higher in Asia and Europe than in North America and Oceania.

- Moderate quality evidence finds augmenting any antipsychotic with aripiprazole can improve symptoms, particularly negative symptoms, when compared to antipsychotic monotherapy in open-label trials, but not when compared to adjunctive placebo in blinded trials.
- 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.

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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. <u>Clozapine plus risperidone vs. clozapine plus ziprasidone</u> 1 RCT, N = 24: no differences in clinical response, PANSS positive, PANSS negative, global state or leaving the study early. <u>Clozapine plus aripiprazole vs. clozapine plus haloperidol</u> 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.

Correll CU, Rummel-Kluge C, Corves C, Kane JM, Leucht S

Antipsychotic Combinations vs. Monotherapy in Schizophrenia: A Meta-analysis of Randomized Controlled Trials

Schizophrenia Bulletin 2009; 35(2): 443-457

View review abstract online

Comparison	**Any antipsychotic vs. combination of the same antipsychotic plus any other antipsychotic for schizophrenia spectrum disorders.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests a small effect of less discontinuation for any reason with combination vs. monotherapy. Moderate quality evidence (inconsistent) suggests a small effect of better clinical response with combination therapy.**
Symptoms	

A small effect of better clinical response with antipsychotic combination therapy; 22 RCTs, N = 1,202, RR = 0.76, 95%CI 0.63 to 0.90, $p = 0.002$, NNT = 7, $I^2 = 79\%$, $p < 0.00001$ Meta-regression showed significant moderators increasing the effects of combination therapy were; comparative rather than reduced co-treatment dose, combination second generation + first generation antipsychotics, and concurrent polypharmacy initiation rather than augmentation with a second antipsychotic. Trending moderators were; combinations involving clozapine, trial duration >10 weeks, and trial blinding. No differences in the results of trials of acute or chronic patients. Authors report possible publication bias.	
Risks	A small effect of less discontinuation for any reason with antipsychotic combination therapy (20 RCTs, N = 1,052, RR = 0.65, 95%CI 0.54 to 0.78, $p < 0.00001$, $I^2 = 0\%$, $p < 0.50$). The only reported difference in adverse events was prolactin levels were significantly higher when sulpiride or risperidone was added to clozapine (2 RCTs, N = 86, WMD = 65.1, 95%CI 51.1 to 79.1, $p < 0.00001$).
Consistency in results	Consistent for discontinuation, inconsistent for clinical response, not reported for prolactin levels.
Precision in results	Precise, unable to assess for prolactin levels (not SMD).
Directness of results	Direct

Gallego JA, Bonetti J, Zhang J, Kane JM, Correll CU

Prevalence and correlates of antipsychotic polypharmacy: A systematic review and meta-regression of global and regional trends from the 1970s to 2009

Schizophrenia Research 2012; 138(1): 18-28

View review abstract online

Comparison	**Use of antipsychotic polypharmacy between 1970 and 2009 in people with schizophrenia.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests antipsychotic polypharmacy is most often associated with the use of first-generation antipsychotics, inpatient status, and a diagnosis of schizophrenia. Polypharmacy use has been higher in Asia and Europe than in North America and Oceania.**

Factors associated with polypharmacy use	
147 studies (N = 1,418,163) Polypharmacy was associated with inpatient status ($p < 0.001$), use of first generation antipsychotics ($p < 0.0001$) and anticholinergics ($p < 0.001$), schizophrenia diagnosis ($p = 0.01$), less antidepressant use ($p = 0.02$), greater long-acting injectable use ($p = 0.04$), shorter study follow-up ($p = 0.001$) and cross-sectional vs. longitudinal study design ($p = 0.03$), although meta-regression showed the most important predictors were inpatient status ($p < 0.0001$), first generation antipsychotics use ($p < 0.046$), and schizophrenia diagnosis ($p < 0.004$) when all other factors were controlled. Polypharmacy was higher in Asia and Europe than North America, and also higher in Asia than Oceania ($p < 0.001$). Polypharmacy increased by 34% in North America from the 1980s (12.7%) to 2000s (17.0%) and decreased significantly in Asia from 1980 (55.5%) to 2000 (19.2%, $p = 0.03$), with non-significant changes in Europe.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Galling B, Roldan A, Hagi K, Rietschel L, Walyzada F, Zheng W, Cao XL, Xiang YT, Zink M, Kane JM, Nielsen J, Leucht S, Correll CU

Antipsychotic augmentation vs. monotherapy in schizophrenia: systematic review, meta-analysis and meta-regression analysis

World Psychiatry 2017; 16: 77-89

View review abstract online

Comparison	**Any antipsychotic polypharmacy vs. any antipsychotic monotherapy.**
Summary of evidence	**Moderate to high quality evidence (large sample, appears inconsistent, precise, direct) finds a medium-sized improvement in overall symptoms with antipsychotic polypharmacy, although the results were only significant in poor quality trials.**
Symptoms	
A significant, medium-sized improvement in overall symptoms with antipsychotic polypharmacy; 16 RCTs, N = 694, SMD = -0.53, 95%CI -0.87 to -0.19, $p = 0.002$ Subgroup analysis found this effect was significant only in open-label (SMD = -0.81) and low-quality	

trials (SMD = -0.83), and not in double-blind (SMD = -0.36) and high-quality trials (SMD = -0.30). The effect was significant only in studies conducted in China (SMD = -0.86), and not studies conducted in Europe (SMD = -0.40), North America (SMD = -0.30). Studies conducted in other regions showed a significant effect (SMD = -0.71). There were no differences according to setting (inpatient vs. outpatient), clozapine or non-clozapine augmentation, partial D2 agonist vs. D2 antagonist augmentation, or strict vs. lenient non-response criteria. Subgroup analyses of symptom clusters showed only negative symptoms improved in studies augmenting D2 antagonists with a partial D2 agonist (SMD = -0.41). There were no differences in positive symptoms (SMD = -0.25). Meta-regressions showed higher augmentation doses relative to monotherapy dose and more severe symptoms were associated with smaller effect sizes.	
Risks	There were no differences in all-cause discontinuation. D2 antagonist augmentation was associated with less insomnia, but more prolactin elevation. Aripiprazole augmentation was associated with reduced prolactin levels and body weight.
Consistency in results	Appears inconsistent
Precision in results	Precise
Directness of results	Direct

Matsui K, Tokumasu T, Takekita Y, Inada K, Kanazawa T, Kishimoto T, Takasu S, Tani H, Tarutani S, Hashimoto N, Yamada H, Yamanouchi Y, Takeuchi H

Switching to antipsychotic monotherapy vs. staying on antipsychotic polypharmacy in schizophrenia: A systematic review and meta-analysis

Schizophrenia Research 2019; 209: 50-57

View review abstract online

Comparison	**Switching to any antipsychotic monotherapy vs. continuing on any two antipsychotics.**
Summary of evidence	**Moderate quality evidence (small sample, consistent, imprecise, direct) finds no differences in relapses, but more study discontinuation with polypharmacy.**
Symptoms	
There were no differences between groups in rates of relapse;	

4 RCTs, N = 123, RR = 1.43, 95%CI 0.38 to 5.32, p = 0.59, I^2 = 0%	
Risks	There was more study discontinuation due to all causes with polypharmacy. There were no significant differences in extrapyramidal symptoms, or bodyweight/BMI.
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Ortiz-Orendain J, Castiello-de Obeso S, Colunga-Lozano LE, Hu Y, Maayan N, Adams CE

Antipsychotic combinations for schizophrenia

Cochrane Database of Systematic Reviews 2017; 6: CD009005

View review abstract online

Comparison	**Any antipsychotic polypharmacy vs. any antipsychotic monotherapy.**
Summary of evidence	**Moderate to high quality evidence (large sample, appears inconsistent, precise, direct) finds a small effect of more clinical response with antipsychotic polypharmacy, particularly with clozapine or other second-generation antipsychotics.**
A significant, small effect of more clinical response with polypharmacy; 29 RCTs, N = 2,398, RR = 0.73, 95%CI 0.64 to 0.83, p < 0.00001, I^2 = 82%, p < 0.001 Subgroup analyses showed the effect was due to studies with clozapine or other second-generation antipsychotics in both the monotherapy and combination groups.	
Risks	There were no differences in all-cause discontinuation or adverse events.
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	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

Taylor DM, Smith L, Gee SH, Nielsen J

Augmentation of clozapine with a second antipsychotic – a meta-analysis

Acta Psychiatrica Scandinavica 2012; 125: 15–24

View review abstract online

Comparison	**Clozapine augmentation vs. placebo augmentation for people with schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests a small effect of improved symptoms with augmentation of clozapine with another antipsychotic vs. placebo.**
Symptoms	
Augmentation of clozapine with a second antipsychotic conferred a small benefit over placebo; 14 RCTs (blinded), N = 734, SMD -0.239, 95%CI -0.452 to -0.026, $p = 0.028$, $I^2 = 40.1\%$, $p < 0.055$ Meta-regression showed no relationship between effect size and length of treatment (6 to 24 weeks). Note: 5 RCTs included risperidone, 3 included aripiprazole and 1 each included amisulpride, pimozide, haloperidol, sertindole, sulpiride, or chlorpromazine. Authors report no publication bias.	
Risks	No differences between groups for discontinuing antipsychotic augmentation.
Consistency in results	Borderline inconsistent
Precision in results	Precise
Directness of results	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.**
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

Zheng W, Zheng YJ, Li XB, Tang YL, Wang CY, Xiang YQ, de Leon J

Efficacy and Safety of Adjunctive Aripiprazole in Schizophrenia: Meta-Analysis of Randomized Controlled Trials

Journal of Clinical Psychopharmacology 2016; 36: 628-36

View review abstract online

Comparison	**Adjunctive aripiprazole (14.0 +/- 7.0 mg/d) vs. adjunctive placebo or antipsychotic monotherapy.** **Treatment ranged from 4 to 24 weeks.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, precise, some indirectness) finds adjunctive aripiprazole can improve symptoms, particularly negative symptoms, compared to antipsychotic monotherapy, but not compared to placebo.**

Symptoms	
Significant, medium-sized effect of improved total symptoms with adjunctive aripiprazole; 43 RCTs, N = 3,351, SMD = -0.48, 95%CI -0.68 to -0.28, $p < 0.00001$, $I^2 = 88\%$ This result remained significant in the subgroup analysis of open-label antipsychotic monotherapy comparison, but not in the subgroup analysis of blinded, placebo-controlled comparison. It was also not significant in the subgroup analysis trials assessed as being high quality. *Significant, improvements in negative and general symptoms with adjunctive aripiprazole;* Negative symptoms: 30 RCTs, N = 2,294, SMD = -0.61, 95%CI -0.91 to -0.31, $p < 0.00001$, $I^2 = 91\%$ General symptoms: 13 RCTs, N = 1,138, WMD = -4.02, 95%CI -7.23 to -0.81, $p = 0.01$, $I^2 = 99\%$ *There were no significant differences in positive symptoms;* 29 RCTs, N = 2,223, SMD = -0.01, 95%CI 0.26 to 0.25, $p = 0.95$, $I^2 = 88\%$	
Risks	There was less weight gain with adjunctive aripiprazole, particularly in females.
Consistency in results	Inconsistent
Precision in results	Precise
Directness	Indirect for placebo and antipsychotic comparisons combined, and where antipsychotic classes are combined.

Explanation of acronyms

BPRS = Brief Psychiatric Rating Scale, CI = confidence interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences (see below for interpretation of effect size) I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, NNT = number needed to treat, *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 = risk ratio, SMD = standardised mean difference, vs. = versus, WMD = weighted mean difference

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[14].

† 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).

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[14].

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[15]. 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.

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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[14];

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

§ 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[16].

‖ 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.

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