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Alprazolam for essential tremor (Review)

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TABLE OF CONTENTS

[Intervention Review]

Alprazolam for essential tremor

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ABSTRACT

Background

Essential tremor (ET) is one of the most common movement disorders. Treatment is based primarily on pharmacological agents. On this basis, although primidone and propranolol are well-established treatments in clinical practice, they could be ineffective in 25% to 55% of patients and can produce serious adverse events (AEs) in a large percentage of individuals. For these reasons, evaluating treatment alternatives for ET may be a worthwhile pursuit. Alprazolam has been suggested as a potentially useful agent for treatment of individuals with ET, but its efficacy and safety are uncertain.

Objectives

Primary

To assess the efficacy and safety of alprazolam in the treatment of individuals with ET.

Secondary

To examine effects of alprazolam treatment on the quality of life of people with ET.

Search methods

We carried out a systematic search without language restrictions to identify all relevant trials. We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (January 1966 to September 2019), EMBASE (January 1988 to September 2019), the National Institute for Health and Care Excellence (NICE) (1999 to September 2019), ClinicalTrials.gov (1997 to September 2019) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (2004 to September 2019). We handsearched grey literature and examined the reference lists of identified studies and reviews.

Selection criteria

We included all randomised controlled trials (RCTs) of alprazolam versus placebo or any other treatment. We included studies in which ET was diagnosed according to accepted and validated diagnostic criteria. We excluded studies that included patients presenting with secondary forms of tremor or reporting only neurophysiological parameters for the purpose of assessing outcomes.

Data collection and analysis

Two review authors independently collected and extracted data using a data collection form. We assessed risk of bias and the body of evidence. We used inverse variance methods for continuous outcomes and measurement scales. We compared differences between treatment groups as mean differences. We used Review Manager software for management and analysis of data.

Main results

We included in this review one trial that compared alprazolam versus placebo (24 participants). It was judged to have high overall risk of bias. We graded the overall quality of evidence as very low. Compared with those given placebo, participants treated with alprazolam showed a significant reduction in tremor severity (mean difference (MD) -0.75, 95% confidence interval (CI) -0.83 to -0.67). Nine alprazolam-treated participants (75%) developed AEs, mainly represented by sedation (50%), constipation (17%) and dry mouth (9%). No participants in the alprazolam group and no participants in the placebo group discontinued treatment and dropped out of the study.

Authors' conclusions

Currently available data reveal evidence insufficient for assessment of the efficacy and safety of alprazolam treatment for individuals with ET.

PLAIN LANGUAGE SUMMARY

Use of alprazolam for treatment of essential tremor

Essential tremor (ET) is the most common movement disorder. Although benign in term of its effect on life expectancy, it is typically progressive and is potentially disabling. Treatment is based primarily on pharmacological agents (propranolol and primidone as first-line therapy) that could be ineffective in 25% to 55% of patients. Alprazolam has been suggested as potentially useful in ET. The authors of this review tried to assess its efficacy and safety in people with ET. One randomized study, which compared alprazolam and placebo in 24 people with head and/or limb ET, was included. Alprazolam produced a reduction in tremor severity associated with a high frequency of adverse events. However, the small number of studies and evidence of many methodological limitations in the one included study prevent firm conclusions on the benefit-risk profile of this treatment. Further research is needed to confirm efficacy and to assess long-term safety of alprazolam for treatment of patients with ET.

SUMMARY OF FINDINGS

Summary of findings 1. Alprazolam for essential tremor

Alprazolam for essential tremor

Patient or population: patients with essential tremor
Settings: outpatients
Intervention: alprazolam

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Alprazolam				
Tremor severity Clinical rating scale. Scale from 0 to 4 Follow-up: 2 weeks	Mean tremor severity in control groups was **2.13 points**	Mean tremor severity in intervention group was **0.75 lower** (0.67 to 0.83 lower)		24 (1 study)	⊕⊖⊖⊖ **Very low** [a,b]	
Withdrawals due to adverse events Follow-up: 2 weeks	None	None		24 (1 study)	⊕⊖⊖⊖ **Very low** [a,b]	
Quality of life Investigator global assessment Scale from 1 to 7 Follow-up: 2 weeks	Mean score in the control group was **3.83 points**	Mean score in the intervention group was **1.16 lower** (0.17 to 2.15 lower)		24 (1 study)	⊕⊖⊖⊖ **Very low** [a,b]	
Quality of life Investigator global assessment Scale from 1 to 7 Follow-up: 2 weeks	Mean score in the control group was **3.5 points**	Mean score in the intervention group was **0.67 lower** (0.27 to 1.61 lower)		24 (1 study)	⊕⊖⊖⊖ **Very low** [a,b]	

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: Confidence interval

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

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[a]Downgraded by 2 levels for very serious risk of bias: allocation and blinding methods not described (selection bias); number of adverse events in the placebo group not reported (reporting bias); essential tremor diagnostic criteria applied to participants not reported; patient exclusion and inclusion criteria not specified. An arbitrary, not validated, clinical rating scale for tremor severity was used for assessment of tremor.
[b]Downgraded by 2 levels for very serious imprecision: small sample size; uncertainty of clinical relevance of results reported and of effects measured.

BACKGROUND

Description of the condition

Essential tremor (ET) is one of the most common movement disorders, presenting an overall estimated prevalence ranging from 0.9% to 2.2%, with a higher rate reported among people over 65 years of age (4.6%) (Louis 2010).

Essential tremor is characterised by postural and kinetic tremor involving the arms and less commonly the head, lower limbs and voice, frequently accompanied by a family history of a similar tremor (Louis 2005). However, ET is a heterogeneous disorder, and little agreement among neurologists can be found regarding both the clinical definition and the diagnostic criteria (Jankovic 2002). Although benign in term of its effect on life expectancy, ET often causes embarrassment and, in a small percentage of patients, serious disability (Koller 1986; Busenbark 1991). Moreover, symptoms are typically progressive and are potentially disabling, often forcing patients to change jobs or to seek early retirement (Deuschl 2000). Treatment is based primarily on pharmacological agents, although surgical intervention may be an option in the most disabling cases. Pharmacotherapy may be used to improve function or to reduce the embarrassment associated with this condition, but treatment should be tailored to the patient's level of disability. Although primidone and propranolol are well-established agents for the treatment of ET, additional medicaments may be useful in reducing tremor (Sullivan 2004). In fact, even though both propranolol and primidone have been reported to improve tremor in about two-thirds of patients (Koller 1989; Wasielewski 1998), these agents tend to lose efficacy over time (Louis 2001a). In addition, their use is limited, particularly in the elderly (> 70 years) (Zesiewicz 2002), because of interactions with commonly used medications (e.g. digoxin, calcium channel blockers, anti-arrhythmics) (Hansten 2004). Benzodiazepines have been suggested as potentially useful agents for the treatment of patients with ET, and they are usually well tolerated.

Description of the intervention

Alprazolam is a triazolo 1,4-benzodiazepine that binds to a specific area of the gamma-aminobutyric acid (GABA)-A receptor, modulating transmission of the inhibitory neurotransmitter GABA as allosteric agonists and facilitating opening of the receptor's chloride channel. Following oral administration, alprazolam is rapidly absorbed with nearly complete bioavailability. Peak concentrations in the plasma occur within 0.3 to 3 hours after administration, and plasma mean half-life ranges from 10 to 14 hours. Alprazolam is excreted primarily in the urine - 50% of the dose within 24 hours, and 94% after 72 hours.

How the intervention might work

Essential tremor may be caused by a deficiency in the α1-subunit of the GABA-A receptor, as demonstrated in a knockout model in mice (Kralic 2005). This mechanism suggests that the GABAergic system could serve as a potential target for pharmacotherapy, and that GABA-A receptor agonists may be effective in ET (Pahwa 2003; Kralic 2005). In fact, in the light of their mechanisms of action, agents that enhance GABAergic neurotransmission have shown some effectiveness in the treatment of patients with ET. A positive effect of 1,4-benzodiazepine (alprazolam, clonazepam) on ET has been reported (Thompson 1984; Huber 1988a) and should be related to allosteric modulation and enhancement of GABA-A receptor function. Moreover, since the time of their discovery, 1,4-benzodiazepines have been demonstrated to present an anxiolytic effect that might be helpful for patients with ET, whose condition is known to be worsened by anxiety.

Why it is important to do this review

In 2005 the American Academy of Neurology published the Practice Parameter for ET (Zesiewicz 2005) and recommended propranolol and primidone as first-line therapy. The quality of evidence was assessed via an arbitrary four-tiered scheme. Alprazolam was considered probably effective in reducing tremor and was given a level B recommendation in a recent update of this work (Zesiewicz 2011). The GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system was used to assess the quality of evidence and the strength of recommendations in another recent work (Zappia 2013), in which alprazolam was indicated as second-line treatment for ET. Given that serious adverse events (AEs) limit the use of primidone or propranolol, and that these agents tend to lose efficacy in long-term therapies, evaluating other treatment alternatives for ET may be a worthwhile pursuit. As uncertainty about the efficacy of alprazolam is ongoing, a systematic review aimed at evaluating whether this agent could be an effective alternative for patients with ET requiring additional drugs may generate clinically useful information.

OBJECTIVES

Primary

- To assess the efficacy and safety of alprazolam in the treatment of individuals with ET.

Secondary

- To examine effects of alprazolam treatment on the quality of life of people with ET.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) based on both parallel-group and cross-over designs.

Types of participants

Adults (aged ≥ 16 years) with ET meeting criteria proposed by the Tremor Investigation Group (Bain 2000a), the Consensus Statement of the Movement Disorder Society on Tremor (Deuschl 1998) or previously accepted and validated clinical criteria (Rejput 1984; Snow 1989; Haerer 1992; Salemi 1994; Chouinard 1997; Louis 1998).

We excluded from our review participants with a secondary form of tremor (e.g. tremor in parkinsonian disorders, dystonia, thyroid disease).

Types of interventions

Alprazolam for ET compared with any other pharmacological treatment or placebo.

We will not exclude trials on the basis of dose or route of administration.

Types of outcome measures

We excluded studies that reported only neurophysiological parameters (e.g. electromyographic recordings, accelerometry, spirography, digitising tablets) when assessing outcomes. These instrumental tests have important limitations, as their accuracy and reproducibility are not well established. Moreover, neurophysiological measures can lead to fallacious assessment of the benefit of treatment, as cross-sectional studies showed weak correlation between those measures and functional disability (Bain 1997; Bain 2000b).

Primary outcomes

- Tremor severity, as measured by the Fahn-Tolosa-Marin Tremor Rating Scale (TRS) (Fahn 1993), at the end of follow-up.
    - The TRS assesses rest and postural and action tremor. The TRS score is derived from three TRS subscales.
        - Examiner-reported upper limb postural and action tremor severity (amplitude), four elements.
        - Examiner-reported ability to perform specific motor tasks (writing, drawing and pouring with dominant and non-dominant hands), nine elements.
        - Patient-reported functional disabilities due to tremor (eating, speaking, drinking, performing hygiene, dressing, writing, working and social activities), eight elements.
- Withdrawals due to adverse events (AEs) as defined in a standard manner in studies, and the number of participants with any AE associated with treatment.

Secondary outcomes

- Quality of life as measured by a validated scale or questionnaire (e.g. Short Form (SF)-36, EuroQoL Quality of Life Questionnaire) or by a patient self evaluation rating scale (e.g. Beck Depression Inventory (BDI), Patient Global Impression (PGI), Clinical Global Impression (CGI)).

Search methods for identification of studies

We carried out a systematic search without language restrictions to identify all relevant published and unpublished RCTs.

Electronic searches

We searched the following databases for relevant trials.

- The Cochrane Central Register of Controlled Trials (CENTRAL) (up to Issue 10).
- MEDLINE (January 1966 to September 2015).
- EMBASE (January 1988 to September 2015).
- National Institute for Health and Care Excellence (NICE) (1999 to September 2015).
- ClinicalTrials.gov (1997 to September 2015).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (2004 to September 2015).

We based search strategies for each database on the strategy developed for MEDLINE, revising it appropriately for each database to take into account differences in controlled vocabulary and syntax rules. See Appendix 1 and Appendix 2.

Searching other resources

In addition to conducting the electronic searches above, we:

- screened the reference lists of all available review articles and primary studies;
- handsearched the references quoted in recent abstract books of European Federation of Neurological Societies (2005 to 2015), American Academy of Neurology (2003 to 2015), American Neurological Association (2006 to 2015), World Federation of Neurology (2008 to 2014) and Movement Disorder Society (2003 to 2015);
- contacted the corresponding authors of relevant trials; and
- contacted drug manufacturers to ask for information on ongoing trials.

Data collection and analysis

Two review authors (EB and GQ) independently assessed the titles and abstracts of all studies identified by electronic searching or by handsearching. We obtained the full text of potentially relevant trials.

Selection of studies

After reading the abstracts, EB and GQ independently selected eligible articles, independently scrutinised the full texts of selected studies and decided which trials met the inclusion criteria for this review. We resolved disagreements concerning inclusion and exclusion of trials by discussion.

Data extraction and management

EB and GQ extracted the following data independently, using a data collecting form.

- Trial design.
- Randomization methods.
- Allocation concealment.
- Blinding of treatments and assessments.
- Comparability of treatment groups in terms of demographic and clinical characteristics.
- Inclusion and exclusion criteria.
- Duration of treatment.
- Length of follow-up.
- Outcome measures (use of validated scales).
- Number of withdrawals and respective causes.
- Descriptions of AEs.

We resolved disagreements on extracted data by discussion.

Assessment of risk of bias in included studies

Review authors independently judged trial quality according to the methods set out in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We considered seven specific domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.

- Incomplete outcome data.
- Selective reporting.
- Other sources of bias.

Two review authors (EB, GQ) independently assessed the risk of bias of each included study and resolved disagreements by discussion to reach consensus. The overall assessment of risk of bias was based on recommendations reported in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If one or more domains were assessed as having high risk of bias, we rated the overall score as high. If all domains were rated as having low risk of bias, we considered the overall score as low. We rated all other combinations as having unclear overall risk of bias.

During interpretation of primary outcome results, we considered the risk of bias of included studies by using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach. We rated the overall quality of evidence as 'high', 'moderate', 'low' or 'very low'. Through the GRADE approach, we assigned RCTs an initially high rating that may be subsequently modified by sequential judgement of limitations, inconsistency of results, indirectness of evidence, imprecision of data and presence of publication bias. Primary outcomes considered were tremor severity, withdrawals and numbers of AEs. We have reported and summarised results of this assessment by preparing a 'Summary of findings' table.

Measures of treatment effect

We analysed as continuous variables measurement scales used to assess ET. We calculated and expressed intervention effects as mean differences (MDs) and standard deviations (SDs). We used changes from baseline for continuous variables and frequencies, and percentages for categorical variables (numbers of withdrawals and numbers of AEs).

Unit of analysis issues

To avoid the 'carry-over' effect that can induce alteration of response to subsequent treatment (Sibbald 1998), we considered only data from the first treatment phase after randomisation for cross-over studies.

Dealing with missing data

To estimate effects of participant withdrawals or loss to follow-up on primary outcomes, we planned to extract available information about incomplete data and about the intention-to-treat analysis performed. We considered the impact of missing data during assessment of risk of bias.

Assessment of reporting biases

We planned to use funnel plots to assess reporting biases.

Data synthesis

We calculated MDs and SDs to assess efficacy, frequency and percentage for withdrawals and AEs. Provided that an outcome of interest was reported by at least two included studies, we combined data in a meta-analysis. We planned to use, in the presence of between-trial homogeneity, a fixed-effect model, and, in cases of heterogeneity, a random-effects model. We used inverse variance methods for continuous outcomes and measurement scales. We compared differences between treatment groups as MDs; we combined results for dichotomous outcomes (withdrawals, AEs) by using Mantel-Haenszel methods and obtained risk differences (RDs) to compare treatment groups. We used Review Manager software for management and analysis of data (RevMan 2012).

Subgroup analysis and investigation of heterogeneity

We planned to investigate effects of potential positive or negative interactions between alprazolam and other anti-tremor medications on primary outcomes by performing a subgroup analysis of trials in which only the experimental anti-tremor medication was allowed (alprazolam or placebo), and of trials including participants using other anti-tremor medications during the study period. For trials in which treatment effects are reported for more than one dose, we planned to investigate effects of different doses reported separately.

For heterogeneity assessment, we planned to use the I^2 statistic (Higgins 2003).

Sensitivity analysis

We performed no sensitivity analysis.

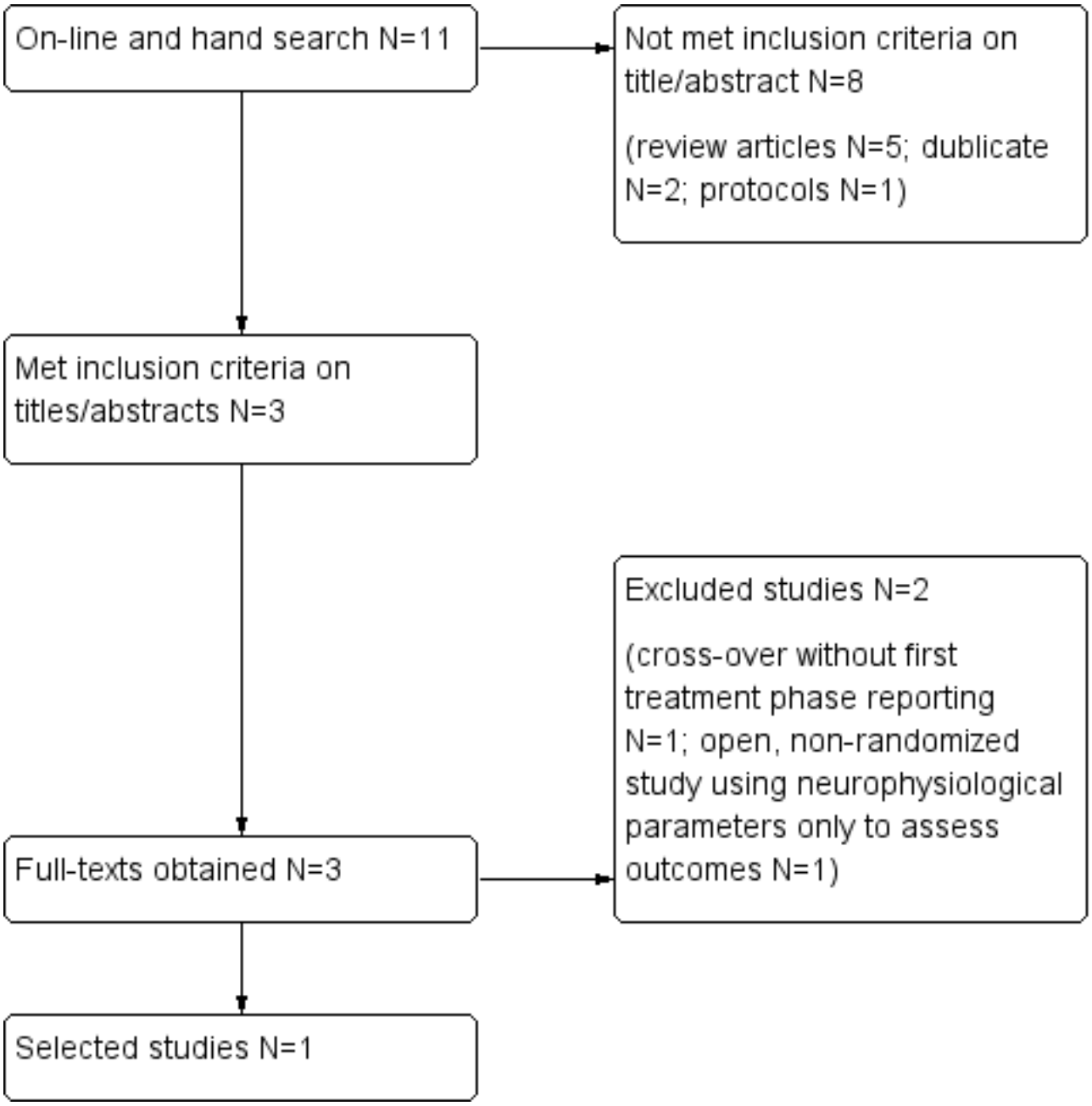
RESULTS

Description of studies

Results of the search

Electronic databases revealed a total of 11 references, six of which we excluded because they were published as review articles or protocols; two were duplicate references. We selected three citations aimed at evaluating alprazolam treatment for ET and obtained the full text. A flowchart presents results of the electronic search in Figure 1. We identified no additional records by searching other resources.

Figure 1. Flowchart of the literature search on alprazolam and essential tremor.



Included studies

We considered one study as eligible for this review (Huber 1988) (Characteristics of included studies). This study was a double-blind parallel RCT comparing alprazolam versus placebo. Duration of follow-up was two weeks. The study included participants with upper limb and head ET (diagnostic criteria were not reported). A total of 24 participants with a mean age of 61.2 years (range 27 to 73 years) were included. Treatment with other anti-tremor medications was stopped one week before entry into the study. A total of 12 participants were randomly assigned to alprazolam treatment, and a second group of 12 participants received placebo. The therapeutic scheme for alprazolam ranged between 0.75 and 3 mg per day, divided into three daily doses. The primary outcome measure used was an arbitrary clinical scale for tremor severity, ranging from 0 (no tremor) to 4 (severe tremor). Clinical ratings at baseline and at study endpoint were reported. A global impression scale was completed by both investigator and participant, and the score ranged from 1 (very much improved) to 7 (very much worse). The number of participants experiencing AEs was reported only for the alprazolam group. No participants dropped out of the study.

Excluded studies

Ibanez 2014 was an open, non-randomised study that included eight participants with a diagnosis of ET and assessed hand tremor and contralateral cortical activity before and after a single dose of alprazolam. Investigators measured outcomes

using neurophysiological parameters only: Tremor on the most affected side was recorded with solid-state gyroscope and surface electromyography (EMG).

Gunal 2000 was a double-blind, cross-over, placebo-controlled trial. Participants with ET received, in random order, alprazolam, acetazolamide, primidone and placebo for four weeks, with a two-week washout period between treatments. This study did not specify, for each participant, the first treatment received and the subsequent order of other treatments. Moreover, data from the first treatment phase after randomisation were not available for analysis. Study authors reported only final scores; therefore the study presented a very high risk of carry-over effect. We contacted the corresponding author of this paper in the attempt to obtain further information but are still awaiting a reply. This study was considered among Studies awaiting classification.

Risk of bias in included studies

We reported the results in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

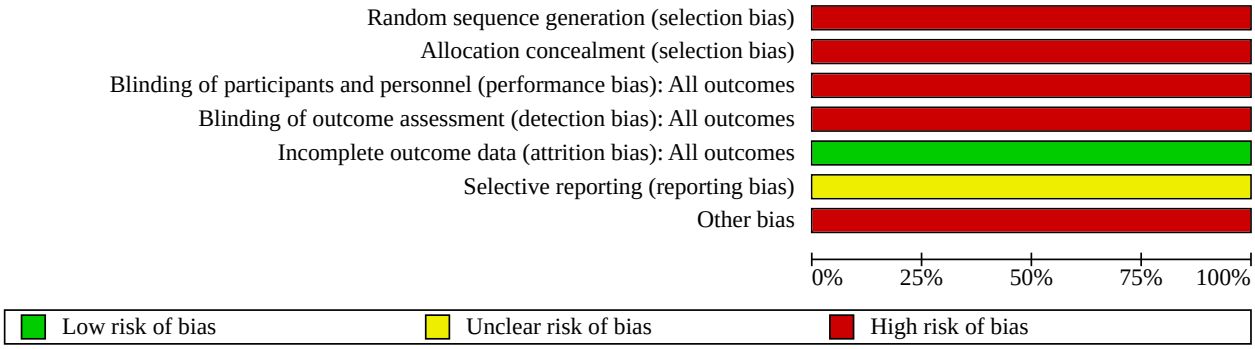
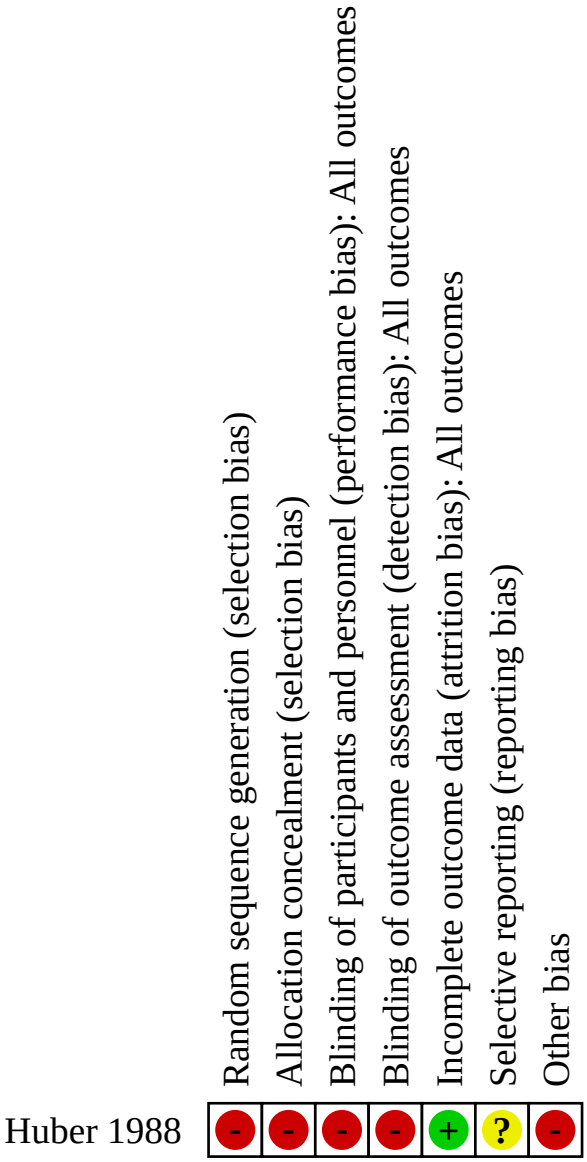


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The trial included did not report methods for sequence generation and allocation concealment and was considered at high risk of bias.

Blinding

The trial included did not report methods for blinding personnel, participants and outcome assessors to treatment allocation and was considered at high risk of bias.

Incomplete outcome data

All participants completed the study and were assessed at study endpoint. We considered the study to have low risk of attrition bias.

Selective reporting

The primary outcome (tremor severity) was reported. Scores of investigator global assessment and participant global assessment were reported. Numbers of AEs in the placebo group were not reported, and the trial was considered overall to have unclear risk of reporting bias.

Other potential sources of bias

Diagnostic criteria for ET as applied to participants were not reported, nor were patient exclusion and inclusion criteria; thus, this was considered an additional source of bias. Moreover, information concerning the validation process for the clinical scale used to assess the primary outcome (tremor severity) was not reported. Finally, the short duration of follow-up was considered another source of bias for the well-known influence of treatment duration and treatment effect related to use of benzodiazepine (long-term tolerance).

Effects of interventions

See: **Summary of findings 1** Alprazolam for essential tremor

See Summary of findings 1, which reports the comparison of alprazolam versus placebo and GRADE assessment results.

The study compared alprazolam and placebo and involved a total of 24 participants (12 alprazolam, 12 placebo). We rated the overall risk of bias as high. We considered the overall quality of evidence as very low.

Primary outcomes

Investigators reported tremor severity and number of withdrawals in the included study. They reported numbers of AEs only for the alprazolam group.

At study end (two weeks), researchers reported mean reduction from baseline on the overall clinical tremor rating scale of 0.79 points for alprazolam and 0.04 for placebo (P value < 0.01). Data analysis showed statistically significant differences between alprazolam and placebo in terms of efficacy measured by the clinical tremor rating scale score (MD -0.75, 95% CI -0.83 to -0.67; Analysis 1.1).

No participants in the alprazolam group and no participants in the placebo group discontinued treatment and dropped out of the study.

In terms of AEs, investigators reported their occurrence only for the alprazolam group, hampering any comparison between groups. Nine alprazolam-treated participants (75%) developed AEs. The most common AE was sedation or drowsiness (50%), followed by constipation (17%) and dry mouth (9%).

We did not perform meta-analysis, as only one study was included. We did not perform subgroup analysis to assess differences in efficacy and safety due to the interaction between combined anti-tremor treatments, as data and the number of trials included were insufficient.

Secondary outcomes

At the study endpoint, investigator global assessment and participant global assessment were completed. The investigator reported better improvement for the alprazolam group, indicated by a mean score of 2.67 (SD 1.5), and less improvement for the placebo group, with a mean score of 3.83 (SD 0.9). These results were similar to those reported by participant global assessment, indicating a mean score of 2.83 (SD 1.4) for alprazolam and 3.5 (SD 1.1) for placebo.

DISCUSSION

Summary of main results

We included in this review one randomised controlled trial (RCT) comparing alprazolam versus placebo for treatment of essential tremor (ET) (Huber 1988). This study involved a group of 24 participants presenting with head and/or limb ET. Investigators reported a positive effect of alprazolam on tremor severity at study endpoint, with a statistically significant difference in terms of efficacy favoring alprazolam versus placebo. A consistent number of participants treated with alprazolam reported adverse events (AEs). However, comparison between groups of the risk to develop AEs was impossible, as no data were reported for participants receiving placebo. The risk of study dropout was negligible in both groups after two weeks of follow-up. These data should be interpreted cautiously because of the small number of trials included, high risk of bias and very low strength of provided evidence.

Overall completeness and applicability of evidence

Important factors limited the validity of results reported in the study. The sample size was very small, and the duration of follow-up was short. This last point should be particularly regarded before alprazolam efficacy and use in patients with ET are considered. As ET is a chronic disease requiring long-term treatment, long-term use of alprazolam should be adequately assessed through studies considering longer duration of follow-up. Tolerance, manifesting with decreased effectiveness, and dependence are well-known effects following long-term use of benzodiazepine and, even in intermittent therapies, could lead to important limitations in use and management of these medications. The short duration of the included study hindered any possible consideration of these issues.

An additional remark pertains to the incomplete presentation of study results and absolute omission of reporting of AEs for the placebo group.

All of these factors represent a limitation in the overall completeness of assessment and hamper the possibility of balancing benefit and risk linked to alprazolam treatment.

Quality of the evidence

Risk of bias evaluation and strength of evidence assessment disclosed a large range of limitations of the study analysed. The global quality of the evidence provided was judged 'very low' and thus insufficient to permit adequate conclusions.

Potential biases in the review process

To minimize biases, we performed a comprehensive systematic review by searching different databases, without language restrictions, to identify all relevant studies. Two review authors performed data management.

Agreements and disagreements with other studies or reviews

Two reviews of the literature analysed alprazolam treatment for ET (Zesiewicz 2005; Zappia 2013). These reviews applied no inclusion/exclusion criteria for considering studies in the review process, and included both of the studies found in the present work.

The paucity of studies evaluating alprazolam for ET, the low quality of studies already under way on this topic and some uncertainty concerning alprazolam use for ET were further discussed in these manuscripts.

The Practice Parameter for Essential Tremor (Zesiewicz 2005) used a four-tired classification scheme based mainly on study design and including uncontrolled studies, case series and case reports. Neurophysiological parameters (electromyographic recordings, accelerometry, spirography, digitising tablets) were considered among outcome measures. Recommendations on alprazolam were formulated on the basis of one class I study (Gunal 2000a) and one class II study (Huber 1988).

The systematic review of evidence and recommendations from the Italian Movement Disorders Association (DISMOV-SIN) (Zappia 2013) was based on the use of GRADE (Grades of Recommendation, Assessment, Development and Evaluation) to assign the level of evidence. Besides RCTs, the review also included case series, case reports and studies using neurophysiological assessment of tremor. Review authors' conclusions on alprazolam are based on evaluation of two studies (Huber 1988; Gunal 2000a) and highlight the very low quality of evidence provided by the literature, attributing a weak recommendation with very low quality of evidence.

AUTHORS' CONCLUSIONS

Implications for practice

Currently no sufficient high-quality evidence is available from the literature for assessment of the efficacy and safety of alprazolam in the treatment of patients with ET. The study included highlighted a positive effect of this agent, without adequately assessing long-term efficacy and safety. Moreover, high risk of bias and lack of other studies on this topic limit firm conclusions.

Implications for research

Assessment of foreseen effectiveness of alprazolam in ET treatment is worth further investigation to enrich the limited and challenging field of ET treatment options. Focus on long-term efficacy and safety of alprazolam is particularly required for a complete evaluation of the risk-benefit linked to use of this agent for patients with a 'chronic disease' such as ET. Future RCTs should be particularly focused on evaluation of tolerance and dependence.

ACKNOWLEDGEMENTS

The review authors would like to express their gratitude to Cristina Sampaio and to Ricardo M. Fernandes for precious comments and guidance provided during development of the final version of this review.

REFERENCES

References to studies included in this review

Huber 1988 *{published data only}*

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CHARACTERISTICS OF STUDIES

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

Huber 1988

Study characteristics	
Methods	Randomised parallel study, double-blind, placebo-controlled
Participants	24 randomly assigned participants (12 alprazolam, 12 placebo); mean age 60.2 years (range 27 to 73 years); 12 men and 12 women, with baseline clinical rating of 2.17 (standard deviation (SD) 0.8)
Interventions	Alprazolam vs placebo; 0.75 to 3 mg/d; follow-up 2 weeks

Huber 1988 *(Continued)*

Outcomes	Clinical rating, investigator global assessment; participant global assessment
Notes	Exclusion criteria not specified; 1-week washout period with no other anti-tremor medication before baseline evaluation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Trial is described as 'randomised', but random sequence generation is not reported
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Trial is described as 'double-blind', but blinding for participants and personnel is not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Presence of a blinded rater is not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	None
Selective reporting (reporting bias)	Unclear risk	Numbers of adverse events in the placebo group are not reported
Other bias	High risk	Diagnostic criteria for essential tremor and patient exclusion and inclusion criteria are not reported; validation process of the clinical scale used to assess the primary outcome (tremor severity) is not reported; short duration of follow-up is described

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

Study	Reason for exclusion
Ibanez 2014	Non-randomised study using neurophysiological parameters only to assess outcomes

Characteristics of studies awaiting classification *[ordered by study ID]*

Gunal 2000

Methods	Double-blind, cross-over, placebo-controlled trial
Participants	22 participants randomly assigned; 19 analysed (3 dropped out before study end); mean age 51.5 years (range 18 to 83 years); 4 men and 15 women; mean tremor duration 24.2 years; baseline functional score 8.00 (standard deviation (SD) 2.36)

Gunal 2000 *(Continued)*

Interventions	Participants with essential tremor received, in random order, alprazolam (starting dose 0.125 mg/d), acetazolamide (starting dose 62.5 mg/d), primidone (starting dose 62.5 mg/d) and placebo for 4 weeks, with a 2-week washout period between treatments
Outcomes	Functional score (including writing a sentence, drawing spirals, feeding, engaging in social activity); participant-rated global improvement score (0 to 3)
Notes	Only final scores were reported (very high risk of carry-over effect), and data from the first treatment phase after randomisation were not available. We contacted the corresponding author of this paper in an attempt to obtain further information and are still awaiting a reply

DATA AND ANALYSES

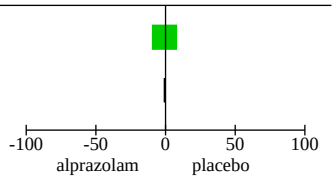
Comparison 1. Comparison for efficacy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Clinical rating scale	1	24	Mean Difference (IV, Fixed, 95% CI)	-0.75 [-0.83, -0.67]

Analysis 1.1. Comparison 1: Comparison for efficacy, Outcome 1: Clinical rating scale

Study or Subgroup	alprazolam Mean	alprazolam SD	alprazolam Total	placebo Mean	placebo SD	placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Huber 1988	-0.79	0.1	12	-0.04	0.1	12	100.0%	-0.75 [-0.83 , -0.67]
Total (95% CI)			**12**			**12**	**100.0%**	**-0.75 [-0.83 , -0.67]**

Heterogeneity: Not applicable
Test for overall effect: Z = 18.37 (P < 0.00001)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. MEDLINE search strategy

1. exp Essential Tremor/ (1183)

2. (essential adj3 tremor*).ab,ti. (2473)

3. (familia* adj3 tremor).ab,ti. (128)

4. 1 or 2 or 3 (2653)

5. exp Alprazolam/ (1618)

6. alprazolam.ab,ti. (1924)

7. Xanax.ab,ti. (63)

8. 5 or 6 or 7 (2260)

9. randomized controlled trial.pt. (367656)

10. controlled clinical trial.pt. (87895)

11. randomized.ab. (287683)

12. placebo.ab. (151722)

13. drug therapy.fs. (1677138)

14. randomly.ab. (208754)

15. trial.ab. (298006)

16. groups.ab. (1332158)

17. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (3287589)

18. exp animals/ not humans.sh. (3903063)

19. 17 not 18 (2818660)

20. 4 and 8 and 19 (7)

Appendix 2. CENTRAL search strategy

1. MeSH descriptor: [Essential Tremor] explode all trees 62

2. essential tremor*:ti,ab,kw (Word variations have been searched) 202

3. familia* tremor*:ti,ab,kw (Word variations have been searched) 7

4. #1 OR #2 OR 3 208

5. MeSH descriptor: [Alprazolam] explode all trees 439

6. "alprazolam":ti,ab,kw (Word variations have been searched) 817

7. #5 OR #6 817

8. #4 AND #7 3

WHAT'S NEW

Date	Event	Description
21 February 2020	Amended	Conflict of intererest and literature search updated

HISTORY

Protocol first published: Issue 3, 2012
Review first published: Issue 12, 2015

Date	Event	Description
6 October 2015	Amended	Amended according to the CEU prepublication screening report
14 March 2015	Amended	Amended according to reviewer's comments

Date	Event	Description
22 May 2014	Amended	Methods and Results sections revised; 1 study included in this review
7 July 2013	Amended	Review updated and completed

CONTRIBUTIONS OF AUTHORS

EB: protocol and review editing, literature searching, study selection, quality assessment, data extraction.

AN: protocol and review editing.

GQ: literature searching, quality assessment, data extraction.

CC: protocol editing, quality assessment, study selection.

GF: protocol editing, editing and revising of the review.

MZ: protocol editing, revising of the review.

DECLARATIONS OF INTEREST

The original review was not compliant with Cochrane Commercial Sponsorship policy for the following reasons:

CC received financial support from Merz (manufacturer of Botulinum toxin), Teva (manufacturer of propranolol) and other pharma companies.
AN received financial support from Lundbeck (manufacturer of benzodiazepine clobazam) and UCB (manufacturer of levetiracetam).
MZ received financial support from Novartis (manufacturer of propranolol [Sandoz]), UCB, Lundbeck and other pharma companies.

Conversely, the current update have a majority of authors and lead author free of conflicts as the lead author and all the other authors have not received payments from manufacturers or marketers of the interventions of interest or potential comparators within the 3 years of the decision to update and none of the authors are/were employed by a company who has a real or potential financial interest in the findings of the review and/or have a relevant patent.

SOURCES OF SUPPORT

Internal sources

- None, Other

External sources

- None, Other

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In an attempt to provide a standardised and reliable assessment of the quality of the evidence on study outcomes, we decided to use the GRADE evidence profile, a systematic and explicit system for grading the evidence according to four quality categories. We reported results obtained through this approach in Summary of findings 1.

Methods for future updates

We did not perform two preplanned analysis because data were insufficient. These analyses will be eventually implemented, if possible, in future updates of the review.

Methods for analysing continuous data: Scales used to assess tremor in most studies are continuous. We will transform ordinal scales with enough categories to continuous scales by assigning a score to each grade, so that we can express the intervention effect as a difference in means, or as a standardised mean difference (SMD). In the case of an ordinal scale with few categories, we will combine data from adjacent categories into two categories, and will use methods for binary data such as odds ratios (ORs) or risk differences (RDs) to evaluate intervention effects.

Sensitivity analysis: We will undertake sensitivity analyses to assess the robustness of results to fixed-effect versus random-effects assumptions, and inclusion or exclusion of studies at high risk of bias (i.e. inadequate allocation concealment and lack of a blinded outcome assessor). We will use best- and worst-case scenarios when taking missing data into account.

INDEX TERMS

Medical Subject Headings (MeSH)

Alprazolam [adverse effects] [*therapeutic use]; Anticonvulsants [adverse effects] [*therapeutic use]; Constipation [chemically induced]; Essential Tremor [*drug therapy]; Randomized Controlled Trials as Topic; Xerostomia [chemically induced]

MeSH check words

Adult; Aged; Humans; Middle Aged