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Keywords:	Essential tremor, Benign essential tremor, Familial tremor, Therapy, Drug therapy, Propranolol

A Study Protocol with Oral Propranolol for Treatment of the Subgroups of Essential Tremor

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The text contains 2111 words.

Abstract

Introduction

Essential tremor (ET) is a tremor disorder that is one of the most common benign dyskinesias. Currently, ET is classified into two categories, “isolated essential tremors” and “essential tremors plus”. Only oral propranolol is still the first-line treatment recommended by FDA. There has been a view that propranolol may effectively reduce the upper limbs action tremor. However, it has a poor effect on axial tremor symptoms, such as essential head tremor

and voice tremor. Whereas, recently studies have provided new evidence that oral propranolol is equally effective against the motional tremor of different anatomical distribution of ET. The purpose of this systematic review is to synthesize these new data to improve the efficacy of propranolol in ET subgroups.

Methods and analysis

Systematic review will be complied by searching for relevant articles in PubMed, MEDLINE, EMBASE, the Cochrane Library, UptoDate, PEDro. Humans who are eligible for criteria, Parkinson, Thyroid patients with a secondary form of tremor, drug-oriented tremor, and toxic tremors will be included in the study. Two independent reviewers will screen the study quality and the Cochrane Collaboration's tool in Review Manager (RevMan) 5.3.3 will be used to evaluate the risk of bias. Narrative and meta-analytical syntheses are planned.

Ethics and dissemination

Published aggregated data is used in this review analysis and therefore no ethical approval is required, the result will be published in peer-reviewed journals, and proliferation activities will include diverse social stakeholders, non-academic groups, and patients.

PROSPERO registration number CRD42018112580

Keywords

Essential tremor; Benign essential tremor; Familial tremor; Hereditary essential tremor; Therapy; Drug therapy; Propranolol; Propranolol hydrochloride

Introduction

Essential tremor is a chronic, progressive movement disorder among adults, with a prevalence ranging from 0.4% of the general population to 5% of the population over the age of 65.[1-3] It appears that the prevalence of ET increases exponentially in aging population.[4] While the direct cause of ET remains unknown, recent reports have indicated that loss or dysfunction of

Purkinje's neurons in the cerebellum likely play a key role in the etiology of ET. Electrophysiological methods reveal abnormal oscillations in the cortical-ponsal-cerebellar-thalamic-cortical loop.[5, 6] It is still unclear why this network involved in the tremor mode; however, it is thought to be associated with abnormalities of gamma-aminobutyric acid (GABA) transmission in brain tissues of ET patients.[7]

Traditionally, ET is defined as a bilateral but systematic kinetic and postural tremors of the upper limbs, voice, head, face, chin, legs or a combination of these symptoms.[8] The incidence of ET usually involves upper limbs(95% of patients) according to anatomical distribution, less common is lower limbs (30%), head (25~34%), sound (12~15%), tongue (7%) face (5%), and trunk (5%), as described in several previous reports.[9-11] There are few ET patients with isolated head tremor.[12, 13] Recently, some studies indicated that some complementary neurological signs (i.e., other than action tremor) exist in patients with ET, such as mild impaired memory, impaired tandem gait, and subtle dystonic body posturing. These clinical symptoms and signs were so mild that they do not suffice for other neurological diagnosis. These presentations are classified as "essential tremor plus" by the International Parkinson and Movement Disorder Society in 2018.[14]

In spite of casting new viewpoints on ET pathogenesis, the treatment of ET still remains merely symptomatic. The therapeutic approach to ET still primarily depends on drugs, although surgery may be an option for patients with refractory essential tremor. As of 2018, propranolol and primidone are still two first-line medications for the treatment of primary tremor, according to the recommendations of the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).[14, 15] In particular, the US Food and Drug Administration only approved propranolol for essential tremor. Conventional wisdom is propranolol is only effective against the upper limbs action tremor, while axial tremor symptoms, such as essential head tremor and voice tremor, usually respond poorly to propranolol treatments.[3, 16]

However, some recent studies provide emerging new evidences for oral propranolol on subgroups of ET, as determined on the basis of anatomical distributions of ET.[17-21] Therefore, it is necessary to integrate these new data to refine the treatment for the efficacy of propranolol in the subgroups of ET.

Methods and analysis

The systematic review protocol is performed under the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines.

Patient and public participation

No patient involved.

Research objective

The purpose of the systematic review and meta-analysis is to address safety and efficacy of propranolol in treating subgroups of ET. The issues of interest to this review are listed below: How effective is the therapy? What is the optimal dosage of the therapy in clinical studies? What are the adverse effects of the therapy? and others?

Methods

Eligibility criteria

Population included

This study includes adult males and females over the age of 16 with ET diagnosed according to the criteria set by the Tremor Investigation Group,[22] and the Consensus Statement of the Movement Disorder Society on Tremor.[14, 23] Parkinson's disease, metabolic tremor, drug tremors, toxicity-related tremor, tonic tremor, neurological tremor, and functional tremor will be excluded(3).

Intervention

The reference intervention is oral propranolol, both long-acting and short-acting formulations. We hypothesize that the oral propranolol treatment is better than other intervention treatments.

Comparators/control

There are many alternative treatment options for essential tremor, including: (1) non-operative care with primidone, topiramate, or other drug therapies, (2) operative care with deep brain stimulation or thalamotomy or gamma knife thalamotomy. Briefly, the comparators group includes all other treatments.

Outcomes

Primary and secondary outcomes

Our primary outcome is functional disability component related to tremors, which is measured by the Fahn-Tolosa-Marin tremor rating scale (TRS) subscales B and C.[24] Secondary outcomes of interest include severity of tremors and quality of life. Specifically, severity of tremors will be measured using the Fahn-Tolosa-Marin TRS subscale A and total score, Patient Global Impression, and Clinical Global Impression. At the same time, we will use a validated QoL scale or questionnaire to measure Quality of life (QoL) , such as 36-item Short Form (SF-36), EuroQol.[24]

Study design

Systematic review of methods of incorporating meta-analysis under the guidance of the Cochrane Handbook. The systematic review protocol is performed under the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines,[25] and will be reported in accordance with the PRISMA Extension Statement in the meta-analysis. The completed PRISMA-P checklist for the current review is provided with Additional file 2. We will include all randomized controlled trials (RCTs) that examine the efficacy and safety of propranolol on essential tremor. We do not use language to identify all relevant RCTs, both published and unpublished. In order to improve the internal validity of the review, the Grades in Recommendation, Assessment, Development and Evaluation (GRADE) approach will be used to evaluate randomized controlled trials. RCTs have the highest level of evidence for this method.

Study registration

The protocol has been successfully registered with PROSPERO, registration number is CRD42018112580.

Patient and public participation

No patient involved.

Search strategy

We will perform a comprehensive electronic search of the medical and rehabilitation literature using medical subject headings (MeSH) and text related to essential tremor and propranolol. A comprehensive electronic search of the following database will be performed, for example, PubMed, MEDLINE, EMBASE, the Cochrane Library, UptoDate, and PEDro, from the beginning to the present. Two different experts developed the search strategy based on the Peer Review of Electronic Search Strategies (PRESS) framework.[26] Professional will be asked to review the strategy if necessary. There is an example for the search strategy using the Medline search (Additional file 1) and will be modified according to the indexing systems of the other databases. Grey documents that meet the inclusion criteria will also be searched, including papers that have been published, reports on relevant agencies, and unpublished data and manuscripts provided by original authors.

Study records:

All standards-compliant articles searched out the database were imported from EndNote X7 for management. All retrieved articles were strictly screened by two independent reviewers accordance with the inclusion criteria. Simultaneously, for some uncertain articles, they browsed the title and abstract to determine whether or not to include. Full texts of each potentially relevant article will adhere the selection criteria strictly during the title and abstract screening phase. The full texts of all potential articles that met the inclusion criteria were obtained and reviewed again. Two independent reviewers will screen the full texts for inclusion. If there is any opposition, we will consult or seek the opinion of the third examiner. Reviewers will have no preference to

the authors or journals when screening articles.

Data extraction

In order to extract the data onto the most relevant article, a predesigned data extraction form will be made， and will continue to update the form to ensure data integrity and relevance. All data were independently extracted by two reviewers and then compared their data onto the end of the review. Divergences were resolved by consultation or discussion with the third examiner. Reviewers were impartial in extracting data. The extracted data form mainly includes the following indicators: the general situation of the publication (author, year), the characteristics of the participants (gender, age, age range, health status), study design, sample size; length of follow-up; the study methods of information regarding; the control group; the forms of tremor; the dose of propranolol; the dose of other drugs; the statistical analyses methods; the effect of the intervention. Only one article will be kept, when there were two and more articles that derived from the same data. In order to ensure the integrity and authenticity of the data, the researchers will contact the author by email or telephone to require the original data when it is found that the data is missing. If no responses after two consecutive emails and calls, the data will not be included.

Outcomes and prioritization

Primary outcome

Our primary outcome is functional disability component related to tremors, which is measured by the Fahn-Tolosa-Marin tremor rating scale (TRS) subscales B and C. Rest, posture, and tremor are the three elements of TRS, and ETs are scored using three subscales to assess the severity of the tremor. The three subscales are: the posture and the magnitude of the tremor, the ability to perform certain actions and disabilities in daily living due to tremor. Each subscale is ranged from 0 to 4, which represents none, mild, moderate, and severe, and overall maximum score is 16, 36, and 32 in each subscale. Finally, the scores of the three subscales were summed to obtain the overall

TRS score.

Secondary outcomes

PGI, CGI, and Fahn-Tolosa-Marin TRS subscale A and total score are used to assess the severity of ET. PGI, also known as patient global impression, is a scale of patients to self-rated the severity. CGI, also known as clinical global impression, is a scale of clinicians to assess the severity. At the same time, we will use a validated QoL scale or questionnaire to measure Quality of life (QoL), such as 36-item Short Form (SF-36), EuroQol

Risk of bias and meta-bias

Two reviewers will separately assess the risk of bias and reporting quality of all included studies. Moreover, each randomized controlled trial will be assessed in Review Manager (RevMan) 5.3.3. Each included study was evaluated using a bias risk table that included seven items, random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias, then according to the results of the table, it is divided into low risk of bias, unclear risk of bias and high risk of bias. In addition, we will resolve disagreements in the assessment through consensus or discussions with a third investigator.

Data synthesis

Strategy for data synthesis

The primary tool for data analysis is Review Manager software (RevMan5.3). A random effects model will be managed with data indicators of overall studies for meta-analysis. We will evaluate and analyze the data onto overall included studies and summarized its 95% CIs using a random effects model. The difference will be considered statistically significant when P is less than 0.05. The funnel plot will be used to evaluate heterogeneity between overall included studies, such as differences of study types, risk of bias, publication bias, differences of measurement resolution, etc.[27]

Analysis of subgroups or subsets

Subgroup analysis will be carried out if the data were enough. Several subgroup analyses will be used to examine differences between the types of ET (e.g. upper limbs, lower limbs, less commonly the head, voice, tongue, face, trunk and others); age; the different dosage of propranolol; side effect of propranolol; the different therapy of ET; and study designs (e.g. treatment groups vs. no control group, randomized vs. non-randomized controlled trial). Among these variables, the dosage of propranolol and the types of ET are assumed to be the most important as it remains unknown what dosage of propranolol is the most effective against different types of ET.

Discussion

Treatments for ET can be mainly subdivided into three categories: medicine (propranolol, primidone, topiramate), surgical treatments (deep brain stimulation, gamma-knife surgery), and other therapies. So far, there has not been major breakthrough in ET treatments. Propranolol and primidone are generally the first treatment option to treat ET. Propranolol was proved to effective against the treatment of ET in 1973.[28] Published controlled trials have shown that the average effective dose of propranolol is 185.2 mg/days, and the daily dose range is 60-800 mg/day.[29, 30] In addition, there is insufficient evidence to indicate that a dose of over 320 mgs per day would bring any benefits. In the treatment of ET, it can be found that about 50%-70% response. Compared with placebo, the average tremor can be reduced by about 50%.[29, 31]

The primary objective of this systematic review is to evaluate the efficacy and safety of propranolol for ET. We will conduct qualitative and quantitative analysis of overall data included in each study, and we hopefully are able to find the optimal drug dose for the treatment of the ET subgroup. What is more, we will summarize as far as possible the role of propranolol in the treatment of ET, especially for axial tremors.

Contributors ZZ, TW, MZ and WL designed the study. The draft agreement

was drafted by ZZ, TW and MZ, and revised by all authors. MZ and WL designed the search strategy. MZ, WL and LH will perform the search. LC, LY, TZ, and HS will be included in the study screening to extract data and assess the risk of bias in the included studies. ZZ and YP will dispute disagreements between reviewers. MZ, WL, SG and ZC will analyze and interpret the data. All authors agree to be responsible for all aspects of the work and have read and approved the final draft.

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Patient consent for publication None.

Competing interests None.

Provenance and peer review Not commissioned.

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Table 1 The list of inclusion and exclusion criterion

	Inclusion	Exclusion
Population	• Adults over the age of 16 • Humans with ET diagnosed	• Parkinson • Metabolic tremor • Toxic-related tremors • Dystonic tremor • Neuropathic tremor • Functional tremor
Intervention	• Oral propranolol • Long-acting or short-acting formulation	• All other intervention types
Comparator	• non-operative care with primidone, topiramate, or other drug therapies • operative care with deep brain stimulation or thalamotomy or gamma knife thalamotomy,or the comparators group includes all other treatments	• N/A
Outcome	Primary • Fahn-Tolosa-Marin Tremor Rating Scale Secondary • tremor severity • quality of life	• N/A
Study designs	• Randomized controlled trials	• Conference proceedings • Only abstracts available

P participants, I intervention, C comparison, O outcome, S study type

Medline

Search strategy

1. randomized control trial.pt. (4,366,033)
2. controlled clinical trial.pt. (92,859)
3. random$.ti.ab. (243,513)
4. placebo.ti.ab. (200,860)
5. clinical trials as topic.mj. (32,507)
6. trial.ti.ab (901,271)
7. or/1-6 (1,300,135)
8. NOT (animals/ not hunmans/) (6,658,452)
9. 7 not 8 (1,117,817)
10. Movement disorder.ti.ab. (16,284)
11. Tremor.ti.ab. (20,602)
12. Essential tremor.ti.ab (3,586)
13. Or/10-11 (34,889)
14. Essential tremor.ti,ab. (3,586)
15. Essential tremor.sh. (1,802)
16. Essential tremor*.ti.ab.(3,587)
17. Benign essential tremor*.ti.ab.(57)
18. Familial tremor*.ti.ab.(194)
19. Hereditary essential tremor*.ti.ab.(39)
20. Or/14-19 (3,838)

21. Therapy.ab.ti (1,788,096)

22. Therapy.sh. (4,069,919)

23. Propranolol.ti.ab. (31,975)

24. Propranolol hydrochloride.ti.ab. (623)

25. Or/21-24 (4,856,447)

26. 7 and 9 and 13 and 20 and 25 (223)

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2

Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	13-14
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	12
Sponsor	#5b	Provide name for the review funder and / or sponsor	n/a
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is	2-3

		already known	
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4-5
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5-6
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is,	6-7

		screening, eligibility and inclusion in meta-analysis)	
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6-7
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	8
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned	8

		exploration of consistency (such as I2, Kendall's τ)	
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8

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Oral Propranolol for Treatment of the Subgroups of Essential Tremor: a systematic review and meta-analysis protocol.

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Abstract

Introduction

Essential tremor (ET) is a tremor disorder that is one of the most common movement disorder. A recent proposal was made to classify ET into two categories，“isolated essential tremors” and “essential tremors plus”. Only oral drugs (propranolol, primidone, topiramate, etc.）are still the first-line treatment recommended by FDA. There has been a view that propranolol may effectively reduce the upper limbs action tremor. However, it has a poor effect on axial

tremor symptoms, such as essential head tremor and voice tremor. Studies have shown that the severity of tremors develops over time, possibly producing other clinical tremors (such as voice tremors) and neurological soft signs (such as memory loss, gait abnormalities, balance disorders, etc.), which makes it even more increase the difficulty of treating tremors. Therefore, we perform subgroup classification based on anatomical distribution and combined with soft signs of the nervous system to find the best choice for drug control of primary tremors. Whereas, some recent studies provide emerging new evidences for oral propranolol on subgroups of ET, which is based on the anatomical distribution of ET (lower extremities, head, sound, tongue, etc.). The purpose of this systematic review is to synthesize these new data to improve the efficacy of propranolol in ET subgroups.

Methods and analysis

Systematic review will be complied by searching for relevant articles in PubMed, MEDLINE, EMBASE, the Cochrane Library, UptoDate, PEDro，from the beginning to the present. Humans who are eligible for criteria, Parkinson, Thyroid patients with a secondary form of tremor, drug-oriented tremor, and toxic tremors will be included in the study. Two independent reviewers will screen the study quality and the Cochrane Collaboration's tool in Review Manager (RevMan) 5.3.3 will be used to evaluate the risk of bias. Narrative and meta-analytical syntheses are planned.

Ethics and dissemination

Published aggregated data is used in this review analysis and therefore no ethical approval is required, the result will be published in peer-reviewed journals, and proliferation activities will include diverse social stakeholders, non-academic groups, and patients.

PROSPERO registration number CRD42018112580

Keywords

Essential tremor; Benign essential tremor; Familial tremor; Hereditary essential tremor; Therapy; Drug therapy; Propranolol; Propranolol

hydrochloride

Article summary

strengths and limitations of this study

The purpose of the systematic review and meta-analysis is to address safety and efficacy of propranolol in treating subgroups of ET, hopefully, we will find the optimal drug dose for the treatment of the ET subgroup.

Different patients, interventions and primary outcome may mean that meta-analysis cannot be conducted, and narrative and meta-analytical syntheses are planned.

Multiple limitations may increase the heterogeneity of the study, thereby hampering the results of the meta-analysis.

Introduction

Essential tremor is a chronic, progressive movement disorder among adults, with a prevalence ranging from 0.4% of the general population to 5% of the population over the age of 65.[1-3] It appears that the prevalence of ET increases exponentially in aging population.[4] While the direct cause of ET remains unknown, recent reports have indicated that loss or dysfunction of Purkinje's neurons in the cerebellum likely play a key role in the etiology of ET.[5-8] Electrophysiological methods reveal abnormal oscillations in the cortical-ponsal-cerebellar-thalamic-cortical loop.[9, 10] It is still unclear why this network involved in the tremor mode; however, it is thought to be associated with abormalities of gamma-aminobutyric acid (GABA) transmission in brain tissues of ET patients.[11]

Traditionally, ET is defined as a bilateral but systematic kinetic and postural tremors of the upper limbs, voice, head, face, chin, legs or a combination of these symptoms.[12] The incidence of ET usually involves upper limbs(95% of patients) according to anatomical distribution, less common is lower limbs (30%), head (25~34%), sound (12~15%), tongue (7%) face (5%), and trunk (5%), as described in several previous reports.[13-15] There are few ET patients with isolated head tremor.[16, 17] Recently, some

studies indicated that some complementary neurological signs (i.e., other than action tremor) exist in patients with ET, such as mild impaired memory, impaired tandem gait, and subtle dystonic body posturing. These clinical symptoms and signs were so mild that they do not suffice for other neurological diagnosis. It was recently proposed that these presentations might be classified as “essential tremor plus” by the International Parkinson and Movement Disorder Society in 2018.[18]

In spite of casting new viewpoints on ET pathogenesis, the treatment of ET still remains merely symptomatic. The therapeutic approach to ET still primarily depends on drugs, although surgery may be an option for patients with refractory essential tremor. As of 2018, propranolol and primidone are still two first-line medications for the treatment of primary tremor, according to the recommendations of the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).[18, 19] In particular, the US Food and Drug Administration only approved propranolol for essential tremor. Conventional wisdom is propranolol is only effective against the upper limbs action tremor, while axial tremor symptoms, such as essential head tremor and voice tremor, usually respond poorly to propranolol treatments.[3, 20] Studies have shown that the severity of tremors develops over time , possibly producing other clinical tremors (such as voice tremors) and neurological soft signs (such as memory loss, gait abnormalities, balance disorders, etc.), which makes it even more increase the difficulty of treating tremors.[21, 22] Therefore, we perform subgroup classification based on anatomical distribution and combined with soft signs of the nervous system to find the best choice for drug control of primary tremors. However, some recent studies provide emerging new evidences for oral propranolol on subgroups of ET, which is based on the anatomical distribution of ET (lower extremities, head, sound, tongue, etc.).[23-27] It is necessary to integrate these new data to refine the treatment for the efficacy of propranolol in the subgroups of ET.

The systematic review protocol is performed under the Preferred

Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines.

Patient and public participation

No patient involved.

Research objective

The purpose of the systematic review and meta-analysis is to address safety and efficacy of propranolol in treating subgroups of ET. The issues of interest to this review are listed below: How effective is the therapy? What is the optimal dosage of the therapy in clinical studies? What are the adverse effects of the therapy? and others?

Methods

Eligibility criteria

Population included

This study includes adult males and females over the age of 16 with ET diagnosed according to the criteria set by the Tremor Investigation Group,[28] and the Consensus Statement of the Movement Disorder Society on Tremor.[18, 29] Parkinson's disease, metabolic tremor, drug tremors, toxicity-related tremor, tonic tremor, neurological tremor, and functional tremor will be excluded(3).

Intervention

The reference intervention is oral propranolol, both long-acting and short-acting formulations. We hypothesize that the oral propranolol treatment is better than other intervention treatments.

Comparators/control

There are many alternative treatment options for essential tremor, including: (1) non-operative care with primidone, topiramate, botulinum toxin injections or other drug therapies, (2) operative care with deep brain stimulation or thalamotomy or gamma knife thalamotomy. Briefly, the comparators group includes all other treatments.

Outcomes

Primary and secondary outcomes

Our primary outcome is functional disability component related to tremors, which is measured by the Fahn-Tolosa-Marin tremor rating scale (TRS) subscales B and C.[30] Secondary outcomes of interest include severity of tremors and quality of life. Specifically, severity of tremors will be measured using the Fahn-Tolosa-Marin TRS subscale A and total score, Patient Global Impression, and Clinical Global Impression. At the same time, we will use a validated QoL scale or questionnaire to measure Quality of life (QoL) , such as 36-item Short Form (SF-36), EuroQol.[30]

Study design

Systematic review of methods of incorporating meta-analysis under the guidance of the Cochrane Handbook. The systematic review protocol is performed under the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines,[31] and will be reported in accordance with the PRISMA Extension Statement in the meta-analysis. The completed PRISMA-P checklist for the current review is provided with supplementary file 1. We will include all randomized controlled trials (RCTs) that examine the efficacy and safety of propranolol on essential tremor. We do not use language to identify all relevant RCTs, both published and unpublished. In order to improve the internal validity of the review, the Grades in Recommendation, Assessment, Development and Evaluation (GRADE) approach will be used to evaluate randomized controlled trials. RCTs have the highest level of evidence for this method.

Table 1 The list of inclusion and exclusion criterion

	Inclusion	Exclusion
Population	● Adults over the age of 16 ● Humans with ET diagnosed	● Parkinson ● Metabolic tremor ● Toxic-related tremors ● Dystonic tremor ● Neuropathic tremor ● Functional tremor
Intervention	● Oral propranolol ● Long-acting or short-acting formulation	● All other intervention types
Comparator	● non-operative care with primidone, topiramate, or other drug therapies ● operative care with deep brain stimulation or thalamotomy or gamma knife thalamotomy,or the comparators group includes all other treatments	● N/A
Outcome	Primary ● Fahn-Tolosa-Marin Tremor Rating Scale Secondary ● tremor severity ● quality of life	● N/A
Study designs	● Randomized controlled trials	● Conference proceedings ● Only abstracts available

P participants, I intervention, C comparison, O outcome, S study type

the planned start and end dates

The start date of the study is April 2019, and the end date is February 2020.

Study registration

The protocol has been successfully registered with PROSPERO, registration number is CRD42018112580.

Patient and public participation

No patient involved.

Search strategy

We will perform a comprehensive electronic search of the medical and rehabilitation literature using medical subject headings (MeSH) and text related to essential tremor and propranolol. A comprehensive electronic search of the following database will be performed, for example, PubMed, MEDLINE, EMBASE, the Cochrane Library, UptoDate, and PEDro, from the beginning to the present. Two different experts developed the search strategy based on the Peer Review of Electronic Search Strategies (PRESS) framework.[32] Professional will be asked to review the strategy if necessary. There is an example for the search strategy using the Medline search (supplementary file 2) and will be modified according to the indexing systems of the other databases. Grey documents that meet the inclusion criteria will also be searched, including papers that have been published, reports on relevant agencies, and unpublished data and manuscripts provided by original authors.

Study records:

All standards-compliant articles searched out the database were imported from EndNote X7 for management. All retrieved articles were strictly screened by two independent reviewers accordance with the inclusion criteria. Simultaneously, for some uncertain articles, they browsed the title and abstract to determine whether or not to include. Full texts of each potentially relevant article will adhere the selection criteria strictly during the title and abstract screening phase. The full texts of all potential articles that met the inclusion

criteria were obtained and reviewed again. Two independent reviewers will screen the full texts for inclusion. If there is any opposition, we will consult or seek the opinion of the third examiner. Reviewers will have no preference to the authors or journals when screening articles.

Data extraction

In order to extract the data onto the most relevant article, a predesigned data extraction form will be made， and will continue to update the form to ensure data integrity and relevance. All data were independently extracted by two reviewers and then compared their data onto the end of the review. Divergences were resolved by consultation or discussion with the third examiner. Reviewers were impartial in extracting data. The extracted data form mainly includes the following indicators: the general situation of the publication (author, year), the characteristics of the participants (gender, age, age range, health status), study design, sample size; length of follow-up; the study methods of information regarding; the control group; the forms of tremor; the dose of propranolol; the dose of other drugs; the statistical analyses methods; the effect of the intervention. Only one article will be kept, when there were two and more articles that derived from the same data. In order to ensure the integrity and authenticity of the data, the researchers will contact the author by email or telephone to require the original data when it is found that the data is missing. If no responses after two consecutive emails and calls, the data will not be included.

Outcomes and prioritization

Primary outcome

Our primary outcome is functional disability component related to tremors, which is measured by the Fahn-Tolosa-Marin tremor rating scale (TRS) subscales B and C. Rest, posture, and tremor are the three elements of TRS, and ETs are scored using three subscales to assess the severity of the tremor. The three subscales are: the posture and the magnitude of the tremor, the ability to perform certain actions and disabilities in daily living due to tremor.

Each subscale is ranged from 0 to 4, which represents none, mild, moderate, and severe, and overall maximum score is 16, 36, and 32 in each subscale. Finally, the scores of the three subscales were summed to obtain the overall TRS score.

Secondary outcomes

PGI, CGI, and Fahn-Tolosa-Marin TRS subscale A and total score are used to assess the severity of ET. PGI, also known as patient global impression, is a scale of patients to self-rated the severity. CGI, also known as clinical global impression, is a scale of clinicians to assess the severity. At the same time, we will use a validated QoL scale or questionnaire to measure Quality of life (QoL), such as 36-item Short Form (SF-36), EuroQol.

Risk of bias and meta-bias

Two reviewers will separately assess the risk of bias and reporting quality of all included studies. Moreover, each randomized controlled trial will be assessed in Review Manager (RevMan) 5.3.3. Each included study was evaluated using a bias risk table that included seven items, random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias, then according to the results of the table, it is divided into low risk of bias, unclear risk of bias and high risk of bias. In addition, we will resolve disagreements in the assessment through consensus or discussions with a third investigator.

Data synthesis

Strategy for data synthesis

The primary tool for data analysis is Review Manager software (RevMan5.3). A random effects model will be managed with data indicators of overall studies for meta-analysis. We will evaluate and analyze the data onto overall included studies and summarized its 95% CIs using a random effects model. The difference will be considered statistically significant when P is less than 0.05. The funnel plot will be used to evaluate heterogeneity between

overall included studies, such as differences of study types, risk of bias, publication bias, differences of measurement resolution, etc.[33]

Analysis of subgroups or subsets

Subgroup analysis will be carried out if the data were enough. Several subgroup analyses will be used to examine differences between the types of ET (e.g. upper limbs, lower limbs, less commonly the head, voice, tongue, face, trunk and others); age; the different dosage of propranolol; side effect of propranolol; the different therapy of ET; and study designs (e.g. treatment groups vs. no control group, randomized vs. non-randomized controlled trial). Among these variables, the dosage of propranolol and the types of ET are assumed to be the most important as it remains unknown what dosage of propranolol is the most effective against different types of ET.

Ethics and dissemination

Published aggregated data is used in this review analysis and therefore no ethical approval is required, the result will be published in peer-reviewed journals, and proliferation activities will include diverse social stakeholders, non-academic groups, and patients.

Discussion

Treatments for ET can be mainly subdivided into three categories: medicine (propranolol, primidone, topiramate), surgical treatments (deep brain stimulation, gamma-knife surgery, MRIgFUS), and other therapies (botulinum toxin, lifestyle management). So far, there has not been major breakthrough in ET treatments. Propranolol and primidone are generally the first treatment option to treat ET. Propranolol was proved to effective against the treatment of ET in 1973.[34] Published controlled trials have shown that the average effective dose of propranolol is 185.2 mg/days, and the daily dose range is 60-800 mg/day.[35, 36] In addition, there is insufficient evidence to indicate that a dose of over 320 mgs per day would bring any benefits. In the treatment of ET, it can be found that about 50%-70% response. Compared with placebo, the average tremor can be reduced by about 50%.[35, 37]

The primary objective of this systematic review is to evaluate the efficacy and safety of propranolol for ET. We will conduct qualitative and quantitative analysis of overall data included in each study, and we hopefully are able to find the optimal drug dose for the treatment of the ET subgroup. What is more, we will summarize as far as possible the role of propranolol in the treatment of ET, especially for axial tremors. The limitations of this systematic review are mainly due to the heterogeneity of the methodology, which may result in some results not being analyzed.

Contributors ZZ, TW, MZ and WL designed the study. The draft agreement was drafted by ZZ, TW and MZ, and revised by all authors. MZ and WL designed the search strategy. MZ, WL and LH will perform the search. LC, LY, TZ, and HS will be included in the study screening to extract data and assess the risk of bias in the included studies. ZZ and YP will dispute disagreements between reviewers. MZ, WL, SG and ZC will analyze and interpret the data. All authors agree to be responsible for all aspects of the work and have read and approved the final draft.

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Competing interests None declared

Provenance and peer review Not commissioned.

Data Sharing Data is available in all public databases. Data are available in a public, open access repository. All data relevant to the study are included in the article or uploaded as supplementary information. At same time, data are

available upon reasonable request.

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Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2

Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	13-14
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	12
Sponsor	#5b	Provide name for the review funder and / or sponsor	n/a
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is	2-3

		already known	
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4-5
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5-6
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is,	6-7

		screening, eligibility and inclusion in meta-analysis)	
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6-7
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	8
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned	8

		exploration of consistency (such as I2, Kendall's τ)	
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8

Medline

Search strategy

1. randomized control trial.pt. (4,366,033)
2. controlled clinical trial.pt. (92,859)
3. random$.ti.ab. (243,513)
4. placebo.ti.ab. (200,860)
5. clinical trials as topic.mj. (32,507)
6. trial.ti.ab (901,271)
7. or/1-6 (1,300,135)
8. NOT (animals/ not hunmans/) (6,658,452)
9. 7 not 8 (1,117,817)
10. Movement disorder.ti.ab. (16,284)
11. Tremor.ti.ab. (20,602)
12. Essential tremor.ti.ab (3,586)
13. Or/10-11 (34,889)
14. Essential tremor.ti,ab. (3,586)
15. Essential tremor.sh. (1,802)
16. Essential tremor*.ti.ab.(3,587)
17. Benign essential tremor*.ti.ab.(57)
18. Familial tremor*.ti.ab.(194)
19. Hereditary essential tremor*.ti.ab.(39)
20. Or/14-19 (3,838)

21. Therapy.ab.ti (1,788,096)

22. Therapy.sh. (4,069,919)

23. Propranolol.ti.ab. (31,975)

24. Propranolol hydrochloride.ti.ab. (623)

25. Or/21-24 (4,856,447)

26. and 9 and 13 and 20 and 25 (223)

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Oral Propranolol for Treatment of the Subgroups of Essential Tremor: a systematic review and meta-analysis protocol.

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Oral Propranolol for Treatment of the Subgroups of Essential Tremor: a systematic review and meta-analysis protocol.

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The text contains 4019 words.

Abstract

Introduction

Essential tremor (ET) is a tremor disorder that is one of the most common movement disorder. A recent proposal was made to classify ET into two categories，“isolated essential tremors” and “essential tremors plus”. Only oral drugs (propranolol, primidone, topiramate, etc.）are still the first-line treatment recommended by FDA. There has been a view that propranolol may effectively reduce the upper limbs action tremor. However, it has a poor effect on axial

tremor symptoms, such as essential head tremor and voice tremor. Studies have shown that the severity of tremors develops over time, possibly producing other clinical tremors (such as voice tremors) and neurological soft signs (such as memory loss, gait abnormalities, balance disorders, etc.), which makes it even more increase the difficulty of treating tremors. Therefore, we perform subgroup classification based on anatomical distribution and combined with soft signs of the nervous system to find the best choice for drug control of primary tremors. Whereas, some recent studies provide emerging new evidences for oral propranolol on subgroups of ET, which is based on the anatomical distribution of ET (lower extremities, head, sound, tongue, etc.). The purpose of this systematic review is to synthesize these new data to improve the efficacy of propranolol in ET subgroups.

Methods and analysis

Systematic review will be complied by searching for relevant articles in PubMed, MEDLINE, EMBASE, the Cochrane Library, UptoDate, PEDro，from the beginning to the present. Humans who are eligible for criteria, Parkinson, Thyroid patients with a secondary form of tremor, drug-oriented tremor, and toxic tremors will be included in the study. Two independent reviewers will screen the study quality and the Cochrane Collaboration's tool in Review Manager (RevMan) 5.3.3 will be used to evaluate the risk of bias. Narrative and meta-analytical syntheses are planned.

Ethics and dissemination

Published aggregated data is used in this review analysis and therefore no ethical approval is required, the result will be published in peer-reviewed journals, and proliferation activities will include diverse social stakeholders, non-academic groups, and patients.

PROSPERO registration number CRD42018112580

Keywords

Essential tremor; Benign essential tremor; Familial tremor; Hereditary essential tremor; Therapy; Drug therapy; Propranolol; Propranolol

hydrochloride

Article summary

strengths and limitations of this study

The purpose of the systematic review and meta-analysis is to address safety and efficacy of propranolol in treating subgroups of ET, hopefully, we will find the optimal drug dose for the treatment of the ET subgroup.

Different patients, interventions and primary outcome may mean that meta-analysis cannot be conducted, and narrative and meta-analytical syntheses are planned.

Multiple limitations may increase the heterogeneity of the study, thereby hampering the results of the meta-analysis.

Introduction

Essential tremor is a chronic, progressive movement disorder among adults, with a prevalence ranging from 0.4% of the general population to 5% of the population over the age of 65.[1-3] It appears that the prevalence of ET increases exponentially in aging population.[4] While the direct cause of ET remains unknown, recent reports have indicated that loss or dysfunction of Purkinje's neurons in the cerebellum likely play a key role in the etiology of ET.[5-8] Electrophysiological methods reveal abnormal oscillations in the cortical-ponsal-cerebellar-thalamic-cortical loop.[9, 10] It is still unclear why this network involved in the tremor mode; however, it is thought to be associated with abormalities of gamma-aminobutyric acid (GABA) transmission in brain tissues of ET patients.[11]

Traditionally, ET is defined as a bilateral but systematic kinetic and postural tremors of the upper limbs, voice, head, face, chin, legs or a combination of these symptoms.[12] The incidence of ET usually involves upper limbs(95% of patients) according to anatomical distribution, less common is lower limbs (30%), head (25~34%), sound (12~15%), tongue (7%) face (5%), and trunk (5%), as described in several previous reports.[13-15] There are few ET patients with isolated head tremor.[16, 17] Recently, some

studies indicated that some complementary neurological signs (i.e., other than action tremor) exist in patients with ET, such as mild impaired memory, impaired tandem gait, and subtle dystonic body posturing. These clinical symptoms and signs were so mild that they do not suffice for other neurological diagnosis. It was recently proposed that these presentations might be classified as “essential tremor plus” by the International Parkinson and Movement Disorder Society in 2018.[18]

In spite of casting new viewpoints on ET pathogenesis, the treatment of ET still remains merely symptomatic. The therapeutic approach to ET still primarily depends on drugs, although surgery may be an option for patients with refractory essential tremor. As of 2018, propranolol and primidone are still two first-line medications for the treatment of primary tremor, according to the recommendations of the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).[18, 19] In particular, the US Food and Drug Administration only approved propranolol for essential tremor. Conventional wisdom is propranolol is only effective against the upper limbs action tremor, while axial tremor symptoms, such as essential head tremor and voice tremor, usually respond poorly to propranolol treatments.[3, 20] Studies have shown that the severity of tremors develops over time , possibly producing other clinical tremors (such as voice tremors) and neurological soft signs (such as memory loss, gait abnormalities, balance disorders, etc.), which makes it even more increase the difficulty of treating tremors.[21, 22] Therefore, we perform subgroup classification based on anatomical distribution and combined with soft signs of the nervous system to find the best choice for drug control of primary tremors. However, some recent studies provide emerging new evidences for oral propranolol on subgroups of ET, which is based on the anatomical distribution of ET (lower extremities, head, sound, tongue, etc.).[23-27] It is necessary to integrate these new data to refine the treatment for the efficacy of propranolol in the subgroups of ET.

The systematic review protocol is performed under the Preferred

Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines.

Patient and public participation

No patient involved.

Research objective

The purpose of the systematic review and meta-analysis is to address safety and efficacy of propranolol in treating subgroups of ET. The issues of interest to this review are listed below: How effective is the therapy? What is the optimal dosage of the therapy in clinical studies? What are the adverse effects of the therapy? and others?

Methods

Eligibility criteria

Population included

This study includes adult males and females over the age of 16 with ET diagnosed according to the criteria set by the Tremor Investigation Group,[28] and the Consensus Statement of the Movement Disorder Society on Tremor.[18, 29] Parkinson's disease, metabolic tremor, drug tremors, toxicity-related tremor, tonic tremor, neurological tremor, and functional tremor will be excluded(3).

Intervention

The reference intervention is oral propranolol, both long-acting and short-acting formulations. We hypothesize that the oral propranolol treatment is better than other intervention treatments.

Comparators/control

There are many alternative treatment options for essential tremor, including: (1) non-operative care with primidone, topiramate, botulinum toxin injections or other drug therapies, (2) operative care with deep brain stimulation or thalamotomy or gamma knife thalamotomy.[30] Briefly, the comparators group includes all other treatments.

Outcomes

Primary and secondary outcomes

Our primary outcome is functional disability component related to tremors, which is measured by the Fahn-Tolosa-Marin tremor rating scale (TRS) subscales B and C.[31] Secondary outcomes of interest include severity of tremors and quality of life. Specifically, severity of tremors will be measured using the Fahn-Tolosa-Marin TRS subscale A and total score, Patient Global Impression, and Clinical Global Impression. At the same time, we will use a validated QoL scale or questionnaire to measure Quality of life (QoL) , such as 36-item Short Form (SF-36), EuroQol.[31]

Study design

Systematic review of methods of incorporating meta-analysis under the guidance of the Cochrane Handbook. The systematic review protocol is performed under the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines,[32] and will be reported in accordance with the PRISMA Extension Statement in the meta-analysis. The completed PRISMA-P checklist for the current review is provided with supplementary file 1. We will include all randomized controlled trials (RCTs) that examine the efficacy and safety of propranolol on essential tremor. We do not use language to identify all relevant RCTs, both published and unpublished. In order to improve the internal validity of the review, the Grades in Recommendation, Assessment, Development and Evaluation (GRADE) approach will be used to evaluate randomized controlled trials. RCTs have the highest level of evidence for this method. In order to more visually express our research criteria, the following Table 1 has been provided.

Table 1 The list of inclusion and exclusion criterion

	Inclusion	Exclusion

Population	● Adults over the age of 16 ● Humans with ET diagnosed	● Parkinson ● Metabolic tremor ● Toxic-related tremors ● Dystonic tremor ● Neuropathic tremor ● Functional tremor
Intervention	● Oral propranolol ● Long-acting or short-acting formulation	● All other intervention types
Comparators	● non-operative care with primidone, topiramate, botulinum toxin injections or other drug therapies ● operative care with deep brain stimulation or thalamotomy or gamma knife thalamotomy, or the comparators group includes all other treatments	● N/A
Outcomes	Primary ● Fahn-Tolosa-Marin Tremor Rating Scale Secondary ● tremor severity ● quality of life	● N/A
Study designs	● Randomized controlled trials	● Conference proceedings ● Only abstracts available

the planned start and end dates

The start date of the study is April 2019, and the end date is February 2020.

Study registration

The protocol has been successfully registered with PROSPERO, registration number is CRD42018112580.

Patient and public participation

No patient involved.

Search strategy

We will perform a comprehensive electronic search of the medical and rehabilitation literature using medical subject headings (MeSH) and text related to essential tremor and propranolol. A comprehensive electronic search of the following database will be performed, for example, PubMed, MEDLINE, EMBASE, the Cochrane Library, UptoDate, and PEDro, from the beginning to the present. Two different experts developed the search strategy based on the Peer Review of Electronic Search Strategies (PRESS) framework.[33] Professional will be asked to review the strategy if necessary. There is an example for the search strategy using the Medline search (supplementary file 2) and will be modified according to the indexing systems of the other databases. Grey documents that meet the inclusion criteria will also be searched, including papers that have been published, reports on relevant agencies, and unpublished data and manuscripts provided by original authors.

Study records:

All standards-compliant articles searched out the database were imported from EndNote X7 for management. All retrieved articles were strictly screened by two independent reviewers accordance with the inclusion criteria. Simultaneously, for some uncertain articles, they browsed the title and abstract to determine whether or not to include. Full texts of each potentially relevant article will adhere the selection criteria strictly during the title and abstract screening phase. The full texts of all potential articles that met the inclusion

criteria were obtained and reviewed again. Two independent reviewers will screen the full texts for inclusion. If there is any opposition, we will consult or seek the opinion of the third examiner. Reviewers will have no preference to the authors or journals when screening articles.

Data extraction

In order to extract the data onto the most relevant article, a predesigned data extraction form will be made， and will continue to update the form to ensure data integrity and relevance. All data were independently extracted by two reviewers and then compared their data onto the end of the review. Divergences were resolved by consultation or discussion with the third examiner. Reviewers were impartial in extracting data. The extracted data form mainly includes the following indicators: the general situation of the publication (author, year), the characteristics of the participants (gender, age, age range, health status), study design, sample size; length of follow-up; the study methods of information regarding; the control group; the forms of tremor; the dose of propranolol; the dose of other drugs; the statistical analyses methods; the effect of the intervention. Only one article will be kept, when there were two and more articles that derived from the same data. In order to ensure the integrity and authenticity of the data, the researchers will contact the author by email or telephone to require the original data when it is found that the data is missing. If no responses after two consecutive emails and calls, the data will not be included.

Outcomes and prioritization

Primary outcome

Our primary outcome is functional disability component related to tremors, which is measured by the Fahn-Tolosa-Marin tremor rating scale (TRS) subscales B and C. Rest, posture, and tremor are the three elements of TRS, and ETs are scored using three subscales to assess the severity of the tremor. The three subscales are: the posture and the magnitude of the tremor, the ability to perform certain actions and disabilities in daily living due to tremor.

Each subscale is ranged from 0 to 4, which represents none, mild, moderate, and severe, and overall maximum score is 16, 36, and 32 in each subscale. Finally, the scores of the three subscales were summed to obtain the overall TRS score.

Secondary outcomes

PGI, CGI, and Fahn-Tolosa-Marin TRS subscale A and total score are used to assess the severity of ET. PGI, also known as patient global impression, is a scale of patients to self-rated the severity. CGI, also known as clinical global impression, is a scale of clinicians to assess the severity. At the same time, we will use a validated QoL scale or questionnaire to measure Quality of life (QoL), such as 36-item Short Form (SF-36), EuroQol.

Risk of bias and meta-bias

Two reviewers will separately assess the risk of bias and reporting quality of all included studies. Moreover, each randomized controlled trial will be assessed in Review Manager (RevMan) 5.3.3. Each included study was evaluated using a bias risk table that included seven items, random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias, then according to the results of the table, it is divided into low risk of bias, unclear risk of bias and high risk of bias. In addition, we will resolve disagreements in the assessment through consensus or discussions with a third investigator.

Data synthesis

Strategy for data synthesis

The primary tool for data analysis is Review Manager software (RevMan5.3). A random effects model will be managed with data indicators of overall studies for meta-analysis. We will evaluate and analyze the data onto overall included studies and summarized its 95% CIs using a random effects model. The difference will be considered statistically significant when P is less than 0.05. The funnel plot will be used to evaluate heterogeneity between

overall included studies, such as differences of study types, risk of bias, publication bias, differences of measurement resolution, etc.[34]

Analysis of subgroups or subsets

Subgroup analysis will be carried out if the data were enough. Several subgroup analyses will be used to examine differences between the types of ET (e.g. upper limbs, lower limbs, less commonly the head, voice, tongue, face, trunk and others); age; the different dosage of propranolol; side effect of propranolol; the different therapy of ET; and study designs (e.g. treatment groups vs. no control group, randomized vs. non-randomized controlled trial). Among these variables, the dosage of propranolol and the types of ET are assumed to be the most important as it remains unknown what dosage of propranolol is the most effective against different types of ET.

Ethics and dissemination

Published aggregated data is used in this review analysis and therefore no ethical approval is required, the result will be published in peer-reviewed journals, and proliferation activities will include diverse social stakeholders, non-academic groups, and patients.

Discussion

Treatments for ET can be mainly subdivided into three categories: medicine (propranolol, primidone, topiramate), surgical treatments (deep brain stimulation, gamma-knife surgery, MRIgFUS), and other therapies (botulinum toxin, lifestyle management).[30] So far, there has not been major breakthrough in ET treatments. Propranolol and primidone are generally the first treatment option to treat ET. Propranolol was proved to effective against the treatment of ET in 1973.[35] Published controlled trials have shown that the average effective dose of propranolol is 185.2 mg/days, and the daily dose range is 60-800 mg/day.[36, 37] In addition, there is insufficient evidence to indicate that a dose of over 320 mgs per day would bring any benefits. In the treatment of ET, it can be found that about 50%-70% response. Compared with placebo, the average tremor can be reduced by about 50%.[36, 38]

The primary objective of this systematic review is to evaluate the efficacy and safety of propranolol for ET. We will conduct qualitative and quantitative analysis of overall data included in each study, and we hopefully are able to find the optimal drug dose for the treatment of the ET subgroup. What is more, we will summarize as far as possible the role of propranolol in the treatment of ET, especially for axial tremors. The limitations of this systematic review are mainly due to the heterogeneity of the methodology, which may result in some results not being analyzed.

Contributors ZZ, TW, MZ and WL designed the study. The draft agreement was drafted by ZZ, TW and MZ, and revised by all authors. MZ and WL designed the search strategy. MZ, WL and LH will perform the search. LC, LY, TZ, and HS will be included in the study screening to extract data and assess the risk of bias in the included studies. ZZ and YP will dispute disagreements between reviewers. MZ, WL, SG and ZC will analyze and interpret the data. All authors agree to be responsible for all aspects of the work and have read and approved the final draft.

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Competing interests None declared

Provenance and peer review Not commissioned.

Data Sharing Data is available in all public databases. Data are available in a public, open access repository. All data relevant to the study are included in the article or uploaded as supplementary information. At same time, data are

available upon reasonable request.

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Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all	13-14

		protocol authors; provide physical mailing address of corresponding author	
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	12
Sponsor	#5b	Provide name for the review funder and / or sponsor	n/a
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	2-3
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
Methods			

Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4-5
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5-6
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6-7
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6-7
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and	7

		simplifications	
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	8
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	8
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in	#17	Describe how the strength of the	8

cumulative evidence	body of evidence will be assessed (such as GRADE)

Medline

Search strategy

1. randomized control trial.pt. (4,366,033)
2. controlled clinical trial.pt. (92,859)
3. random$.ti.ab. (243,513)
4. placebo.ti.ab. (200,860)
5. clinical trials as topic.mj. (32,507)
6. trial.ti.ab (901,271)
7. or/1-6 (1,300,135)
8. NOT (animals/ not hunmans/) (6,658,452)
9. 7 not 8 (1,117,817)
10. Movement disorder.ti.ab. (16,284)
11. Tremor.ti.ab. (20,602)
12. Essential tremor.ti.ab (3,586)
13. Or/10-11 (34,889)
14. Essential tremor.ti,ab. (3,586)
15. Essential tremor.sh. (1,802)
16. Essential tremor*.ti.ab.(3,587)
17. Benign essential tremor*.ti.ab.(57)
18. Familial tremor*.ti.ab.(194)
19. Hereditary essential tremor*.ti.ab.(39)
20. Or/14-19 (3,838)
21. Therapy.ab.ti (1,788,096)
22. Therapy.sh. (4,069,919)
23. Propranolol.ti.ab. (31,975)
24. Propranolol hydrochloride.ti.ab. (623)
25. Or/21-24 (4,856,447)
26. and 9 and 13 and 20 and 25 (223)

BMJ Open

Oral Propranolol for Treatment of the Subgroups of Essential Tremor: a systematic review and meta-analysis protocol.

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Oral Propranolol for Treatment of the Subgroups of Essential Tremor: a systematic review and meta-analysis protocol.

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The text contains 3121 words.

Abstract

Introduction

Essential tremor (ET), a tremor disorder, is one of the most common movement disorders. Only oral drugs (propranolol, primidone, topiramate, etc.) are still the first-line treatment recommended by the FDA. Propranolol is thought to potentially reduce upper limb action tremor. However, it has a poor effect on axial tremor symptoms, such as essential head tremor and voice tremor. Studies have shown that tremor severity develops over time, possibly

producing other clinical tremors and neurological soft signs (such as memory loss, gait abnormalities, balance disorders, etc.), which further increases the difficulty of treating tremors. However, some recent studies provide emerging evidence for oral propranolol on subgroups of ET, which is based on the anatomical distribution of ET (lower extremities, head, sound, tongue, etc.). This systematic review aims to synthesize these new data to improve the efficacy of propranolol in ET subgroups.

Methods and analysis

We will search for randomized controlled trials from the PubMed, MEDLINE, EMBASE, Cochrane Library, UptoDate, and PEDro databases from inception to June 2019. All data will be extracted independently by two reviewers and compared at the end of the review. The two reviewers will screen the study quality, and the Cochrane Collaboration's tool in Review Manager (RevMan) 5.3.3 will be used to evaluate risk of bias. Our primary outcome will be the functional disability component related to tremors, as measured by the Fahn-Tolosa-Marin tremor rating scale (TRS) subscales B and C. Secondary outcomes will include severity of tremors and quality of life. Narrative and meta-analytical syntheses are planned.

Ethics and dissemination

Published aggregated data will be used in this review analysis and therefore no ethical approval is required. The results will be published in peer-reviewed journals, and proliferation activities will include diverse social stakeholders, non-academic groups, and patients.

PROSPERO registration number CRD42018112580

Keywords

Essential tremor; Benign essential tremor; Familial tremor; Hereditary essential tremor; Therapy; Drug therapy; Propranolol; Propranolol hydrochloride

Article summary

Strengths and limitations of this study

A continuously updated data extraction form will be used to ensure data integrity and relevance.

We will resolve disagreements during the assessment through consensus or discussions with a third investigator.

Although we will include research published in any language, translation difficulties may occur, which will cause these studies to be excluded.

Differences in patients, interventions and primary outcomes may mean that meta-analysis cannot be conducted, and narrative and meta-analytical syntheses are planned.

Multiple limitations may increase the heterogeneity of the study, thereby hampering the results of the meta-analysis.

Introduction

Essential tremor is a chronic, progressive movement disorder occurring in adults, with a prevalence ranging from 0.4% of the general population to 5% of the population over the age of 65.[1-3] It appears that the prevalence of ET increases exponentially in the aging population.[4] While the direct cause of ET remains unknown, recent reports have indicated that loss or dysfunction of Purkinje's neurons in the cerebellum likely plays a key role in the aetiology of ET,[5-8] and electrophysiological methods reveal abnormal oscillations in the cortical-ponsal-cerebellar-thalamic-cortical loop.[9, 10] It is still unclear why this network is involved in tremor; however, it is thought to be associated with abnormalities in gamma-aminobutyric acid (GABA) transmission in brain tissues of ET patients.[11]

Traditionally, ET is defined as bilateral but systematic kinetic and postural tremors of the upper limbs, voice, head, face, chin, legs or a combination of these symptoms.[12] The incidence of ET usually involves the upper limbs (95% of patients) according to anatomical distribution; less commonly affected are the lower limbs (30%), head (25~34%), sound (12~15%), tongue (7%) face (5%), and trunk (5%), as described in several previous reports.[13-15] There are few ET patients with isolated head tremor.[16, 17] Recently, some studies

indicated that some complementary neurological signs (i.e., other than action tremor), such as mild impaired memory, impaired tandem gait, and subtle dystonic body posturing, are present in patients with ET. These clinical symptoms and signs were so mild that they did not suffice for other neurological diagnoses. It was recently proposed that these presentations might be classified as “essential tremor plus” by the International Parkinson and Movement Disorder Society in 2018.[18]

Despite the presentation of new viewpoints on ET pathogenesis, the treatment of ET remains merely symptomatic. The therapeutic approach to ET still primarily depends on drugs, although surgery may be an option for patients with refractory essential tremor. As of 2018, propranolol and primidone are still two first-line medications for the treatment of primary tremor, according to the recommendations of the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).[18, 19] In particular, the US FDA approved only propranolol for essential tremor. Conventional wisdom is propranolol is only effective against the upper limb action tremor, while axial tremor symptoms, such as essential head tremor and voice tremor, usually respond poorly to propranolol treatments.[3, 20] Studies have shown that the severity of tremors develops over time , possibly producing other clinical tremors (such as voice tremors) and neurological soft signs (such as memory loss, gait abnormalities, balance disorders, etc.), which makes it even more difficult to tremors.[21, 22] Therefore, we performded subgroup classification based on anatomical distribution and combined it with soft signs of the nervous system to find the best choice for drug control of primary tremors. However, some recent studies provide emerging evidence for oral propranolol on subgroups of ET, which is based on the anatomical distribution of ET (lower extremities, head, sound, tongue, etc.).[23-27] Integration of these new data is necessary to refine the treatment for the efficacy of propranolol in the subgroups of ET.

The systematic review protocol is performed under the Preferred

Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines.

Patient and public participation

No patients will be involved.

Research objective

The purpose of the systematic review and meta-analysis will be to address the safety and efficacy of propranolol in treating subgroups of ET. The issues of interest to this review are listed below: How effective is the therapy? What is the optimal dosage of the therapy in clinical studies? What are the adverse effects of the therapy? and others.

Methods

Eligibility criteria

Population included

This study will include adult males and females over the age of 16 with ET diagnosed according to the criteria set by the Tremor Investigation Group,[28] and the Consensus Statement of the Movement Disorder Society on Tremor.[18, 29] Individuals with Parkinson's disease, metabolic tremor, drug tremors, toxicity-related tremor, tonic tremor, neurological tremor, and functional tremor will be excluded(3).

Intervention

The reference intervention is oral propranolol, both long-acting and short-acting formulations. We hypothesize that oral propranolol treatment will be better than other intervention treatments.

Comparators/control

There are many alternative treatment options for essential tremor, including: (1) non-operative care with primidone, topiramate, botulinum toxin injections or other drug therapies, and (2) operative care with deep brain stimulation or thalamotomy or gamma knife thalamotomy.[30] Briefly, the comparator group will include all other treatments.

Outcomes

Primary and secondary outcomes

Our primary outcome will be the functional disability component related to tremors, which is measured by the Fahn-Tolosa-Marin tremor rating scale (TRS) subscales B and C.[31] Secondary outcomes of interest will include the severity of tremors and quality of life (QoL). Specifically, the severity of tremors will be measured using the Fahn-Tolosa-Marin TRS subscale A and total score, Patient Global Impression, and Clinical Global Impression. At the same time, we will use a validated QoL scale or questionnaire to measure QoL, such as the 36-item Short Form (SF-36), EuroQol.[31]

Study design

The systematic review protocol will be performed under the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines[32] and will be reported in accordance with the PRISMA Extension Statement in the meta-analysis. The completed PRISMA-P checklist for the current review is provided with supplementary file 1. We will include all randomized controlled trials (RCTs) that examine the efficacy and safety of propranolol for the treatment of essential tremor. We will not limit language in order to identify all relevant RCTs, both published and unpublished. To improve the internal validity of the review, the Grades in Recommendation, Assessment, Development and Evaluation (GRADE) approach will be used to evaluate RCTs. RCTs have the highest level of evidence for this method. To express our research criteria in a more visual manner, the following Table 1 has been provided.

Table 1 The list of inclusion and exclusion criterion

	Inclusion	Exclusion
Population	● Adults over the age of 16 ● Individuals with diagnosed ET	● Parkinsonian tremor ● Metabolic tremor ● Toxicity-related tremors ● Dystonic tremor ● Neuropathic tremor ● Functional tremor
Intervention	● Oral propranolol ● Long-acting or short-acting formulation	● All other intervention types
Comparators	● Non-operative care with primidone, topiramate, botulinum toxin injections or other drug therapies ● Operative care with deep brain stimulation, thalamotomy or gamma knife thalamotomy, or the comparators group includes all other treatments	● N/A
Outcomes	Primary ● Fahn-Tolosa-Marin Tremor Rating Scale Secondary ● Tremor severity ● Quality of life	● N/A
Study designs	● Randomized controlled trials	● Conference proceedings ● Availability of only the abstract

The planned start and end dates

The start date of the study is April 2019, and the end date is February 2020.

Study registration

The protocol has been successfully registered with PROSPERO, and the registration number is CRD42018112580.

Patient and public participation

No patients will be involved.

Search strategy

We will perform a comprehensive electronic search of the medical and rehabilitation literature using medical subject headings (MeSH) and text related to essential tremor and propranolol. A comprehensive electronic search of the following databases will be performed, including PubMed, MEDLINE, EMBASE, the Cochrane Library, UptoDate, and PEDro, from the beginning of each database to June 2019. Two different experts developed the search strategy based on the Peer Review of Electronic Search Strategies (PRESS) framework.[33] Professionals will be asked to review the strategy if necessary. There is an example for the search strategy using the Medline search (supplementary file 2) that will be modified according to the indexing systems of the other databases. Grey documents that meet the inclusion criteria will also be searched, including papers that have been published, reports on relevant agencies, and unpublished data and manuscripts provided by the original authors.

Study records:

All standards-compliant articles identified in the databases will be imported to EndNote X7 for management. All retrieved articles will be strictly screened by two independent reviewers according to the inclusion criteria. Simultaneously, for some uncertain articles, the reviewers will browse the title and abstract to determine eligibility. The full texts of each potentially relevant article will strictly adhere to the selection criteria during the title and abstract

screening phase. The full texts of all potential articles that meet the inclusion criteria will be obtained and reviewed again. Two independent reviewers will screen the full texts for inclusion. If there is any opposition, we will consult or seek the opinion of the third examiner. The reviewers will have no preferences for authors or journals when screening articles.

Data extraction

To extract the most relevant data from the article, a predesigned data extraction form will be constructed and will continue to be updated to ensure data integrity and relevance. All data will be independently extracted by the two reviewers and then compared at the end of the review. Divergences will be resolved by consultation or discussion with the third examiner. Reviewers will be impartial in extracting the data. The extracted data form will mainly include the following information: the general information on the publication (author, year), the characteristics of the participants (sex, age, age range, health status), study design, sample size; length of follow-up; the study methods used; the control group; the forms of tremor; the dose of propranolol; the dose of other drugs; the statistical analysis methods; and the effect of the intervention. Only one article will be kept when there are two or more articles derived from the same data. To ensure the integrity and authenticity of the data, the researchers will contact the author by email or telephone to request the original data when data are found to be missing. If there are no responses after two consecutive emails and calls, the data will not be included.

Outcomes and prioritization

Primary outcome

Our primary outcome will be the functional disability component related to tremors, which is measured by the Fahn-Tolosa-Marin TRS subscales B and C. Rest, posture, and tremor are the three elements of TRS, and ETs will be scored using three subscales to assess the severity of the tremor. The three subscales are the posture and the magnitude of the tremor, the ability to perform certain actions and disabilities in daily living due to tremor. Each

subscale ranges from 0 to 4, which represents none, mild, moderate, and severe, and the overall maximum scores are 16, 36, and 32 in each subscale. Finally, the scores of the three subscales will be summed to obtain the overall TRS score.

Secondary outcomes

PGI, CGI, and Fahn-Tolosa-Marin TRS subscale A and total score are used to assess the severity of ET. PGI, also known as patient global impression, is a scale for patients to self-rate the severity. CGI, also known as Clinical Global Impression, is a scale for clinicians to assess the severity. At the same time, we will use a validated QoL scale or questionnaire to measure QoL, such as the 36-item Short Form (SF-36) or EuroQol.

Risk of bias and meta-bias

Two reviewers will separately assess the risk of bias and reporting quality of all included studies. Moreover, each randomized controlled trial will be assessed in Review Manager (RevMan) 5.3.3. Each included study will be evaluated using a bias risk table that includes seven items, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Then, according to the results of the table, it is divided into low risk of bias, unclear risk of bias and high risk of bias. In addition, we will resolve disagreements in the assessment through consensus or discussions with a third investigator.

Data synthesis

Strategy for data synthesis

The primary tool for data analysis will be Review Manager software (RevMan5.3). A random-effects model will be managed with data indicators from all of the studies for meta-analysis. We will evaluate and analyse the data on the overall included studies and summarize its 95% CIs using a random-effects model. Differences will be considered statistically significant when P is less than 0.05. The funnel plot will be used to evaluate

heterogeneity between overall included studies, such as differences in study types, risk of bias, publication bias, differences in measurement resolution, etc.[34]

Analysis of subgroups or subsets

Subgroup analysis will be carried out if there are sufficient data. Several subgroup analyses will be used to examine differences between the types of ET (e.g., upper limbs, lower limbs, and less commonly, the head, voice, tongue, face, trunk and others); age; the different dosages of propranolol; side effects of propranolol; the different therapies for ET; and study designs (e.g., treatment groups vs. no control group, randomized vs. non-randomized controlled trial). Among these variables, the dosage of propranolol and the types of ET are assumed to be the most important, as it remains unknown what dosage of propranolol is the most effective against different types of ET.

Ethics and dissemination

Published aggregated data will be used in this review analysis and therefore no ethical approval is required. The results will be published in peer-reviewed journals, and proliferation activities will include diverse social stakeholders, non-academic groups, and patients.

Discussion

Treatments for ET can be mainly subdivided into three categories: medicine (propranolol, primidone, topiramate), surgical treatments (deep brain stimulation, gamma knife surgery, MRIgFUS), and other therapies (botulinum toxin, lifestyle management).[30] Thus far, there has not been a major breakthrough in ET treatments. Propranolol and primidone are generally the first treatment options in treating ET. Propranolol was proven to be effective against the treatment of ET in 1973.[35] Furthermore, published controlled trials have shown that the average effective dose of propranolol is 185.2 mg/day, and the daily dose range is 60-800 mg/day.[36, 37] In addition, there is insufficient evidence indicating that a dose over 320 mg per day would provide any benefits. In the treatment of ET, an approximately 50%-70%

response was observed. Compared with placebo, the average tremor can be reduced by approximately 50%.[36, 38]

The primary objective of this systematic review will be to evaluate the efficacy and safety of propranolol in the treatment of ET. We will conduct a qualitative and quantitative analysis of the overall data included in each study, and we will hopefully find the optimal drug dose for the treatment of the ET subgroup. Furthermore, we will summarize as much as possible the role of propranolol in the treatment of ET, especially for axial tremors. The limitations of this systematic review are mainly due to the heterogeneity of the methodology, which may result in some results not being analysed.

Contributors ZZ, TW, MZ and WL designed the study. The draft agreement was drafted by ZZ, TW and MZ, and revised by all authors. MZ and WL designed the search strategy. MZ, WL and LH will perform the search. LC, LY, TZ, and HS will be included in the study screening to extract data and assess the risk of bias in the included studies. ZZ and YP will dispute disagreements between reviewers. MZ, WL, SG and ZC will analyse and interpret the data. All authors agree to be responsible for all aspects of the work and have read and approved the final draft.

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Competing interests None declared

Provenance and peer review Not commissioned.

Data Sharing Data are available in all public databases. Data are available in a public, open access repository. All data relevant to the study are included in

the article or uploaded as supplementary information. At same time, data are available upon reasonable request.

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Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all	13-14

		protocol authors; provide physical mailing address of corresponding author	
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	12
Sponsor	#5b	Provide name for the review funder and / or sponsor	n/a
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	2-3
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
Methods			

Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4-5
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5-6
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6-7
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6-7
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and	7

		simplifications	
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	8
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	8
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in	#17	Describe how the strength of the	8

cumulative evidence	body of evidence will be assessed (such as GRADE)

Medline

Search strategy

1. randomized control trial.pt. (4,366,033)
2. controlled clinical trial.pt. (92,859)
3. random$.ti.ab. (243,513)
4. placebo.ti.ab. (200,860)
5. clinical trials as topic.mj. (32,507)
6. trial.ti.ab (901,271)
7. or/1-6 (1,300,135)
8. NOT (animals/ not hunmans/) (6,658,452)
9. 7 not 8 (1,117,817)
10. Movement disorder.ti.ab. (16,284)
11. Tremor.ti.ab. (20,602)
12. Essential tremor.ti.ab (3,586)
13. Or/10-11 (34,889)
14. Essential tremor.ti,ab. (3,586)
15. Essential tremor.sh. (1,802)
16. Essential tremor*.ti.ab.(3,587)
17. Benign essential tremor*.ti.ab.(57)
18. Familial tremor*.ti.ab.(194)
19. Hereditary essential tremor*.ti.ab.(39)
20. Or/14-19 (3,838)
21. Therapy.ab.ti (1,788,096)
22. Therapy.sh. (4,069,919)
23. Propranolol.ti.ab. (31,975)
24. Propranolol hydrochloride.ti.ab. (623)
25. Or/21-24 (4,856,447)
26. and 9 and 13 and 20 and 25 (223)