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Therapeutic monitoring of antiepileptic drugs for epilepsy (Review)

Tomson T, Dahl ML, Kimland E

Tomson T, Dahl ML, Kimland E.
Therapeutic monitoring of antiepileptic drugs for epilepsy.
Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD002216.
DOI: 10.1002/14651858.CD002216.pub2.

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[Intervention Review]

Therapeutic monitoring of antiepileptic drugs for epilepsy

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Editorial group: Cochrane Epilepsy Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 5, 2010.

Citation: Tomson T, Dahl ML, Kimland E. Therapeutic monitoring of antiepileptic drugs for epilepsy. *Cochrane Database of Systematic Reviews* 2007, Issue 2. Art. No.: CD002216. DOI: 10.1002/14651858.CD002216.pub2.

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ABSTRACT

Background

This is an updated version of the original Cochrane review published in Issue 1, 2007.

The aim of drug treatment for epilepsy is to prevent seizures without causing adverse effects. To achieve this, drug dosages need to be individualised. Measuring antiepileptic drug levels in body fluids (therapeutic drug monitoring) is frequently used to optimise drug dosage for individual patients.

Objectives

To review the evidence regarding the effects of therapeutic drug monitoring upon outcomes in epilepsy.

Search methods

We searched the Cochrane Epilepsy Group Specialised Register (February 2010), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 1) and MEDLINE (1950 to January week 4, 2010). No language restrictions were imposed. We checked the reference lists of retrieved articles for additional reports of relevant studies.

Selection criteria

Randomised controlled trials comparing the outcomes of antiepileptic drug monotherapy guided by therapeutic drug monitoring with drug treatment without the aid of therapeutic drug monitoring.

Data collection and analysis

We based this review on published aggregate data. The main outcomes measured were the proportions of patients achieving a 12-month remission from seizures, reporting adverse effects, and being withdrawn from the treatment they had been randomised to receive.

Main results

Only one study met the inclusion criteria for the review. In this open study, 180 patients with newly-diagnosed, untreated epilepsy were randomised to treatment with the antiepileptic drug selected by their physician either with or without therapeutic drug serum level monitoring as an aid to dosage adjustments. The antiepileptic drugs used were carbamazepine, valproate, phenytoin, phenobarbital and primidone. A 12-month remission from seizures was achieved by 60% of the patients randomised to therapeutic drug monitoring (intervention group) and by 61% in the control group. A total of 56% in the intervention group and 58% in the control group were seizure free during the last 12 months of follow up. Adverse effects were reported by 48% in the intervention group and 47% of the control group

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patients. Of those randomised to therapeutic drug monitoring, 62% completed the two-year follow up compared with 67% of the control group.

Authors' conclusions

We found no clear evidence to support routine antiepileptic drug serum concentration measurement with the aim of reaching predefined target ranges for the optimisation of treatment of patients with newly-diagnosed epilepsy with antiepileptic drug monotherapy. However, this does not exclude the possible usefulness of therapeutic drug monitoring of specific antiepileptic drugs during polytherapy, in special situations or in selected patients, although evidence is lacking.

PLAIN LANGUAGE SUMMARY

Therapeutic monitoring of antiepileptic drugs for epilepsy

No evidence to support routine therapeutic monitoring of antiepileptic drugs in the treatment of epilepsy.

No evidence was found to indicate that the routine measurement of serum drug concentrations to inform drug dose adjustments is superior to drug dose adjustments made on clinical grounds alone in newly-diagnosed epilepsy patients treated with a single drug: carbamazepine, valproate, phenytoin, phenobarbital or primidone. One under-powered study was found, and this review does not exclude the possibility that therapeutic drug monitoring might be useful in patients with newly-diagnosed epilepsy, nor does it exclude the possible usefulness of monitoring in special situations or in selected patients.

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BACKGROUND

This review is an update of a previously published review in The Cochrane Database of Systematic Reviews (Issue 1, 2007) on 'Therapeutic monitoring of antiepileptic drugs for epilepsy'.

Epilepsy is a disorder characterised by spontaneously occurring recurrent epileptic seizures. It has been estimated that more than 40 million people in the world have epilepsy; the main treatment is with antiepileptic drugs. The aim of treatment is to prevent seizures without causing side effects. The treatment of epilepsy needs to be individualised with respect to both choice of drugs and drug dosage. The latter became apparent during the 1960s when methods for measuring serum concentrations of antiepileptic drugs were developed (Buchtal 1960). The serum concentration of an antiepileptic drug varies markedly between patients given the same dosage; the reason for this is that people differ in their ability to absorb, distribute, metabolise and excrete drugs. These processes are summarised in the term 'pharmacokinetics'. The rate at which these pharmacokinetic processes proceed may be influenced by factors such as the formulation of the drug, concurrent disease, concomitant medication and genetic variables of the individual patient. Thus, many factors contribute to differences in pharmacokinetics and to the individual variability in the serum concentration of a drug. As a consequence of this variability, there may be a wide variation in response to a drug given in a standard dose. Some patients may suffer from poor efficacy whereas others may experience toxic effects unless the dosage is individualised.

Phenytoin was the drug of choice for most seizure types when drug level measurements were introduced in the 1960s and it was found to exhibit particularly complex dose-dependent pharmacokinetics. As a consequence, it is extremely difficult to predict the effect of a dose change of this drug. Studies carried out in the 1960s and 1970s demonstrated a correlation between the concentration of phenytoin in serum and its therapeutic and toxic effects, thus measuring the serum concentration of phenytoin was soon established as a guide to individualised dosing (Kutt 1968; Kutt 1974; Lund 1974). Since then, drug level monitoring (therapeutic drug monitoring) has been established as a routine aid to optimising treatment with other antiepileptic drugs. The goal of therapeutic drug monitoring is to optimise a patient's clinical outcome by managing the medication regimen, assisted by the measurement of drug concentrations. In general, therapeutic drug monitoring is considered to be of potential value when there is a need for individualised dosing owing to marked inter-individual differences in drug response when such differences are accounted for by variations in pharmacokinetics, and when it is difficult to monitor drug treatment by direct observation of the therapeutic response and adverse effects, as is sometimes the case in epilepsy. Although most antiepileptic drugs do not share the problems of dose-dependent kinetics that phenytoin has, many display pronounced inter-individual variability in pharmacokinetics that suggest the need for individualised dosing. Furthermore, the serum concentration of many antiepileptic drugs can be affected by interactions with other drugs. Therapeutic drug monitoring may facilitate the identification of such interactions.

The concept of therapeutic drug monitoring rests on the assumption that drug concentration correlates better with clinical effects than dose. For some antiepileptic drugs, target ranges of serum concentration have been determined. These are drug concentrations known to be associated with a high probability of seizure control and low risk of toxicity. However, comparatively few studies have been designed specifically to explore the relationship between serum concentrations and effects of antiepileptic drugs, and the documentation in this respect for many of the drugs is scarce (Tomson 2000). Provided there is a distinct concentration-effect relationship within the individual, therapeutic drug monitoring may be justifiable to control for changes due to drug interactions. This is also possible in the absence of a defined target drug concentration range. It is, however, likely that the value of therapeutic drug monitoring will vary with the different antiepileptic drugs, depending on their pharmacological properties.

The therapeutic drug monitoring service may vary in its methods. Drug concentrations can be measured in specimens other than serum, such as saliva, while analytical methods with varying specificities may also be used. Moreover, there are different ways in which the results of the analysis are presented to the treating physician. This may be just the crude drug concentration or, in some settings, it may be part of a more comprehensive pharmacokinetic service with suggestions for dose adjustments.

Given the heterogeneity in the concept of therapeutic drug monitoring and in the pharmacological characteristics of antiepileptic drugs, it is not surprising that the use of therapeutic drug monitoring varies markedly and that we lack consensus concerning the value of its application in epilepsy (Chadwick 1987). The focus of this review is, therefore, on studies assessing the extent to which therapeutic drug monitoring contributes towards the greater effectiveness of antiepileptic drug treatment.

OBJECTIVES

To assess if the use of therapeutic drug monitoring improves the outcome of drug treatment for epilepsy in terms of improved seizure control and reduced adverse drug effects.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials comparing the outcomes of antiepileptic drug therapy guided by therapeutic drug monitoring with drug treatment without the aid of drug monitoring. Both adequately and quasi-randomised, and blinded and unblinded trials were to be included.

Types of participants

People with epilepsy who were receiving treatment with antiepileptic drugs as monotherapy. The review included patients of all ages with different seizure types and the use of all established antiepileptic drugs to prevent seizures. Two separate cohorts of patients were to be analysed:
(1) patients with newly-diagnosed epilepsy starting treatment;
(2) patients with established epilepsy on continuous treatment with antiepileptic drugs.
Children (under 16 years of age) and adults were to be analysed separately, if sufficient data were available.

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Types of interventions

The use of therapeutic drug monitoring to optimise antiepileptic drug therapy versus drug therapy without guidance by therapeutic drug monitoring.

It is recognised that antiepileptic drug levels may be analysed in many ways. Drug concentrations may be measured in different specimens, such as serum, plasma or saliva. Total as well as unbound serum concentrations may be analysed, and various analytical methods can be used. Moreover, the results of the analysis can be presented to the treating physician in different ways: as the actual drug concentration, as the drug level together with a suggested target range, or together with an interpretation with suggestions for dose adjustments as part of a more comprehensive pharmacokinetic service.

In this review any measurement of antiepileptic drug concentration that was made in order to assist the treating physician in his or her therapeutic decision making was to be considered.

Types of outcome measures

(1) Proportion of patients achieving a 12-month remission from seizures.
(2) Proportion of patients reporting adverse effects considered by the investigator to be drug related during the observation period.
(3) Proportion of patients withdrawn from the treatment to which they had been randomised.
(4) Proportion of patients achieving at least a 50% reduction in number of seizures during the period of observation. This outcome measure is not applicable to cohorts with newly-diagnosed epilepsy.
The review did not consider surrogate outcomes such as number of patients achieving serum concentrations of antiepileptic drugs within a specific target range.

Search methods for identification of studies

The original search methods for earlier versions of this review have been archived in Appendix 1.

For the most recent update of this review, we searched as follows:

(a) Cochrane Epilepsy Group Specialised Register (6 February 2010);

(b) CENTRAL (The Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 1, 2010) using the search strategy outlined in Appendix 2;

(c) MEDLINE (Ovid, 1950 to January week 4, 2010) using the search strategy outlined in Appendix 3.

No language restrictions were imposed. We checked the reference lists of retrieved articles for additional reports of relevant studies.

Data collection and analysis

Selection of studies
Two review authors (TT and MD) discarded irrelevant citations based on the titles of publications and their abstracts. If there was any suggestion that an article could possibly be relevant it was retrieved for further assessment.

The same two review authors assessed independently the methodological quality of each trial. They recorded details of method of randomisation, concealment of randomisation and use of intention-to-treat analysis. Disagreements were resolved by discussion.

Data extraction
Descriptive characteristics and study data were extracted by the same two review authors using a standard form.

Data analysis plan
(1) The two cohorts, patients with newly-diagnosed epilepsy starting treatment and patients with established epilepsy on continuous treatment with antiepileptic drugs, were analysed separately; a separate analysis for children and adults was also undertaken.
(2) The primary analysis was to include therapeutic drug monitoring of all drugs. However, it was envisaged that the impact of drug monitoring may vary with different drugs, depending at least in part on the pharmacokinetic and pharmacodynamic properties of the drugs. Subgroup analyses were, therefore, undertaken separately for the different drugs.
(3) Clinical heterogeneity between trials was to be assessed by comparing the following:
(a) Patient characteristics: age; type of epilepsy; aetiology of epilepsy.
(b) Therapeutic drug monitoring method: measurement of bound or unbound drug concentrations; nature of specimens analysed (for example, saliva versus plasma); relation of timing of taking sample for analysis and dosing; whether the therapeutic drug monitoring results given to treating physicians included interpretation of results and suggestions for dose adjustments versus provision of crude drug levels only; whether the laboratory analysing drug levels was taking part in a quality control program or not.
(4) Statistical heterogeneity was to be assessed using the chi-squared test for heterogeneity and I^2 statistic. Provided no significant heterogeneity was found, results were to be summarised in a fixed-effect meta-analysis.
(5) The primary analysis was by intention to treat, including all patients randomised to treatment guided by therapeutic drug monitoring or treatment without drug monitoring, whether the randomised patients completed the evaluation period or not.
(6) Dichotomous data was to be presented as odds ratios and relative risks, and analysed using both fixed-effect and random-effects models.
(7) Sensitivity analyses were to be made including all studies and also only those using adequate methods of randomisation.

RESULTS

Description of studies

Only one prospective randomised study was identified that met the main inclusion criteria of this review (Jannuzzi 2000). The focus of that study was on the clinical impact of therapeutic drug monitoring in patients with newly-diagnosed epilepsy. One hundred and eighty patients, aged 6 to 65 years, with untreated partial or idiopathic generalised non-absence epilepsy, and who had a history of at least two seizures in the previous month, were enrolled in this unblinded, prospective parallel-group study. The ability of prospective participants to comply with the study protocol was evaluated and informed consent obtained from the patients or their guardians. All participants who met the eligibility criteria were randomised through a central office into two groups using a stratification procedure aimed at ensuring a balanced distribution

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of different types of epilepsy between groups. All participants were prescribed the antiepileptic drug selected as the most appropriate by their physician, including carbamazepine, valproate, phenytoin, phenobarbital or primidone. In one group, dosage was adjusted to achieve a steady-state serum antiepileptic drug concentration within a target range during a period of three months or less, whereas, in the other groups, dosage was adjusted on purely clinical grounds aimed at achieving optimal seizure control over the shortest reasonable period.

Exclusion criteria were: pregnancy; history of drug or alcohol abuse; previous treatment with any antiepileptic drug; presence of any known progressive disease or a diagnosis of benign rolandic epilepsy; absence epilepsy; and epileptic encephalopathy.

The target ranges used were 10 to 20 µg/ml (40 to 80 µM) for phenytoin, 15 to 40 µg/ml (64 to 172 µM) for phenobarbital, 4 to 11 µg/ml (17 to 46 µM) for carbamazepine, and 40 to 100 µg/ml (280 to 700 µM) for valproate. For primidone treated patients, only metabolically derived phenobarbital was used for therapeutic monitoring purposes. Blood samples for determination of antiepileptic drug levels were collected in both groups in a similar way but the results were not made available to the treating physician in one of the groups. If no satisfactory response was achieved after 6 to 12 months of treatment, and the physician thought that knowledge of serum drug concentration was necessary to continue treatment, patients randomised to the control group could be crossed over to the intervention group. However, only one patient crossed over, after one month. Hence, this is not likely to have had a significant effect on the overall results of the study. Patients were followed up for 24 months or until a change in treatment strategy was clinically indicated. The primary efficacy endpoint was the proportion of patients achieving complete seizure remission during the previous 12 months of follow up and the analyses based on the intention-to-treat population.

One additional prospective randomised study assessing the effect of monitoring plasma anticonvulsant levels was identified (Fröscher 1981). In this, 127 outpatients with epilepsy were randomly assigned to two groups. In one, the treating physician was not informed of the results of plasma concentration determinations, whereas, in the other, plasma levels were reported and the treating physician was asked to try to keep plasma concentrations within a therapeutic range. Each patient was followed for one year. This study included patients with chronic epilepsy and those who had been on treatment for a considerable time before enrolment. However, this study was excluded from the review since the majority of patients were treated with a combination of different antiepileptic drugs (on average 2.5 per patient). In all, only 14 patients taking part in this study received monotherapy.

Risk of bias in included studies

The only study that met our criteria was an open, prospective randomised study with a parallel-group design. The randomisation procedure was adequate and the two treatment groups comparable with respect to age, seizure frequency and type of epilepsy. The study design was open, but there would have been considerable practical problems associated with blinding procedures, and this is not likely to have had a major impact on the results. The selected primary efficacy endpoint, the proportion of participants achieving complete seizure remission during the previous 12 months, is relevant and the two-year follow up was adequate. The sample size calculations were based on the assumption of a 50% seizure freedom rate in the control group and in the intervention group a 25% absolute improvement corresponding to a 75% seizure freedom rate. A sample size of 146 patients was thus considered adequate for a power of 80% at the $P < 0.05$ level. The investigators nevertheless enrolled 180 patients. The reasons for this are not declared. Although the expected seizure response rate in the control group was close to the one observed in the study, the assumed effect of therapeutic drug monitoring on the primary efficacy outcome variable could be considered as unrealistically high. The limited number of patients may thus have contributed to the failure to demonstrate an effect of the intervention in the present study. Additionally, although the potential value of drug level monitoring is likely to vary between drugs, comparisons were made between the two groups regardless of type of treatment. Most patients in both the intervention group (52/93; 56%) and the control group (48/87; 55%) were treated with carbamazepine, while the number receiving other antiepileptic drugs was much lower. A substantial proportion (64/180; 36%) of the enrolled patients exited the study prematurely. Of these, 43 were lost to follow up. However, the proportion of completers was similar in the two groups, and the analyses in the study of Januzzi et al used the intention-to-treat population.

Effects of interventions

The proportion of patients who achieved a 12-month remission from seizures was 60% (56/93) (95% CI 50 to 70) in the group with treatment supported by drug monitoring data, which was not significantly different from the 61% (53/87) (95% CI 50 to 71) in the control group, relative risk (RR) 0.99 (95% CI 0.78 to 1.25). As for the primary endpoint of the study, seizure freedom rates during the last 12 months of follow up, the results were also very close: 56% (52/93) (95% CI 45 to 66) in the intervention group and 58% (50/87) (95% CI 48 to 68) in the control group (not statistically significant), RR 0.97 (95% CI 0.75 to 1.26). Adverse effects were reported in 45 of 93 patients (48%, 95% CI 38 to 59) in the drug level monitoring group compared with 41 of the 87 in the control group (47%, 95% CI 36 to 58) (not statistically significant), RR 0.84 (95% CI 0.64 to 1.11). The rates of the most frequently reported types of side effects (somnolence, dizziness, headache, irritability and fatigue) were also very similar in the two groups. Among the 93 patients in the intervention group, 58 (62%, 95% CI 52 to 72) completed the two-year follow up compared with 58/87 (67%, 95% CI 56 to 76) in the control group, RR 0.94 (95% CI 0.75 to 1.16). Of the 64 patients who exited the study prematurely, 43 were lost to follow up, 10 exited due to insufficient efficacy and/or adverse events, and 11 for other reasons.

Exclusion of all patients who did not complete the two-year follow up from the analysis of the primary endpoint of the study, seizure freedom rates during the last 12 months of follow up, resulted in a RR of 1.04 (95% CI 0.91 to 1.19).

Serum drug levels

The mean serum concentrations of carbamazepine and valproate at nearly all time points were within the predefined target ranges for patients in both groups; there were no significant differences between the groups in this respect. Serum phenobarbital levels below the target range were twice as common in the control group as in the intervention group, but the numbers of participants were low. After the last dosage adjustment, general serum drug levels

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outside the target range were found in 6% of those participants in the drug monitored group compared with 22% of the control participants (P < 0.01). Of the patients who continued to have seizures during the last 12 months of follow up, 1 out of 10 in the therapeutic drug monitoring group and 4 out of 11 in the control group had serum drug levels below the target range.

DISCUSSION

This review has demonstrated the lack of relevant randomised studies assessing the impact of therapeutic drug monitoring in efforts to optimise the drug treatment of newly-diagnosed epilepsy. The only identified study meeting our inclusion criteria provides no evidence for the effectiveness of the routine use of therapeutic monitoring of antiepileptic drugs during the first two years after the initiation of monotherapy treatment for patients with newly-diagnosed epilepsy. This does not exclude the possibility that therapeutic monitoring of antiepileptic drugs may be useful in individual patients, in other stages of epilepsy, in patients on polytherapy or in other specific clinical situations. Nor do the results of this included study exclude some impact of therapeutic drug monitoring on the outcome of the treatment of patients with newly-diagnosed epilepsy.

The study failed to demonstrate a difference between the two treatment groups, with and without monitoring, but was powered to detect only an improvement in response rate from 50% to 75%. More realistic, less pronounced effects may still be of clinical relevance. Such effects are not excluded, although they may seem unlikely considering the very similar rates of seizure remission and side effects in the two treatment groups. Furthermore, although it is likely that the value of therapeutic drug monitoring varies between drugs, owing to their individual pharmacokinetic properties, all antiepileptic drugs were analysed together in the identified study. Phenytoin, the antiepileptic drug for which therapeutic drug monitoring is potentially most important, was used by a small fraction of the patients and was unevenly distributed between the two groups. Additionally, although a two-year follow up is unusually long for an intervention study in epilepsy, it should be recognised that treatment continues for considerably longer for the vast majority of patients. Potential long-term benefits of therapeutic drug monitoring have, therefore, not been addressed in the included study. The risk of chronic toxicity and the management of late treatment failure are examples of situations where drug level monitoring might play a role that could not be assessed in the present study. A further special feature of the included study is the key role of the target ranges of antiepileptic drug serum concentrations. In the intervention group, dosage was adjusted to achieve serum concentrations within predefined target ranges. The outcome thus partly depended on the validity of the selected target ranges. Their relevance for patients with newly-diagnosed epilepsy has in fact been questioned (Tomson 2000) and therapeutic monitoring is, therefore, often employed without strict adherence to target ranges but rather using the individual patient's optimal drug concentration as a reference for future therapeutic decisions. Such use of drug-level monitoring has not been evaluated in the included study. Neither can it be said that therapeutic drug monitoring would not prove more useful as an aid for physicians who are less experienced in the treatment of epilepsy and thus less skilled in individualising drug dosage on clinical grounds alone.

AUTHORS' CONCLUSIONS

Implications for practice

The result of this review, with only one study meeting our inclusion criteria, provides no clear evidence to support the routine use of therapeutic drug monitoring for the optimisation of treatment with antiepileptic drugs of patients with newly-diagnosed epilepsy. However, benefits of therapeutic drug monitoring in newly-diagnosed patients cannot be excluded, neither can its usefulness in special situations or in selected patients, although strict evidence is lacking.

Implications for research

This review has demonstrated the shortage of data from randomised controlled studies concerning the effectiveness of using therapeutic drug monitoring as an aid to dosage adjustment in antiepileptic drug monotherapy for newly-diagnosed epilepsy. Future studies should be appropriately powered, ideally analysing individual antiepileptic drugs, and could consider not using strict adherence to poorly defined target ranges of drug concentrations as part of the intervention. Although the practical and ethical difficulties would be considerable, the extension of follow up beyond two years would be of interest.

ACKNOWLEDGEMENTS

Mrs Jeannette Grünstein, Department of Clinical Pharmacology, Karolinska University Hospital-Huddinge, for assistance with collecting the articles.

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Jannuzzi 2000 *{published data only}*

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CHARACTERISTICS OF STUDIES

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

Jannuzzi 2000

Methods	Randomised, open, parallel study over a 24-month study period
Participants	Patients of both sexes, aged 6 to 65 years with partial or generalised epilepsy The median number of seizures was 3 during 4 months before intervention
Interventions	Monotherapy with carbamazepine, phenytoin, valproate, phenobarbital or primidone guided by therapeutic drug monitoring versus without support of drug level monitoring
Outcomes	Proportion achieving seizure remission in the last 12 months Proportion remaining seizure free since initiation of treatment Proportion with side effects at any time
Notes	Under powered Not possible to evaluate individual drugs

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

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

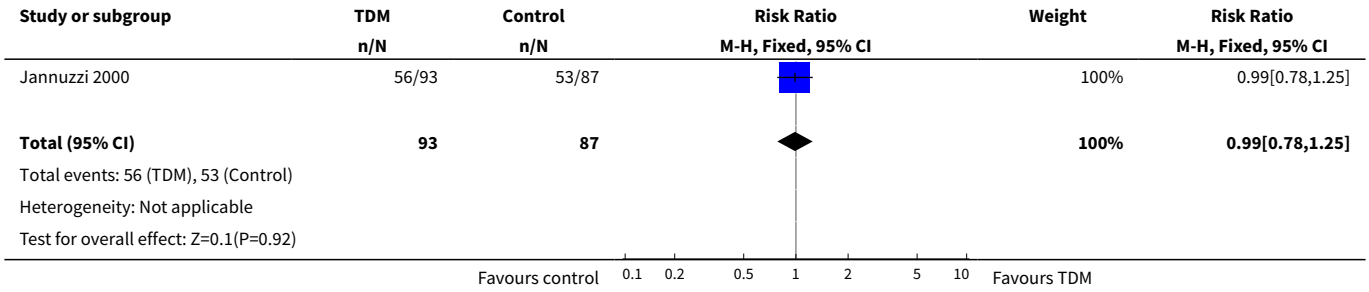
Study	Reason for exclusion
Fröscher 1981	Patients treated with antiepileptic drugs in polytherapy

DATA AND ANALYSES

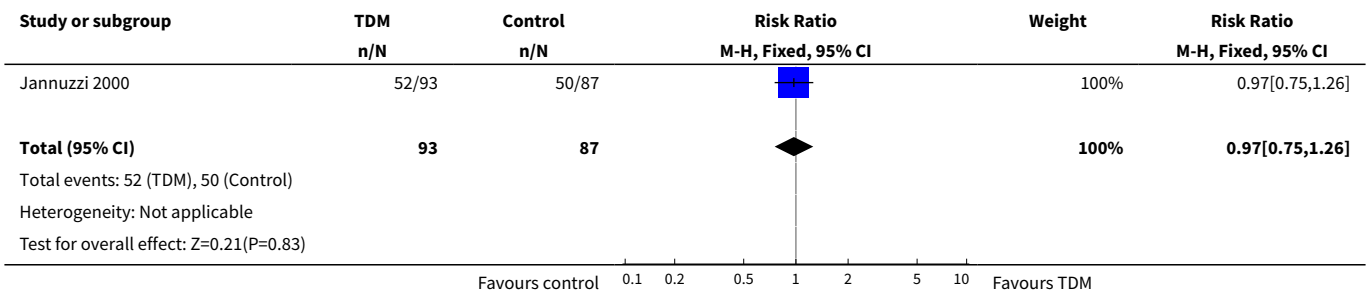
Comparison 1. TDM versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 12-month remission	1	180	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.78, 1.25]
2 Seizure free last 12-month follow up	1	180	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.75, 1.26]
3 Adverse effects	1	180	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.64, 1.11]
4 Completed 2-year follow up	1	180	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.75, 1.16]

Analysis 1.1. Comparison 1 TDM versus control, Outcome 1 12-month remission.



Analysis 1.2. Comparison 1 TDM versus control, Outcome 2 Seizure free last 12-month follow up.



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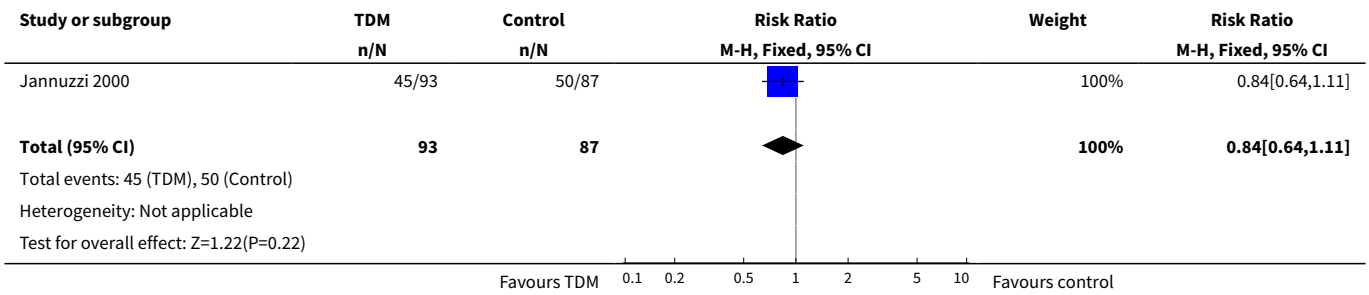
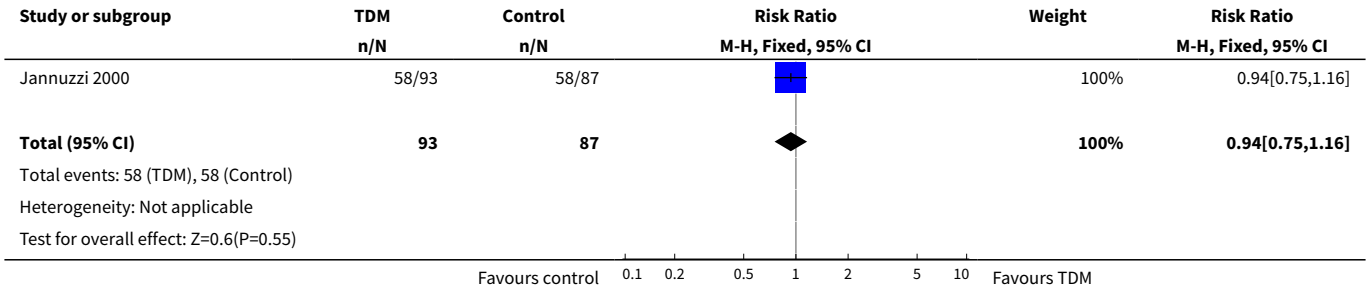
Analysis 1.3. Comparison 1 TDM versus control, Outcome 3 Adverse effects.



Analysis 1.4. Comparison 1 TDM versus control, Outcome 4 Completed 2-year follow up.



APPENDICES

Appendix 1. Search methods for original version of this review

We searched the Cochrane Epilepsy Group Specialised Register (4 September 2006). This register contains reports of trials identified from regular searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and of MEDLINE. Relevant reports are also identified by handsearching selected journals and conference proceedings.

In addition, we searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 4, 2005), MEDLINE (January 1966 to April 2005) and EMBASE (1974 to May 2005). Details of the search strategy used are given below. No language restrictions were imposed. We checked the reference lists of retrieved articles for additional reports of relevant studies.

The following search strategy was used for MEDLINE and was modified for other databases.

1 RANDOMISED-CONTROLLED TRIAL in Publication Type
2 CONTROLLED-CLINICAL TRIAL in Publication Type
3 RANDOMISED-CONTROLLED-TRIALS / ALL
4 RANDOM-ALLOCATION / ALL
5 DOUBLE-BLIND-METHOD / ALL
6 SINGLE-BLIND-METHOD / ALL
7 #1 or #2 or #3 or #4 or #5 or #6
8 TG=ANIMAL not (TG=HUMAN and TG=ANIMAL)
9 #7 not #8
10 CLINICAL TRIAL in PT
11 Explode CLINICAL-TRIALS / ALL
12 CLIN* and TRIAL* in TI
13 CLIN* and TRIAL* in AB
14 (SINGL* or DOUBL* or TREBL* or TRIPL*) and (BLIND* or MASK*) in TI

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15 (SINGL* or DOUBL* or TREBL* or TRIPL*) and (BLIND* or MASK*) in AB
16 PLACEBOS / ALL
17 PLACEBO*in TI
18 PLACEBO* in AB
19 RANDOM* in TI
20 RANDOM* in AB
21 Explode RESEARCH-DESIGN / ALL
22 #10 or #11or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
23 #22 not #8
24 #23 or #9
25 TDM
26 DRUG-MONITORING (MeSH)
27 (THERAP* or DRUG*) and MONITOR*
28 (SERUM or PLASMA) and MONITOR*
29 (SALIVA and MONITOR*)
30 #25 or #26 or #27 or #28 or #29
31 DRUG-ADMINISTRATION-SCHEDULE (MeSH)
32 DOSE-RESPONSE-RELATIONSHIP-DRUG (MeSH)
33 PHARMACOKINETICS (MeSH)
34 (DRUG and ANALYSIS)
35 (SERUM or PLASMA) and DRUG-CONCENTRATION
36 (THERAPEUTIC and RANGE)
37 EPILEPSY (MeSH)
38 EPILEP*
39 ANTICONVULSANTS (MeSH)
40 ANTICONVULSANT*
41 ANTIEPILEP*
42 SEIZURE (MeSH)
43 SEIZURE*
44 CONVULSION*
45 PHENOBARBITAL (MeSH)
46 PHENOBARBITA*
47 PHENYTOIN (MeSH)
48 PHENYTOIN
49 CARBAMAZEPINE (MeSH)
50 CARBAMAZEPIN*
51 TOPIRAMATE
52 GABAPENTIN
53 FELBAMATE
54 OXCARBAZEPIN*
55 TIAGABINE
56 ZONISAMIDE
57 # 30 or #31 or #32 or #33 or #34 or #35 or #36
58 #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56
59 #57 and #58
60 #59 and #24

Appendix 2. CENTRAL search strategy

#1 (epilep* or seizure* or convulsion*)

#2 MeSH descriptor Epilepsy explode all trees

#3 MeSH descriptor Seizures explode all trees

#4 anticonvulsant*

#5 MeSH descriptor Anticonvulsants explode all trees

#6 antiepilep*

#7 phenytoin

#8 valpro*

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#9 carbamazepine

#10 phenobarbit*

#11 MeSH descriptor Phenobarbital explode all trees

#12 MeSH descriptor Phenytoin explode all trees

#13 MeSH descriptor Carbamazepine explode all trees

#14 ethosuximide

#15 primidone

#16 topiramate

#17 gabapentin

#18 felbamate

#19 oxcarbazepin*

#20 tiagabine

#21 zonisamide

#22 levetiracetam

#23 lacosamide

#24 pregabalin

#25 rufinamide

#26 TDM

#27 MeSH descriptor Drug Monitoring explode all trees

#28 (therap* or drug*) NEAR/2 (monitor*)

#29 (serum or plasma) NEAR/2 (monitor*)

#30 saliva* NEAR/2 monitor*

#31 MeSH descriptor Drug Administration Schedule explode all trees

#32 MeSH descriptor Dose-Response Relationship, Drug explode all trees

#33 pharmacokinetics

#34 drug NEAR/2 analysis

#35 (serum or plasma) NEAR/2 (drug NEXT concentration)

#36 therapeutic NEXT range

#37 MeSH descriptor Pharmacokinetics explode all trees

#38 (#1 OR #2 OR #3)

#39 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25)

#40 (#26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR# 36 OR #37)

#41 (#38 AND #39 AND #40)

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Appendix 3. MEDLINE search strategy

This strategy is based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials published in Lefebvre 2009.

1. randomized controlled trial.pt.

2. controlled clinical trial.pt.

3. randomized.ab.

4. placebo.ab.

5. clinical trials as topic.sh.

6. randomly.ab.

7. trial.ti.

8. 1 or 2 or 3 or 4 or 5 or 6 or 7

9. exp animals/ not humans.sh.

10. 8 not 9

11. exp Epilepsy/

12. Seizures/

13. (epilep$ or seizure$ or convuls$).tw.

14. 11 or 12 or 13

15. exp Anticonvulsants/

16. anticonvulsant$.tw.

17. antiepilep$.tw.

18. phenytoin.tw.

19. valpro$.tw.

20. carbamazepine.tw.

21. ethosuximide.tw.

22. phenobarbit$.tw.

23. exp Phenobarbital/

24. primidone.tw.

25. exp Phenytoin/

26. exp Carbamazepine/

27. topiramate.tw.

28. gabapentin.tw.

29. felbamate.tw.

30. oxcarbazepin$.tw.

31. tiagabine.tw.

32. zonisamide.tw.

33. levetiracetam.tw.

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34. lacosamide.tw.

35. pregabalin.tw.

36. rufinamide.tw.

37. or/15-36

38. TDM.tw.

39. exp Drug Monitoring/

40. ((therap$ or drug$) adj2 monitor$).tw.

41. ((serum or plasma) adj2 monitor$).tw.

42. (saliva$ adj2 monitor$).tw.

43. or/38-42

44. exp Drug Administration Schedule/

45. exp Dose-Response Relationship, Drug/

46. exp Pharmacokinetics/

47. (drug adj2 analysis).tw.

48. ((serum or plasma) adj2 (drug adj concentration)).tw.

49. (therapeutic adj range).tw.

50. or/43-49

51. 10 and 14 and 37 and 50

WHAT'S NEW

Date	Event	Description
6 February 2010	New search has been performed	Searches updated 6th February 2010; no new trials identified.

HISTORY

Protocol first published: Issue 4, 2006
Review first published: Issue 1, 2007

Date	Event	Description
10 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Dr Tomson was primarily responsible for all aspects of the protocol design. Dr Dahl commented on the draft stage of the protocol. Dr Kimland performed the literature search. Dr Tomson and Dr Dahl selected the studies according to the protocol. All authors participated in writing the review.

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DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- The Swedish Council on Technology Assessment in Health Care, Sweden.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [*administration & dosage] [blood]; Carbamazepine [administration & dosage] [blood]; Drug Monitoring; Epilepsy [blood] [*drug therapy]; Phenobarbital [administration & dosage] [blood]; Phenytoin [administration & dosage] [blood]; Primidone [administration & dosage] [blood]; Valproic Acid [administration & dosage] [blood]

MeSH check words

Humans

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