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Mood stabilisers

Introduction

Mood stabilisers, including lithium and anticonvulsants (such as valproate, carbamazepine, and lamotrigine) have been proposed as an adjunctive therapy to standard antipsychotic treatments when individuals have sub-optimal responses to treatment. Mood stabilisers may be implemented as an immediate therapy for acute symptoms of psychosis, but they may also be used as part of an ongoing treatment regime.

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

Lithium

- Moderate to high quality evidence suggests a small effect of adjunctive lithium for improvements in overall symptoms as measured by BPRS reduction scores.
- Moderate quality evidence suggests a small effect of improvements in global state, reflected by clinical response. There is a medium-sized effect of adjunctive lithium for

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increasing the risk of people leaving a study early.

Lamotrigine

- Moderate quality evidence suggests no benefit of adjunctive lamotrigine for symptoms however some benefit may be seen in treatment-resistant patients who are receiving clozapine.

Valproate

- Moderate quality evidence suggests no benefit of adjunctive valproate compared to placebo for study attrition or mental state, Valproate may lower the risk of constipation and tardive dyskinesia and increase the risk of sedation. Lower quality evidence suggests no benefit of valproate for reducing aggressive behaviour.

Carbamazepine

- Moderate to low quality evidence suggests a medium-sized effect of improvements in global state with adjunctive carbamazepine.

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Goedhard LE, Stolker JJ., Heerdink ER, Nijman HLI, Olivier B, Egberts TCG

Pharmacotherapy for the treatment of aggressive behavior in general adult psychiatry: A systematic review

Journal of Clinical Psychiatry 2006; 67(7): 1013-1024

View review abstract online

Comparison	**Valproate plus antipsychotics (unspecified) vs. placebo plus antipsychotics.**
Summary of evidence	**Moderate to low quality evidence (medium-sized sample, unable to assess consistency or precision, direct) suggests short term (1 week) benefit of valproate for improving aggressive behaviour, but no benefit by 4 weeks. There were no difference in adverse effect.**
Aggressive behaviour	
1 RCT (N = 249) was identified which compared adjunctive valproate with placebo over 4 weeks. PANSS-Hostility scores were better in the adjunctive valproate group up to one week, but were not significantly different at the 4-week endpoint.	
Risks	No significant group differences were reported for adverse effects.
Consistency in results	Not applicable – 1 RCT
Precision in results	No measure of precision is reported.
Directness of results	Direct

Leucht S, Kissling W, McGrath J, White P

Carbamazepine for schizophrenia

Cochrane Database of Systematic Reviews 2007; (3): CD001258

View review abstract online

Comparison	**Anticonvulsants (carbamazepine, 800-1200mg/day) plus antipsychotics (mostly haloperidol, also clozapine and**

	unspecified others) vs. antipsychotics alone (mostly haloperidol, also clozapine and unspecified others). Treatment duration range 18 days to 5 weeks, sample included schizophrenia and spectrum psychoses, treatment resistant schizophrenia.
Summary of evidence	**Moderate to low quality evidence (small samples, imprecise, consistent, direct) suggests a medium-sized improvement in global state with adjunctive carbamazepine, with unclear effects on mental state or adverse effects.**
Leaving the study early	
No significant difference in study attrition was reported between groups; 8 RCTs, N = 182, RR = 0.47, 95%CI 0.16 to 1.35, *p* = 0.16, Q = 3.54, *p* = 0.32, I^2 = 15%	
Global state	
Medium effect size significantly favoured the carbamazepine plus antipsychotic group over antipsychotics alone for rate of improvement in global state; 2 RCTs, N = 38, RR = 0.57, 95%CI 0.37 to 0.88, *p* = 0.01, Q = 1.79, *p* = 0.18, I^2 = 44%	
Mental state **Measured by BPRS, IMPS, PANSS, SANS, HAM D**	
Significant effect favoured antipsychotics alone over adjunctive carbamazepine for average PANSS endpoint score (positive subscale); 1 RCT, N = 18, WMD = 4.22, 95%CI 0.75 to 7.69, *p* = 0.017 *No significant difference in average BPRS endpoint score was reported between groups;* 3 RCTS, N = 79, WMD = 0.30, 95%CI -12.49 to 13.09, *p* = 0.96, Q = 12.89, *p* = 0.002, I^2 = 84% *No significant difference in degree of BPRS score reduction was reported between groups;* Less than 20% reduction: 6 RCTs, N = 147, RR = 0.69, 95%CI 0.44 to 1.07, *p* = 0.096, Q = 6.63, *p* = 0.16, I^2 = 40% Less than 35% reduction: 6 RCTs, N = 147, RR = 0.78, 95%CI 0.57 to 1.05, *p* = 0.10, Q = 6.81, *p* = 0.23, I^2 = 27% Less than 50% reduction: 6 RCTs, N = 147, RR = 0.86, 95%CI 0.67 to 1.12, *p* = 0.27, Q = 14.31, *p* = 0.01, I^2 = 65% *No significant difference in average IMPS endpoint score was reported between groups;* 2 RCTs, N = 50, WMD = 5.18, 95%CI -11.09 to 21.44, *p* = 0.53, Q = 24.08, *p* = 0.00001, I^2 = 96%	

No significant difference in average SANS endpoint score was reported between groups; 2 RCTs, N = 53, WMD = -2.75, 95%CI -6.71 to 1.22, *p* = 0.17, Q = 0.17, *p* = 0.68, I^2 = 0% *No significant difference in average HAM D (depression) endpoint score was reported between groups;* 1 RCT, N = 26, WMD = -0.35, 95%CI -2.20 to 1.50, *p* = 0.71	
Risks	1 RCT, N = 20, reported a trend for a medium effect size suggesting a lower rate of movement disorder in the adjunctive carbamazepine group compared to antipsychotic alone, RR = 0.38, 95%CI 0.14 to 1.02, *p* = 0.054. In 1 RCT, N = 41, there was no difference in rate of allergic reaction (RR 3.79, 95%CI 0.16 to 87.86), ECG deterioration (RR 2.13, 95%CI 0.59 to 7.75), liver enzyme elevation (RR 2.56, 95%CI 0.53 to 12.42), or white blood cell decline (RR 1.28, 95%CI 0.09 to 19.06).
Consistency in results	Consistent for attrition, global state, most mental state outcomes (except BPRS endpoint and 50% reduction; IMPS endpoint). Not applicable where 1 RCT.
Precision in results	Imprecise for all, unable to assess WMD
Directness of results	Direct

Leucht S, Kissling W, McGrath J

Lithium for schizophrenia

Cochrane Database of Systematic Reviews 2007; (3): CD001258

View review abstract online

Comparison	**Adjunctive lithium (various doses) + antipsychotics (various doses) vs. antipsychotic alone or with placebo. Treatment duration ranged from 3 to 8 weeks.**
Summary of evidence	**Moderate to high quality evidence (medium-sized sample, consistent, precise, direct) suggests a small effect of adjunctive lithium in combination with antipsychotics for improving overall schizophrenia symptom severity when measured by BPRS reduction scores, however low erquality evidence (imprecise, very small samples) is unable to determine any benefit when measuring specific symptoms of schizophrenia.**

	Moderate quality evidence (imprecise) suggests greater improvement in global state in in patients taking adjunctive lithium (small effect size), reflected by clinical response. However a medium effect size suggests adjunctive lithium may result in an increased risk of patients leaving a study early for any reason.
Leaving the study early	
Significant, medium effect size of increased rates of leaving the study early risk with adjunctive lithium; All reasons: 11 RCTs, N = 320, RR = 2.01, 95%CI 1.31 to 3.08, *p* = 0.0014, Q = 12.94, *p* = 0.17, I^2 = 30% Due to adverse effects: 1 RCT, N = 39, RR = 4.32, 95%CI 0.22 to 84.48, *p* = 0.33	
Global state	
Significant, small effect size of greater overall improvement with adjunctive lithium; No clinically important response: 8 RCTs, N = 244, RR = 0.84, 95%CI 0.73 to 0.97, *p* = 0.017, Q = 6.91, *p* = 0.44, I^2 = 0% Not improved or worse: 4 RCTs, N = 115, RR = 0.62, 95%CI 0.42 to 0.94, *p* = 0.024, Q = 4.30, *p* = 0.23, I^2 = 30% Relapse: 1 RCT, N = 29, RR = 0.21, 95%CI 0.015 to 4.76, *p* = NS	
Mental state – schizophrenia symptoms **Measured by BPRS, MS, SANS, PANSS**	
<u>Overall symptoms</u> *Significant, small effect size for lower risk of a less than 50% reduction in BPRS overall scores (but not significant for endpoint scores) reflecting greater mental state improvements in the lithium group;* Less than 20% reduction: 5 RCTs, N = 131, RR = 0.89, 95%CI 0.67 to 1.19, *p* = 0.43, Q = 1.99, *p* = 0.74, I^2 = 0% Less than 35% reduction: 5 RCTs, N = 131, RR = 0.80, 95%CI 0.64 to 1.00, *p* = 0.053, Q = 4.65, *p* = 0.32, I^2 = 14% Less than 50% reduction: 5 RCTs, N = 131, RR = 0.79, 95%CI 0.66 to 0.94, *p* = 0.0068, Q = 4.16, *p* = 0.38, I^2 = 4% BPRS endpoint scores: 4 RCTs, N = 102, SMD = -0.31, 95%CI -0.70 to 0.09, *p* = 0.13, Q = 0.93, *p* = 0.82, I^2 = 0% *No significant differences in MS overall score reduction or endpoint scores;*	

Less than 20% reduction: 1 RCT, N = 45, RR = 2.09, 95%CI 0.42 to 10.29, *p* = 0.36

Less than 35% reduction: 1 RCT, N = 45, RR = 1.25, 95%CI 0.45 to 3.52, *p* = 0.67

Less than 50% reduction: 1 RCT, N = 45, RR = 1.05, 95%CI 0.40 to 2.75, *p* = 0.93

MS endpoint score: 1 RCT, N = 45, MD = 0.18, 95%CI -0.41 to 0.77, *p* = 0.55

Negative symptoms

No significant differences in BPRS negative symptom endpoint scores;

2 RCTs, N = 61, MD = 0.60, 95%CI -1.13 to 2.32, *p* = 0.50, Q = 1.14, *p* = 0.28, I^2 = 13%

No significant differences in MS negative symptom score reduction or negative endpoint scores;

Less than 20% reduction: 1 RCT, N = 45, RR = 2.09, 95%CI 0.20 to 21.45, *p* = 0.53

Less than 35% reduction: 1 RCT, N = 45, RR = 1.05, 95%CI 0.16 to 6.79, *p* = 0.96

Less than 50% reduction: 1 RCT, N = 45, RR = 1.05, 95%CI 0.16 to 6.79, *p* = 0.96

MS negative endpoint score: 1 RCT, N = 45, MD = 0.29, 95%CI -0.31 to 0.89, *p* = 0.34

No significant differences in SANS negative symptom score reduction, but a significant difference between groups in SANS endpoint scores, favouring the lithium group;

Less than 20% reduction: 3 RCTs, N = 70, RR = 0.73, 95%CI 0.33 to 1.65, *p* = 0.46, Q = 4.81, *p* = 0.09, I^2 = 58%

Less than 35% reduction: 3 RCTs, N = 70, RR = 0.93, 95%CI 0.64 to 1.34, *p* = 0.69, Q = 2.21, *p* = 0.33, I^2 = 10%

Less than 50% reduction: 3 RCTs, N = 70, RR = 0.99, 95%CI 0.74 to 1.33, *p* = 0.94, Q = 0.43, *p* = 0.81, I^2 = 0%

SANS negative endpoint score: 2 RCTs, N = 41, MD = -4.50, 95%CI -8.81 to -0.19, *p* = 0.041, Q = 0.95, *p* = 0.33, I^2 = 0%

No significant differences in PANSS negative symptom score reduction or negative endpoint scores;

Less than 20% reduction: 1 RCT, N = 20, RR = 1.33, 95%CI 0.74 to 2.41, *p* = 0.34

Less than 35% reduction: 1 RCT, N = 20, RR = 1.00, 95%CI 0.75 to 1.34, *p* = 1.00

Less than 50% reduction: 1 RCT, N = 20, RR = 0.90, 95%CI 0.69 to 1.18, *p* = 0.46

PANSS negative endpoint score: 1 RCT, N = 20, MD = 1.00, 95%CI -3.43 to 5.43, *p* = 0.66

Positive symptoms

No significant differences in BPRS positive symptom score reduction;

Less than 20% reduction: 2 RCTs, N = 49, RR = 0.55, 95%CI 0.24 to 1.25, *p* = 0.15, Q = 0.00, *p* = 0.97, I^2 = 0%

Less than 35% reduction: 2 RCTs, N = 49, RR = 0.86, 95%CI 0.50 to 1.47, *p* = 0.58, Q = 0.02, *p* = 0.89, I^2 = 0%

Less than 50% reduction: 2 RCTs, N = 49, RR = 0.80, 95%CI 0.48 to 1.35, *p* = 0.41, Q = 0.02, *p* = 0.88, I^2 = 0%

BPRS positive endpoint score: 1 RCT, N = 41, MD = 0.14, 95%CI -3.45 to 3.75, *p* = 0.94
No significant differences in MS negative symptom score reduction or negative endpoint scores;
Less than 20% reduction: 1 RCT, N = 45, RR = 0.35, 95%CI 0.01 to 8.11, *p* = 0.51
Less than 35% reduction: 1 RCT, N = 45, RR = 1.39, 95%CI 0.35 to 5.53, *p* = 0.64
Less than 50% reduction: 1 RCT, N = 45, RR = 2.09, 95%CI 0.60 to 7.35, *p* = 0.25
MS positive endpoint score: 1 RCT, N = 45, MD = 0.23, 95%CI -1.34 to 1.80, *p* = 0.77
No significant differences in PANSS positive symptom score reduction or negative endpoint scores;
Less than 20% reduction: 1 RCT, N = 20, RR = 1.00, 95%CI 0.42 to 2.40, *p* = 1.00
Less than 35% reduction: 1 RCT, N = 20, RR = 1.00, 95%CI 0.49 to 2.05, *p* = 1.00
Less than 50% reduction: 1 RCT, N = 20, RR = 0.86, 95%CI 0.45 to 1.64, *p* = 0.64
PANSS positive endpoint score: 1 RCT, N = 20, MD = -2.80, 95%CI -7.84 to 2.24, *p* = 0.28
Mental state – Depressive symptoms **Measured by MADRS, BPRS, HS and MAS**
No significant differences in depressive symptoms were reported between groups on any scale;
MADRS, less than 20% reduction: 1 RCT, N = 45, RR = 1.05, 95%CI 0.35 to 3.12, *p* = 0.94
MADRS, less than 35% reduction: 1 RCT, N = 45, RR = 1.05, 95%CI 0.44 to 2.49, *p* = 0.92
MADRS, less than 50% reduction: 1 RCT, N = 45, RR = 0.91, 95%CI 0.40 to 2.10, *p* = 0.83
BPRS-Depression, less than 20% reduction: 1 RCT, N = 22, RR = 1.04, 95%CI 0.38 to 2.87, *p* = 0.94
BPRS-Depression, less than 35% reduction: 1 RCT, N = 22, RR = 0.83, 95%CI 0.33 to 2.08, *p* = 0.70
BPRS-Depression, less than 50% reduction: 1 RCT, N = 22, RR = 0.83, 95%CI 0.33 to 2.08, *p* = 0.70
HS, endpoint score: 1 RCT, N = 16, MD = 3.40, 95%CI -7.66 to 14.46, *p* = 0.55
MAS, endpoint score: 1 RCT, N = 44, MD = -0.34, 95%CI -1.64 to 0.96, *p* = 0.61
Q_B = 0.43, *p*= 0.51, I^2 =0.0%
Mental state – mania symptoms **Measured by Bech-Rafaelsen scale**
No significant difference was reported between groups;
Less than 20% reduction: 1 RCT, N = 44, RR = 0.90, 95%CI 0.36 to 2.25, *p* = 0.82
Less than 35% reduction: 1 RCT, N = 44, RR = 0.84, 95%CI 0.41 to 1.72, *p* = 0.63
Less than 50% reduction: 1 RCT, N = 44, RR = 0.84, 95%CI 0.41 to 1.72, *p* = 0.63

Risks	No significant differences in rates of delirium (N = 50, RR = 2.56, 95%CI 0.28 to 23.28, *p* = 0.40, I^2 = 0%), movement disorders (N = 49, RR = 0.99, 95%CI 0.57 to 1.72, *p* = 0.98, I^2 = 0%), or non-specific discomfort (N = 22, RR = 2.54, 95%CI 0.11 to 56.25, *p* = 0.56).
Consistency in results	Consistent where applicable.
Precision in results	Imprecise apart from reduction in BPRS overall scores.
Directness of results	Direct

Porcelli S, Balzarro B, Seretti A

Clozapine resistance: augmentation strategies

Neuropsychopharmacology 2012; 22: 165-182

View review abstract online

Comparison	**Efficacy of augmented clozapine therapy for improving outcomes in people with treatment-resistant schizophrenia.**
Summary of evidence	**Moderate quality evidence (small sample, consistent, imprecise, direct) suggests no benefit of augmenting clozapine therapy with lamotrigine compared to augmentation with placebo.**

Clozapine plus mood stabilisers

No benefit of augmenting clozapine therapy with lamotrigine over placebo;

3 RCTs, N = 97, OR = 1.22, 95%CI 0.47 to 3.17, *p* = 0.69, Q = 1.27, *p* = 0.53, I^2 = 0%

2 of 3 studies (N = 64) found no benefits of topiramate augmentation for improving symptom severity; 1 of 3 studies found positive results for topiramate.

2 of 3 studies (no placebo groups) (N = 111) reported benefits of lithium augmentation for improving symptom severity; 1 study found no benefit of lithium over placebo.

Consistency in results	Consistent where applicable.
Precision in results	Imprecise
Directness of results	Direct

Premkumar TS, Pick J

Lamotrigine for schizophrenia

Cochrane Database of Systematic Reviews; 2006(4): CD005962

View review abstract online

Comparison	**Anticonvulsant (lamotrigine, dose range 125-400mg/day) plus second generation antipsychotics (unspecified) vs. placebo plus antipsychotics (unspecified). Treatment duration range 8-28 weeks.**
Summary of evidence	**Moderate quality evidence (small samples, mostly consistent, imprecise or unable to assess, direct) suggests no differences in PANSS response scores, but significantly lower PANSS endpoint scores in the lamotrigine group. No differences were reported for endpoint scores in other measures of mental state (BPRS, SANS, HAM D) or cognition (BACS). There were no differences between groups for study attrition, risk of fatalistic impulses or any other adverse effects.**

Global state

No difference in global state scores, measured using CGI-I;

1 RCT, N = 208, RR = 1.06, 95%CI 0.73 to 1.54, $p = 0.77$

Mental state

Significantly lower PANSS endpoint scores were reported in the lamotrigine group, at end of treatment (range 8-28 weeks);

PANSS total: 2 RCTs, N = 67, WMD = -16.88, 95%CI -25.18 to -8.57, $p = 0.000068$, Q = 0.00, $p = 1.00$, $I^2 = 0\%$

PANSS-Positive: 2 RCTs, N = 65, WMD = -5.10, 95%CI -8.86 to -1.34, $p = 0.0078$, Q = 0.13, $p = 0.72$, $I^2 = 0\%$

PANSS-Negative: 2 RCTs, N = 67, WMD = -5.25, 95%CI -7.07 to -3.43, $p = 0.00001$, Q = 0.51, $p = 0.47$, $I^2 = 0\%$

PANSS-Psychopathology: 2 RCTs, N = 67, WMD = -10.74, 95%CI -16.53 to -4.96, $p = 0.00027$, Q = 0.27, $p = 0.60$, $I^2 = 0\%$

No difference in PANSS response, measured as > 20% reduction in PANSS score;

3 RCTs, N = 297, RR = 1.26, 95%CI 0.81 to 1.97, $p = 0.30$, Q = 2.57, $p = 0.28$, $I^2 = 22\%$

No difference in BPRS endpoint score, measured at 10 weeks;

1 RCT, N = 31, WMD = -2.80, 95%CI -12.44 to 6.84, *p* = 0.57 *No difference in SANS endpoint score, measured at 10 weeks;* 1 RCT, N = 31, WMD = -8.80, 95%CI -19.73 to 2.13, *p* = 0.11 *No difference in HAM-D endpoint score, measured at 10 weeks;* 1 RCT, N = 31, WMD = 0.10, 95%CI -3.69 to 3.89, *p* = 0.96	
Cognitive state	
Significant improvements in colour naming time and error on the Stroop task, but not in word naming time or error; Colour naming time: 1 RCT, N = 36, WMD = -29.45, 95%CI -53.69 to -5.21, *p* = 0.0017 Colour naming error: 1 RCT, N = 36, WMD = -8.28, 95%CI -12.85 to -3.71, *p* = 0.00038 Word naming time: 1 RCT, N = 36, WMD = 0.61, 95%CI -10.81 to 12.03, *p* = 0.92 Word naming error: 1 RCT, N = 36, WMD = -0.33, 95%CI -2.46 to 1.80, *p* = 0.76 *No difference in cognitive state, measured using BACS;* 2 RCT, N = 329, RR = 1.10, 95%CI 0.59 to 2.04, *p* = 0.77, Q = 4.66, *p* = 0.03, I^2 = 79%	
Leaving the study early	
No difference between groups for study attrition; 5 RCTs, N = 537, RR = 0.96, 95%CI 0.71 to 1.29, *p* = 0.78, Q = 1.17, *p* = 0.88, I^2 = 0%	
Fatalistic impulses	
There was no significant difference between groups in risk of: Fatalistic impulses: 2 RCTs, N = 429, RR 2.38, 95%CI 0.90 to 6.30, *p* = 0.081, I^2 = 4%, *p* = 0.31 Suicide attempt: 1 RCT, N = 217, RR 2.97, 95%CI 0.12 to 72.18, *p* = 0.50 Homicidal ideation: 1 RCT, N = 217, RR 4.95, 95%CI 0.24 to 102.01, *p* = 0.30 Suicidal ideation: 2 RCTs, N = 429, RR 1.05, 95%CI 0.15 to 7.06, I^2 = 0% *p* = 0.96, I^2 = 0%, *p* = 0.38	
Risks	2 RCTs (N = 429) report significantly lower risk of any adverse effect in the placebo group (RR = 1.19, 95%CI 1.02 to 1.38, *p* = 0.027, I^2 = 0%). There was no significant difference in chest pain (N = 429, RR 1.68, 95%CI 0.18 to 15.99 I^2 = 50%), abnormal ECG (N = 212, RR 3.00, 95%CI 0.12 to 72.18), hypertension (N = 212, RR 2.50, 95%CI 0.50 to 12.60), tachycardia (N = 212, RR 0.33, 95%CI 0.01 to 8.09), hair loss (N = 36, RR 3.00, 95%CI 0.13 to 69.69), itching (N = 36, RR 4.00, 95%CI 0.49 to 32.39), rash (N = 465, RR 0.74, 95%CI 0.24 to

	2.28 I^2 = 0%), constipation (N = 212, RR 0.33, 95%CI 0.04 to 3.15), decreased appetite (N = 217, RR 0.11, 95%CI 0.01 to 2.02), diarrhoea (N = 465, RR 1.56, 95%CI 0.39 to 6.16 I^2 = 31%), dyspepsia (N = 212, RR 4.00, 95%CI 0.45 to 35.20), nausea (N = 465, RR 2.26, 95%CI 1.05 to 4.88 I^2 = 0%), vomiting (N = 253, RR 3.17, 95%CI 0.77 to 13.02 I^2 = 0%), increased levels of alanine aminotransferase (N = 217, RR 2.97, 95%CI 0.12 to 72.18), aspartate aminotransferase (N = 217, RR 2.97, 95%CI 0.12 to 72.18), creatine kinase (N = 212, RR 0.33, 95%CI 0.01 to 8.09), glucose (N = 212, RR 1.50, 95%CI 0.26 to 8.80), ataxia (N = 36, RR 5.00, 95%CI 0.26 to 97.37), blurred vision (N = 36, RR 2.00, 95%CI 0.20 to 20.15), dizziness (N = 465, RR 1.17, 95%CI 0.51 to 2.70 I^2 = 0%), headache (N = 465, RR 1.36, 95%CI 0.88 to 2.08 I^2 = 0%), loss of consciousness (N = 212, RR 5.00, 95%CI 0.24 to 102.92), paraesthesia (N = 212, RR 3.00, 95%CI 0.12 to 72.82), hypoaesthesia (N = 212, RR 7.00, 95%CI 0.37 to 133.88), tremor (N = 217, RR 4.95, 95%CI 0.59 to 41.71), aggression (N = 217, RR 2.97, 95%CI 0.12 to 72.18), agitation (N = 212, RR 0.50, 95%CI 0.09 to 2.67), anxiety (N = 429, RR 0.73, 95%CI 0.09 to 5.76 I^2 = 17%), crying (N = 212, RR 0.33, 95%CI 0.01 to 8.09), auditory hallucination (N = 217, RR 10.90, 95%CI 0.61 to 194.74), insomnia (N = 429, RR 2.02, 95%CI 0.04 to 96.25 I^2 = 78%(p = 0.03)), paranoia (N = 429, RR 1.99, 95%CI 0.37 to 10.75), somnolence (N = 429, RR 1.21, 95%CI 0.51 to 2.87 I^2 = 0%), cough (N = 212, RR 7.00, 95%CI 0.37 to 133.88), influenza (N = 212, RR 1.00, 95%CI 0.06 to 15.78), abnormal dreams (N = 217, RR 0.33, 95%CI 0.01 to 8.02), asthenia (N = 217, RR 0.33, 95%CI 0.01 to 8.02), back pain (N = 217, RR 0.99, 95%CI 0.30 to 3.33), dry mouth (N = 212, RR 1.00, 95%CI 0.21 to 4.84), fatigue (N = 212, RR 1.39, 95%CI 0.45 to 4.24), lymphadenopathy (N = 429, RR 2.99, 95%CI 0.31 to 28.48 I^2 = 0%), abnormal urine (N = 212, RR 3.00, 95%CI 0.12 to 72.82), weight increase (N = 212, RR 3.00, 95%CI 0.12 to 72.82).
Consistency in results	Consistent for all except BACS cognition and insomnia. Not applicable where 1 RCT.
Precision in results	Imprecise for all, except unable to assess WMD
Directness of results	Direct

Schwarz C, Volz A, Li C, Leucht S

Valproate for schizophrenia

Cochrane Database of Systematic Reviews; 2008(3): CD004028

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Comparison	**Anticonvulsant (valproate, dose range 300-1500mg/day) plus antipsychotics (mostly haloperidol, also olanzapine, risperidone, and others unspecified) vs. placebo plus antipsychotics (mostly haloperidol, also olanzapine, risperidone, and others unspecified). Treatment duration range 12 days to 12 weeks, sample included schizophrenia spectrum disorders and unspecified psychosis.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, mostly consistent, imprecise or unable to assess, direct) suggests no differences between valproate and placebo in study attrition or mental state, but a lower risk of constipation and tardive dyskinesia in the valproate group and a higher risk of sedation.**

Leaving the study early

No difference between groups for study attrition;

6 RCTs, N = 270, RR = 1.68, 95%CI 0.88 to 3.21, $p = 0.12$, Q = 2.58, $p = 0.28$, $I^2 = 23\%$

Mental state

No difference in clinically significant response (study-defined);

2 RCTs, N = 307, RR = 0.85, 95%CI 0.69 to 1.04, $p = 0.11$, Q = 0.75, $p = 0.39$, $I^2 = 0\%$

No difference in BPRS endpoint scores at 4 weeks;

3 RCTs, N = 101, WMD = -2.81, 95%CI -7.72 to 2.11, $p = 0.26$, Q = 8.84, $p = 0.01$, $I^2 = 77\%$

No difference in IMPS change scores at 4 weeks;

1 RCT, N = 18, WMD = -5.11, 95%CI -26.04 to 15.82, $p = 0.63$

No differences in PANSS change scores at 4 weeks;

PANSS-total change: 1 RCT, N = 242, WMD = -1.50, 95%CI -9.81 to 6.81, $p = 0.72$

PANSS-positive change: 2 RCTs, N = 260, WMD = -1.42, 95%CI -3.91 to 1.07, $p = 0.26$, $I^2 = 0\%$

Behaviour - aggression

Significantly lower OAS scores by 28 days; 1 RCT, N = 60, WMD = -3.79, 95%CI -5.05 to -2.53, *p* < 0.00001	
Risks	1 RCT (N = 429) report no significant difference in risk of general adverse effects (RR = 1.11, 95%CI 0.98 to 1.26, p = 0.08). There was a significantly lower risk of constipation (N = 249, RR 0.36, 95%CI 0.15 to 0.87, p = 0.024), and tardive dyskinesia in the valproate group (N = 79, WMD -3.31, 95%CI -4.91 to -1.71 p = 0.000049), and a higher risk of sedation (N = 296, RR 1.52, 95%CI 1.04 to 2.22 p = 0.029, I^2 = 0%). There was no significant difference in use of additional medication (N = 249, RR 0.94, 95%CI 0.77 to 1.15), anxiety (N = 249, RR 0.40, 95%CI 0.13 to 1.25), asthenia (N = 249, RR 1.58, 95%CI 0.63 to 3.95), ataxia (N = 47, RR 3.39, 95%CI 0.15 to 79.22), anxiety (N = 249, RR 0.40, 95%CI 0.13 to 1.25), eosinophilia (N = 42, RR 1.38, 95%CI 0.43 to 4.42), monocytosis (N = 42, RR 5.48, 95%CI 0.28 to 107.62), anxiety (N = 249, RR 0.40, 95%CI 0.13 to 1.25), transient lymphocytosis (N = 42, RR 3.30, 95%CI 0.37 to 29.21), dizziness (N = 249, RR 1.61, 95%CI 0.76 to 3.41), dyspepsia (N = 249, RR 1.05, 95%CI 0.62 to 1.79), headache (N = 249, RR 1.09, 95%CI 0.66 to 1.79), incontinence (N = 47, RR 3.39, 95%CI 0.15 to 79.22), increased levels of alaninaminotransferase (N = 249, RR 0.20, 95%CI 0.02 to 1.70), anxiety (N = 249, RR 0.40, 95%CI 0.13 to 1.25), gamma-GT (N = 42, RR 0.55, 95%CI 0.05 to 5.61), nausea (N = 249, RR 1.01, 95%CI 0.50 to 2.03), pain (N = 249, RR 0.62, 95%CI 0.30 to 1.25), rhinitis (N = 249, RR 0.30, 95%CI 0.09 to 1.07), vegetative effect (N = 47, RR 1.70, 95%CI 0.55 to 5.27), vomiting (N = 249, RR 0.92, 95%CI 0.40 to 2.08), weight gain (N = 249, RR 1.08, 95%CI 0.54 to 2.14).
Consistency in results	Consistent for all, not applicable where 1 RCT.
Precision in results	Imprecise for all except clinically significant response, unable to assess WMD.
Directness of results	Direct

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Soares-Weiser KV, Joy C

Miscellaneous treatments for neuroleptic-induced tardive dyskinesia

Cochrane Database of Systematic Reviews 2003; 2: CD000208

View review abstract online

Comparison	**Lithium (dose not reported) plus ongoing antipsychotic treatment, vs. placebo plus ongoing antipsychotics for 15 days.**
Summary of evidence	**Low quality evidence (very small sample, imprecise, direct) is unclear as to any benefit of lithium for improving symptoms of tardive dyskinesia in schizophrenia.**
Leaving the study early	
There was no difference in the risk of study attrition between groups; 1 RCT, N = 11, RR = 2.57, 95%CI 0.13 to 52.12, *p* = 0.54	
Tardive dyskinesia symptoms	
No difference in improving TD symptoms; 1 RCT, N = 11, RR = 4.29, 95%CI 0.25 to 72.90, *p* = 0.31 *No difference in deterioration of TD symptom severity;* 1 RCT, N = 11, RR = 4.29, 95%CI 0.25 to 72.90, *p* = 0.31	
Risks	No significant difference was reported in the risk of adverse effects, 1 RCT, N = 11, RR = 6.00, 95%CI 0.38 to 94.35, *p* = 0.20.
Consistency in results	Not applicable - 1 RCT.
Precision in results	Imprecise
Directness of results	Direct

Tiihonen J, Wahlbeck K, Kiviniemi V

The efficacy of lamotrigine in clozapine-resistant schizophrenia: A systematic review and meta-analysis

Schizophrenia Research 2009; 109(1-3): 10-14 View review abstract online	
Comparison	**Anticonvulsant (lamotrigine, dose range 100-400mg/day) plus clozapine (dose unspecified) vs. placebo plus clozapine (dose unspecified). Treatment duration range 12-24 weeks.**
Summary of evidence	**Moderate quality evidence (small samples, consistent, imprecise, direct) suggests some benefit of lamotrigine for improving symptom severity in patients receiving clozapine.**
Mental state	
Significant improvement in mental state outcomes in the lamotrigine group at the end of treatment; PANSS or BPRS difference scores: 5 RCTs, N = 81, *d* = -0.57, 95%CI -0.89 to -0.25, *p* = 0.0006, Q = 6.35, *p* = 0.17, I^2 = 37% Positive scales (PANSS, BPRS, SAPS): 5 RCTs, N = 81, *d* = 0.34, 95%CI 0.02 to 0.65, *p* = 0.04 Negative scales (PANSS, BPRS, SANS): 5 RCTs, N = 81, *d* = 0.43, 95%CI 0.11 to 0.76, *p* = 0.008 *Lamotrigine was associated with a significantly higher treatment response rate than placebo;* OR = 0.19, 95%CI 0.09 to 0.43, *p* = 0.001 (NNT 4, CI 3-6)	
Leaving the study early	
There was no significant difference between groups for study attrition; 5 RCTs, N = 81, OR = 0.59, 95%CI 0.27 to 1.29	
Risks	From five RCT, three patients reported severe adverse events following lamotrigine, OR = 1.58, 95%CI 0.24 to 10.60 (NS). There was also no significant difference in risk of rash (OR 1.75, 95%CI 0.39 to 7.94).
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Veerman SRT, Schulte PFJ, Begemann MJH, Engelsbel F, de Haan L

Clozapine Augmented with Glutamate Modulators in Refractory

Schizophrenia: A Review and Meta-analysis

Pharmacopsychiatry 2014; 47: 185-194

View review abstract online

Comparison	**Clozapine plus glutamate modulators compared to clozapine and placebo for people with treatment-resistant schizophrenia.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, inconsistent or imprecise, direct) suggests augmenting clozapine with lamotrigine, topiramate or glycine provides no benefit over clozapine plus placebo.**

There were no significant differences between clozapine plus lamotrigine and clozapine plus placebo;

Overall symptoms: 6 RCTs, N = 185, *g* = 0.31, 95%CI -0.28 to 0.91, *p* = 0.29, I^2 75%

Positive symptoms: 6 RCTs, N = 185, *g* = 0.31, 95%CI -0.02 to 0.65, *p* = 0.07, I^2 26%

Negative symptoms: 6 RCTs, N = 185, *g* = 0.37, 95%CI -0.15 to 0.88, *p* = 0.16, I^2 68%

Affective symptoms: 3 RCTs, N = 126, *g* = 0.07, 95%CI -0.39 to 0.53, *p* = 0.77, I^2 43%

Authors report that after excluding 2 outliers, effect sizes for overall symptoms and negative symptoms increased to trend level and heterogeneity reduced to 0%.

There were no significant differences between clozapine plus topiramate and clozapine plus placebo;

Overall symptoms: 4 RCTs, N = 152, *g* = 0.75, 95%CI -0.06 to 1.56, *p* = 0.07, I^2 69%

Positive symptoms: 4 RCTs, N = 152, *g* = 0.41, 95%CI -0.15 to 0.98, *p* = 0.15, I^2 65%

Negative symptoms: 4 RCTs, N = 152, *g* = 0.40, 95%CI -0.39 to 1.19, *p* = 0.32, I^2 81%

Clozapine plus glycine showed a worsening of positive symptoms, with no significant differences in overall or negative symptoms;

Overall symptoms (PANSS/BPRS): 3 RCTs, N = 57, *g* = -0.16, 95%CI -0.62 to 0.30, *p* = 0.499, I^2 0%

Positive symptoms: 3 RCTs, N = 57, *g* = -0.64, 95%CI -1.12 to -0.17, *p* = 0.008, I^2 0%

Negative symptoms: 3 RCTs, N = 57, *g* = -0.07, 95%CI -0.53 to 0.39, *p* = 0.77, I^2 0%

Consistency in results	Consistent for glycine only.
Precision in results	Precise for glycine overall and negative symptoms, and lamotrigine positive, negative and affective symptoms only.
Directness	Direct

Explanation of acronyms

BACS = Brief Assessment of Cognition in Schizophrenia, BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impression scale, CI = confidence interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences (see below for interpretation of effect size), ECG = Electrocardiogram, HAM-D and HS = Hamilton Scale for Depression, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), IMPS = Inpatient Multidimensional Rating Scale, MAS = Montgomery Asberg Scale, MD = mean difference, MS = Manchester Scale, N = number of participants, OAS = Overt Aggression Scale, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PANSS = Positive and Negative Syndrome Scale, Q = Q statistic for the test of heterogeneity, RR = Risk ratio, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms, vs. = versus, WMD = Weighted mean difference

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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[12].

† 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[12].

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[13]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

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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[12];

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

§ 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[14].

‖ 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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