Carbamazepine for schizophrenia (Review)

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[Intervention Review]

Carbamazepine for schizophrenia

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ABSTRACT

Background

Many people with schizophrenia do not achieve a satisfactory treatment response with just antipsychotic drug treatment and various adjunct medications are used to promote additional response. The antiepileptic carbamazepine is one such drug.

Objectives

To evaluate the effects of carbamazepine and its derivatives for the treatment of schizophrenia and related psychoses.

Search strategy

For the original version we searched Biological Abstracts (1980-2001), The Cochrane Library (Issue 3, 2001), The Cochrane Schizophrenia Group's Register of Trials (December 2001), EMBASE (1980-2001), MEDLINE (1966-2001), PsycLIT (1886-2001) and PSYNDEX (1974-2001). For the current update we searched the Cochrane Schizophrenia Group's Register of Trials in March 2005 and in December 2006. We also inspected references of all identified studies for further trials and contacted relevant pharmaceutical companies and authors for additional data.

Selection criteria

We included all randomised controlled trials comparing carbamazepine or compounds of the carbamazepine family to placebo or no intervention, whether as sole treatment or as an adjunct to antipsychotic medication for the treatment of schizophrenia and/or schizoaffective psychoses.

Data collection and analysis

We extracted data independently. For homogenous dichotomous data we calculated random effects, relative risk (RR), 95% confidence intervals (CI) and, where appropriate, numbers needed to treat (NNT) on an intention-to-treat basis. For continuous data, we calculated weighted mean differences (WMD).

Main results

The update search did not reveal any further studies that met our inclusion criteria. The number of included studies therefore remains at ten with the number of participants randomised still 258. One study comparing carbamazepine with placebo as the sole treatment

for schizophrenia was abandoned early due to high relapse rate with 26 out of 31 participants relapsing by three months. No effect of carbamazepine was evident with no difference in relapse between the two groups (1 RCT n=31, RR 4.1 CI 0.8 to 1.5).

Another study compared carbamazepine with antipsychotics as the sole treatment for schizophrenia. No differences in terms of mental state were found when comparing 50% reduction in BPRS scores (1 RCT n=38, RR 1.2 CI 0.8 to 1.9). A favourable effect for carbamazepine was found when more people who received the antipsychotic (perphenazine) had parkinsonism (1 RCT n=38, RR 0.03 CI 0.00 to 0.04, NNH 1 CI 0.9 to 1.4).

Eight studies compared adjunctive carbamazepine versus adjunctive placebo. Adding carbamazepine to antipsychotic treatment was as acceptable as adding placebo with no difference between the numbers leaving the study early from each group (8 RCTs n=182, RR 0.5 CI 0.2 to 1.4). Carbamazepine augmentation was superior compared with antipsychotics alone in terms of overall global improvement, but participant numbers were low (2RCTs n=38, RR 0.6 CI 0.4 to 0.9, NNT 2 CI 1 to 5). There were no differences for the mental state outcome of 50% reduction in BPRS scores (6 RCTs n=147, RR 0.9 CI 0.7 to 1.1). Less people in the carbamazepine augmentation group had movement disorders than those taking haloperidol alone (1 RCT n=20, RR 0.4 CI 0.1 to 1.0). No data were available for the effects of carbamazepine on subgroups of people with schizophrenia and aggressive behaviour, negative symptoms or EEG abnormalities or with schizoaffective disorder.

Authors' conclusions

Based on currently available randomised trial-derived evidence, carbamazepine cannot be recommended for routine clinical use for treatment or augmentation of antipsychotic treatment of schizophrenia. At present large, simple well-designed and reported trials are justified especially if focusing on those with violent episodes and people with schizoaffective disorders or those with both schizophrenia and EEG abnormalities.

PLAIN LANGUAGE SUMMARY

Carbamazepine for schizophrenia

Carbamazepine is an antiepileptic drug, which is also used as an adjunct to antipsychotics for schizophrenia. Although the original patient data from eight out of ten included studies could be re-analysed, we found no significant benefit of carbamazepine, either as a sole treatment or as an adjunct to antipsychotics. However, as the total number of patients included was small, further randomised trials seem to be warranted.

BACKGROUND

Despite the introduction of antipsychotic (neuroleptic) medication in the 1950s, there is still a sizeable minority of people with schizophrenia and related conditions that do not have complete remission of symptoms (Schooler 1993). Over the last 40 years a variety of adjunctive treatments have been used to treat schizophrenia (Christison 1991). These are often used in addition to antipsychotics, in order to augment any alleviation of symptoms of schizophrenia, but can be used instead of antipsychotics. Treatments such as lithium (indicated for bipolar affective disorder), carbamazepine (or related compounds such as oxcarbazepine), benzodiazepines, beta-blockers (Ahonen 1998) and electroconvulsive therapy (Tharyan 2002) have all been used for people whose psychoses did not respond to traditional therapy. The situation has improved somewhat in recent years with the re-introduction of clozapine which has proven efficacy for those that have not responded to traditional medications (Wahlbeck 1998). However, many people with psychoses have sub-optimal responses to treatment, and clinicians are faced with the choice of changing to alternate types of medication, or augmenting existing neuroleptics with other drugs or treatments.

Carbamazepine is traditionally used for the treatment of epilepsy, but is also used to prevent relapse, as a 'mood stabiliser', in bipolar affective illness in a similar fashion to lithium (Dardennes 1995). Oxcarbazepine is a related compound that is said to be an improvement on the older 'parent' drug (Tiihonen 1995). In this review we do not examine the efficacy of carbamazepine for mood disorders and the affective psychoses. However in two companion reviews the impact of lithium and benzodiazepines as sole or adjunctive treatment for schizophrenia and schizoaffective psychoses is examined.

OBJECTIVES

To examine whether carbamazepine/oxcarbazepine alone is an effective treatment for schizophrenia and schizoaffective psychoses and whether carbamazepine/oxcarbazepine augmentation of neuroleptic medication is an effective treatment for the same illnesses.

METHODS

Criteria for considering studies for this review

Types of studies

We included all relevant randomised controlled trials. Where a trial was described as 'double-blind', but it was implied that the study was randomised, we included the trial in a sensitivity analysis. If there was no substantive difference within primary outcomes (see 'types of outcome measures') when these 'implied randomisation' studies were added, then we included these in the final analysis. If there was a substantive difference, we only analysed clearly randomised trials and described the results of the sensitivity analysis in the text. We excluded quasi-randomised studies, such as those allocating by using alternate days of the week.

Types of participants

People with schizophrenia, schizophreniform psychoses, delusional disorder and schizoaffective psychoses as diagnosed by any criteria.

Types of interventions

1. Carbamazepine/oxcarbazepine alone: any dose.
2. Placebo (or no intervention).
3. Carbamazepine/oxcarbazepine in combination with any antipsychotic treatment: any dose.
4. Placebo (or no intervention) in combination with any antipsychotic treatment.
5. Antipsychotics alone: any dose.

Types of outcome measures

1. Leaving the study early
1.1 For specific reasons
1.2 For general reasons
2. Service utilisation
2.1 Hospital admission
2.2 Days in hospital
2.3 Change in hospital status
3. Global state
3.1 Relapse - as defined by each of the studies
3.2 Time to relapse
3.3 No clinically important change in global state*
3.4 Not any change in global state
3.5 Average endpoint global state score
3.6 Average change in global state scores
4. Mental state
4.1 General mental state
4.1.1 No clinically important change in general mental state - as defined by each of the studies
4.1.2 Not any change in general mental state
4.1.3 Average endpoint general mental state score
4.1.4 Average change in general mental state scores
4.2 Specific aspects of mental state
4.2.1 No clinically significant response in positive symptoms - as defined by each of the studies
4.2.2 Not any change in positive symptoms
4.2.3 Average endpoint positive symptom score
4.2.4 Average change in positive symptom scores
4.2.5 No clinically significant response in negative symptoms - as defined by each of the studies
4.2.6 Not any change in negative symptoms
4.2.7 Average endpoint negative symptom score
4.2.8 Average change in negative symptom scores
4.2.9 No clinically significant response in depressive symptoms - as defined by each of the studies
4.2.10 Not any change in depressive symptoms
4.2.11 Average endpoint depressive symptom score
4.2.12 Average change in depressive symptom scores
4.2.13 No clinically significant response in manic symptoms - as defined by each of the studies
4.2.14 Not any change in manic symptoms
4.2.15 Average endpoint manic symptom score
4.2.16 Average change in manic symptom scores
5. Behaviour
5.1 General behaviour
5.1.1 No clinically important change in general behaviour
5.1.2 Not any change in general behaviour
5.1.3 Average endpoint general behaviour score
5.1.4 Average change in general behaviour scores
5.1.5 Compulsory administrations of treatment
5.1.6 Use of further doses of medication
5.2 Specific behaviours
5.2.1 Self-harm, including suicide
5.2.2 Injury to others
5.2.3 Aggression
5.2.3.1 No clinically important change in aggression
5.2.3.2 Not any change in aggression
5.2.3.3 Average endpoint aggression score
5.2.3.4 Average change in aggression scores
5.2.4 Self care
5.2.4.1 No clinically important change in self care
5.2.4.2 Not any change in self care
5.2.4.3 Average endpoint self care score

5.2.4.4 Average change in self care scores
5.2.5 Compliance
5.2.5.1 No clinically important change in compliance
5.2.5.2 Not any change in compliance
5.2.5.3 Average endpoint compliance score
5.2.5.4 Average change in compliance scores
6. Social functioning
6.1 No clinically important effects for social function
6.2 Not any effects for social function
6.3 Average endpoint social functioning score
6.4 Average change social functioning scores
6.5 Employment status during trial (employed / unemployed)
7. Adverse effects
7.1 Clinically important general adverse effects*
7.2 Any general adverse effects
7.3 Average endpoint general adverse effect score
7.4 Average change in general adverse effect scores
7.5 Clinically important change in specific adverse effects such as movement disorders
7.6 Any change in specific adverse effects
7.7 Average endpoint specific adverse effects
7.8 Average change in specific adverse effects
7.9 Use of antiparkinsonian treatment
8. Sudden and unexpected death
9. Economic outcomes
9.1 Direct costs
9.2 Indirect costs
10. Satisfaction with treatment
10.1 Recipient of care not satisfied with treatment
10.2 Recipient of care average satisfaction score
10.3 Recipient of care average change in satisfaction scores
10.4 Carer not satisfied with treatment
10.5 Carer average satisfaction score
10.6 Carer average change in satisfaction scores
11. Quality of life
11.1 No clinically important change in quality of life
11.2 Not any change in quality of life
11.3 Average endpoint quality of life score
11.4 Average change in quality of life scores
11.5 No clinically important change in specific aspects of quality of life
11.6 Not any change in specific aspects of quality of life
11.7 Average endpoint specific aspects of quality of life
11.8 Average change in specific aspects of quality of life
12. Pharmacokinetic interactions - change of haloperidol plasma-levels.
* Primary outcomes of interest were overall improvement and side effects.
We grouped all outcomes by time - short term (up to 12 weeks), medium term (13 to 26 weeks) and long term (over 26 weeks).

Search methods for identification of studies

#
1. Update searches in March 2005 and in December 2006
For the update we searched the Cochrane Schizophrenia Group's Register of Trials (March 2005 and November 2006) using the phrase: [((*carbama* or *amizepine* or *carbag* or *carbap* or *carbaz* or *carbymal* or *carpaz* or *cephalon* or *degranol* or *epitol* or *finlepsin* or *fokalepsin* or *hermolepsin* or *neurotol* or *neurotop* or *nordotol* or *sirtal* or *tardotol* or *tegret* or *teril* or *timonil* or *trimonil* or *trialeptal* or *trilpetal*) in Ti, Ab and In fields in References) AND (carbama* in Intervention field in Study)]
This register is compiled by systematic searches of major databases, hand searches and conference proceedings (see Group Module)
2. Original search
2.1 Electronic searching
2.1.1 We searched Biological Abstracts (January 1980 - August 2001) using the Cochrane Schizophrenia Group's phrase for both randomised controlled trials and schizophrenia (see Group search strategy) combined with the phrase:
[and carbamazepine* or tegretol or tardotol or tegretal or carbagamma or carbymal or carpaz or carbapin or degranol or finlepsin or fokalepsin or hermolepsin or neurotol or neurotop or nordotol or oxcarbazepine or sirtal or tardotol or timonil or trimonil or "10,11-dihydro-10-oxo-5H-dobenz[b,f]azepine-5-carboxamide" or "5H-dibenz[b,f]azepine-5-carboxamide" or (GP near1 (49.023 or 10.000 or 47.779 or 47.680)) or trialeptal or trileptal or "trans-10,11-dihydro-10,11-epoxy-5h-dibenz[b,f]azepine-5-carboxamide"]
2.1.2 We searched The Cochrane Library (Issue 3, 2001) using the phrase:
[and carbamazepine* or tegretol or tardotol or tegretal or carbagamma or carbymal or carpaz or carbapin or degranol or finlepsin or fokalepsin or hermolepsin or neurotol or neurotop or nordotol or oxcarbazepine or sirtal or tardotol or timonil or trimonil or "10,11-dihydro-10-oxo-5H-dobenz[b,f]azepine-5-carboxamide" or "5H-dibenz[b,f]azepine-5-carboxamide" or (GP and (49.023 or 10.000 or 47.779 or 47.680)) or trialeptal or trileptal or "trans-10,11-dihydro-10,11-epoxy-5h-dibenz[b,f]azepine-5-carboxamide" or explode CARBAMAZEPINE / all]
2.1.3 We searched the Cochrane Schizophrenia Group's Register of Trials (December 2001) using the phrase:
[and carbamazepine* or tegretol or tardotol or tegretal or carbagamma or carbymal or carpaz or carbapin or degranol or finlepsin or fokalepsin or hermolepsin or neurotol or neurotop or nordotol or oxcarbazepine or sirtal or tardotol or timonil or trimonil or "10,11-dihydro-10-oxo-5H-dobenz[b,f]azepine-5-carboxamide" or "5H-dibenz[b,f]azepine-5-carboxamide" or (GP and (49.023 or 10.000 or 47.779 or 47.680)) or trialeptal or trileptal or "trans-10,11-dihydro-10,11-epoxy-5h-dibenz[b,f]azepine-5-carboxamide"or #42 = 684 or #42=20]
#42 is the intervention field within the register and 684 and 20

are the codes for carbamazepine.
2.1.4 We searched EMBASE (January 1980 - August 2001) using the Cochrane Schizophrenia Group's phrase for both randomised controlled trials and schizophrenia (see Group search strategy) combined with the phrase:
[and carbamazepine* or tegretol or tardotol or tegretal or carbagamma or carbymal or carpaz or carbapin or degranol or finlepsin or fokalepsin or hermolepsin or neurotol or neurotop or nordotol or oxcarbazepine or sirtal or tardotol or timonil or trimonil or "10,11-dihydro-10-oxo-5H-dobenz[b,f]azepine-5-carboxamide" or "5H-dibenz[b,f]azepine-5-carboxamide" or (GP near1 (49.023 or 10.000 or 47.779 or 47.680)) or trialeptal or trileptal or "trans-10,11-dihydro-10,11-epoxy-5h-dibenz[b,f]azepine-5-carboxamide"or explode CARBAMAZEPINE / all]
2.1.5 We searched MEDLINE (January 1966 - August 2001) using the Cochrane Schizophrenia Group's phrase for both randomised controlled trials and schizophrenia (see Group search strategy) combined with the phrase:
[and carbamazepine* or tegretol or tardotol or tegretal or carbagamma or carbymal or carpaz or carbapin or degranol or finlepsin or fokalepsin or hermolepsin or neurotol or neurotop or nordotol or oxcarbazepine or sirtal or tardotol or timonil or trimonil or "10,11-dihydro-10-oxo-5H-dobenz[b,f]azepine-5-carboxamide" or "5H-dibenz[b,f]azepine-5-carboxamide" or (GP near1 (49.023 or 10.000 or 47.779 or 47.680)) or trialeptal or trileptal or "trans-10,11-dihydro-10,11-epoxy-5h-dibenz[b,f]azepine-5-carboxamide"or explode CARBAMAZEPINE / all]
2.1.6 We searched PsycLIT (1886 - August 2001) using the Cochrane Schizophrenia Group's phrase for both randomised controlled trials and schizophrenia (see Group search strategy) combined with the phrase:
[and carbamazepine* or tegretol or tardotol or tegretal or carbagamma or carbymal or carpaz or carbapin or degranol or finlepsin or fokalepsin or hermolepsin or neurotol or neurotop or nordotol or oxcarbazepine or sirtal or tardotol or timonil or trimonil or "10,11-dihydro-10-oxo-5H-dobenz[b,f]azepine-5-carboxamide" or "5H-dibenz[b,f]azepine-5-carboxamide" or (GP near1 (49.023 or 10.000 or 47.779 or 47.680)) or trialeptal or trileptal or "trans-10,11-dihydro-10,11-epoxy-5h-dibenz[b,f]azepine-5-carboxamide"or explode "CARBAMAZEPINE" / all]
2.1.7 We searched PSYNDEX (January 1974 - August 2001) using the Cochrane Schizophrenia Group's phrase for both randomised controlled trials and schizophrenia (see Group search strategy) combined with the phrase:
[and carbamazepine* or tegretol or tardotol or tegretal or carbagamma or carbymal or carpaz or carbapin or degranol or finlepsin or fokalepsin or hermolepsin or neurotol or neurotop or nordotol or oxcarbazepine or sirtal or tardotol or timonil or trimonil or "10,11-dihydro-10-oxo-5H-dobenz[b,f]azepine-5-carboxamide" or "5H-dibenz[b,f]azepine-5-carboxamide" or (GP near1 (49.023 or 10.000 or 47.779 or 47.680)) or trialeptal or trileptal or "trans-10,11-dihydro-10,11-epoxy-5h-dibenz[b,f]azepine-5-carboxamide]
2.2 Reference lists
We searched all references of articles selected for inclusion for further relevant trials.
2.3 Pharmaceutical companies
We contacted companies performing trials with carbamazepine to obtain data on unpublished trials.
2.4 Personal contact
We contacted the first author of each included study for more data of their study and any information regarding unpublished trials.

Data collection and analysis

[For definitions of terms used in this, and other sections, please refer to the Glossary.]
1. Selection of trials
SL independently inspected all reports identified by the search and JM re-inspected these to ensure reliable selection. Where agreement could not be reached, we acquired the full report was for more detailed scrutiny. Once the full reports were obtained we independently inspected them to assess their relevance to this review. Again, if disagreement could not be resolved by discussion or from published information, we added the article to those awaiting assessment and contacted the authors of the study for clarification.
2. Assessment of methodological quality
We assessed the methodological quality of included trials in this review using the criteria described in the Cochrane Handbook (Higgins 2005) and the Jadad Scale (Jadad 1996). The former is based on the evidence of a strong relationship among the potential for bias in the results and the allocation concealment (Schulz 1995) and is defined as below:
A. Low risk of bias (adequate allocation concealment)
B. Moderate risk of bias (some doubt about the results)
C. High risk of bias (inadequate allocation concealment)
The Jadad Scale measures a wider range of factors that impact on the quality of a trial. The scale includes three items:
1. Was the study described as randomised?
2. Was the study described as double-blind?
3. Was there a description of withdrawals and drop outs?
Each item receives one point if the answer is positive. In addition, a point can be deducted if either the randomisation or the blinding/masking procedures described were inadequate or added if random number generation adequate or blinding appropriate. Scores on item 1 and 2 can therefore be 0, 1 or 2.
For the purpose of the analysis in this review, we included trials if they met the criteria A or B of the Cochrane Handbook. We did not us the Jadad scale to exclude trials in this review, but we used it to explore potential heterogeneity as a result of trial quality.
3. Data collection
We independently extracted the data from included studies. Again, we discussed any disagreement and documented decisions. When this was not possible, we sought further information from authors

of the studies and did not enter data from these trials but added them to the list of those awaiting assessment.

4. Data synthesis

4.1 Data types

Outcomes are assessed using continuous (for example changes on a behaviour scale), categorical (for example, one of three categories on a behaviour scale, such as 'little change', 'moderate change' or 'much change') or dichotomous measures (for example, either 'no important changes' or 'important changes' in a person's behaviour). Currently RevMan does not support categorical data so they were presented only in the text of the review.

4.2 Incomplete data

For studies that did not specify the reasons for people leaving the study early (dropped out), we assumed that these people had no change in the clinical outcome variables. If over 50% of people dropped out, and the study did not provide intention-to-treat results for continuous data, we excluded these data.

4.3 Crossover design

We expected that some trials would use a crossover design. In order to exclude the potential additive effect in the second or more stages on these trials, we only analysed data from the first stage.

4.4 Dichotomous - yes/no data

We carried out an intention to treat analysis. On the condition that more than 50% of people completed the study, everyone allocated to the intervention were counted, whether they completed the follow up or not. We assumed that those who dropped out had the negative outcome, with the exception of death.

Where possible efforts were made to convert outcome measures to dichotomous data. This may be done by identifying cut off points on rating scales and dividing subjects accordingly into 'clinically improved' or 'not clinically improved'. If the authors of a study had used a designated cut off point for determining clinical effectiveness we used this where appropriate.

For dichotomous outcomes, a relative risk (RR) with the 95% confidence interval (CI) based on a fixed effects model was estimated. This is different to previous versions of this review. The reason for the change is that it has been shown that relative risks are more intuitive to clinicians than odds ratios (Boissel 1999). Furthermore, clinicians tend to interpret odds ratios as relative risks. This misinterpretation leads to an overestimate of effect (Deeks 2000). When overall results were significant we calculated the Number Needed to Treat (NNT) and/or the Number Needed to Harm (NNH) as the inverse of the absolute risk difference.

4.5 Continuous data

4.5.1 Normally distributed data: Continuous data on outcomes in trials relevant to mental health issues are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data the following standards were applied to data derived from continuous measures of endpoint ('state' data). The criteria were used before inclusion:

i. standard deviations and means were reported in the paper or were obtainable from the authors and ii. the standard deviation (SD), when multiplied by 2, was less than the mean (as otherwise the mean was unlikely to be an appropriate measure of the centre of the distribution) (Altman 1996). If a scale starts from a positive value (such as PANSS which can have values from 30 to 210) the calculation described above in ii) should be modified to take the scale starting point into account. In these cases skewness is present if 2SD>(S-Smin), where S is the mean score and Smin is the minimum score. We did not enter data that did not meet the first or second standard into RevMan software for analysis, but reported the data in the text of the results section.

4.5.2 Scale derived data: A wide range of rating scales is available to measure outcomes in mental health trials. These scales vary in quality and many are questionably validated, or even ad hoc. It is generally accepted that measuring instruments should have the properties of reliability (the extent to which a test effectively measures anything at all) and validity (the extent to which a test measures that which it is supposed to measure). Before publication of an instrument, most scientific journals insist that reliability and validity be demonstrated to the satisfaction of referees. We therefore decided, as a minimum standard, not to include any data from a rating scale in this review unless its properties had been published in a peer-reviewed journal. In addition, we set the following minimum standards for rating scales; the rating scale should either be i. a self-report or ii. completed by an independent rater or relative. We may set more stringent standards for instruments in future updates of this review.

Whenever possible we took the opportunity to make direct comparisons between trials that used the same measurement instrument to quantify specific outcomes. Where continuous data was presented from different scales rating the same effect, we presented both sets of data and inspected the general direction of effect.

4.5.3 Endpoint versus change data: For continuous mean change data (endpoint minus baseline) the situation is even more problematic. In the absence of individual patient data it is impossible to know if change data is skewed. The RevMan meta-analyses of continuous data are based on the assumption that the data are, at least to a reasonable degree, normally distributed. It is quite feasible that change data is skewed but, after consulting the ALL-STAT electronic statistics mailing list, it was entered into RevMan in order to summarise the available information. In doing this it is assumed that either data were not skewed or that the analyses within RevMan could cope with the unknown degree of skewness.

4.6 Individual patient data

For this update we requested the individual patient data from the original authors. Most of these were data derived from the BPRS, a scale measuring mental state. We tried to convert these results to dichotomous data (see 4.3.1). As it seemed impossible to us to predefine which level of reduction of the total score is clinically meaningful, three levels were analysed: a relatively low level (at least 20% BPRS reduction), an intermediate level (at least 35% BPRS reduction) and a relatively high level (at least 50% BPRS reduction).

4.7 Data display
We entered data into RevMan in such a way that the area to the left of the line of no effect indicated a favourable outcome for carbamazepine alone or carbamazepine augmentation.
4.8 Cluster trials
Studies increasingly employ "cluster randomisation" (such as randomisation by clinician or practice) but analysis and pooling of clustered data poses problems. Firstly, authors often fail to account for intra class correlation in clustered studies, leading to a "unit of analysis" error (Divine 1992) whereby p values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This causes type 1 errors (Bland 1997, Gulliford 1999).
Where clustering was not accounted for in primary studies, we presented the data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. in subsequent versions of this review we will seek to contact first authors of studies to obtain intra-class correlation co-efficients of their clustered data and to adjust for this using accepted methods (Gulliford 1999). Where clustering was incorporated into the analysis of primary studies, we presented these data as if from a non-cluster randomised study, but adjusted for the clustering effect.
We sought statistical advice and were advised that the binary data as presented in a report should be divided by a "design effect". This is calculated using the mean number of participants per cluster (m) and the intraclass correlation co-efficient (ICC) [Design effect=1+(m-1)*ICC] (Donner 2002). If the ICC was not reported, we assumed it to be 0.1 (Ukoumunne 1999).

If cluster studies had been appropriately analysed taking into account intra-class correlation coefficients and relevant data documented in the report, synthesis with other studies would have been possible using the generic inverse variance technique.
5. Investigation for heterogeneity
Firstly, we visually inspected graphs to investigate the possibility of statistical heterogeneity. This was supplemented using, primarily, the I-squared statistic. This provides an estimate of the percentage of variability due to heterogeneity rather than chance alone. Where the I-squared estimate was greater than or equal to 50% we interpreted this as indicating the presence of considerable levels of heterogeneity (Higgins 2005). The I-squared statistic has been described to be a more appropriate indicator of heterogeneity than the Chi-square test that was used in the previous version of the review (Higgins 2005). If either the I-squared statistic was higher than 50% or the p-value of the Chi-square test, for reasons of consistency we did not deviate from the rule as to when the fixed and when the random effect model has to be applied, although we would now rather use the random effects model throughout.
6. Publication bias
We entered data from all included trials into a funnel graph (trial effect versus trial size or 'precision') in an attempt to investigate the likelihood of overt publication bias. A formal test of funnel plot asymmetry (suggesting potential publication bias) was undertaken, where appropriate (Egger 1997). Significance levels of $p < 0.1$ were set a priori to accept the presence of asymmetry. Where only three or four studies reported an outcome or there was little variety in sample size (or precision estimate) between studies tests of asymmetry were not appropriate.
7. Where possible, we entered data in such a way that the area to the left of the line of no effect indicated a favourable outcome for carbamazepine.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
Please also see tables of included and excluded studies.
1. Excluded studies
We excluded 89 studies. The main reasons for exclusion were that studies were not randomised trials, or allocated in a way that was too open to the inclusion of bias (n=42). Several papers, mainly reviews, did not contain any original data (n=19), one other did not include people with schizophrenia or similar disorders or and five did not include a placebo or no-intervention group. This latter group all involved lithium as the comparator. One of these five studies was the only trial which used oxcarbazepine instead of carbamazepine. Two studies examined participants with several diagnoses, but no data specifically for people with schizophrenia only could be extracted (de Vogelaer 1981, Dehing 1968). Three studies randomised appropriate participant groups to relevant interventions, but no data could be extracted from the original publications (Kidron 1985, Klein 1984, Möller 1989). We contacted the authors of these studies who replied explaining that the data were no longer available; we therefore had to exclude these studies.
2. Studies awaiting assessment
We have not heard back from the author of the study classified as awaiting assessment in the 2002 update (Lee 1996). In the 2005 update we found another potentially relevant study (Kamisada 1988), but it is only available as an abstract and the design is unclear; we therefore classified it as awaiting assessment. We have contacted the first author for more information, but did not receive any reply.
3. Ongoing studies
We are not aware of any ongoing studies.
4. Included studies
We included ten studies in the current version of this review. Most studies used a parallel group designs but Carpenter 1991, Llorca 1993, Svestka 1989 and Neppe 1983 were crossover studies. Of the latter, we used only the results of the first phase.

4.1 Length of trials
One study was a medium-term study with a duration of 14 weeks (Carpenter 1991) but all others were in the 'short-term' category being between one and six weeks long within a single treatment phase.
4.2 Participants
These studies included a total of 258 people. Most suffered from schizophrenia but there were also some with schizoaffective disorder (n=12), other diagnoses (n=3) and 23 patients where the diagnosis was not clearly indicated. Four studies included only people with sub-types of serious mental illnesses: treatment resistant illness (Llorca 1993, Simhandl 1996), "residual patients" suffering from negative symptoms (Nachshoni 1994) and "psychotic patients with EEG abnormalities" (Neppe 1983). Diagnostic criteria varied to a considerable degree, because the studies were carried out over a long period of time, but most studies used some sort of standard diagnostic criteria. Where possible we excluded participants with affective disorder or dementia.
4.3 Setting
Only Carpenter 1991was undertaken in the community and all others were carried out with people currently in hospital.
4.4 Study size
The number of people in each study was low and ranged from between 13 and 41.
4.5 Interventions
One study examined carbamazepine as a sole agent in relapse prevention (Carpenter 1991), and a second compared carbamazepine as a sole treatment with perphenazine for acutely ill people with schizophrenia (Svestka 1989). All other studies investigated carbamazepine as an adjunct to antipsychotic drug treatment. The most commonly used dose of carbamazepine was about 6600 mg day and haloperidol was commonly used as the standard antipsychotic treatment (doses ranging from 6-665 mg day).
4.6 Outcomes
In the original reports many different scales were used to assess outcome parameters which makes the summation of results difficult. Furthermore, different ways of analysing the same scale were used, for example, comparison of mean changes or comparison of endpoint values. Only one study (Neppe 1983) presented dichotomised data on number of patients "improved or not improved". Few of the studies used specific scales to assess side effects. For this reason, we requested the individual patient data and received this from eight out of ten included trials. This allowed an analysis of the available data in a uniform way. However, even after receiving individual patient data, adverse effects remained poorly reported.
4.6.1 Outcome scales: details of the scales that provided useful data are shown below. We have reported reasons for exclusion of data under 'Outcomes' in the 'Included studies' table.
4.6.1.1 Global state
Clinical Global Impression - CGI (NIMH 1970)
A rating instrument commonly used in studies on schizophrenia that enables clinicians to quantify severity of illness and overall clinical improvement during therapy. A seven-point scoring system is usually used with low scores indicating decreased severity and/or greater recovery.
4.6.1.2 Mental state
Brief Psychiatric Rating Scale - BPRS (Overall 1962)
A brief rating scale used to assess the severity of a range of psychiatric symptoms, including psychotic symptoms. The scale has 16 items, and each item can be defined on a seven-point scale varying from 'not present' (1) to 'extremely severe' (7). Scoring goes from 24 -168.
Inpatient Multidimensional Rating Scale (Lorr 1962)
A rating scale used to assess the severity of a range of psychiatric symptoms. Higher scores indicate more symptoms. We were unable to obtain further details.

Positive and Negative Symptom Scale - PANSS (Kay 1987)
This scale was developed to evaluate the positive, negative and general symptoms in schizophrenia. The scale has 30 items, and each item can be defined on a seven-point scoring system varying from one (absent) to seven (extreme). This scale can be divided into three subscales for measuring the severity of general psychopathology, positive symptoms (PANSS-P) and negative symptoms (PANSS-N). Higher scores indicate more symptoms.
Scale for the Assessment of Negative Symptoms - SANS (Andreasen 1982).
This six-point scale gives a global rating of the following negative symptoms alogia, affective blunting, avolition-apathy, anhedonia-asociality and attention impairment. Higher scores indicate more symptoms.
Scale for the Assessment of Positive Symptoms - SAPS (Andreasen 1984)
This six-point scale gives a global rating of positive symptoms such as delusions, hallucinations, and disordered thinking. Higher scores indicate more symptoms.
Hamilton Rating Scale for Depression - HDRS (Hamilton 1960)
The instrument is designed to be used only on patients already diagnosed as suffering from affective disorder of depressive type. It is used for quantifying the results of an interview, and its value depends entirely on the skill of the interviewer in eliciting the necessary information. The scale contains 17 variables measured on either a five-point or a three-point rating scale, the latter being used where quantification of the variable is either difficult or impossible. Among the variables are: depressed mood, suicide, work and loss of interest, retardation, agitation, gastro-intestinal symptoms, general somatic symptoms, hypochondriasis, loss of insight, and loss of weight. It is useful to have two raters independently scoring a patient at the same interview. The scores of the patient are obtained by summing the scores of the two physicians.

Risk of bias in included studies

1. Randomisation
Six studies achieved an 'A' category for randomisation concealment (Heßlinger 1998, Nachshoni 1994, Carpenter 1991, Heßlinger 1998, Llorca 1993, Martin-Munoz 1989). All others studies were allocated to the 'B' quality score.
2. Blindness
All but two studies were double-blind (Heßlinger 1998, Mair 1990), although there was no description as to how blindness was assured and never was it tested. In the methods section of this review it was planned that only ratings carried out by independent raters would be accepted. No study stuck to this rule. As data were so sparse excluding further data would have not done a service to the reader, this principle was no longer followed. There is little danger of bias creeping in for this reason alone.
3. Loss to follow up
Only little data were given on patients who left the studies early.
4. Overall
Overall, the quality of the included trials varied, with the older studies tending to use designs which would not be regarded as excellent by modern research standards. Jadad scores of between two (poor quality) and four (good quality) were reached by the studies. Jadad score maximum is five.

Effects of interventions

1. The search
The original strategy identified hundreds of citations but only 10 studies met our inclusion criteria. In the update searches in 2005 and 2007 there were 24 and 23 new references respectively. One report could be a further relevant randomised trial (Kamisada 1988), but due to insufficient information it had to be classified as awaiting assessment. We have written to the first author. Five references were further reports of studies that had been already included or excluded in the first version of this review. They were added as additional references. All other reports had to be excluded.
2. COMPARISON 01: CARBAMAZEPINE AS SOLE TREATMENT versus PLACEBO AS SOLE TREATMENT
Only one trial Carpenter 1991compared carbamazepine as a sole agent with placebo in maintenance treatment.
2.1 Leaving the study early
One person receiving carbamazepine left early due to a rash and another due to leukopenia. Two people also left early from the placebo group, due to a conduction defect on the ECG and headache, respectively. No difference between groups was found (1 RCT n=31, RR 1.1 CI 0.2 to 6.6).
2.2 Relapse
Data from the first 27 people included into this study showed that carbamazepine was no more effective than placebo in preventing relapse(1 RCT n=31, RR 1.1 CI 0.8 to 1.5). As the majority of those in both groups (26 out of 31) did relapse, the study was halted by three months.
2.3 Mental state
There was no significant difference in terms of mental state as measured by the number of patients with less than 20% BPRS reduction (1 RCT n=31, RR 0.99 CI 0.8 to 1.3) or the mean BPRS at endpoint between both groups (1 RCT n=27, WMD -0.1 CI -0.5 to 0.3).
2.4 Adverse effects
Carpenter 1991 reported transient sedation and nausea in the carbamazepine group, although no figures were presented. Three people treated with carbamazepine, this difference was not statistically significant (1 RCT n=31, RR 7.4 CI 0.4 to 133) developed a rash and one leukopenia, again differences between treatment groups were not significant (1RCT n=31, RR 3.2 CI 0.1 to 73).
3. COMPARISON 02: CARBAMAZEPINE AS SOLE TREATMENT versus ANTIPSYCHOTICS AS SOLE TREATMENT
Again, only one trial was found that compared carbamazepine with perphenazine in acutely ill patients with schizophrenia and schizoaffective disorder (Svestka 1989).
3.1 Leaving the study early
Two patients on carbamazepine versus none on perphenazine left the study before its end, this difference is not statistically significant (1 RCT n=38, RR 4.5 CI 0.2 to 88).
3.2 Mental state
No significant differences in terms of mental state were found. A similar number of people treated with carbamazepine and perphenazine reached less than 20% (1RCT n=38, RR 1.3 CI 0.6 to 2.7), 35% (1RCT n=38, RR 1.7 CI 0.9 to 3.2) or 50% (1RCT n=38, RR 1.2 CI 0.8 to 1.9) BPRS reduction. Again, no significant difference in terms of mean BPRS at endpoint was found (1RCT n=38, WMD 2.3 CI -3.8 to 8.4). However, when those with schizoaffective disorder were excluded, a statistically significant inferiority of carbamazepine in terms of 20% BPRS reduction (1RCT n=28, RR 3.1 CI 1.2 to 7.8, NNT 2 CI 1 to 6) and 35% BPRS reduction (1RCT n=28, RR 2.3 CI 1.2 to 4.7, NNT 2 CI 1 to 7) was found. This effect was not as evident for 50% BPRS reduction scores and the difference between groups just failed to reach significance (1RCT n=28, RR 1.4 CI 0.9 to 2.1). Since only ten participants had schizoaffective disorder, an analysis of this subgroup was not thought to be meaningful.
3.3 Adverse effects
3.3.1 Movement disorders
Significantly more participants who received perphenazine needed antiparkinson medication (1 RCT n=38, RR 0.2 CI 0.09 to 0.6, NNH 1 CI 1 to 2) or had parkinsonism (1 RCT n=38, RR 0.03 CI 0.00 to 0.4, NNH 1 CI 0.9 to 1.4). No significant difference in terms of number of participants with akathisia (1 RCT,n=38, RR 0.1 CI 0.01 to 2.3) or tremor (1 RCT n=38, RR 0.3 CI 0.01 to 7.0) was found.
3.3.2 Other adverse effects
The following other adverse effects were reported: collapse, dizziness, blurred vision, dryness of mouth, fatigue, nausea, constipation, salivation, tachycardia. Studies found no significant differences between groups.

4. COMPARISON 03: ADJUNCTIVE CARBAMAZEPINE + ANTIPSYCHOTICS versus PLACEBO/NO ADJUNCTIVE TREATMENT + ANTIPSYCHOTICS

Eight studies compared adding carbamazepine to antipsychotic treatment with adding a placebo to antipsychotic treatment just antipsychotic treatment alone.

4.1 Leaving the study early

Eight studies were able to contribute to the outcome of 'number leaving the study early', although four of these studies had no one leave early in either group. No difference was found (8 RCTs n=182, RR 0.5 CI 0.2 to 1.4) between those allocated to the augmentation group and those taking placebo adjunctive therapy.

4.2 Global state

Only Neppe 1983 and Simhandl 1996 provided data on the outcome 'no general improvement'. Carbamazepine augmentation of neuroleptics was superior compared to various antipsychotics alone, but the number of patients included was very low (2 RCTs n=38, RR 0.6 CI 0.4 to 0.9, NNT 2, CI 1 to 5).

4.3 Mental state

4.3.1 General

The individual patient data from six studies could be used for the analysis of various degrees of BPRS reduction. No significant differences in terms of number of participants with less than 20% (6 RCTs n=147, RR 0.7 CI 0.4 to 1.1), 35% (6 RCTs n=147, RR 0.8 CI 0.6 to 1.1) or 50% BPRS reduction (6 RCTs n=147, RR 0.9 CI 0.7 to 1.1) were found. The results at the 50% BPRS reduction level were significantly heterogeneous because two studies (Heßlinger 1998, Dose 1987) showed contrary results. No obvious reasons for this heterogeneity could be derived from the publications. Similar equivocal results were found when the mean BPRS (3 RCTs n=79, WMD 0.3 CI -12.5 to 13.1) or IMPS at endpoint (2 RCTs n=50, WMD 5.2 CI -11.1 to 21.4) were analysed.

4.3.2 Specific - positive symptoms, negative symptoms and depression

Only very few data for specific symptoms of schizophrenia could be extracted. In the Heßlinger 1998 study the participants of the carbamazepine group had, on average, more positive symptoms at endpoint than those in the control group (1 RCT n=18, WMD 4.2 CI 0.8 to 7.7). The Dose 1987 study showed oppositional results, but the data could only be presented in the 'other data' table because they were skewed. No significant superiority of carbamazepine augmentation in terms of negative symptoms (2 RCTs n=53, WMD -2.8 CI -6.7 to 1.2) or depression (1 RCT n=26, WMD -0.4 CI -2.2 to 1.5) could be found.

4.4 Behaviour

Two studies presented data on the average dose of additional medication needed for the treatment of agitated behaviour. In Dose 1987 people receiving carbamazepine augmentation needed less additional medication, whereas in Heßlinger 1998 they needed more additional medication than in the control group. Data were skewed and could therefore only be presented in the other data table.

4.5 Adverse effects

Side effects were not well reported in the studies.

4.5.1 Movement disorders

The effect of adjunctive carbamazepine on movement disorders is not clear. One small study (Martin-Munoz 1989) reported on the binary outcome of 'movement disorder present'. Less people in the carbamazepine augmentation group had movement disorders than those taking haloperidol alone but the result just failed to reach significance (1 RCT n=20, RR 0.4 CI 0.1 to 1.0). Skewed data from the Simpson-Angus Scale were equivocal from three studies (Dose 1987, Nachshoni 1994, Simhandl 1996).

Three studies (Dose 1987, Heßlinger 1998, Simhandl 1996) presented data on the mean dose of antiparkinson medication used. These data are presented in the 'other data' tables, because they are skewed. No consistent trend can be derived from these data.

4.5.2 Other side effects

Two studies used scales in order to assess side-effects (Martin-Munoz 1989, Mair 1990) but data were reported in such a way as to be unusable for this review. Dose 1987 reported several carbamazepine-associated adverse effects (allergic reactions, elevation of liver enzymes, leucopoenia, EEG change). Although these tended to be more prevalent in the carbamazepine augmented group, none reached the level of statistical significance.

4.6 Physiological effects

Dose 1987 and Heßlinger 1998 describe mean plasma haloperidol to be lower in the carbamazepine-augmented group but again these data are in the 'other data' tables.

4.7 Missing outcomes

Carbamazepine is said to have an effect upon aggression. Neppe 1983 reports that overt aggression was rated twice as severe with placebo compared to carbamazepine but no quantitative data were reported. Llorca 1993 did not find between-group differences in SAPS or BPRS hostility and aggressiveness items but only 'p' values were presented. No data were found for 'service' outcomes such as 'duration of hospital stay'. Nor were there data on satisfaction with treatment or costs.

4.8 Schizophrenia sub-types

4.8.1 People with treatment resistant schizophrenia: Llorca 1993 examined the effectiveness of adjunctive carbamazepine in those with treatment resistant schizophrenia (Kane 1988 criteria) using a crossover design. No mental state data were directly reported (p-values only) but carbamazepine was not stated to be better than placebo in this small study (n=12). Simhandl 1996 also included only those with schizophrenia who had fulfilled specific criteria of neuroleptic non-response. Significantly more patients treated with adjunctive carbamazepine improved according to the CGI and reached at least 20% BPRS reduction. However, this result is not consistent, because there was not significantly more patients treated with carbamazepine augmentation than with placebo augmentation reaching 35% and 50% BPRS reduction.

4.8.2 People with EEG abnormalities: Neppe 1983 examined a small group of 13 relatively non-responsive patients with EEG

abnormalities of which nine had schizophrenia. In this crossover trial, more patients fared somewhat better in the carbamazepine than in the placebo phase for 'leaving the study earlier', 'no global clinical improvement' and the mental state ratings (BPRS). The patient population was quite heterogeneous and diagnostic criteria were not indicated.

4.8.3 People with negative symptoms: Nachshoni 1994 carried out a double blind randomised controlled trial in 28 residual patients who were suffering predominantly from negative symptoms. After 5 weeks no superiority of adjunctive carbamazepine compared to placebo on negative symptoms could be found.

4.8.4 People with schizoaffective disorder: Only 12 people included in this review had schizoaffective disorder so analyses of this subgroup did not appear to be meaningful.

DISCUSSION

1. General

Although much original data were received from trialists, a total of 258 participants is still a small base upon which to judge the effectiveness of carbamazepine. Trials with small sample sizes lack sufficient power to detect a small to moderate effect, and thus results from such trials are often inconclusive, even when a real effect does exist. A recent review has suggested that meta-analyses based on summation of small trials should be interpreted as inconclusive, regardless of whether the combined estimate was significant (Davey Smith 1998). The included studies in this review, were therefore unable to provide sufficient data to clarify the role of carbamazepine for the treatment or augmentation of antipsychotic treatment of schizophrenia and schizoaffective disorder.

2. COMPARISON 01. CARBAMAZEPINE AS SOLE TREATMENT versus PLACEBO AS SOLE TREATMENT (Carpenter 1991)

The little available data suggest that carbamazepine is no better than placebo for maintenance treatment. Considering that the single study contributing data was stopped early, because the majority of those in both groups relapsed, these data are unlikely to be supplemented.

3. COMPARISON 02. CARBAMAZEPINE AS SOLE TREATMENT versus ANTIPSYCHOTICS AS SOLE TREATMENT (Svestka 1989)

In the only small study available, carbamazepine was not inferior when compared with perphenazine in terms of improvement of mental state and carbamazepine was associated with fewer extrapyramidal side effects than perphenazine. However, due to the small sample size of this trial (n=38) carbamazepine can not be considered as a reasonable alternative to antipsychotics, and in the subgroup analysis in which those with schizoaffective disorder were excluded, perphenazine was superior to carbamazepine in some efficacy outcomes.

4. COMPARISON 03. ADJUNCTIVE CARBAMAZEPINE + ANTIPSYCHOTICS versus PLACEBO/NO ADJUNCTIVE TREATMENT + ANTIPSYCHOTICS

4.1 Leaving the study early

Only 13 out of 180 people left the studies before completion with no difference between groups. This very low rate of attrition is rare within trials relevant to the care of those with schizophrenia. Adjunctive therapy of this sort seems to be very acceptable to people with schizophrenia, at least within the confines of a trial.

4.2 General improvement

Two small trials (Neppe 1983, Simhandl 1996) presented data on the outcome of 'no general improvement', and found a slight, but statistically significant difference between groups favouring the carbamazepine group (NNT 2 CI 1-5). Little can be concluded from two small trials including 38 schizophrenia patients. It is disappointing that more trials did not report this simple outcome.

4.3 Mental state

The interpretation of results on mental state has been improved by the analysis of individual patient data in a uniform way. The meta-analysis of the data of six out of eight trials did not show a significant superiority of carbamazepine according to several levels of reduction of the Brief Psychiatric Rating Scale (Overall 1962). Furthermore, there was a significant heterogeneity of the study results with one study (Heßlinger 1998) showing especially bad results associated with carbamazepine augmentation. The inspection of the methods of each study did not reveal clear reasons for this heterogeneity. Therefore, current data suggests that carbamazepine augmentation of antipsychotic drugs for people with schizophrenia does not seem to have a clinically meaningful effect on mental state. However, since there was a non-significant trend in terms of 20% BPRS reduction and since the total number of patients is still low, more trials are warranted. Specific symptoms of schizophrenia (positive symptoms, negative symptoms and depression) were only reported by one or two trials so that any meaningful statement was not possible.

4.4 Adverse effects

Most data about movement disorders were too skewed to summate and individual studies reported conflicting results. As a result, no firm conclusion can be drawn. The fact that some studies found that carbamazepine augmentation leads to fewer movement disorders might be explained by a reduction of haloperidol plasma levels. This lowering of plasma levels might be the expression of an induction of liver enzymes related to carbamazepine. Two of the included studies (Dose 1987, Heßlinger 1998), one trial excluded because it did not provide any usable data (Kidron 1985), and

several uncontrolled trials (Kahn 1990, Jann 1985, Otani 1997) suggest that this enzyme induction occurs. This interaction must be carefully taken into account whenever carbamazepine augmentation is tried.

Carbamazepine augmentation may well cause more allergic reactions, elevation of liver enzymes, leucopoenia, and deterioration in the EEG than placebo augmentation. Adverse effects were, however, poorly reported and the only small trial (Dose 1987, n=41) that clearly reported these important events had limited power to investigate differences between groups.

4.5 Missing outcomes

Currently, there are no data relating to the effect of carbamazepine augmentation on aggression, 'service' outcomes such as 'duration of hospital stay', satisfaction with treatment or costs.

4.6 Schizophrenia sub-types

Carbamazepine augmentation was not more effective when subgroups of people with schizophrenia were the focus of the studies. People with a schizophrenic illness designated as resistant to treatment were not consistently better when they received carbamazepine augmentation. Those with negative symptoms were not different in their response to antipsychotic augmentation compared with people whose illness did not have a predominance of negative symptoms. The small Neppe 1983 study (n=9) suggested that a relatively non-responsive heterogeneous group of patients with EEG abnormalities did fare somewhat better with carbamazepine augmentation than with placebo. This should be considered as hypothesis-generating only.

It is not clear whether it makes sense to use carbamazepine in schizophrenia(-like) patients with 'excited states'. One randomised controlled study (Klein 1984) suggested that this could be useful, but data from this trial could not be used in this review as the treatment allocation of people who left the study early is unclear. In a letter the authors stated that they do not remember how to interpret the data sheets of the study. Furthermore, a large controlled study of adjunctive carbamazepine to antipsychotics in 'excited psychoses' (Okuma 1989a, n=162) had to be excluded because of the potential for inclusion of bias at the point of randomisation. Forty three percent of those in the carbamazepine augmentation group showed marked and moderate improvement compared to 27% in the placebo group (not statistically significant). A post hoc analysis of individual mental state scale items suggested that this was related to an effect on disturbances of affective or emotional functions, whereas other items like hallucinatory behaviour worsened with adjunctive carbamazepine.

Finally, carbamazepine augmentation for those with schizoaffective disorder has been surprisingly poorly studied, although it is frequently used in the daily routine for this condition. Only 12 participants included in this review had schizoaffective disorder so any judgment on the effects of carbamazepine for this important subgroup are impossible.

AUTHORS' CONCLUSIONS

Implications for practice

1. For clinicians

Based on currently available randomised trial-derived evidence, carbamazepine cannot be recommended for routine clinical use for treatment or augmentation of antipsychotic treatment of schizophrenia. For patients with a past history of response to carbamazepine, a trial of the drug may be warranted. For health care professionals currently caring for patients who have been receiving carbamazepine as a putative treatment for schizophrenia, clinicians need to weigh up whether this treatment should be stopped. Carbamazepine is associated with a range of adverse effects. If there is no evidence that the treatment has been effective, then it should be gradually tapered off and then stopped altogether. The dose of concomitant antipsychotics may need to be revised in light of the potential pharmacokinetic interactions between carbamazepine and some antipsychotics as antipsychotic plasma levels may rise upon withdrawal.

2. For people with schizophrenia

People with schizophrenia should know of the lack of a strong empirical basis for the use of carbamazepine in their illness. If its recommendation is still perused, the recipient of this treatment should expect clear endpoints and duration of treatment to be agreed upon.

3. For managers and policy makers

Although idiosyncratic positive responses are always possible, there are no data to support the use of carbamazepine for those with schizophrenia as a routine measure.

Implications for research

1. General

Any future studies should respect standards of measuring outcomes and of reporting data in order to enhance the comparability of study results (Begg 1996). The fact that several authors (see acknowledgement) shared their data with us very much improved the quality of this review. We would like to encourage similar collaboration in the future.

2. Specific

There seems to be little need to undertake randomised trials investigating the effects of carbamazepine augmentation for people with uncomplicated schizophrenia. Some special indications might, however, still be of research interest.

2.1 People whose illness is resistant to treatment

Despite the reintroduction of clozapine, the only drug proven to have superior efficacy than standard drugs for those with treatment resistant illness (Wahlbeck 1998), there is a need for the development of treatment strategies when clozapine does not work. The two randomised trials investigating the effects of carbamazepine augmentation for people with treatment resistant schizophrenia (Simhandl 1996, Llorca 1993) only randomised a total of 66 patients. Even the combined totals lack the power to identify anything but gross differences between groups. Even small differences in outcome may be of great importance in this sub-group and therefore a large simple trial is justified.

2.2 People with psychoses and EEG abnormalities

Clarification of the role of carbamazepine for the treatment of people with both schizophrenia and EEG abnormalities may be warranted.

2.3 People with psychoses and aggressive behaviour

Carbamazepine is used for those with aggressive or violent episodes and its evaluation within trials in this sub-group of people with schizophrenia would be valuable.

2.4 People with schizoaffective disorders

Carbamazepine is also used for those with schizoaffective disorders but data from placebo-controlled trials do not exist. The bipolar type of schizoaffective disorder especially warrants further studies.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Carpenter 1991

Methods	Allocation: randomised - no further details. Blinding: double - no further information. Design: cross-over. Duration: 95 days each phase. Setting: outpatient department.
Participants	Diagnosis: schizophrenia (DSM-III & RDC). N=34.* Sex: 18 M, 9 F.* Age: mean ~ 33 years. History: stabilised on neuroleptic maintenance, hospitalised ~3 times, ill ~10 years.
Interventions	1. Carbamazepine: dose 800-1200 mg/day. N~15.* 2. Placebo (neuroleptics withdrawn over 1-5 days when study medication dose was reached). N~16.*
Outcomes	1. Leaving the study early. 2. Relapse.* 3. Mental state: BPRS (mean and number with 20% reduction).* 4. Side effects - allergic reactions, blood dyscrasia.*
Notes	Data analysed on 31 patients, no information about treatment status of 3 people. Jadad score = 4. Interim analyses showed high relapse rates in both arms of study - study stopped.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Dose 1987

Methods	Allocation: randomised - no further details. Blinding: double - no further information. Design: parallel. Duration: 5 weeks (at week 4 interventions withdrawn). Setting: in hospital.

Dose 1987 (*Continued*)

Participants	Diagnosis: acute schizophrenia (ICD-9 & DSM-III). N=41. Sex: not reported. Age: not reported. History: hospitalised ~1.2 times, ill ~6 years.
Interventions	1. Adjunctive carbamazepine: dose 200mg, increased to 600-1200mg/day (target plasma level 8-12 micrograms/dL) + haloperidol 6mg/day then titrated to clinical judgement. N=18. 2. Placebo additional treatment + haloperidol 6mg/day then titrated to clinical judgement. N=23.
Outcomes	1. Leaving the study early 2. Mental state: (BPRS 20%, 35%, 50% reduction, mean at endpoint; mean IMPS at endpoint). 3. Side-effects: allergic reactions, substantial white blood cell decline, increase of liver enzymes, worsening of EEG. Unable to use: Medication use (mean haloperidol dose - no SD, biperiden, chlorprothixene - data skewed). Movement disorder (SAS - data skewed). Haloperidol plasma-levels - data skewed.
Notes	Jadad score = 4. ** Two people taking carbamazepine had falls in white cell counts, but not below usual reference range.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Heßlinger 1998

Methods	Allocation: randomised - sealed envelopes. Blinding: single. Design: parallel. Duration: 4 weeks. Setting: in hospital.
Participants	Diagnosis: schizophrenia (n=16) or schizoaffective (n=2) psychosis (ICD-10). N=18. Sex: 12 M, 6F.
Interventions	1. Adjunctive carbamazepine: dose mean 567mg/day, titrated in week 1 to plasma-level of 6-12mg/ml + constant haloperidol dose: dose mean ~ 15mg/day, higher in this group to maintain effective plasma-levels. N=9. 2. No additional treatment + constant haloperidol dose. N=9.

Heßlinger 1998 (*Continued*)

Outcomes	1. Leaving the study early. 2. Mental state (BPRS 20%, 35%, 50% reduction and mean at endpoint, PANSS positive score at endpoint). Unable to use: Haloperidol plasma levels - data skewed. Mean biperiden and chlorprothixen dose - data skewed.
Notes	Jadad score = 2.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Llorca 1993

Methods	Allocation: randomised - no further details. Blindness: double - no further information. Design: cross-over, no wash-out. Duration: 4 X 5 week crossovers (preceeded by 5 weeks no adjunctive treatment). Setting: in hospital.
Participants	Diagnosis: treatment resistant schizophrenia patients (DSM-III-R, Kane criteria). N=24. Sex: 18 M, 6 F. Age: mean ~44 years.
Interventions	1. Adjunctive carbamazepine: dose 2 weeks 200mg/day, 3 weeks 400mg/day + constant haloperidol (15-65mg/day). N=6. 2. Adjunctive bromocriptine: dose 2.5mg/day + constant haloperidol (15-65mg/day). N=6.* 3. Adjunctive cyproheptadine: 12-24mg/day + constant haloperidol (15-65mg/day). N=6.* 4. Placebo additional treatment + constant haloperidol (15-65mg/day). N=6.
Outcomes	1. Leaving the study early. Unable to use: Mental state (BPRS, SAPS, SANS - p values only). Movement disorder (SAS, AIMS - p values only).
Notes	Jadad score = 2. * Data from groups 2 & 3 not used in this review.

Risk of bias

Llorca 1993 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Mair 1990

Methods	Allocation: randomised - no further details. Blinding: open. Design: parallel. Duration: 5 weeks. Setting: in hospital.
Participants	Diagnosis: schizophrenia & schizophrenia-like psychoses (ICD-9). N=23. Age: range 31-44 years. History: "acutely ill", unresponsive to 5 days clozapine or haloperidol, admitted 4-9 times.
Interventions	1. Adjunctive carbamazepine: dose 600mg/day + titrated dose of haloperidol or clozapine. N=13. 2. No additional treatment + titrated dose of haloperidol or clozapine. N=10.
Outcomes	1. Leaving the study early. Unable to use: General functioning (CGI - no SD). Mental state (BPRS - no SD). Extrapyramidal side-effects (Webster scale - no data). Other side-effects (FSUCL - no data). Mean haloperidol/clozapine dose - no SD.
Notes	Jadad score = 2.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Martin-Munoz 1989

Methods	Allocation: randomised - no further information. Blinding: not stated. Design: parallel. Duration: 18 days. Setting: in hospital.
Participants	Diagnosis: paranoid schizophrenia (RDC). N=20. Age: mean ~29 years. Sex: 18 M, 2 F.
Interventions	1. Adjunctive carbamazepine: dose initially 600mg/day, adjusted to plasma-levels of 8-12ng/ml + haloperidol, 30mg/day, fixed dose. N=10. 2. No additional treatment + haloperidol, 30mg/day, fixed dose. N=10.
Outcomes	1. Leaving the study early. 2. Mental state (20%, 35%, 50% BPRS reduction). 3. Movement disorder. Unable to use: Side effects (UKU-scale - no data).
Notes	Jadad score = 2.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Nachshoni 1994

Methods	Allocation: randomised - random allocation list. Blinding: double - no further details. Design: parallel. Duration: 5 weeks. Setting: in hospital.
Participants	Diagnosis: residual schizophrenia (DSM-III-R). N=30*. Age: mean ~46 years. Sex: 15 M, 13 F. History: predominant negative symptoms, ill mean ~19 years.

Nachshoni 1994 (*Continued*)

Interventions	1. Adjunctive carbamazepine: dose increased to 600mg/day during week 1, then adjustment to plasma-levels of 4-12ng/ml + 300-800 chlorpromazine equivalent antipsychotic treatment. N=15. 2. Placebo adjunctive treatment + 300-800 chlorpromazine equivalent antipsychotic treatment. N=15.
Outcomes	1. Leaving the study early. 2. Mental state (20%, 35%, 50% BPRS reduction, HRSD, SANS at endpoint). Unable to use: EPS (SAS - no data).
Notes	Jadad score = 4.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Neppe 1983

Methods	Allocation: randomised - no further information. Blinding: double - no further information. Design: cross-over. Duration: 2 X 6 weeks (preceeded by 3 week baseline). Setting: in hospital.
Participants	Diagnosis: schizophrenia (10), non-progressive dementia (2), rapid cycling (1) (diagnostic criteria unclear). N=13*. Age: mean ~34 years. Sex: 8 M, 5 F. History: chronic, "poor-responders", EEG abnormalities.
Interventions	1. Adjunctive carbamazepine: dose 600mg/day + various antipsychotics (constant dose). N=3. 2. Placebo adjunctive treatment + various antipsychotics (constant dose). N=6.
Outcomes	1. Leaving the study early. 2. Global impression (CGI). 3. Mental state (20%, 35%, 50% BPRS reduction). Unable to use: General improvement (Global Assessment, OCR unpublished scales).
Notes	*Data extracted for 9 subjects with schizophrenia from published data. Jadad score = 3.

Risk of bias

Neppe 1983 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Simhandl 1996

Methods	Allocation: randomised - no further details. Blindness: double. Design: parallel. Duration: 8 weeks (intervention withdrawn at week 6). Setting: not indicated.
Participants	Diagnosis: schizophrenia (DSM-III-R). N=42. Age: mean ~35 years. Sex: 30 M, 12 F. History: "chronic", non-response to > 3 neuroleptics (2 different chemical classes) in last 2 years, duration ill ~ 10 years.
Interventions	1. Adjunctive carbamazepine: dose increased week 1-2 until plasma-levels = 15-42 micromol/L + constant dose of antipsychotics. N=15. 2. Lithium*: dose increased week 1-2 until plama level = 0.6-1.2 myml/L) + constant dose of antipsychotics. N = 13. 3. Placebo + constant dose of antipsychotics. N=14.
Outcomes	1. Leaving the study early. 2. Global impression (CGI). 3. Mental state (20%, 35%, 50% BPRS reduction, SANS at endpoint). Unable to use: Plasma-levels of antipsychotics - skewed data.
Notes	Jadad = 4. *This group was not used in the analysis.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Svestka 1989

Methods	Allocation: randomised - no further details. Blindness: single (raters). Design: cross-over. Duration: 6 weeks (2 weeks placebo - 3 weeks carbamazepin/perphenazine - 1 week placebo - 3 weeks carbamazepin/perphenazine). Setting: hospital.
Participants	Diagnosis: ICD-9 schizophrenia (n=28) or schizoaffective disorder (n=10). History: "acutely ill", duration ill ~9 years. N=38. Age: mean ~38 years. Sex: 30 M, 8 F (the gender of 2 people who left early is unknown).
Interventions	1. Carbamazepine, flexible dose, mean = 1374 SD = 334, N=22. 2. Perphenazine, flexible dose, mean = 53, SD = 12 . N = 18. Then 1 week placebo and 3 week cross-over to other treatment.
Outcomes	1. Leaving the study early. 2. Mental state (20%, 35%, 50% BPRS reduction and BPRS at endpoint) 3. Various side-effects.
Notes	Jadad = 4.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

General abbreviations:
CBZ - carbamazepine
HPL - haloperidol
EPS - Extrapyramidal side effects.
EEG - electroencephalogram
M - males
F - females
N = number
Mg = milligram
Diagnostic tools:
DSM-III-R - Diagnostic and Statistical Manual of Mental disorders, third edition,revised.
ICD-9/10 - International Classification of Diseases, ninth/tenth revision.
RDC - Research Diagnostic Criteria
Global effect scales:
CGI - Clinical Global Impression (Guy 1976 (2))
OCR - Overall Clinical Rating
Mental state scales:
BPRS - Brief Psychiatric Rating Scale (Overall and Gorham 1970)
IMPS - Inpatient Multidimensional Rating Scale (Lorr 1962)

PANSS - Positive and Negative Symptoms Scale (Kay 1987)
BRMAS - Bech-Rafaelsen Scale for Mania
MSM - Murphy Scale for Mania
SANS - Scale for Assessment of Negative Symptoms (Andreasen 1989)
SAPS - Scale for Assessment of Positive Symptoms (Andreasen 1984)
Side effect scales:
CGI - Clinical Global Impression, side effects (Guy 1976)
UKU - UKU Side effect Scale (Lingjaerde et al. 1987)
AIMS - Abnormal Involuntary Movement Scale (Guy 1976)
SAS - Simpson and Angus Scale (Simpson and Angus 1970)
FSUCL - Fischers Somatische Symptome oder Unerwünschte Effekte Check List (Fischer-Cornellson 1986)

Characteristics of excluded studies *[ordered by study ID]*

Arana 1986	Allocation: not randomised, A-B design.
Azorin 1986	Allocation: not randomised, A-B design.
Ballenger 1984	Allocation: not randomised, case series.
Barnes 1996	Allocation: not randomised, review.
Bellaire 1990	Allocation: randomised. Participants: people with schizoaffective disorders or bipolar illness. Interventions: lithium versus carbamazepine, no placebo group.
Birkheimer 1985	Allocation: not randomised, review.
Borison 1991	Allocation: randomised. Participants: people with schizophrenia. Interventions: rimcazole, no carbamazepine.
Botte 1988	Allocation: not randomised, A-B design.
Cabrera 1986	Allocation: randomised. Participants: people with schizoaffective disorders and bipolar illness. Interventions: oxcarbazepine versus lithium, no placebo group.
Cegalis 1984	Allocation: not randomised, case report.
Chouinard 1990	Allocation: not randomised, case series.
Costa 1986	Allocation: not randomised, case report.

(*Continued*)

Covell 2004	Allocation: randomised. Participants: people with schizophrenia. Interventions: clozapine versus typical antipsychotics, no carbamazepine group.
Dalby 1971	Allocation: not randomised, A-B design.
de Vogelaer 1981	Allocation: randomised. Participants: very heterogeneous group of patients, some with "behavioral disorders", some with "psychotic" disorders. No clear diagnoses, study focuses on character disorders. Interventions: not entirely clear, but probably carbamazepine or placebo were added to antipsychotic drugs Outcomes: impossible to extract data just for people with serious mental illness. As yet, no response from the author to a letter.
Dehing 1968	Allocation: randomised (random number list). Participants: mixed group, no data on people with schizophrenia, the focus of the study was on 'character disorders'. Interventions: Carbamazepine or placebo added to ongoing treatment Outcomes: according to the authors no original data are available and therefore no single outcome parameter can be used for this review.
Denicoff 1994	Allocation: not randomised, clinical practice survey/audit.
Elphick 1985	Allocation: not randomised, A-B-A design.
Frankenburg 1988	Allocation: not randomised, case series.
Gadow 1992	Allocation: not randomised, review.
Galletly 1997	Allocation: not randomised, case series.
Ginestet 1996	Allocation: not randomised, review.
Goncalves 1985	Allocation: randomised. Participants: manic people, seven with bipolar disorder, five with schizoaffective disorder. Interventions: carbamazepine versus placebo, but most participants also received haloperidol. The trial could therefore not be classified according to the three comparisons analysed in this review and no data could be extracted.
Greil 1997	Allocation: randomised. Participants: people with schizoaffective disorder. Interventions: carbamazepine versus lithium, no placebo group.
Hakola 1982	Allocation: not randomised, A-B design.
Hermle 1993	Allocation: not randomised, case report.

(*Continued*)

Herrera 1987	Allocation: not randomised, A-B-A design.
Iwahashi 1995	Allocation: not randomised, case-control study.
Iwahashi 1996	Allocation: not randomised, case series.
Jann 1985	Allocation: not randomised, A-B design.
Johns 1995	Allocation: not randomised, review.
Kahn 1990	Allocation: randomised. Participants: people with schizophrenia. Intervention: carbamazepine plus neuroleptics versus lithium plus neuroleptics, no placebo group.
Karper 1992	Allocation: not randomised, case report.
Keck 1996	Allocation: not randomised, review.
Kessler 1989	Allocation: not randomised, case series.
Kidron 1985	Allocation: randomised, cross-over. Participants: people with schizophrenia or schizoaffective disorders and excited states. Interventions: haloperidol + carbamazepine versus haloperidol + placebo. Outcomes: no usable data.
Klein 1984	Allocation: randomised, parallel (participants with poor response were crossed-over at the end). Participants: those with schizophrenia or schizoaffective disorders and excited states. Interventions: haloperidol + carbamazepine versus haloperidol + placebo. Outcomes: no usable data.
Kraft 1984	Allocation: not randomised, case report.
Lambert 1987	Allocation: review.
Lapensee 1992	Allocation: not randomised, review.
Lenzi 1986	Allocation: randomised. Participants: mixed affective and nonaffective psychoses. Interventions: carbamazepine + chlorpromazine versus lithium + chlorpromazine, no placebo group.
Llorca 1992	Allocation: not randomised, review.
Luchins 1983	Allocation: not randomised, case series.
Luchins 1984	Allocation: not randomised, case report.

(*Continued*)

Makaric 2000	Allocation: controlled clinical trial, but not randomised.
McAllister 1985	Allocation: not randomised, case series.
McKee 1989	Allocation: not randomised, case report.
Meltzer 1992	Allocation: not randomised, review.
Meshel 1967	Allocation: randomised. Participants: people with psychosis. Interventions: tybamate versus placebo, no carbamazepine group.
Meshel 1968	Allocation: randomised. Participants: people with schizophrenia. Interventions: tybamate versus placebo, no carbamazepine group.
Miceli 2000	Allocation: randomised. Participants: healthy volunteers.
Miller 1965	Allocation: unclear. Participants: people with schizophrenia. Interventions: hydroxyphenamate, no carbamazepine group.
Miodownik 2003	Allocation: unclear, but probably randomised. Participants: people with schizophrenia. Interventions: vitamin B6, no carbamazepine group.
Mokrusch 1987	Allocation: not randomised, review.
Morinigo 1992	Allocation: randomised. Participants: people with mania.
Mosca 1998	Allocation: randomised. Participants: people with violent behaviour or impulsivity. Interventions: carbamazepine versus valproate, no placebo.
Munetz 1989	Allocation: randomised. Participants: people with schizophrenia. Interventions: rimcazole, no carbamazepine group.
Möller 1989	Allocation: randomised, cross-over. Participants: people with schizophrenia or schizoaffective disorders and excited states. Interventions: haloperidol + carbamazepine versus haloperidol + placebo. Outcomes: no usable data.

(*Continued*)

Möller 1996	Allocation: not randomised, review.
Nasser 1990	Allocation: not randomised, case series.
Nelson 1993	Allocation: not randomised, review.
Neppe 1988a	Allocation: not randomised, review.
Neppe 1988b	Allocation: not randomised, review.
Neppe 1988c	Allocation: not randomised, case report.
Neppe 1991	Allocation: not randomised, case series.
Nijdam 1992	Allocation: unclear. Participants: people with mental retardation and psychoses. Interventions: comparison of two different formulations of carbamazepine, no placebo.
Okuma 1989a	Allocation: alternate allocation, category C, inadequate randomisation.
Okuma 1989b	Allocation: not randomised, A-B design.
Ortega 1991	Allocation: randomised (aleatory numbers list generated with a computer program) Participants: inhalant induced psychotic disorders, not schizophrenia. Interventions: carbamazepine as a sole treatment versus haloperidol as a sole treatment.
Otani 1997	Allocation: not randomised, A-B design.
Pantelis 1996	Allocation: not randomised, review.
Panu 1984	Allocation: not randomised, case series.
Placidi 1986	Allocation: randomised. Participants: mixed affective and nonaffective psychoses. Intervention: carbamazepine versus lithium, no placebo.
Raitasuo 1994	Allocation: not randomised, case report.
Rankel 1988	Allocation: not randomised, case series.
Rittmannsberger 1990	Allocation: not randomised, review.
Scher 1983	Allocation: not randomised, case series.

(*Continued*)

Schulz 1990	Allocation: randomised. Participants: people with schizophrenia. Interventions: antipsychotics + carbamazepine versus antipsychotics versus lithium, no placebo.
Simhandl 1992	Allocation: not randomised, review.
Siris 1993	Allocation: not randomised, review.
Sramek 1988	Allocation: not randomised, A-B design.
Sugerman 1970	Allocation: unclear, probably randomised. Participants: people with schizophrenia. Interventions: adrenochrome semicarbazone, no carbamazepine group.
Svestka 1985	Allocation: not randomised, A-B design.
Svestka 1988	Allocation: not randomised, A-B design.
Tohen 1994	Allocation: not randomised, case series.
Walden 1996	Allocation: not randomised, review.
Wetterling 1987	Allocation: not randomised, A-B-A design.
Wunderlich 1983	Allocation: not randomised, A-B design.
Yassa 1983	Allocation: not randomised, case report.

DATA AND ANALYSES

Comparison 1. CARBAMAZEPINE AS SOLE TREATMENT vs PLACEBO AS SOLE TREATMENT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early	1	31	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.17, 6.64]
2 Relapse (by 3 months)	1	31	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.78, 1.45]
3 Mental state: 1. Less than 20% BPRS reduction	1	31	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.75, 1.30]
4 Mental state: 2. Average endpoint score of the BPRS at 3 months	1	27	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.46, 0.32]
5 Adverse effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 allergic reactions	1	31	Risk Ratio (M-H, Fixed, 95% CI)	7.44 [0.42, 132.95]
5.2 blood dyscrasia	1	31	Risk Ratio (M-H, Fixed, 95% CI)	3.19 [0.14, 72.69]

Comparison 2. CARBAMAZEPINE AS SOLE TREATMENT vs ANTIPSYCHOTICS AS SOLE TREATMENT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early	1	38	Risk Ratio (M-H, Fixed, 95% CI)	4.52 [0.23, 88.38]
2 Mental state: 1. Categories of reduction on BPRS scores	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 less than 20% reduction	1	38	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.62, 2.66]
2.2 less than 35% reduction	1	38	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.86, 3.24]
2.3 less than 50% reduction	1	38	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.78, 1.92]
3 Mental state: 2. Mean BPRS at endpoint	1	38	Mean Difference (IV, Fixed, 95% CI)	2.30 [-3.84, 8.44]
4 Adverse effects: 1. Movement disorders	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 akathisia	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 2.34]
4.2 parkinsonism	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.03 [0.00, 0.43]
4.3 tremor	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.01, 6.97]
4.4 use of anticholinergic drugs	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.09, 0.55]
5 Adverse effects: 2. Others	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 blurred vision	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.04, 4.55]
5.2 collapse	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.3 [0.03, 2.63]
5.3 constipation	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.04, 4.55]
5.4 dizziness	1	38	Risk Ratio (M-H, Fixed, 95% CI)	4.52 [0.23, 88.38]
5.5 dry mouth	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.04, 4.55]
5.6 fatigue	1	38	Risk Ratio (M-H, Fixed, 95% CI)	5.4 [0.72, 40.66]
5.7 nausia	1	38	Risk Ratio (M-H, Fixed, 95% CI)	2.71 [0.12, 62.70]
5.8 salivation	1	38	Risk Ratio (M-H, Fixed, 95% CI)	2.71 [0.12, 62.70]

5.9 tachycardia	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.28, 2.04]
6 Subgroup analysis - schizoaffective disorder excluded - Mental state: Categories of reduction on BPRS score	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 less than 20% reduction	1	28	Risk Ratio (M-H, Fixed, 95% CI)	3.09 [1.22, 7.84]
6.2 less than 35% reduction	1	28	Risk Ratio (M-H, Fixed, 95% CI)	2.32 [1.15, 4.67]
6.3 less than 50% reduction	1	28	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.94, 2.09]

Comparison 3. ADJUNCTIVE CARBAMAZEPINE + ANTIPSYCHOTICS vs PLACEBO/NO ADJUNCTIVE TREATMENT + ANTIPSYCHOTICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early	8	182	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.16, 1.35]
2 Global state: No improvement	2	38	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.37, 0.88]
3 Mental state: 1a. General - categories of reduction on BPRS scores	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 less than 20% reduction	6	147	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.44, 1.07]
3.2 less than 35% reduction	6	147	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.57, 1.05]
3.3 less than 50% reduction	6	147	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.67, 1.12]
4 Mental state: 1b. General - average BPRS endpoint score (high = poor)	3	79	Mean Difference (IV, Random, 95% CI)	0.30 [-12.49, 13.09]
5 Mental state: 1c. General - average BPRS endpoint score (high = poor, skewed data)			Other data	No numeric data
6 Mental state: 1d. General - average IMPS endpoint score (high = poor)	2	50	Mean Difference (IV, Random, 95% CI)	5.18 [-11.09, 21.44]
7 Mental state: 2a. Specific - positive symptoms (PANSS subscale at endpoint, high = poor)	1	18	Mean Difference (IV, Fixed, 95% CI)	4.22 [0.75, 7.69]
8 Mental state: 2b. Specific - positive symptoms (IMPS score at endpoint, high = poor)			Other data	No numeric data
9 Mental state: 2c. Specific - negative symptoms (SANS at endpoint, high = poor)	2	53	Mean Difference (IV, Fixed, 95% CI)	-2.75 [-6.71, 1.22]
10 Mental state: 2d. Specific - depression (Hamilton scale at endpoint, high = poor)	1	26	Mean Difference (IV, Fixed, 95% CI)	-0.35 [-2.20, 1.50]
11 Behaviour: Average dose of medication used for agitation (chlorprothixene, skewed data)			Other data	No numeric data

12 Adverse effects: 1a Movement disorders - at least one movement disorder	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.14, 1.02]
13 Adverse effects: 1b. Movement disorders - average dose of antiparkinsonism drugs (biperiden, skewed data)			Other data	No numeric data
14 Adverse effects: 1c. Movement disorders - average endpoint score (SAS, high = poor, skewed data)			Other data	No numeric data
15 Adverse effects: 1d. Movement disorders - average endpoint TD rating (high = poor, skewed data)			Other data	No numeric data
16 Adverse effects: 2. Others	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 allergic reaction	1	41	Risk Ratio (M-H, Fixed, 95% CI)	3.79 [0.16, 87.86]
16.2 EEG deterioration	1	41	Risk Ratio (M-H, Fixed, 95% CI)	2.13 [0.59, 7.75]
16.3 liver enzyme elevation	1	41	Risk Ratio (M-H, Fixed, 95% CI)	2.56 [0.53, 12.42]
16.4 white blood cell decline (substantial)	1	41	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.09, 19.06]
17 Physiological effect: Haloperidol plasma levels			Other data	No numeric data

WHAT'S NEW

Last assessed as up-to-date: 20 May 2007.

26 April 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 1998

Review first published: Issue 4, 1999

21 May 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Stefan Leucht - protocol development, searching, data extraction, analysis, data interpretation and writing the final report.

John McGrath - protocol development, data checking, data interpretation.

Paul White - protocol development, data interpretation.

Werner Kissling - protocol development, data interpretation.

DECLARATIONS OF INTEREST

Stefan Leucht has received honoraria and/or travel support and/or research support from BMS, Janssen/Johnson & Johnson, Sanofi Aventis, Eli Lilly, Lundbeck and Pfizer.

John McGrath is a member of the following advisory boards: Eli Lilly Australia, Lundbeck Australia and Pfizer Australia. In addition JM has been a co-investigator on studies of neuroleptic medications produced by the following companies: Astra, Janssen-Cilag, Eli Lilly, Zeneca (ICI), Sandoz and Pfizer. The same companies have provided travel and accommodation expenses for John McGrath to attend relevant investigator meetings and scientific symposia. No funds have been paid directly to Dr McGrath. Payments related to participation in drug trials and board attendances have been paid to a Government-audited trust account to support schizophrenia research.

Paul White is a member of the advisory boards for Janssen Australia and Zeneca Australia. The same companies have provided travel and accommodation expenses for Dr White to attend relevant investigator meetings and scientific symposia.

Werner Kissling has received honoraria and/or research support from Janssen-Cilag, SanofiAventis, Johnson & Johnson, Pfizer, BMS, Astra Zeneca, Lundbeck, Novartis and Eli Lilly. Dr Kissling is an investigator on one of the excluded trials in this review (Möller 1989).

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External sources

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INDEX TERMS

Medical Subject Headings (MeSH)

Antimanic Agents [*therapeutic use]; Carbamazepine [*therapeutic use]; Randomized Controlled Trials as Topic; Schizophrenia [*drug therapy]

MeSH check words

Humans