TECHNICAL COMMENTARY

Anticonvulsants

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Introduction

A supplementary, or adjunctive, treatment is administered in conjunction with a patient's ongoing antipsychotic therapy.

Anticonvulsants have been proposed as an additional therapy to standard antipsychotic treatments in an attempt to improve functional outcomes and treat symptoms that are not addressed by the antipsychotic medication alone. Anticonvulsant medications influence the actions of neurotransmitters including glutamate and GABA, leading to a decrease in brain cell (neuron) excitability.

Anticonvulsants may be implemented as an immediate adjunct to normal medication in order to treat acute symptoms of psychosis, such as aggressive behaviour. They may also be used as part of an ongoing treatment regime in order to supplement antipsychotic effects or combat side effects such as movement disorder. Anticonvulsant medications assessed in this topic primarily include valproate, carbamazepine, and lamotrigine.

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 have been given priority 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).

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Results

We found seven systematic reviews that met our inclusion criteria[3-9].

- Moderate to low quality evidence suggests a medium-sized effect of improved mental state (as measured by the PANSS but not the BPRS, SANS or HAM-D), and reduced risk of any adverse effect with adjunctive lamotrigine. There were no differences between groups (vs. placebo) in global state, study attrition, or fatalistic impulses.
- Moderate quality evidence suggests a small benefit for overall symptoms with valproate augmentation, particularly over the short term, although this result was found only in open trials and not RCTs.
- Moderate to low quality evidence suggests some benefit of adjunctive valproate for reducing aggressive behaviour in the short term (1 week), but not in the longer term (4 weeks) compared to placebo. There may also be a lower risk of constipation and tardive dyskinesia, but an increased risk of sedation.
- Moderate to low quality evidence suggests no improvement in symptoms after augmenting clozapine with lamotrigine or topiramate in treatment-resistant patients.

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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	**Anticonvulsant valproate plus antipsychotics (unspecified) vs. placebo plus antipsychotics for improving aggressive behaviour.**
Summary of evidence	**Moderate to low quality evidence (medium-sized sample, unable to assess consistency or precision, direct) suggests a benefit of valproate for improving aggressive behaviour in the short term (1 week), but not in the longer term (4 weeks). There were no differences between groups in adverse effects.**
Aggressive behaviour	
One RCT (N = 249) reported PANSS-Hostility scores were lower in the adjunctive valproate group at one week, but were not significantly different at the 4-week endpoint.	
Risks	Authors report no significant differences in adverse effects.
Consistency in results	Not applicable – 1 RCT.
Precision in results	Unable to assess; no statistics are 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	**Anticonvulsant carbamazepine (800-1200mg/day) plus antipsychotics (mostly haloperidol, also clozapine and unspecified others) vs. antipsychotics alone. Treatment duration**

	ranged from 18 days to 5 weeks.
Summary of evidence	**Moderate to low quality evidence (medium-sized sample, consistent, direct, imprecise) suggests no differences between groups for study attrition. Low quality evidence (small samples, some imprecision or inconsistency) is unable to determine the benefits of carbamazepine for global or mental state, or for adverse effects.**
Leaving the study early	
No significant difference 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 significantly favoured the carbamazepine plus antipsychotic group over antipsychotics alone for 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	
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 differences between groups;* BPRS endpoint score: 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% Less than 20% reduction: 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: 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: RR = 0.86, 95%CI 0.67 to 1.12, *p* = 0.27, Q = 14.31, *p* = 0.01, I^2 = 65% IMPS endpoint score: 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% SANS endpoint score: 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% HAM D (depression) endpoint score: 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 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).

	1 RCT (N = 41), reported no differences in the 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, and most mental state outcomes (except BPRS endpoint and 50% reduction; IMPS endpoint). Not applicable with 1 RCT.
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. Treatment duration ranged from 8 to 28 weeks.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, some inconsistency, imprecise, direct) suggests improved PANSS endpoint scores, but an increased risk of any adverse effect. There were no differences between groups on BPRS, SANS, or HAM-D scales, global state, study attrition, or fatalistic impulses.**
Global state	
No differences between groups; 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;	

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 differences between groups for;
> 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%
BPRS endpoint score: 1 RCT, N = 31, WMD = -2.80, 95%CI -12.44 to 6.84, *p* = 0.57
SANS endpoint score: 1 RCT, N = 31, WMD = -8.80, 95%CI -19.73 to 2.13, *p* = 0.11
HAM-D endpoint score: 1 RCT, N = 31, WMD = 0.10, 95%CI -3.69 to 3.89, *p* = 0.96
Cognitive state
Improved 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 differences between groups for;
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 differences between groups;
5 RCT, 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 impulse

No differences between groups for; 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
Directness of results	Direct

Schwarz C, Volz A, Li C, Leucht S

Valproate for schizophrenia

Cochrane Database of Systematic Reviews 2008; 3: CD004028

View review abstract online

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 ranged from 12 days to 12 weeks.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, some inconsistency, imprecise, direct) suggests no difference between valproate and placebo in study attrition or mental state, with a lower risk of constipation and tardive dyskinesia in the valproate group and a higher risk of sedation.**
Leaving the study early	
No differences between groups; 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 differences between groups for; Clinically significant response: 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% 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% IMPS change scores at 4 weeks: 1 RCT, N = 18, WMD = -5.11, 95%CI -26.04 to 15.82, p = 0.63 PANSS-total change at 4 weeks*:* 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	
Improved OAS scores by 28 days with valproate: 1 RCT, N = 60, WMD = -3.79, 95%CI -5.05 to -2.53, p < 0.00001	
Risks	1 RCT (N = 428) 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 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).

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Consistency in results	Consistent for all, not applicable where 1 RCT.
Precision in results	Imprecise, apart from clinically significant response.
Directness of results	Direct

Sommer IE, Begemann MJH, Temmerman A, Leucht S

Pharmacological Augmentation Strategies for Schizophrenia Patients With Insufficient Response to Clozapine: A Quantitative Literature Review

Schizophrenia Bulletin 2012; 38(5): 1003-1011

View review abstract online

Comparison	**Clozapine plus antiepileptics vs. placebo for people with insufficient response to clozapine.**
Summary of evidence	**Moderate to low quality evidence (small samples, some inconsistency, some imprecision, direct) suggests no improvements in symptoms after augmentation with lamotrigine or topiramate.**

Mental state

No significant improvements with lamotrigine augmentation;

Total symptoms (PANSS/BPRS): 5 RCTs, N = 143, g = 0.53, 95%CI 0.03 to 1.04, $p < 0.05$, I^2 60%

Excluding 1 outlier: 4 RCTs, N = 92, g = 0.27, 95%CI -0.10 to 0.65, $p > 0.05$, I^2 0%

Positive symptoms: 5 RCTs, N = 143, g = 0.38, 95%CI -0.02 to 0.78, $p > 0.05$, I^2 39%

Excluding 1 outlier: 4 RCTs, N = 92, g = 0.15, 95%CI -0.22 to 0.52, $p > 0.05$, I^2 0%

Negative symptoms: 5 RCTs, N = 143, g = 0.41, 95%CI -0.13 to 0.94, $p > 0.05$, I^2 64%

Excluding 1 outlier: 4 RCTs, N = 92, g = 0.12, 95%CI -0.25 to 0.49, $p > 0.05$, I^2 0%

No significant improvements with topiramate augmentation;

Total symptoms (PANSS/BPRS): 3 RCTs, N = 89, g = 0.75, 95%CI -0.05 to 1.56, $p > 0.05$, I^2 69%

Excluding 1 outlier: 2 RCTs, N = 57, g = 0.27, 95%CI -0.13 to 0.89, $p > 0.05$, I^2 0%

Positive symptoms: 3 RCTs, N = 89, g = 0.63, 95%CI 0.03 to 1.23, $p < 0.05$, I^2 47%

Excluding 1 outlier: 2 RCTs, N = 57, g = 0.39, 95%CI -0.24 to 1.01, $p > 0.05$, I^2 25%

Negative symptoms: 3 RCTs, N = 89, g = 0.66, 95%CI -0.17 to 1.50, $p > 0.05$, I^2 71%

Consistency in results	Consistent for all antiepileptic analyses without outliers.
Precision in results	Precise for all lamotrigine analyses without outliers. Imprecise for topiramate analyses.
Directness	Direct

Tseng PT, Chen YW, Chung W, Tu KY, Wang HY, Wu CK, Lin PY

Significant Effect of Valproate Augmentation Therapy in Patients With Schizophrenia: A Meta-analysis Study

Medicine 2016; 95(4): e2475

View review abstract online

Comparison	**Valproate plus antipsychotics vs. antipsychotics with or without placebo in people with schizophrenia spectrum disorders.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, some imprecision, direct) suggests a small benefit for overall symptoms with valproate augmentation, particularly over the short term, although this result was found only in open trials and not RCTs.**

Mental state

PANSS or BPRS

Significant, small effect of greater improvement in overall symptoms with valproate augmentation;

Overall symptoms: 11 studies, N = 889, *g* = 0.31, 95%CI 0.05 to 0.57, *p* = 0.02, Q = 24.35, *p* = 0.007, I^2 = 59%

Similar results were observed when patients with schizoaffective disorder were excluded from the analysis.

Significant, medium-sized effect of greater improvement in overall symptoms with valproate augmentation in studies with drug naive or drug free patients;

3 studies, N = 48, *g* = 0.66, 95%CI 0.11 to 1.22, *p* = 0.14

No significant differences between groups were found when positive and negative symptoms were analysed separately or in studies of patients with moderate to severe symptoms;

Positive symptoms: 4 studies, N = 573, *g* = 0.26, 95%CI -0.14 to 0.66, *p* = 0.203

Negative symptoms: 4 studies, N = 567, *g* = 0.24, 95%CI -0.18 to 0.66, *p* = 0.263

Moderate to severe symptoms: 5 studies, N = 510, *g* = 0.28, 95%CI -0.03 to 0.59, *p* = 0.075 Subgroup analyses revealed results from open trials (*g* = 0.60, 95%CI 0.13 to 1.06, *p* = 0.01), but not from randomised controlled trials (*g* = 0.19, 95%CI -0.10 to 0.47, *p* = 0.20) and in the studies with a shorter treatment duration (< 4 weeks, *g* = 1.17, 95%CI 0.64 to 1.70, *p* < 0.001) and not longer treatment duration (> 4 weeks, *g* = 0.10, 95%CI -0.06 to 0.26, *p* = 0.23). Meta-regression revealed longer treatment duration (*β* = -0.06, *p* < 0.001), older mean age (*β* = -0.06, *p* = 0.014), and greater valproate dosage (*β* = -0.0005, *p* = 0.002) were significantly associated with smaller effect sizes. Authors report possible publication bias.
Leaving the study early
No significant differences between groups; 6 studies, N = 653, RR = 0.71, 95%CI 0.45 to 1.12, *p* = 0.14

Risks	Authors report that the three studies that used a longer duration of treatment (< 4 weeks) revealed no severe side effects in the groups receiving antipsychotics augmented with valproate.
Consistency in results	Inconsistent for overall symptoms, consistency measure is not reported for other analyses.
Precision in results	Precise for symptoms, long treatment duration, open trials, and RCTs analyses. Imprecise for drug free and short treatment duration analyses.
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 to low 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, β = meta-regression coefficient, 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 = 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, 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, Q_w = test for within group differences (heterogeneity in study results within a group of studies – measure of study consistency), Q_B = test for between group differences (heterogeneity between groups of studies for an outcome of interest), 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[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).

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[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.

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 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, 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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