TECHNICAL COMMENTARY

Polypharmacy

Introduction

Medication combination treatment, also called polypharmacy, has been utilised in clinical practice for patients who are unresponsive or partially responsive to monotherapies. This topic covers antipsychotic, mood stabiliser, and/or antidepressant combinations for people with bipolar disorder.

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 2010 that report results separately for people with a diagnosis of bipolar or related disorders. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, the most recent and/or most comprehensive review 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 that describes a preferred way to present a meta-analysis[1]. Reviews reporting less than 50% of items 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 seven reviews that met our inclusion criteria[3-9].

Any combination therapy vs. placebo

- Moderate quality evidence suggests fewer relapses with combination therapy than with monotherapy or placebo. The risk of relapse is highest in the first year of treatment.
- Moderate quality evidence finds the following combination medications reduced overall relapse rates more than placebo (in descending order of effectiveness); aripiprazole + valproate, lithium + oxcarbazepine, lithium + valproate, and aripiprazole + lamotrigine.

Antipsychotic olanzapine + antidepressant fluoxetine vs. placebo, olanzapine or anticonvulsant lamotrigine

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- Moderate to high quality evidence suggests greater improvement in depression with combined olanzapine + fluoxetine therapy.

Second-generation antidepressants + mood stabilisers or antipsychotics vs. placebo + mood stabilisers or antipsychotics

- Moderate to high quality evidence suggests adjunctive second generation antidepressants were associated with a small, significant effect of greater improvement in depressive symptoms, but only over the short-term (< 12 weeks). There was also an increased risk of switching to mania/hypomania in the longer term (~52 weeks).

Second generation antipsychotics + mood stabilisers vs. placebo + mood stabilisers

- Moderate quality evidence finds a medium-sized reduction in relapse to any mood episode after 6 months of treatment with second-generation antipsychotics plus mood stabilisers (mostly lithium and valproate) compared to placebo plus mood stabilisers. The effect size was similar for relapse to depression or relapse to mania. Aripiprazole + mood stabilisers and quetiapine + mood stabilisers prevented both depression and mania relapses, while lurasidone + mood stabilisers was more effective for preventing relapse to depression, and ziprasidone + mood stabilisers was more effective for preventing relapse to mania.

Mood stabilisers + antipsychotics vs. mood stabilisers

- Moderate to high quality evidence suggests mood stabilisers + antipsychotics resulted in small effects of better response and remission, and improved mania and depression symptoms. However, there are also increased rates of discontinuation due to adverse effects, in particular, sleepiness, somnolence, weakness, faintness, dizzyness, appetite, weight gain, tremor, use of antiparkinsonian drugs, dry mouth and thirst, and changes in triglycerides, fasting glucose, and HbA1c levels.

Mood stabilisers + antipsychotics vs. antipsychotics

- Moderate quality evidence suggests mood stabilisers + antipsychotics results in small effects of better response and remission, and improved mania but not depression. However, there are medium-sized to large effects of more tremor, sleepiness, and vomiting.

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Farooq S, Singh SP

Fixed dose-combination products in psychiatry: Systematic review and meta-analysis

Journal of Psychopharmacology 2015; 29: 556-64

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Comparison	**7-8 weeks of olanzapine + fluoxetine vs. placebo, olanzapine or lamotrigine.**
Summary of evidence	**Moderate to high quality evidence (large samples, imprecise, consistent, direct) suggests greater improvement in depression with combined olanzapine + fluoxetine therapy than with placebo, olanzapine or lamotrigine.**
Depression	
Greater improvement in depression scores with combination therapy; 3 RCTs, N = 1,300, SMD = -0.32, 95%CI -0.45 to -0.19, $p < 0.001$, NNT = 16 *Results were similar in each comparison/trial;* Olanzapine + fluoxetine vs. placebo; 1 RCT, N = 463, SMD = -0.44, 95%CI 0.68 to -0.20, $p < 0.001$ Olanzapine + fluoxetine vs. lamotrigine; 1 RCT, N = 381, SMD = -0.27, 95%CI 0.47 to -0.07, $p = 0.01$ Olanzapine + fluoxetine vs. olanzapine; 1 RCT, N = 456, SMD = -0.26, 95%CI -0.50 to -0.03, $p = 0.03$	
Risks	Not reported
Consistency in results‡	Consistent
Precision in results§	Imprecise
Directness of results‖	Direct for individual comparisons.

Frecska E, Kovacs AI, Balla P, Falussy L, Ferencz A, Varga Z

The message of the survival curves: I. Composite analysis of long-term treatment studies in bipolar disorder

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Neuropsychopharmacologia Hungarica 2012; 14: 155-64 View review abstract online	
Comparison	**Any combination therapy vs. any monotherapy vs. placebo.**
Summary of evidence	**Moderate quality evidence (large sample, precise for NNTs, unable to assess consistency, indirect) suggests fewer relapses with any combination therapy than any monotherapy or placebo. The risk of relapse is highest in the first year.**
Relapse	
28 studies, N = 5,231 *Fewer relapses with combination therapy than with placebo or monotherapy;* Combination vs. placebo: $chi^2 = 283.3$, $p < 0.0001$ Combination vs. monotherapy: $chi^2 = 55.2$, $p < 0.001$ Monotherapy NNT = 6, 95%CI 5.9 to 6.1 Combination NNT = 3, 95%CI 2.9 to 3.1 By 1 year: 48% relapsed with monotherapy vs. 35% with combination therapy By 2 years: 57% relapsed with monotherapy vs. 42% with combination therapy Authors report that from 12 to 28 months, relapse rates decrease, with rates being similar between the three groups; 15% with monotherapy,14% with combination therapy,14% with placebo. However, within the group of patients who remained stable until 1 year, the NNTs after one year were 14 with monotherapy and 8 with combination therapy.	
Risks	Not reported
Consistency in results	No measure of consistency is reported.
Precision in results	NNTs appear precise.
Directness of results	Indirect; mixed treatment and control classes.

Galling B, Garcia MA, Osuchukwu U, Hagi K, Correll CU

Safety and tolerability of antipsychotic-mood stabilizer co-treatment in the management of acute bipolar disorder: results from a systematic review and exploratory meta-analysis

Expert Opinion on Drug Safety 2015; 14: 1181-99

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Comparison 1	**3-12 weeks of mood stabilisers + antipsychotics vs. mood stabilisers alone.**
Summary of evidence	**Moderate to high quality evidence (large samples, imprecise or inconsistent, direct) suggests that compared to mood stabilisers alone, mood stabilisers + antipsychotics results in increased discontinuation due to adverse effects, in particular; more tremor and use of antiparkinsonian drugs; dry mouth/thirst; sleepiness, weakness, and faintness/dizzyness; greater appetite and weight gain; and more change in triglycerides, fasting glucose, and HbA1c levels.**
Discontinuation	
Small effect of more discontinuation due to adverse effects with combination therapy; 15 RCTs, N = 3,997, RR = 1.541, 95%CI 1.095 to 2.171, $p = 0.013$, test for heterogeneity $p = 0.041$	
Movement disorders	
Small to medium-sized effects of more extrapyramidal adverse effects with combination therapy, in particular tremor and use of antiparkinsonian drugs; At least one extrapyramidal adverse effect: 10 RCTs, N = 2,448, RR = 1.804, 95%CI 1.144 to 2.845, $p = 0.011$, test for heterogeneity $p < 0.001$ Tremor: 14 RCTs, N = 3,950, RR = 1.354, 95%CI 1.067 to 1.717, $p = 0.013$, test for heterogeneity $p = 0.501$ Use of antiparkinsonian drugs: 6 RCTs, N = 1990, RR = 2.839, 95%CI 1.983 to 4.065, $p < 0.001$, test for heterogeneity $p = 0.911$ There were no significant differences between groups in levels of akathisia, dyskinesia, hypokinesia, dystonia, parkinsonism, rigidity, or tardive dyskinesia.	
Anticholinergic	
Medium-sized effect of more thirst or dry mouth with combination therapy; Thirst, dry mouth: 11 RCTs, N = 2311, RR = 3.241, 95%CI 2.197 to 4.781, $p < 0.001$, test for heterogeneity $p = 0.173$ There were no significant differences between groups in levels of blurred vision.	
Arousal	
Medium-sized effect of more sleepiness or somnolence with combination therapy; Sleepiness/somnolence: 15 RCTs, N = 3,875, RR = 2.830, 95%CI 2.226 to 3.598, $p < 0.001$, test for heterogeneity $p = 0.130$	

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There were no significant differences between groups in levels of excitement, insomnia, or sedation.
Cardiovascular
Small effect of more faintness or dizziness with combination therapy; Faintness/dizziness: 12 RCTs, N = 2,908, RR = 1.838, 95%CI 1.360 to 2.483, $p < 0.001$, test for heterogeneity $p = 0.949$ There were no significant differences between groups in levels of electrocardiography abnormalities, orthostasis, or QTc average change.
Central nervous system
Small effect of more weakness or fatigue with combination therapy; 8 RCTs, N = 1,885, RR = 1.693, 95%CI 1.155 to 2.480, $p = 0.007$, test for heterogeneity $p = 0.344$ There were no significant differences between groups in levels of anxiety, nervousness, depression, mania, or headache.
Appetite and weight adverse events
Medium-sized effects of more appetite and weight gain with combination therapy; Increased appetite: 5 RCTs, N = 1,297, RR = 2.366, 95%CI 1.539 to 3.637, $p < 0.001$, test for heterogeneity $p = 0.612$ Any weight gain: 9 RCTs, N = 2,484, RR = 2.905, 95%CI 1.746 to 4.835, $p < 0.001$, test for heterogeneity $p = 0.131$ Weight gain > 7%: 9 RCTs, N = 2,413, RR = 3.674, 95%CI 2.273 to 5.939, $p < 0.001$, test for heterogeneity $p = 0.075$
Metabolic and endocrine
Small effects of more change in triglycerides, fasting glucose and HbA1c with combination therapy; Triglycerides: 5 RCTs, N = 1271, SMD = 0.212, 95%CI 0.102 to 0.323, $p < 0.001$, test for heterogeneity $p = 0.507$ Fasting glucose: 5 RCTs, N = 1340, SMD = 0.201, 95%CI 0.085 to 0.317, $p = 0.001$, test for heterogeneity $p = 0.333$ HbA1c: 3 RCTs, N = 911, SMD = 0.252, 95%CI 0.082 to 0.421, $p = 0.004$, test for heterogeneity $p = 0.193$ There were no differences between groups in levels of cholesterol, fasting glucose, insulin, prolactin or ALT levels.
Other adverse events

There were no differences between groups in levels of gastrointestinal, exanthema/Rash, rhinitis/ nasopharyngitis/, upper respiratory tract infection or oedema.	
Consistency in results	Consistent, apart from extrapyramidal adverse effects and discontinuation.
Precision in results	Imprecise, apart from metabolic and endocrine.
Directness of results	Direct
Comparison 2	**3-6 weeks of mood stabilisers + antipsychotics vs. antipsychotics alone.**
Summary of evidence	**Moderate quality evidence (medium-sized samples, imprecise, direct) suggests that, compared to antipsychotics alone, mood stabilisers + antipsychotics results in increased medium-sized to large effects of more tremor, sleepiness, and vomiting.**
Movement disorders	
Medium-sized effect of more tremor with combination therapy; Tremor: 1 RCT, N = 356, RR = 3.173, 95%CI 1.537 to 6.554, *p* = 0.002	
Arousal	
Medium-sized effect of more sleepiness with combination therapy; Sleepiness/somnolence: 1 RCT, N = 356, RR = 2.327, 95%CI 1.135 to 4.772, *p* = 0.021	
Gastrointestinal	
Large effect of more vomiting with combination therapy; Vomiting: 1 RCT, N = 356, RR = 17.977, 95%CI 1.045 to 309.1, *p* = 0.047 There were no differences between groups in levels of constipation, diarrhea, nausea, and dyspepsia	
Other adverse events	
There were no differences between groups in levels of discontinuation, thirst, dry mouth, insomnia, cardiovascular factors, central nervous system factors, appetite and weight, prolactin, and exanthema/rash factors.	
Consistency in results	Not applicable; 1 RCT.
Precision in results	Imprecise
Directness of results	Direct

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

Kishi T, Ikuta T, Matsuda Y, Sakuma K, Okuya M, Mishima K, Iwata N

Mood stabilizers and/or antipsychotics for bipolar disorder in the maintenance phase: a systematic review and network meta-analysis of randomized controlled trials

Molecular Psychiatry 2021; 26(8): 4146-57

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Comparison 1	**Any combination medications vs. placebo or other medications.** **Mean study duration 70.5 weeks.**
Summary of evidence	**Moderate quality evidence (large sample, consistent, mostly imprecise, indirect) finds the following combination medications reduced overall relapse rates more than placebo (in descending order of effectiveness); aripiprazole + valproate, lithium + oxcarbazepine, lithium + valproate, and aripiprazole + lamotrigine.**
Relapse to any mood episode	
42 RCTs, N = 9,821 *The following combination treatments reduced overall relapse rates more than placebo (in descending order of effectiveness);* Aripiprazole + valproate: RR = 0.292, 95%CI 0.114 to 0.748, $p < 0.05$ Lithium + oxcarbazepine: RR = 0.409, 95%CI 0.212 to 0.792, $p < 0.05$ Lithium + valproate: RR = 0.525, 95%CI 0.363 to 0.760, $p < 0.05$ Aripiprazole + lamotrigine: RR = 0.530, 95%CI 0.324 to 0.868, $p < 0.05$	
Consistency in results	Authors report results are reasonably consistent
Precision in results	Precise for lithium + valproate only.
Directness of results	Indirect; network meta-analysis.
Comparison 2	**Second-generation antipsychotics plus lithium or valproate vs. placebo plus lithium or valproate.**
Summary of evidence	**Moderate quality evidence (large sample, consistent, some imprecision, indirect) finds the following antipsychotics added to lithium or valproate reduced overall relapse rates more than placebo added to lithium or valproate (in descending order of effectiveness); quetiapine, lurasidone, aripiprazole and ziprasidone. Adding olanzapine performed no better than adding**

	placebo. **For mania relapse, adding aripiprazole or quetiapine outperformed placebo. For depression relapse, adding lurasidone or quetiapine outperformed placebo, aripiprazole, and ziprasidone.** **For all-cause discontinuation, adding lurasidone or quetiapine outperformed placebo.**
Relapse to any mood episode	
5 RCTs, N = 2,399 *The following treatments reduced overall relapse rates more than placebo (in descending order of effectiveness);* Quetiapine + lithium or valproate: RR = 0.383, 95%CI 0.322 to 0.456, $p < 0.05$ Lurasidone + lithium or valproate: RR = 0.402, 95%CI 0.306 to 0.528, $p < 0.05$ Aripiprazole + lithium or valproate: RR = 0.595, 95%CI 0.396 to 0.894, $p < 0.05$ Ziprasidone + lithium or valproate: RR = 0.607, 95%CI 0.390 to 0.944, $p < 0.05$ Olanzapine + lithium or valproate performed no better than placebo. Lurasidone + lithium or valproate and quetiapine + lithium or valproate outperformed olanzapine + lithium or valproate. For mania relapse, aripiprazole + lithium or valproate and quetiapine + lithium or valproate outperformed placebo + lithium or valproate. For depression relapse, lurasidone + lithium or valproate and quetiapine + lithium or valproate outperformed placebo + lithium or valproate, aripiprazole + lithium or valproate, and ziprasidone + lithium or valproate.	
Risks	Lurasidone + lithium or valproate and quetiapine + lithium or valproate outperformed placebo + lithium or valproate for all-cause discontinuation. Quetiapine + lithium or valproate was associated with a higher incidence of somnolence compared with placebo + lithium or valproate. Olanzapine + lithium or valproate and quetiapine + lithium or valproate were associated with a lower incidence of insomnia compared with placebo + lithium or valproate. Olanzapine + lithium or valproate and quetiapine + lithium or valproate were associated with a higher incidence of increased weight compared with placebo + lithium or valproate and Aripiprazole + lithium or valproate.
Consistency in results	Authors report results are reasonably consistent.

Precision in results	Precise for quetiapine and lurasidone analyses only.
Directness of results	Indirect; network meta-analysis.

Kishi T, Sakuma K, Okuya M, Matsuda Y, Esumi S, Hashimoto Y, Hatano M, Miyake N, Miura I, Mishima K, Iwata N

Effects of a conventional mood stabilizer alone or in combination with second-generation antipsychotics on recurrence rate and discontinuation rate in bipolar I disorder in the maintenance phase: A systematic review and meta-analysis of randomized, placebo-controlled trials

Bipolar Disorders: 2021; doi: 10.1111/bdi.13053

View review abstract online

Comparison	**Second-generation antipsychotics (aripiprazole, lurasidone, olanzapine, quetiapine, or ziprasidone) + mood stabilisers (lithium, valproate, lamotrigine, or divalproex) vs. placebo + mood stabilisers.** **Mean study duration = 58.25 ± 33.63 weeks**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, imprecise, direct) finds a medium-sized reduction in relapse to any mood episode after 6 months of treatment with second-generation antipsychotics plus mood stabilisers compared to placebo plus mood stabilisers. The effect size was similar for relapse to depression or relapse to mania. Aripiprazole + mood stabilisers and quetiapine + mood stabilisers prevented both depression and mania relapses, while lurasidone + mood stabilisers was more effective for preventing relapse to depression, and ziprasidone + mood stabilisers was more effective for preventing relapse to mania.**

Relapse to any mood episode

A medium-sized effect showed second-generation antipsychotics plus mood stabilisers showed lower rates of any relapse by 6 months than placebo plus mood stabilisers;

8 RCTs, N = 2,850, RR = 0.51, 95%CI 0.39 to 0.86, $p < 0.05$, $I^2 = 73\%$

Subgroup analysis showed similar effect sizes for relapse to mania (RR = 0.42) and depression (RR = 0.39).

Results were similar to the overall results for aripiprazole + mood stabilisers and quetiapine + mood

stabilisers, while lurasidone + mood stabilisers was more effective for preventing relapse to depression than mania, and ziprasidone + mood stabilisers was more effective for preventing relapse to mania than depression.	
Risks	There was less all-cause discontinuation with second-generation antipsychotics + mood stabilisers.
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

McGirr A, Vohringer PA, Ghaemi SN, Lam RW, Yatham LN

Safety and efficacy of adjunctive second-generation antidepressant therapy with a mood stabiliser or an atypical antipsychotic in acute bipolar depression: a systematic review and meta-analysis of randomised placebo-controlled trials

The Lancet Psychiatry 2016; 3: 1138-46

View review abstract online

Comparison	**6-12 weeks of adjunctive second-generation antidepressants (+ mood stabilsers or second-generation antipsychotics) vs. adjunctive placebo (+ mood stabilsers or second-generation antipsychotics) in people with bipolar depression.**
Summary of evidence	**Moderate to high quality evidence (large samples, imprecise, consistent, direct) suggests adjunctive second-generation antidepressants (+ mood stabilisers or antipsychotics) were associated with a small, significant effect of greater improvement in depressive symptom scores than with placebo (+ mood stabilisers or antipsychotics), but only over the short-term (< 12 weeks). There is also an increased risk of mania/hypomania switching in the longer term (~52 weeks).**
Symptoms	
Adjunctive second-generation antidepressants (+ mood stabilisers or antipsychotics) were associated with a small, significant effect of greater improvement in depressive symptom scores than with placebo (+ mood stabilisers or antipsychotics), but only over the short-term; 6 RCTs, N = 1,383, SMD = 0.165, 95%CI 0.051 to 0.278, $p = 0.004$, $I^2 = 0\%$, $p < 0.05$ There were no differences between groups in clinical response or remission rates, and meta-	

regression found decreasing efficacy with increasing trial duration. Authors report no evidence of publication bias.	
Risks	There were no differences between groups in risk of treatment-emergent mania or hypomania in the short term (6-12 weeks), but in the longer term (follow-up ~52 weeks) there was a small increased risk of emergent mania/hypomania (2 RCTs, N = 463, OR = 1.774, 95%CI 1.018 to 3.091, *p* = 0.043).
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct for adjunctive antidepressants.

Ogawa Y, Tajika A, Takeshima N, Hayasaka Y, Furukawa TA

Mood stabilizers and antipsychotics for acute mania: a systematic review and meta-analysis of combination/augmentation therapy versus monotherapy

CNS Drugs 2014; 28: 989-1003

View review abstract online

Comparison 1	**3-12 weeks of mood stabilisers + antipsychotics vs. mood stabilisers alone.**
Summary of evidence	**Moderate to high quality evidence (large samples, some inconsistency or imprecision, direct) suggests small effects of better response and remission rates, and improved mania and depression symptoms with combined mood stabilisers + antipsychotics compared to mood stabilisers alone. However, more participants in the combination therapy group experienced at least one side effect, in particular somnolence and weight gain. Adding haloperidol or aripiprazole significantly increased extrapyramidal symptoms.**
Response and remission	
Small, significant effects of better response and remission rates with mood stabilisers + antipsychotics than mood stabilisers alone; Remission: 12 RCTs, N = 3,164, RR = 1.17, 1.07 to 1.28, $p < 0.05$, $I^2 = 23\%$ Response: 11 RCTs, (N not reported), RR 1.25, 1.14 to 1.36, $p < 0.05$, $I^2 = 6\%$	

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Mania	
Small, significant effect of improved mania symptoms with mood stabilisers + antipsychotics than mood stabilisers alone; 12 RCTs, N = 3,164, SMD = -0.26, 95%CI -0.36 to -0.15, $p < 0.05$, $I^2 = 47\%$, $p = 0.03$ Results were similar for individual adjunctive antipsychotics haloperidol, asenapine, olanzapine, quetiapine, risperidone and ziprasidone. Results for adjunctive aripiprazole and paliperidone were were not significantly different to mood stabilisers alone.	
Depression	
Small, significant effect of improved depression symptoms with mood stabilisers + antipsychotics than mood stabilisers alone; 6 RCTs, (N not reported), SMD = -0.21, 95%CI -0.37 to -0.06, $p < 0.05$, I^2 not reported This result was particularly relevant for mood stabilisers + olanzapine.	
Risks	The dropout rates due to inefficacy showed a statistically significant superiority for the combination therapy (12 RCTs, N = 3,164, RR = 0.62, 95%CI 0.47 to 0.82, $p < 0.05$, I^2 not reported). However, significantly more participants in the combination therapy group experienced at least one side effect (8 RCTs, RR = 1.18, 95%CI 1.08 to 1.30, $p < 0.05$, $I^2 = 28\%$), in particular somnolence (9 RCTs, RR = 2.46, 95%CI 1.91 to 3.18, $p < 0.05$, $I^2 = 0\%$) and weight gain (7 RCTs, RR - 3.72, 95%CI 2.46 to 5.63, $p < 0.05$, $I^2 = 0\%$). Adding haloperidol (2 RCTs, RR = 6.01, 95%CI 1.55 to 23.4, $p < 0.05$, I^2 not reported) and aripiprazole (1 RCT, RR = 2.03, 95%CI 1.26 to 3.25, $p < 0.05$) significantly increased extrapyramidal symptoms. There were no differences between groups in tremor and depression.
Consistency in results	Inconsistent for mania symptoms.
Precision in results	Precise, apart from somnolence, weight gain, and extrapyramidal symptoms.
Directness of results	Direct
Comparison 2	**3-6 weeks of mood stabilisers + antipsychotics vs. antipsychotics alone.**
Summary of evidence	**Moderate quality evidence (medium-sized samples, some inconsistency or imprecision, direct) suggests small effects of better response and remission rates, and improved mania with combined mood stabilisers + antipsychotics compared to antipsychotics alone.**

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Response and remission	
Small, significant effects of better response and remission rates with lithium or valproate + antipsychotics than antipsychotics alone; Response: 4 RCTs, (N not reported), RR = 1.24, 1.11 to 1.39, $p < 0.05$, I^2 not reported Remission: 2 RCTs, (N not reported), RR = 1.28, 1.12 to 1.47, $p < 0.05$, I^2 not reported	
Mania	
Small, significant effects of more improved symptoms with lithium + antipsychotics than antipsychotics alone; 3 RCTs, N = 426, SMD -0.31, 95%CI -0.50 to -0.12, $p = 0.001$, $I^2 = 0\%$, $p > 0.05$ *Medium-sized, significant effects of more improved symptoms with valproate + antipsychotics than antipsychotics alone;* 1 RCT, N = 136, SMD -0.50, 95%CI -0.85 to -0.16, $p = 0.004$	
Depression	
No significant differences between lithium + quetiapine vs. quetiapine; 1 RCT, N not reported, SMD = -0.15, 95%CI -0.35 to 0.06, $p > 0.05$	
Risks	Adding lithium to quetiapine increased tremor (1 RCT, N not reported, RR = 3.17, 95%CI 1.54 to 6.55, $p < 0.05$) and somnolence (1 RCT, N not reported, RR = 2.33, 95%CI 1.13 to 4.77, $p < 0.05$). There were no differences between groups in extrapyramidal symptoms, depression or weight gain.
Consistency in results	Consistent where reported (mania).
Precision in results	Precise for symptoms and response, imprecise for side effects.
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, 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, OR = odds ratio, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RCT = randomised controlled trial, RR = risk ratio, SMD = standardised mean difference, vs. = versus

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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[10].

† 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[10].

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[11]. 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.

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

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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[10];

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

§ 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[12].

‖ 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 that 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.

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

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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. McGirr A, Vohringer PA, Ghaemi SN, Lam RW, Yatham LN (2016): Safety and efficacy of adjunctive second-generation antidepressant therapy with a mood stabiliser or an atypical antipsychotic in acute bipolar depression: a systematic review and meta-analysis of randomised placebo-controlled trials. *The Lancet Psychiatry* 3: 1138-46.
4. Farooq S, Singh SP (2015): Fixed dose-combination products in psychiatry: Systematic review and meta-analysis. *Journal of Psychopharmacology* 29: 556-64.
5. Ogawa Y, Tajika A, Takeshima N, Hayasaka Y, Furukawa TA (2014): Mood stabilizers and antipsychotics for acute mania: a systematic review and meta-analysis of combination/augmentation therapy versus monotherapy. *CNS Drugs* 28: 989-1003.
6. Galling B, Garcia MA, Osuchukwu U, Hagi K, Correll CU (2015): Safety and tolerability of antipsychotic-mood stabilizer co-treatment in the management of acute bipolar disorder: results from a systematic review and exploratory meta-analysis. *Expert Opinion on Drug Safety* 14: 1181-99.
7. Frecska E, Kovacs AI, Balla P, Falussy L, Ferencz A, Varga Z (2012): The message of the survival curves: I. Composite analysis of long-term treatment studies in bipolar disorder. *Neuropsychopharmacologia Hungarica* 14: 155-64.
8. Kishi T, Ikuta T, Matsuda Y, Sakuma K, Okuya M, Mishima K*, et al.* (2020): Mood stabilizers and/or antipsychotics for bipolar disorder in the maintenance phase: a systematic review and network meta-analysis of randomized controlled trials. *Molecular Psychiatry* 26: 4146-57.
9. Kishi T, Sakuma K, Okuya M, Matsuda Y, Esumi S, Hashimoto Y*, et al.* (2021): Effects of a conventional mood stabilizer alone or in combination with second-generation antipsychotics on recurrence rate and discontinuation rate in bipolar I disorder in the maintenance phase: A systematic review and meta-analysis of randomized, placebo-controlled trials. *Bipolar Disorders*: doi: 10.1111/bdi.13053.
10. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
11. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
12. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*