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

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

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4 A Study Protocol with Oral Propranolol for Treatment of the Subgroups of
5 Essential Tremor
6

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38
39 The text contains 2111 words.

40 41 42 **Abstract**

43 44 **Introduction**

45
46 Essential tremor (ET) is a tremor disorder that is one of the most common
47 benign dyskinesias. Currently, ET is classified into two categories, “isolated
48 essential tremors” and “essential tremors plus”. Only oral propranolol is still the
49 first-line treatment recommended by FDA. There has been a view that
50 propranolol may effectively reduce the upper limbs action tremor. However, it
51 has a poor effect on axial tremor symptoms, such as essential head tremor
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4 and voice tremor. Whereas, recently studies have provided new evidence that
5 oral propranolol is equally effective against the motional tremor of different
6 anatomical distribution of ET. The purpose of this systematic review is to
7 synthesize these new data to improve the efficacy of propranolol in ET
8 subgroups.
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13 **Methods and analysis**

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

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33 Published aggregated data is used in this review analysis and therefore no
34 ethical approval is required, the result will be published in peer-reviewed
35 journals, and proliferation activities will include diverse social stakeholders,
36 non-academic groups, and patients.
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40 **PROSPERO registration number** CRD42018112580

41 **Keywords**

42
43 Essential tremor; Benign essential tremor; Familial tremor; Hereditary
44 essential tremor; Therapy; Drug therapy; Propranolol; Propranolol
45 hydrochloride
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50 **Introduction**

51
52 Essential tremor is a chronic, progressive movement disorder among
53 adults, with a prevalence ranging from 0.4% of the general population to 5% of
54 the population over the age of 65.[1-3] It appears that the prevalence of ET
55 increases exponentially in aging population.[4] While the direct cause of ET
56 remains unknown, recent reports have indicated that loss or dysfunction of
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4 Purkinje's neurons in the cerebellum likely play a key role in the etiology of ET.
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6 Electrophysiological methods reveal abnormal oscillations in the
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8 cortical-ponsal-cerebellar-thalamic-cortical loop.[5, 6] It is still unclear why this
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10 network involved in the tremor mode; however, it is thought to be associated
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12 with abnormalities of gamma-aminobutyric acid (GABA) transmission in brain
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14 tissues of ET patients.[7]

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16 Traditionally, ET is defined as a bilateral but systematic kinetic and
17
18 postural tremors of the upper limbs, voice, head, face, chin, legs or a
19
20 combination of these symptoms.[8] The incidence of ET usually involves upper
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22 limbs(95% of patients) according to anatomical distribution, less common is
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24 lower limbs (30%), head (25~34%), sound (12~15%), tongue (7%) face (5%),
25
26 and trunk (5%), as described in several previous reports.[9-11] There are few
27
28 ET patients with isolated head tremor.[12, 13] Recently, some studies
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30 indicated that some complementary neurological signs (i.e., other than action
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32 tremor) exist in patients with ET, such as mild impaired memory, impaired
33
34 tandem gait, and subtle dystonic body posturing. These clinical symptoms and
35
36 signs were so mild that they do not suffice for other neurological diagnosis.
37
38 These presentations are classified as "essential tremor plus" by the
39
40 International Parkinson and Movement Disorder Society in 2018.[14]

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42 In spite of casting new viewpoints on ET pathogenesis, the treatment of
43
44 ET still remains merely symptomatic. The therapeutic approach to ET still
45
46 primarily depends on drugs, although surgery may be an option for patients
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48 with refractory essential tremor. As of 2018, propranolol and primidone are still
49
50 two first-line medications for the treatment of primary tremor, according to the
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52 recommendations of the US Food and Drug Administration (FDA) and the
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54 European Medicines Agency (EMA).[14, 15] In particular, the US Food and
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56 Drug Administration only approved propranolol for essential tremor.
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58 Conventional wisdom is propranolol is only effective against the upper limbs
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60 action tremor, while axial tremor symptoms, such as essential head tremor and
voice tremor, usually respond poorly to propranolol treatments.[3, 16]

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

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15 The systematic review protocol is performed under the Preferred
16 Reporting Items for Systematic review and Meta-Analysis Protocols
17 (PRISMA-P) guidelines.
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21 **Patient and public participation**

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23 No patient involved.
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25 **Research objective**

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

38 **Eligibility criteria**

39 **Population included**

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

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

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4 the authors or journals when screening articles.

5 6 **Data extraction**

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

41 Primary outcome

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

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6 Secondary outcomes

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

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

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42 Strategy for data synthesis

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

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

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23 Treatments for ET can be mainly subdivided into three categories:
24 medicine (propranolol, primidone, topiramate), surgical treatments (deep brain
25 stimulation, gamma-knife surgery), and other therapies. So far, there has not
26 been major breakthrough in ET treatments. Propranolol and primidone are
27 generally the first treatment option to treat ET. Propranolol was proved to
28 effective against the treatment of ET in 1973.[28] Published controlled trials
29 have shown that the average effective dose of propranolol is 185.2 mg/days,
30 and the daily dose range is 60-800 mg/day.[29, 30] In addition, there is
31 insufficient evidence to indicate that a dose of over 320 mgs per day would
32 bring any benefits. In the treatment of ET, it can be found that about 50%-70%
33 response. Compared with placebo, the average tremor can be reduced by
34 about 50%.[29, 31]
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46 The primary objective of this systematic review is to evaluate the efficacy
47 and safety of propranolol for ET. We will conduct qualitative and quantitative
48 analysis of overall data included in each study, and we hopefully are able to
49 find the optimal drug dose for the treatment of the ET subgroup. What is more,
50 we will summarize as far as possible the role of propranolol in the treatment of
51 ET, especially for axial tremors.
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Contributors ZZ, TW, MZ and WL designed the study. The draft agreement

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4 was drafted by ZZ, TW and MZ, and revised by all authors. MZ and WL
5 designed the search strategy. MZ, WL and LH will perform the search. LC, LY,
6 TZ, and HS will be included in the study screening to extract data and assess
7 the risk of bias in the included studies. ZZ and YP will dispute disagreements
8 between reviewers. MZ, WL, SG and ZC will analyze and interpret the data. All
9 authors agree to be responsible for all aspects of the work and have read and
10 approved the final draft.
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36 **Competing interests** None.

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Table 1 The list of inclusion and exclusion criterion

	Inclusion	Exclusion
Population	<ul style="list-style-type: none"> Adults over the age of 16 Humans with ET diagnosed 	<ul style="list-style-type: none"> Parkinson Metabolic tremor Toxic-related tremors Dystonic tremor Neuropathic tremor Functional tremor
Intervention	<ul style="list-style-type: none"> Oral propranolol Long-acting or short-acting formulation 	<ul style="list-style-type: none"> All other intervention types
Comparator	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> N/A
Outcome	<p>Primary</p> <ul style="list-style-type: none"> Fahn-Tolosa-Marin Tremor Rating Scale <p>Secondary</p> <ul style="list-style-type: none"> tremor severity quality of life 	<ul style="list-style-type: none"> N/A
Study designs	<ul style="list-style-type: none"> Randomized controlled trials 	<ul style="list-style-type: none"> 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 humans/) (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)

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4 21. Therapy.ab.ti (1,788,096)
5

6 22. Therapy.sh. (4,069,919)
7

8
9 23. Propranolol.ti.ab. (31,975)
10

11 24. Propranolol hydrochloride.ti.ab. (623)
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14 25. Or/21-24 (4,856,447)
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17 26. 7 and 9 and 13 and 20 and 25 (223)
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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.

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

In your methods section, say that you used the PRISMA-Preorting 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

1 **Authors**

2

3

4 Contact [#3a](#) Provide name, institutional 13-14

5 affiliation, e-mail address of all

6 protocol authors; provide physical

7 mailing address of corresponding

8 author

9

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11

12

13 Contribution [#3b](#) Describe contributions of protocol 12

14 authors and identify the guarantor

15 of the review

16

17

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19 **Amendments**

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22 [#4](#) If the protocol represents an n/a

23 amendment of a previously

24 completed or published protocol,

25 identify as such and list changes;

26 otherwise, state plan for

27 documenting important protocol

28 amendments

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35 **Support**

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38 Sources [#5a](#) Indicate sources of financial or 12

39 other support for the review

40

41

42 Sponsor [#5b](#) Provide name for the review n/a

43 funder and / or sponsor

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46

47 Role of [#5c](#) Describe roles of funder(s), n/a

48 sponsor or sponsor(s), and / or institution(s), if

49 funder any, in developing the protocol

50

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53 **Introduction**

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56 Rationale [#6](#) Describe the rationale for the 2-3

57 review in the context of what is

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already known

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3	Objectives	#7	4
4		Provide an explicit statement of	
5		the question(s) the review will	
6		address with reference to	
7		participants, interventions,	
8		comparators, and outcomes	
9		(PICO)	
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14	Methods		
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17	Eligibility	#8	4-5
18	criteria	Specify the study characteristics	
19		(such as PICO, study design,	
20		setting, time frame) and report	
21		characteristics (such as years	
22		considered, language, publication	
23		status) to be used as criteria for	
24		eligibility for the review	
25			
26			
27			
28			
29	Information	#9	5-6
30	sources	Describe all intended information	
31		sources (such as electronic	
32		databases, contact with study	
33		authors, trial registers or other	
34		grey literature sources) with	
35		planned dates of coverage	
36			
37			
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39			
40	Search	#10	6
41	strategy	Present draft of search strategy to	
42		be used for at least one electronic	
43		database, including planned limits,	
44		such that it could be repeated	
45			
46			
47	Study records -	#11a	6
48	data	Describe the mechanism(s) that	
49	management	will be used to manage records	
50		and data throughout the review	
51			
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54	Study records -	#11b	6-7
55	selection	State the process that will be used	
56	process	for selecting studies (such as two	
57		independent reviewers) through	
58		each phase of the review (that is,	
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1		screening, eligibility and inclusion	
2		in meta-analysis)	
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4			
5	Study records -	#11c	Describe planned method of
6	data collection		extracting data from reports (such
7	process		as piloting forms, done
8			independently, in duplicate), any
9			processes for obtaining and
10			confirming data from investigators
11			
12			
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14			
15	Data items	#12	List and define all variables for
16			which data will be sought (such as
17			PICO items, funding sources), any
18			pre-planned data assumptions and
19			simplifications
20			
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23			
24	Outcomes and	#13	List and define all outcomes for
25	prioritization		which data will be sought,
26			including prioritization of main and
27			additional outcomes, with rationale
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32	Risk of bias in	#14	Describe anticipated methods for
33	individual		assessing risk of bias of individual
34	studies		studies, including whether this will
35			be done at the outcome or study
36			level, or both; state how this
37			information will be used in data
38			synthesis
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44	Data synthesis	#15a	Describe criteria under which
45			study data will be quantitatively
46			synthesised
47			
48			
49			
50	Data synthesis	#15b	If data are appropriate for
51			quantitative synthesis, describe
52			planned summary measures,
53			methods of handling data and
54			methods of combining data from
55			studies, including any planned
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exploration of consistency (such as I², Kendall's τ)

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5	Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
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12	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned
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18	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
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26	Confidence in	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)
27	cumulative		
28	evidence		
29			
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The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution License CC-BY 4.0. This checklist was completed on 02. June 2019 using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-032096.R1
Article Type:	Protocol
Date Submitted by the Author:	14-Oct-2019
Complete List of Authors:	<p>yu, Zhang; Hainan Medical University, Department of Neurology, First Affiliated Hospital Wei, Li; Hainan Medical University, Department of Neurology, First Affiliated Hospital Lan, Hu; Hainan Medical University, Department of Neurology, First Affiliated Hospital Li, Chen; Hainan Medical University, Department of Neurology, First Affiliated Hospital Liu, Yang; Hainan Medical University, Department of Neurology, First Affiliated Hospital Tian, Zhang; Hainan Medical University, Department of Neurology, First Affiliated Hospital Hui, Shen; Hainan Medical University, Department of Neurology, First Affiliated Hospital Nan, Peng; Hainan Medical University, Department of Neurology, First Affiliated Hospital Jun, Gao; Hainan Medical University, Department of Neurology, First Affiliated Hospital Bin, Chen; Hainan Medical University, Department of Neurology, First Affiliated Hospital Tan, Wang; Hainan Medical University, Department of Neurology, First Affiliated Hospital Qiang, Zhao; Hainan Medical University, Department of Neurology, First Affiliated Hospital</p>
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	Essential tremor, Benign essential tremor, Familial tremor, Therapy, Drug therapy, Propranolol

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4 Oral Propranolol for Treatment of the Subgroups of Essential Tremor: a
5 systematic review and meta-analysis protocol.
6

7 Manyu Zhang^{1†}, Wei Li^{1†}, Lan Hu², Li Chen¹, Liu Yang¹, Tian Zhang¹,
8 Hui Shen¹, Yanan Peng¹, Shijun Gao¹, Zhibin Chen¹, Tan Wang^{1*}, Zhenqiang
9 Zhao ^{1*}
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38
39 The text contains 4019 words.

40 41 **Abstract**

42 43 **Introduction**

44
45 Essential tremor (ET) is a tremor disorder that is one of the most common
46 movement disorder. A recent proposal was made to classify ET into two
47 categories, “isolated essential tremors” and “essential tremors plus”. Only oral
48 drugs (propranolol, primidone, topiramate, etc.) are still the first-line treatment
49 recommended by FDA. There has been a view that propranolol may effectively
50 reduce the upper limbs action tremor. However, it has a poor effect on axial
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4 tremor symptoms, such as essential head tremor and voice tremor. Studies
5 have shown that the severity of tremors develops over time, possibly
6 producing other clinical tremors (such as voice tremors) and neurological soft
7 signs (such as memory loss, gait abnormalities, balance disorders, etc.), which
8 makes it even more increase the difficulty of treating tremors. Therefore, we
9 perform subgroup classification based on anatomical distribution and
10 combined with soft signs of the nervous system to find the best choice for drug
11 control of primary tremors. Whereas, some recent studies provide emerging
12 new evidences for oral propranolol on subgroups of ET, which is based on the
13 anatomical distribution of ET (lower extremities, head, sound, tongue, etc.).
14 The purpose of this systematic review is to synthesize these new data to
15 improve the efficacy of propranolol in ET subgroups.

26 **Methods and analysis**

27
28 Systematic review will be complied by searching for relevant articles in
29 PubMed, MEDLINE, EMBASE, the Cochrane Library, UptoDate, PEDro, from
30 the beginning to the present. Humans who are eligible for criteria, Parkinson,
31 Thyroid patients with a secondary form of tremor, drug-oriented tremor, and
32 toxic tremors will be included in the study. Two independent reviewers will
33 screen the study quality and the Cochrane Collaboration's tool in Review
34 Manager (RevMan) 5.3.3 will be used to evaluate the risk of bias. Narrative
35 and meta-analytical syntheses are planned.

44 **Ethics and dissemination**

45
46 Published aggregated data is used in this review analysis and therefore no
47 ethical approval is required, the result will be published in peer-reviewed
48 journals, and proliferation activities will include diverse social stakeholders,
49 non-academic groups, and patients.

54 **PROSPERO registration number** CRD42018112580

56 **Keywords**

57
58 Essential tremor; Benign essential tremor; Familial tremor; Hereditary
59 essential tremor; Therapy; Drug therapy; Propranolol; Propranolol
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4 hydrochloride

5 **Article summary**

6 strengths and limitations of this study

7
8 The purpose of the systematic review and meta-analysis is to address safety
9 and efficacy of propranolol in treating subgroups of ET, hopefully, we will find
10 the optimal drug dose for the treatment of the ET subgroup.
11

12
13 Different patients, interventions and primary outcome may mean that
14 meta-analysis cannot be conducted, and narrative and meta-analytical
15 syntheses are planned.
16

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18 Multiple limitations may increase the heterogeneity of the study, thereby
19 hampering the results of the meta-analysis.
20

21 **Introduction**

22
23 Essential tremor is a chronic, progressive movement disorder among
24 adults, with a prevalence ranging from 0.4% of the general population to 5% of
25 the population over the age of 65.[1-3] It appears that the prevalence of ET
26 increases exponentially in aging population.[4] While the direct cause of ET
27 remains unknown, recent reports have indicated that loss or dysfunction of
28 Purkinje's neurons in the cerebellum likely play a key role in the etiology of
29 ET.[5-8] Electrophysiological methods reveal abnormal oscillations in the
30 cortical-ponsal-cerebellar-thalamic-cortical loop.[9, 10] It is still unclear why
31 this network involved in the tremor mode; however, it is thought to be
32 associated with abnormalities of gamma-aminobutyric acid (GABA)
33 transmission in brain tissues of ET patients.[11]
34

35
36 Traditionally, ET is defined as a bilateral but systematic kinetic and
37 postural tremors of the upper limbs, voice, head, face, chin, legs or a
38 combination of these symptoms.[12] The incidence of ET usually involves
39 upper limbs(95% of patients) according to anatomical distribution, less
40 common is lower limbs (30%), head (25~34%), sound (12~15%), tongue (7%)
41 face (5%), and trunk (5%), as described in several previous reports.[13-15]
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43 There are few ET patients with isolated head tremor.[16, 17] Recently, some
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4 studies indicated that some complementary neurological signs (i.e., other than
5 action tremor) exist in patients with ET, such as mild impaired memory,
6 impaired tandem gait, and subtle dystonic body posturing. These clinical
7 symptoms and signs were so mild that they do not suffice for other
8 neurological diagnosis. It was recently proposed that these presentations
9 might be classified as “essential tremor plus” by the International Parkinson
10 and Movement Disorder Society in 2018.[18]
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17 In spite of casting new viewpoints on ET pathogenesis, the treatment of
18 ET still remains merely symptomatic. The therapeutic approach to ET still
19 primarily depends on drugs, although surgery may be an option for patients
20 with refractory essential tremor. As of 2018, propranolol and primidone are still
21 two first-line medications for the treatment of primary tremor, according to the
22 recommendations of the US Food and Drug Administration (FDA) and the
23 European Medicines Agency (EMA).[18, 19] In particular, the US Food and
24 Drug Administration only approved propranolol for essential tremor.
25 Conventional wisdom is propranolol is only effective against the upper limbs
26 action tremor, while axial tremor symptoms, such as essential head tremor and
27 voice tremor, usually respond poorly to propranolol treatments.[3, 20] Studies
28 have shown that the severity of tremors develops over time, possibly
29 producing other clinical tremors (such as voice tremors) and neurological soft
30 signs (such as memory loss, gait abnormalities, balance disorders, etc.), which
31 makes it even more increase the difficulty of treating tremors.[21, 22]
32 Therefore, we perform subgroup classification based on anatomical
33 distribution and combined with soft signs of the nervous system to find the best
34 choice for drug control of primary tremors. However, some recent studies
35 provide emerging new evidences for oral propranolol on subgroups of ET,
36 which is based on the anatomical distribution of ET (lower extremities, head,
37 sound, tongue, etc.).[23-27] It is necessary to integrate these new data to
38 refine the treatment for the efficacy of propranolol in the subgroups of ET.
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The systematic review protocol is performed under the Preferred

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4 Reporting Items for Systematic review and Meta-Analysis Protocols
5 (PRISMA-P) guidelines.
6

7 **Patient and public participation**

8 No patient involved.
9

10 **Research objective**

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

24 **Eligibility criteria**

25 **Population included**

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

41 The reference intervention is oral propranolol, both long-acting and
42 short-acting formulations. We hypothesize that the oral propranolol treatment
43 is better than other intervention treatments.
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47

48 **Comparators/control**

49 There are many alternative treatment options for essential tremor,
50 including: (1) non-operative care with primidone, topiramate, botulinum toxin
51 injections or other drug therapies, (2) operative care with deep brain
52 stimulation or thalamotomy or gamma knife thalamotomy. Briefly, the
53 comparators group includes all other treatments.
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60 **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	<ul style="list-style-type: none"> Adults over the age of 16 Humans with ET diagnosed 	<ul style="list-style-type: none"> Parkinson Metabolic tremor Toxic-related tremors Dystonic tremor Neuropathic tremor Functional tremor
Intervention	<ul style="list-style-type: none"> Oral propranolol Long-acting or short-acting formulation 	<ul style="list-style-type: none"> All other intervention types
Comparator	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> N/A
Outcome	<p>Primary</p> <ul style="list-style-type: none"> Fahn-Tolosa-Marin Tremor Rating Scale <p>Secondary</p> <ul style="list-style-type: none"> tremor severity quality of life 	<ul style="list-style-type: none"> N/A
Study designs	<ul style="list-style-type: none"> Randomized controlled trials 	<ul style="list-style-type: none"> Conference proceedings Only abstracts available

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

the planned start and end dates

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4 The start date of the study is April 2019, and the end date is February
5 2020.
6

7 **Study registration**

8
9 The protocol has been successfully registered with PROSPERO,
10 registration number is CRD42018112580.
11

12 **Patient and public participation**

13
14 No patient involved.
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16 **Search strategy**

17
18 We will perform a comprehensive electronic search of the medical and
19 rehabilitation literature using medical subject headings (MeSH) and text
20 related to essential tremor and propranolol. A comprehensive electronic
21 search of the following database will be performed, for example, PubMed,
22 MEDLINE, EMBASE, the Cochrane Library, UptoDate, and PEDro, from the
23 beginning to the present. Two different experts developed the search strategy
24 based on the Peer Review of Electronic Search Strategies (PRESS)
25 framework.[32] Professional will be asked to review the strategy if necessary.
26 There is an example for the search strategy using the Medline search
27 (supplementary file 2) and will be modified according to the indexing systems
28 of the other databases. Grey documents that meet the inclusion criteria will
29 also be searched, including papers that have been published, reports on
30 relevant agencies, and unpublished data and manuscripts provided by original
31 authors.
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46 **Study records:**

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48 All standards-compliant articles searched out the database were imported
49 from EndNote X7 for management. All retrieved articles were strictly screened
50 by two independent reviewers accordance with the inclusion criteria.
51 Simultaneously, for some uncertain articles, they browsed the title and abstract
52 to determine whether or not to include. Full texts of each potentially relevant
53 article will adhere the selection criteria strictly during the title and abstract
54 screening phase. The full texts of all potential articles that met the inclusion
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4 criteria were obtained and reviewed again. Two independent reviewers will
5 screen the full texts for inclusion. If there is any opposition, we will consult or
6 seek the opinion of the third examiner. Reviewers will have no preference to
7 the authors or journals when screening articles.
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10 11 **Data extraction**

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

47 **Primary outcome**

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49 Our primary outcome is functional disability component related to tremors,
50 which is measured by the Fahn-Tolosa-Marin tremor rating scale (TRS)
51 subscales B and C. Rest, posture, and tremor are the three elements of TRS,
52 and ETs are scored using three subscales to assess the severity of the tremor.
53 The three subscales are: the posture and the magnitude of the tremor, the
54 ability to perform certain actions and disabilities in daily living due to tremor.
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4 Each subscale is ranged from 0 to 4, which represents none, mild, moderate,
5 and severe, and overall maximum score is 16, 36, and 32 in each subscale.
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7 Finally, the scores of the three subscales were summed to obtain the overall
8 TRS score.
9

10 11 Secondary outcomes

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

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

47 Strategy for data synthesis

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49 The primary tool for data analysis is Review Manager software
50 (RevMan5.3). A random effects model will be managed with data indicators of
51 overall studies for meta-analysis. We will evaluate and analyze the data onto
52 overall included studies and summarized its 95% CIs using a random effects
53 model. The difference will be considered statistically significant when P is less
54 than 0.05. The funnel plot will be used to evaluate heterogeneity between
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4 overall included studies, such as differences of study types, risk of bias,
5 publication bias, differences of measurement resolution, etc.[33]

6 7 Analysis of subgroups or subsets

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

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

37
38 Treatments for ET can be mainly subdivided into three categories:
39 medicine (propranolol, primidone, topiramate), surgical treatments (deep brain
40 stimulation, gamma-knife surgery, MRIGFUS), and other therapies (botulinum
41 toxin, lifestyle management). So far, there has not been major breakthrough in
42 ET treatments. Propranolol and primidone are generally the first treatment
43 option to treat ET. Propranolol was proved to effective against the treatment of
44 ET in 1973.[34] Published controlled trials have shown that the average
45 effective dose of propranolol is 185.2 mg/days, and the daily dose range is
46 60-800 mg/day.[35, 36] In addition, there is insufficient evidence to indicate
47 that a dose of over 320 mgs per day would bring any benefits. In the treatment
48 of ET, it can be found that about 50%-70% response. Compared with placebo,
49 the average tremor can be reduced by about 50%.[35, 37]
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4 The primary objective of this systematic review is to evaluate the efficacy
5 and safety of propranolol for ET. We will conduct qualitative and quantitative
6 analysis of overall data included in each study, and we hopefully are able to
7 find the optimal drug dose for the treatment of the ET subgroup. What is more,
8 we will summarize as far as possible the role of propranolol in the treatment of
9 ET, especially for axial tremors. The limitations of this systematic review are
10 mainly due to the heterogeneity of the methodology, which may result in some
11 results not being analyzed.
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19 **Contributors** ZZ, TW, MZ and WL designed the study. The draft agreement
20 was drafted by ZZ, TW and MZ, and revised by all authors. MZ and WL
21 designed the search strategy. MZ, WL and LH will perform the search. LC, LY,
22 TZ, and HS will be included in the study screening to extract data and assess
23 the risk of bias in the included studies. ZZ and YP will dispute disagreements
24 between reviewers. MZ, WL, SG and ZC will analyze and interpret the data. All
25 authors agree to be responsible for all aspects of the work and have read and
26 approved the final draft.
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52 **Competing interests** None declared
53

54 **Provenance and peer review** Not commissioned.
55

56 **Data Sharing** Data is available in all public databases. Data are available in a
57 public, open access repository. All data relevant to the study are included in
58 the article or uploaded as supplementary information. At same time, data are
59
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4 available upon reasonable request.

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12 13 14 15 16 17 18 19 **References**

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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.

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

In your methods section, say that you used the PRISMA-Preorting 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 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

1		screening, eligibility and inclusion	
2		in meta-analysis)	
3			
4			
5	Study records -	#11c	Describe planned method of
6	data collection		extracting data from reports (such
7	process		as piloting forms, done
8			independently, in duplicate), any
9			processes for obtaining and
10			confirming data from investigators
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15	Data items	#12	List and define all variables for
16			which data will be sought (such as
17			PICO items, funding sources), any
18			pre-planned data assumptions and
19			simplifications
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24	Outcomes and	#13	List and define all outcomes for
25	prioritization		which data will be sought,
26			including prioritization of main and
27			additional outcomes, with rationale
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32	Risk of bias in	#14	Describe anticipated methods for
33	individual		assessing risk of bias of individual
34	studies		studies, including whether this will
35			be done at the outcome or study
36			level, or both; state how this
37			information will be used in data
38			synthesis
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44	Data synthesis	#15a	Describe criteria under which
45			study data will be quantitatively
46			synthesised
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50	Data synthesis	#15b	If data are appropriate for
51			quantitative synthesis, describe
52			planned summary measures,
53			methods of handling data and
54			methods of combining data from
55			studies, including any planned
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1 exploration of consistency (such
2 as I², Kendall's τ)
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5	Data synthesis	#15c	Describe any proposed additional	8
6			analyses (such as sensitivity or	
7			subgroup analyses, meta-	
8			regression)	
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12	Data synthesis	#15d	If quantitative synthesis is not	8
13			appropriate, describe the type of	
14			summary planned	
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18	Meta-bias(es)	#16	Specify any planned assessment	8
19			of meta-bias(es) (such as	
20			publication bias across studies,	
21			selective reporting within studies)	
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26	Confidence in	#17	Describe how the strength of the	8
27	cumulative		body of evidence will be assessed	
28	evidence		(such as GRADE)	
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32 The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution License
33 CC-BY 4.0. This checklist was completed on 02. June 2019 using <https://www.goodreports.org/>, a
34 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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6 Search strategy

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- 9 1. randomized control trial.pt. (4,366,033)
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- 15 4. placebo.ti.ab. (200,860)
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- 17 5. clinical trials as topic.mj. (32,507)
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- 25 9. 7 not 8 (1,117,817)
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- 27 10. Movement disorder.ti.ab. (16,284)
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- 29 11. Tremor.ti.ab. (20,602)
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- 31 12. Essential tremor.ti.ab (3,586)
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- 35 14. Essential tremor.ti.ab. (3,586)
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- 37 15. Essential tremor.sh. (1,802)
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- 39 16. Essential tremor*.ti.ab.(3,587)
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- 41 17. Benign essential tremor*.ti.ab.(57)
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- 43 18. Familial tremor*.ti.ab.(194)
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- 45 19. Hereditary essential tremor*.ti.ab.(39)
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9 23. Propranolol.ti.ab. (31,975)
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11 24. Propranolol hydrochloride.ti.ab. (623)
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For peer review only

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-032096.R2
Article Type:	Protocol
Date Submitted by the Author:	23-Oct-2019
Complete List of Authors:	<p>yu, Zhang; Hainan Medical University, Department of Neurology, First Affiliated Hospital Wei, Li; Hainan Medical University, Department of Neurology, First Affiliated Hospital Lan, Hu; Hainan Medical University, Department of Neurology, First Affiliated Hospital Li, Chen; Hainan Medical University, Department of Neurology, First Affiliated Hospital Liu, Yang; Hainan Medical University, Department of Neurology, First Affiliated Hospital Tian, Zhang; Hainan Medical University, Department of Neurology, First Affiliated Hospital Hui, Shen; Hainan Medical University, Department of Neurology, First Affiliated Hospital Nan, Peng; Hainan Medical University, Department of Neurology, First Affiliated Hospital Jun, Gao; Hainan Medical University, Department of Neurology, First Affiliated Hospital Bin, Chen; Hainan Medical University, Department of Neurology, First Affiliated Hospital Tan, Wang; Hainan Medical University, Department of Neurology, First Affiliated Hospital Qiang, Zhao; Hainan Medical University, Department of Neurology, First Affiliated Hospital</p>
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	Essential tremor, Benign essential tremor, Familial tremor, Therapy, Drug therapy, Propranolol

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4 Oral Propranolol for Treatment of the Subgroups of Essential Tremor: a
5 systematic review and meta-analysis protocol.
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38
39 The text contains 4019 words.

40 41 **Abstract**

42 43 **Introduction**

44
45 Essential tremor (ET) is a tremor disorder that is one of the most common
46 movement disorder. A recent proposal was made to classify ET into two
47 categories, “isolated essential tremors” and “essential tremors plus”. Only oral
48 drugs (propranolol, primidone, topiramate, etc.) are still the first-line treatment
49 recommended by FDA. There has been a view that propranolol may effectively
50 reduce the upper limbs action tremor. However, it has a poor effect on axial
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4 tremor symptoms, such as essential head tremor and voice tremor. Studies
5 have shown that the severity of tremors develops over time, possibly
6 producing other clinical tremors (such as voice tremors) and neurological soft
7 signs (such as memory loss, gait abnormalities, balance disorders, etc.), which
8 makes it even more increase the difficulty of treating tremors. Therefore, we
9 perform subgroup classification based on anatomical distribution and
10 combined with soft signs of the nervous system to find the best choice for drug
11 control of primary tremors. Whereas, some recent studies provide emerging
12 new evidences for oral propranolol on subgroups of ET, which is based on the
13 anatomical distribution of ET (lower extremities, head, sound, tongue, etc.).
14 The purpose of this systematic review is to synthesize these new data to
15 improve the efficacy of propranolol in ET subgroups.
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27 **Methods and analysis**

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

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47 Published aggregated data is used in this review analysis and therefore no
48 ethical approval is required, the result will be published in peer-reviewed
49 journals, and proliferation activities will include diverse social stakeholders,
50 non-academic groups, and patients.
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54 **PROSPERO registration number** CRD42018112580

55 **Keywords**

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58 Essential tremor; Benign essential tremor; Familial tremor; Hereditary
59 essential tremor; Therapy; Drug therapy; Propranolol; Propranolol
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5 **Article summary**

6 strengths and limitations of this study

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8 The purpose of the systematic review and meta-analysis is to address safety
9 and efficacy of propranolol in treating subgroups of ET, hopefully, we will find
10 the optimal drug dose for the treatment of the ET subgroup.
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13 Different patients, interventions and primary outcome may mean that
14 meta-analysis cannot be conducted, and narrative and meta-analytical
15 syntheses are planned.
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18 Multiple limitations may increase the heterogeneity of the study, thereby
19 hampering the results of the meta-analysis.
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21 **Introduction**

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23 Essential tremor is a chronic, progressive movement disorder among
24 adults, with a prevalence ranging from 0.4% of the general population to 5% of
25 the population over the age of 65.[1-3] It appears that the prevalence of ET
26 increases exponentially in aging population.[4] While the direct cause of ET
27 remains unknown, recent reports have indicated that loss or dysfunction of
28 Purkinje's neurons in the cerebellum likely play a key role in the etiology of
29 ET.[5-8] Electrophysiological methods reveal abnormal oscillations in the
30 cortical-ponsal-cerebellar-thalamic-cortical loop.[9, 10] It is still unclear why
31 this network involved in the tremor mode; however, it is thought to be
32 associated with abnormalities of gamma-aminobutyric acid (GABA)
33 transmission in brain tissues of ET patients.[11]
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36 Traditionally, ET is defined as a bilateral but systematic kinetic and
37 postural tremors of the upper limbs, voice, head, face, chin, legs or a
38 combination of these symptoms.[12] The incidence of ET usually involves
39 upper limbs(95% of patients) according to anatomical distribution, less
40 common is lower limbs (30%), head (25~34%), sound (12~15%), tongue (7%)
41 face (5%), and trunk (5%), as described in several previous reports.[13-15]
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43 There are few ET patients with isolated head tremor.[16, 17] Recently, some
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4 studies indicated that some complementary neurological signs (i.e., other than
5 action tremor) exist in patients with ET, such as mild impaired memory,
6 impaired tandem gait, and subtle dystonic body posturing. These clinical
7 symptoms and signs were so mild that they do not suffice for other
8 neurological diagnosis. It was recently proposed that these presentations
9 might be classified as “essential tremor plus” by the International Parkinson
10 and Movement Disorder Society in 2018.[18]
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17 In spite of casting new viewpoints on ET pathogenesis, the treatment of
18 ET still remains merely symptomatic. The therapeutic approach to ET still
19 primarily depends on drugs, although surgery may be an option for patients
20 with refractory essential tremor. As of 2018, propranolol and primidone are still
21 two first-line medications for the treatment of primary tremor, according to the
22 recommendations of the US Food and Drug Administration (FDA) and the
23 European Medicines Agency (EMA).[18, 19] In particular, the US Food and
24 Drug Administration only approved propranolol for essential tremor.
25 Conventional wisdom is propranolol is only effective against the upper limbs
26 action tremor, while axial tremor symptoms, such as essential head tremor and
27 voice tremor, usually respond poorly to propranolol treatments.[3, 20] Studies
28 have shown that the severity of tremors develops over time, possibly
29 producing other clinical tremors (such as voice tremors) and neurological soft
30 signs (such as memory loss, gait abnormalities, balance disorders, etc.), which
31 makes it even more increase the difficulty of treating tremors.[21, 22]
32 Therefore, we perform subgroup classification based on anatomical
33 distribution and combined with soft signs of the nervous system to find the best
34 choice for drug control of primary tremors. However, some recent studies
35 provide emerging new evidences for oral propranolol on subgroups of ET,
36 which is based on the anatomical distribution of ET (lower extremities, head,
37 sound, tongue, etc.).[23-27] It is necessary to integrate these new data to
38 refine the treatment for the efficacy of propranolol in the subgroups of ET.
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The systematic review protocol is performed under the Preferred

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4 Reporting Items for Systematic review and Meta-Analysis Protocols
5 (PRISMA-P) guidelines.
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7 **Patient and public participation**

8 No patient involved.
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10 **Research objective**

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

24 **Eligibility criteria**

25 **Population included**

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

41 The reference intervention is oral propranolol, both long-acting and
42 short-acting formulations. We hypothesize that the oral propranolol treatment
43 is better than other intervention treatments.
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48 **Comparators/control**

49 There are many alternative treatment options for essential tremor,
50 including: (1) non-operative care with primidone, topiramate, botulinum toxin
51 injections or other drug therapies, (2) operative care with deep brain
52 stimulation or thalamotomy or gamma knife thalamotomy.[30] Briefly, the
53 comparators group includes all other treatments.
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60 **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
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Population	<ul style="list-style-type: none"> ● Adults over the age of 16 ● Humans with ET diagnosed 	<ul style="list-style-type: none"> ● Parkinson ● Metabolic tremor ● Toxic-related tremors ● Dystonic tremor ● Neuropathic tremor ● Functional tremor
Intervention	<ul style="list-style-type: none"> ● Oral propranolol ● Long-acting or short-acting formulation 	<ul style="list-style-type: none"> ● All other intervention types
Comparators	<ul style="list-style-type: none"> ● 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 	<ul style="list-style-type: none"> ● N/A
Outcomes	<p>Primary</p> <ul style="list-style-type: none"> ● Fahn-Tolosa-Marin Tremor Rating Scale <p>Secondary</p> <ul style="list-style-type: none"> ● tremor severity ● quality of life 	<ul style="list-style-type: none"> ● N/A
Study designs	<ul style="list-style-type: none"> ● Randomized controlled trials 	<ul style="list-style-type: none"> ● Conference proceedings ● Only abstracts available

the planned start and end dates

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4 The start date of the study is April 2019, and the end date is February
5 2020.
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7 **Study registration**

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9 The protocol has been successfully registered with PROSPERO,
10 registration number is CRD42018112580.
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12 **Patient and public participation**

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14 No patient involved.
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16 **Search strategy**

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

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48 All standards-compliant articles searched out the database were imported
49 from EndNote X7 for management. All retrieved articles were strictly screened
50 by two independent reviewers accordance with the inclusion criteria.
51 Simultaneously, for some uncertain articles, they browsed the title and abstract
52 to determine whether or not to include. Full texts of each potentially relevant
53 article will adhere the selection criteria strictly during the title and abstract
54 screening phase. The full texts of all potential articles that met the inclusion
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4 criteria were obtained and reviewed again. Two independent reviewers will
5 screen the full texts for inclusion. If there is any opposition, we will consult or
6 seek the opinion of the third examiner. Reviewers will have no preference to
7 the authors or journals when screening articles.
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10 11 **Data extraction**

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

47 **Primary outcome**

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49 Our primary outcome is functional disability component related to tremors,
50 which is measured by the Fahn-Tolosa-Marin tremor rating scale (TRS)
51 subscales B and C. Rest, posture, and tremor are the three elements of TRS,
52 and ETs are scored using three subscales to assess the severity of the tremor.
53 The three subscales are: the posture and the magnitude of the tremor, the
54 ability to perform certain actions and disabilities in daily living due to tremor.
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4 Each subscale is ranged from 0 to 4, which represents none, mild, moderate,
5 and severe, and overall maximum score is 16, 36, and 32 in each subscale.
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7 Finally, the scores of the three subscales were summed to obtain the overall
8 TRS score.
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10 11 Secondary outcomes

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

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

47 Strategy for data synthesis

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49 The primary tool for data analysis is Review Manager software
50 (RevMan5.3). A random effects model will be managed with data indicators of
51 overall studies for meta-analysis. We will evaluate and analyze the data onto
52 overall included studies and summarized its 95% CIs using a random effects
53 model. The difference will be considered statistically significant when P is less
54 than 0.05. The funnel plot will be used to evaluate heterogeneity between
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3 overall included studies, such as differences of study types, risk of bias,
4 publication bias, differences of measurement resolution, etc.[34]
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7 Analysis of subgroups or subsets 8

9 Subgroup analysis will be carried out if the data were enough. Several
10 subgroup analyses will be used to examine differences between the types of
11 ET (e.g. upper limbs, lower limbs, less commonly the head, voice, tongue,
12 face, trunk and others); age; the different dosage of propranolol; side effect of
13 propranolol; the different therapy of ET; and study designs (e.g. treatment
14 groups vs. no control group, randomized vs. non-randomized controlled trial).
15 Among these variables, the dosage of propranolol and the types of ET are
16 assumed to be the most important as it remains unknown what dosage of
17 propranolol is the most effective against different types of ET.
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27 **Ethics and dissemination** 28

29 Published aggregated data is used in this review analysis and therefore no
30 ethical approval is required, the result will be published in peer-reviewed
31 journals, and proliferation activities will include diverse social stakeholders,
32 non-academic groups, and patients.
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36 **Discussion** 37

38 Treatments for ET can be mainly subdivided into three categories:
39 medicine (propranolol, primidone, topiramate), surgical treatments (deep brain
40 stimulation, gamma-knife surgery, MRIGFUS), and other therapies (botulinum
41 toxin, lifestyle management).[30] So far, there has not been major
42 breakthrough in ET treatments. Propranolol and primidone are generally the
43 first treatment option to treat ET. Propranolol was proved to effective against
44 the treatment of ET in 1973.[35] Published controlled trials have shown that
45 the average effective dose of propranolol is 185.2 mg/days, and the daily dose
46 range is 60-800 mg/day.[36, 37] In addition, there is insufficient evidence to
47 indicate that a dose of over 320 mgs per day would bring any benefits. In the
48 treatment of ET, it can be found that about 50%-70% response. Compared
49 with placebo, the average tremor can be reduced by about 50%.[36, 38]
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4 The primary objective of this systematic review is to evaluate the efficacy
5 and safety of propranolol for ET. We will conduct qualitative and quantitative
6 analysis of overall data included in each study, and we hopefully are able to
7 find the optimal drug dose for the treatment of the ET subgroup. What is more,
8 we will summarize as far as possible the role of propranolol in the treatment of
9 ET, especially for axial tremors. The limitations of this systematic review are
10 mainly due to the heterogeneity of the methodology, which may result in some
11 results not being analyzed.
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19 **Contributors** ZZ, TW, MZ and WL designed the study. The draft agreement
20 was drafted by ZZ, TW and MZ, and revised by all authors. MZ and WL
21 designed the search strategy. MZ, WL and LH will perform the search. LC, LY,
22 TZ, and HS will be included in the study screening to extract data and assess
23 the risk of bias in the included studies. ZZ and YP will dispute disagreements
24 between reviewers. MZ, WL, SG and ZC will analyze and interpret the data. All
25 authors agree to be responsible for all aspects of the work and have read and
26 approved the final draft.
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52 **Competing interests** None declared
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54 **Provenance and peer review** Not commissioned.
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56 **Data Sharing** Data is available in all public databases. Data are available in a
57 public, open access repository. All data relevant to the study are included in
58 the article or uploaded as supplementary information. At same time, data are
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4 available upon reasonable request.

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For peer review only

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-Preorting 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

1		protocol authors; provide physical	
2		mailing address of corresponding	
3		author	
4			
5	Contribution	#3b Describe contributions of protocol	12
6		authors and identify the guarantor	
7		of the review	
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10	Amendments		
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13		#4 If the protocol represents an	n/a
14		amendment of a previously	
15		completed or published protocol,	
16		identify as such and list changes;	
17		otherwise, state plan for	
18		documenting important protocol	
19		amendments	
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24	Support		
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26	Sources	#5a Indicate sources of financial or	12
27		other support for the review	
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30	Sponsor	#5b Provide name for the review	n/a
31		funder and / or sponsor	
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34	Role of	#5c Describe roles of funder(s),	n/a
35	sponsor or	sponsor(s), and / or institution(s), if	
36	funder	any, in developing the protocol	
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39	Introduction		
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42	Rationale	#6 Describe the rationale for the	2-3
43		review in the context of what is	
44		already known	
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47	Objectives	#7 Provide an explicit statement of	4
48		the question(s) the review will	
49		address with reference to	
50		participants, interventions,	
51		comparators, and outcomes	
52		(PICO)	
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57	Methods		
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1	Eligibility	#8	Specify the study characteristics	4-5
2	criteria		(such as PICO, study design,	
3			setting, time frame) and report	
4			characteristics (such as years	
5			considered, language, publication	
6			status) to be used as criteria for	
7			eligibility for the review	
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12	Information	#9	Describe all intended information	5-6
13	sources		sources (such as electronic	
14			databases, contact with study	
15			authors, trial registers or other	
16			grey literature sources) with	
17			planned dates of coverage	
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22	Search	#10	Present draft of search strategy to	6
23	strategy		be used for at least one electronic	
24			database, including planned limits,	
25			such that it could be repeated	
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29	Study records -	#11a	Describe the mechanism(s) that	6
30	data		will be used to manage records	
31	management		and data throughout the review	
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34	Study records -	#11b	State the process that will be used	6-7
35	selection		for selecting studies (such as two	
36	process		independent reviewers) through	
37			each phase of the review (that is,	
38			screening, eligibility and inclusion	
39			in meta-analysis)	
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44	Study records -	#11c	Describe planned method of	6-7
45	data collection		extracting data from reports (such	
46	process		as piloting forms, done	
47			independently, in duplicate), any	
48			processes for obtaining and	
49			confirming data from investigators	
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54	Data items	#12	List and define all variables for	7
55			which data will be sought (such as	
56			PICO items, funding sources), any	
57			pre-planned data assumptions and	
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		simplifications	
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3	Outcomes and	#13	List and define all outcomes for
4	prioritization		which data will be sought,
5			including prioritization of main and
6			additional outcomes, with rationale
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9	Risk of bias in	#14	Describe anticipated methods for
10	individual		assessing risk of bias of individual
11	studies		studies, including whether this will
12			be done at the outcome or study
13			level, or both; state how this
14			information will be used in data
15			synthesis
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20	Data synthesis	#15a	Describe criteria under which
21			study data will be quantitatively
22			synthesised
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26	Data synthesis	#15b	If data are appropriate for
27			quantitative synthesis, describe
28			planned summary measures,
29			methods of handling data and
30			methods of combining data from
31			studies, including any planned
32			exploration of consistency (such
33			as I ² , Kendall's τ)
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39	Data synthesis	#15c	Describe any proposed additional
40			analyses (such as sensitivity or
41			subgroup analyses, meta-
42			regression)
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45	Data synthesis	#15d	If quantitative synthesis is not
46			appropriate, describe the type of
47			summary planned
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51	Meta-bias(es)	#16	Specify any planned assessment
52			of meta-bias(es) (such as
53			publication bias across studies,
54			selective reporting within studies)
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58	Confidence in	#17	Describe how the strength of the
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1 cumulative body of evidence will be assessed
2 evidence (such as GRADE)
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5 CC-BY 4.0. This checklist was completed on 02. June 2019 using <https://www.goodreports.org/>, a
6 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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4 Search strategy

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8 3. random\$.ti.ab. (243,513)
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10 5. clinical trials as topic.mj. (32,507)
11 6. trial.ti.ab (901,271)
12 7. or/1-6 (1,300,135)
13 8. NOT (animals/ not humans/) (6,658,452)
14 9. 7 not 8 (1,117,817)
15 10. Movement disorder.ti.ab. (16,284)
16 11. Tremor.ti.ab. (20,602)
17 12. Essential tremor.ti.ab (3,586)
18 13. Or/10-11 (34,889)
19 14. Essential tremor.ti.ab. (3,586)
20 15. Essential tremor.sh. (1,802)
21 16. Essential tremor*.ti.ab.(3,587)
22 17. Benign essential tremor*.ti.ab.(57)
23 18. Familial tremor*.ti.ab.(194)
24 19. Hereditary essential tremor*.ti.ab.(39)
25 20. Or/14-19 (3,838)
26 21. Therapy.ab.ti (1,788,096)
27 22. Therapy.sh. (4,069,919)
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BMJ Open

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

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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	Essential tremor, Benign essential tremor, Familial tremor, Therapy, Drug therapy, Propranolol

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4 Oral Propranolol for Treatment of the Subgroups of Essential Tremor: a
5 systematic review and meta-analysis protocol.
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38
39 The text contains 3121 words.

40 41 42 **Abstract**

43 44 45 **Introduction**

46
47 Essential tremor (ET), a tremor disorder, is one of the most common
48 movement disorders. Only oral drugs (propranolol, primidone, topiramate, etc.)
49 are still the first-line treatment recommended by the FDA. Propranolol is
50 thought to potentially reduce upper limb action tremor. However, it has a poor
51 effect on axial tremor symptoms, such as essential head tremor and voice
52 tremor. Studies have shown that tremor severity develops over time, possibly
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4 producing other clinical tremors and neurological soft signs (such as memory
5 loss, gait abnormalities, balance disorders, etc.), which further increases the
6 difficulty of treating tremors. However, some recent studies provide emerging
7 evidence for oral propranolol on subgroups of ET, which is based on the
8 anatomical distribution of ET (lower extremities, head, sound, tongue, etc.).
9 This systematic review aims to synthesize these new data to improve the
10 efficacy of propranolol in ET subgroups.
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17 **Methods and analysis**

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19 We will search for randomized controlled trials from the PubMed, MEDLINE,
20 EMBASE, Cochrane Library, UptoDate, and PEDro databases from inception
21 to June 2019. All data will be extracted independently by two reviewers and
22 compared at the end of the review. The two reviewers will screen the study
23 quality, and the Cochrane Collaboration's tool in Review Manager (RevMan)
24 5.3.3 will be used to evaluate risk of bias. Our primary outcome will be the
25 functional disability component related to tremors, as measured by the
26 Fahn-Tolosa-Marin tremor rating scale (TRS) subscales B and C. Secondary
27 outcomes will include severity of tremors and quality of life. Narrative and
28 meta-analytical syntheses are planned.
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38 **Ethics and dissemination**

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40 Published aggregated data will be used in this review analysis and therefore
41 no ethical approval is required. The results will be published in peer-reviewed
42 journals, and proliferation activities will include diverse social stakeholders,
43 non-academic groups, and patients.
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48 **PROSPERO registration number** CRD42018112580

49 **Keywords**

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51 Essential tremor; Benign essential tremor; Familial tremor; Hereditary
52 essential tremor; Therapy; Drug therapy; Propranolol; Propranolol
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58 **Article summary**

59 Strengths and limitations of this study
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4 A continuously updated data extraction form will be used to ensure data
5 integrity and relevance.

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

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

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

16
17 Multiple limitations may increase the heterogeneity of the study, thereby
18 hampering the results of the meta-analysis.

25 **Introduction**

26
27 Essential tremor is a chronic, progressive movement disorder occurring in
28 adults, with a prevalence ranging from 0.4% of the general population to 5% of
29 the population over the age of 65.[1-3] It appears that the prevalence of ET
30 increases exponentially in the aging population.[4] While the direct cause of ET
31 remains unknown, recent reports have indicated that loss or dysfunction of
32 Purkinje's neurons in the cerebellum likely plays a key role in the aetiology of
33 ET,[5-8] and electrophysiological methods reveal abnormal oscillations in the
34 cortical-ponsal-cerebellar-thalamic-cortical loop.[9, 10] It is still unclear why
35 this network is involved in tremor; however, it is thought to be associated with
36 abnormalities in gamma-aminobutyric acid (GABA) transmission in brain
37 tissues of ET patients.[11]

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39 Traditionally, ET is defined as bilateral but systematic kinetic and postural
40 tremors of the upper limbs, voice, head, face, chin, legs or a combination of
41 these symptoms.[12] The incidence of ET usually involves the upper limbs
42 (95% of patients) according to anatomical distribution; less commonly affected
43 are the lower limbs (30%), head (25~34%), sound (12~15%), tongue (7%) face
44 (5%), and trunk (5%), as described in several previous reports.[13-15] There
45 are few ET patients with isolated head tremor.[16, 17] Recently, some studies
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4 indicated that some complementary neurological signs (i.e., other than action
5 tremor), such as mild impaired memory, impaired tandem gait, and subtle
6 dystonic body posturing, are present in patients with ET. These clinical
7 symptoms and signs were so mild that they did not suffice for other
8 neurological diagnoses. It was recently proposed that these presentations
9 might be classified as “essential tremor plus” by the International Parkinson
10 and Movement Disorder Society in 2018.[18]
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17 Despite the presentation of new viewpoints on ET pathogenesis, the
18 treatment of ET remains merely symptomatic. The therapeutic approach to ET
19 still primarily depends on drugs, although surgery may be an option for
20 patients with refractory essential tremor. As of 2018, propranolol and
21 primidone are still two first-line medications for the treatment of primary tremor,
22 according to the recommendations of the US Food and Drug Administration
23 (FDA) and the European Medicines Agency (EMA).[18, 19] In particular, the
24 US FDA approved only propranolol for essential tremor. Conventional wisdom
25 is propranolol is only effective against the upper limb action tremor, while axial
26 tremor symptoms, such as essential head tremor and voice tremor, usually
27 respond poorly to propranolol treatments.[3, 20] Studies have shown that the
28 severity of tremors develops over time, possibly producing other clinical
29 tremors (such as voice tremors) and neurological soft signs (such as memory
30 loss, gait abnormalities, balance disorders, etc.), which makes it even more
31 difficult to tremors.[21, 22] Therefore, we performed subgroup classification
32 based on anatomical distribution and combined it with soft signs of the nervous
33 system to find the best choice for drug control of primary tremors. However,
34 some recent studies provide emerging evidence for oral propranolol on
35 subgroups of ET, which is based on the anatomical distribution of ET (lower
36 extremities, head, hand, tongue, etc.).[23-27] Integration of these new data is
37 necessary to refine the treatment for the efficacy of propranolol in the
38 subgroups of ET.
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The systematic review protocol is performed under the Preferred

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4 Reporting Items for Systematic review and Meta-Analysis Protocols
5 (PRISMA-P) guidelines.
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7 **Patient and public participation**

8 No patients will be involved.
9

10 **Research objective**

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

24 **Eligibility criteria**

25 **Population included**

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

42 The reference intervention is oral propranolol, both long-acting and
43 short-acting formulations. We hypothesize that oral propranolol treatment will
44 be better than other intervention treatments.
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48 **Comparators/control**

49 There are many alternative treatment options for essential tremor,
50 including: (1) non-operative care with primidone, topiramate, botulinum toxin
51 injections or other drug therapies, and (2) operative care with deep brain
52 stimulation or thalamotomy or gamma knife thalamotomy.[30] Briefly, the
53 comparator group will include all other treatments.
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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	<ul style="list-style-type: none"> ● Adults over the age of 16 ● Individuals with diagnosed ET 	<ul style="list-style-type: none"> ● Parkinsonian tremor ● Metabolic tremor ● Toxicity-related tremors ● Dystonic tremor ● Neuropathic tremor ● Functional tremor
Intervention	<ul style="list-style-type: none"> ● Oral propranolol ● Long-acting or short-acting formulation 	<ul style="list-style-type: none"> ● All other intervention types
Comparators	<ul style="list-style-type: none"> ● 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 	<ul style="list-style-type: none"> ● N/A
Outcomes	<p>Primary</p> <ul style="list-style-type: none"> ● Fahn-Tolosa-Marin Tremor Rating Scale <p>Secondary</p> <ul style="list-style-type: none"> ● Tremor severity ● Quality of life 	<ul style="list-style-type: none"> ● N/A
Study designs	<ul style="list-style-type: none"> ● Randomized controlled trials 	<ul style="list-style-type: none"> ● 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

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

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

47 **Primary outcome**

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49 Our primary outcome will be the functional disability component related to
50 tremors, which is measured by the Fahn-Tolosa-Marin TRS subscales B and
51 C. Rest, posture, and tremor are the three elements of TRS, and ETs will be
52 scored using three subscales to assess the severity of the tremor. The three
53 subscales are the posture and the magnitude of the tremor, the ability to
54 perform certain actions and disabilities in daily living due to tremor. Each
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4 subscale ranges from 0 to 4, which represents none, mild, moderate, and
5 severe, and the overall maximum scores are 16, 36, and 32 in each subscale.
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7 Finally, the scores of the three subscales will be summed to obtain the overall
8 TRS score.
9

10 11 Secondary outcomes

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

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

47 Strategy for data synthesis

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49 The primary tool for data analysis will be Review Manager software
50 (RevMan5.3). A random-effects model will be managed with data indicators
51 from all of the studies for meta-analysis. We will evaluate and analyse the data
52 on the overall included studies and summarize its 95% CIs using a
53 random-effects model. Differences will be considered statistically significant
54 when P is less than 0.05. The funnel plot will be used to evaluate
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4 heterogeneity between overall included studies, such as differences in study
5 types, risk of bias, publication bias, differences in measurement resolution,
6 etc.[34]
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8 9 Analysis of subgroups or subsets 10

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

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

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41 Treatments for ET can be mainly subdivided into three categories:
42 medicine (propranolol, primidone, topiramate), surgical treatments (deep brain
43 stimulation, gamma knife surgery, MRIGFUS), and other therapies (botulinum
44 toxin, lifestyle management).[30] Thus far, there has not been a major
45 breakthrough in ET treatments. Propranolol and primidone are generally the
46 first treatment options in treating ET. Propranolol was proven to be effective
47 against the treatment of ET in 1973.[35] Furthermore, published controlled
48 trials have shown that the average effective dose of propranolol is 185.2
49 mg/day, and the daily dose range is 60-800 mg/day.[36, 37] In addition, there
50 is insufficient evidence indicating that a dose over 320 mg per day would
51 provide any benefits. In the treatment of ET, an approximately 50%-70%
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4 response was observed. Compared with placebo, the average tremor can be
5 reduced by approximately 50%.[36, 38]
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8 The primary objective of this systematic review will be to evaluate the
9 efficacy and safety of propranolol in the treatment of ET. We will conduct a
10 qualitative and quantitative analysis of the overall data included in each study,
11 and we will hopefully find the optimal drug dose for the treatment of the ET
12 subgroup. Furthermore, we will summarize as much as possible the role of
13 propranolol in the treatment of ET, especially for axial tremors. The limitations
14 of this systematic review are mainly due to the heterogeneity of the
15 methodology, which may result in some results not being analysed.
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18
19 **Contributors** ZZ, TW, MZ and WL designed the study. The draft agreement
20 was drafted by ZZ, TW and MZ, and revised by all authors. MZ and WL
21 designed the search strategy. MZ, WL and LH will perform the search. LC, LY,
22 TZ, and HS will be included in the study screening to extract data and assess
23 the risk of bias in the included studies. ZZ and YP will dispute disagreements
24 between reviewers. MZ, WL, SG and ZC will analyse and interpret the data. All
25 authors agree to be responsible for all aspects of the work and have read and
26 approved the final draft.
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29
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34 Teaching Reform in Colleges and Universities of Hainan Province of China
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36 Department of Hainan Province of China (grant number 2018-10); Educational
37 Research Projects of Hainan Medical University (grant number HYZ201705);
38

39
40 **Competing interests** None declared
41
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44 **Provenance and peer review** Not commissioned.
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48 **Data Sharing** Data are available in all public databases. Data are available in
49 a public, open access repository. All data relevant to the study are included in
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4 the article or uploaded as supplementary information. At same time, data are
5 available upon reasonable request.
6

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13 <http://creativecommons.org/licenses/by-nc/4.0/>.
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For peer review only

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	13-14

1		protocol authors; provide physical	
2		mailing address of corresponding	
3		author	
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5	Contribution	#3b Describe contributions of protocol	12
6		authors and identify the guarantor	
7		of the review	
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9			
10	Amendments		
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12			
13		#4 If the protocol represents an	n/a
14		amendment of a previously	
15		completed or published protocol,	
16		identify as such and list changes;	
17		otherwise, state plan for	
18		documenting important protocol	
19		amendments	
20			
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24	Support		
25			
26	Sources	#5a Indicate sources of financial or	12
27		other support for the review	
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30	Sponsor	#5b Provide name for the review	n/a
31		funder and / or sponsor	
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34	Role of	#5c Describe roles of funder(s),	n/a
35	sponsor or	sponsor(s), and / or institution(s), if	
36	funder	any, in developing the protocol	
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39	Introduction		
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42	Rationale	#6 Describe the rationale for the	2-3
43		review in the context of what is	
44		already known	
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47	Objectives	#7 Provide an explicit statement of	4
48		the question(s) the review will	
49		address with reference to	
50		participants, interventions,	
51		comparators, and outcomes	
52		(PICO)	
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57	Methods		
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1	Eligibility	#8	Specify the study characteristics	4-5
2	criteria		(such as PICO, study design,	
3			setting, time frame) and report	
4			characteristics (such as years	
5			considered, language, publication	
6			status) to be used as criteria for	
7			eligibility for the review	
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12	Information	#9	Describe all intended information	5-6
13	sources		sources (such as electronic	
14			databases, contact with study	
15			authors, trial registers or other	
16			grey literature sources) with	
17			planned dates of coverage	
18				
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22	Search	#10	Present draft of search strategy to	6
23	strategy		be used for at least one electronic	
24			database, including planned limits,	
25			such that it could be repeated	
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29	Study records -	#11a	Describe the mechanism(s) that	6
30	data		will be used to manage records	
31	management		and data throughout the review	
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34	Study records -	#11b	State the process that will be used	6-7
35	selection		for selecting studies (such as two	
36	process		independent reviewers) through	
37			each phase of the review (that is,	
38			screening, eligibility and inclusion	
39			in meta-analysis)	
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44	Study records -	#11c	Describe planned method of	6-7
45	data collection		extracting data from reports (such	
46	process		as piloting forms, done	
47			independently, in duplicate), any	
48			processes for obtaining and	
49			confirming data from investigators	
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52				
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54	Data items	#12	List and define all variables for	7
55			which data will be sought (such as	
56			PICO items, funding sources), any	
57			pre-planned data assumptions and	
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		simplifications	
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3	Outcomes and	#13	List and define all outcomes for
4	prioritization		which data will be sought,
5			including prioritization of main and
6			additional outcomes, with rationale
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8			
9	Risk of bias in	#14	Describe anticipated methods for
10	individual		assessing risk of bias of individual
11	studies		studies, including whether this will
12			be done at the outcome or study
13			level, or both; state how this
14			information will be used in data
15			synthesis
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20	Data synthesis	#15a	Describe criteria under which
21			study data will be quantitatively
22			synthesised
23			
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25			
26	Data synthesis	#15b	If data are appropriate for
27			quantitative synthesis, describe
28			planned summary measures,
29			methods of handling data and
30			methods of combining data from
31			studies, including any planned
32			exploration of consistency (such
33			as I ² , Kendall's τ)
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39	Data synthesis	#15c	Describe any proposed additional
40			analyses (such as sensitivity or
41			subgroup analyses, meta-
42			regression)
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46	Data synthesis	#15d	If quantitative synthesis is not
47			appropriate, describe the type of
48			summary planned
49			
50			
51	Meta-bias(es)	#16	Specify any planned assessment
52			of meta-bias(es) (such as
53			publication bias across studies,
54			selective reporting within studies)
55			
56			
57			
58	Confidence in	#17	Describe how the strength of the
59			
60			

1 cumulative body of evidence will be assessed
2 evidence (such as GRADE)
3

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5 CC-BY 4.0. This checklist was completed on 02. June 2019 using <https://www.goodreports.org/>, a
6 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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3 Medline

4 Search strategy

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