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Review articles

Effectiveness of nonsurgical treatments for trigeminal neuralgia: an overview protocol

David Sildes Fidelis Florêncio[1]
https://orcid.org/0000-0002-2153-0698

Ana Luiza Caldas Garcia[1]
https://orcid.org/0000-0003-4817-4539

Edna Pereira Gomes de Morais[2]
https://orcid.org/0000-0002-0034-0166

Silvia Damasceno Benevides[1]
https://orcid.org/0000-0002-4877-0835

Giorvan Ânderson dos Santos Alves[1]
https://orcid.org/0000-0003-1619-0139

[1] Universidade Federal da Paraíba - UFPB, João Pessoa, Paraíba, Brasil.

[2] Universidade Estadual de Ciências da Saúde de Alagoas - UNCISAL, Maceió, Alagoas, Brasil.

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Corresponding address:
Giorvan Ânderson dos Santos Alves
Rua Dr. Ivanildo Guedes Pessoa, 184, Apto 901 - Jardim Oceania
CEP: 58037-325 - João Pessoa, Paraíba, Brasil
E-mail: anderson_ufpb@yahoo.com.br

ABSTRACT

Purpose: to present an overview protocol for systematic reviews to synthesize and describe available evidence on the effectiveness of nonsurgical treatments for trigeminal neuralgia.

Methods: the protocol follows the method proposed by PRISMA-P guidelines for protocol reports. The search will be made in MEDLINE, EMBASE, LILACS, Cochrane, Web of Science, Scopus, SpeechBITE, PeDRO, and the grey literature (Google Scholar and ProQuest Dissertations and Theses), with no restriction on language or time of publication. A search strategy developed for MEDLINE will be adapted for each database. Two independent reviewers will screen the articles by title and abstract. Then, they will read the full texts of included articles, following the eligibility criteria. In case of disagreements, a third reviewer will come to a consensus. The data will be extracted with a standardized form. Information on the risk of bias and GRADE assessment will be recorded. AMSTAR-2 will assess the overall result reliability of the systematic reviews. Results will be presented in a flowchart, tables, and a narrative description.

Final Considerations: once carried out, this protocol will describe the current body of research on the topic and identify existing gaps on the basis of evidence.

Keywords: Trigeminal Neuralgia; Complementary Therapies; Meta-Analysis as Topic; Systematic Review; Meta-Analysis

INTRODUCTION

Trigeminal neuralgia (TN) is a rare disease that affects the fifth cranial nerve (trigeminal nerve). It is one of the facial neuropathic pain syndromes, which are divided into three etiological categories: idiopathic TN with no neurovascular contact or neurovascular contact without morphological changes in the trigeminal root; classic TN, caused by neurovascular compression with morphological changes in the trigeminal root; and TN secondary to an underlying pathology. Based on this classification, primary TN describes patients with either idiopathic or classic TN[1-5].

About 4.3 to 27 new cases of this disease per 100,000 people are identified every year. Women, especially after the fourth decade of life, have the highest incidence of the disease[6].

Painful symptomatology runs through one or two of the three trigeminal nerve branches – V_2 and V_3 are the most affected ones, usually on only one side of the face. The pain is classified into two phenotypes: TN with paroxysmal pain and TN with continuous pain. The pain is intense and lasts from a few seconds to 2 minutes; however, episodes can be recurrent. These episodes are triggered by non-painful stimuli, such as touching, moving, smiling, brushing the teeth, combing the hair, putting makeup on, shaving, wind blowing or water dropping on the face, and so forth. This condition also changes essential orofacial functions, such as speaking, chewing, and swallowing[2,6,7].

TN is a disabling disease, and its impact on the quality of life may easily progress to a psychiatric disorder. Wu et al.[8] conducted a retrospective cohort study on Taiwanese people to explore the relationship between TN and the subsequent development of psychiatric disorders, including schizophrenia, bipolar disorder, depressive disorder, anxiety disorder, and sleep disorder. Patients with and without TN were matched for age and sex. The cohorts comprised 3,273 patients with TN and 13,092 without TN. The study concluded that TN may increase the risk of depressive disorder, anxiety disorder, and sleep disorder[8].

The first-line treatment for this disease is pharmacotherapy, which can immediately control it. However, long-term use diminishes its effectiveness after the pain had been subdued, thus requiring new drug management. Adverse drug effects also limit adherence to this therapy – for instance, patients report changes in cognition, lack of concentration and memory, sleepiness, instability, nausea, skin rash, and blood dyscrasia[8-10].

A cohort study by Benoliel et al.[10] aimed to analyze demographic and clinical characteristics associated with pharmacotherapy results in classic TN patients. The researchers concluded that prolonged disease duration and autonomic signs are indicators of a poor prognosis. The study also pointed out that long episode duration is yet another sign of a negative prognosis related to pharmacotherapy[10].

When pharmacotherapy does not control TN as desired, surgical interventions are indicated. Nevertheless, despite the evidence that surgical procedures variably relieve the pain, there are also side effects, sensory loss, and pain recurrence rates in the long run. The literature still lacks evidence to support comparative decision-making regarding the best surgical procedure[11].

The literature indicates that even after successful surgery, some patients suffer pain recurrence in different degrees during follow-up. A large-scale formal meta-analysis by Holste et al.[12] demonstrated that 76.0% of patients reported being pain-free after microvascular decompression surgery[12]. Other studies showed great variability in recurrence rate reports following this surgical procedure, ranging from 0 to 26.6%[13,14].

Nonsurgical interventions can be recommended as treatment alternatives prior to surgical indication. There are various nonsurgical, complementary therapy interventions – e.g., pharmacotherapy, exercise therapy, psychological therapy, musculoskeletal manipulation, manual therapy, mindfulness, mind-body therapy, relaxation therapy, cognitive-behavioral therapy, photobiomodulation, botulinum toxin, and acupuncture[6,15-17].

It is indispensable to investigate the available high-quality information on the strength of evidence for the effectiveness, efficacy, and safety of nonsurgical interventions in TN treatment and systematically synthesize such evidence in an overview to guide decision-making by TN patients, physicians, therapists, researchers, and health policymakers.

Therefore, this paper aimed at presenting an overview protocol for systematic reviews to synthesize evidence and identify areas that remain unclear and gaps in the evidence on the effectiveness of nonsurgical TN treatment.

METHODS

The protocol for this overview was constructed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols

(PRISMA-P)[18] and then submitted to the International Prospective Register of Systematic Reviews (PROSPERO) on October 30, 2021, under approval number CRD42021282682. Given the interactive nature of this type of study, there may be methodological changes in the protocol, which will be reported in the overview.

The PICOS strategy – encompassing population, intervention, comparison, outcome, and study type[19] – will be used to include studies, as follows: a) Population – individuals 18 years or older, diagnosed with idiopathic or classic TN; b) Intervention – systematic reviews addressing randomized clinical trials of nonsurgical interventions (e.g., pharmacotherapy, exercise therapy, psychological therapy, musculoskeletal manipulation, manual therapy, mindfulness, mind-body therapy, relaxation therapy, cognitive-behavioral therapy, photobiomodulation, botulinum toxin, and acupuncture) to ease the pain and improve functions in people with TN; c) Comparison – studies comparing intervention A with intervention B, intervention group with control or placebo group, or combined interventions A + B with placebo; d) Outcome – the pain will be assessed as primary outcome; and masticatory function, mandibular function, and the quality of life, as secondary outcome; e) Study types – systematic reviews of interventions. This strategy will be used to answer the following research question: "What is the effectiveness of nonsurgical TN treatments?".

Eligibility criteria

The inclusion criteria were as follows: systematic reviews with no restriction on time or language, with subjects 18 years or older, diagnosed with idiopathic or classic TN, approaching any nonsurgical treatments; studies comparing intervention A with intervention B, intervention group with control or placebo group, or combined interventions A + B with placebo. Systematic reviews must completely report randomized clinical trials, assessing the effectiveness of nonsurgical TN treatments. In the case of updated reviews, only the most recent version will be included.

Systematic reviews including articles whose subjects had comorbidities or TN secondary to another pathology, studies whose full text is inaccessible, and reviews including studies with participants under 18 years old (unless they reported separate results for participants 18 years or older) will be excluded.

Search strategy and sources of information

Systematic reviews will be retrieved through a comprehensive and systematic approach with bibliographic search in the following databases: MEDLINE via PubMed, LILACS via VHL (Virtual Health Library), EMBASE, Cochrane Library, Web of Science, Scopus, SpeechBITE, and PeDRO, besides additional search in the grey literature (Google Scholar and ProQuest Dissertations and Theses).

Researchers constructed the search strategy in MEDLINE via PubMed (Chart 1) and will adapt it to each database, applying specific descriptors and previously testing their sensitivity (Chart 1) to retrieve eligible studies. The terms were selected by searching descriptors in PubMed Medical Subject Headings (MeSH) and ENTRY Terms, considering the pathology, interventions, and outcomes researched in this review. No search restriction on time and language of publication will be used.

Study selection

Identified articles will be imported to reference management Mendeley Desktop software 1.19.8, which identifies and removes duplicate papers. Then, studies will be imported to Rayyan (Qatar Computing Research Institute, Doha, Qatar), a free online software application for the web and mobile phones, which blinds reviewers and improves data screening. Two reviewers blind to each other's judgments will classify each article for inclusion or exclusion based on its title and abstract, recording their decisions on the platform. Articles whose abstracts were included will be retrieved in full text and considered for this review.

The above stages will be conducted by two initially independent reviewers. In case of divergences regarding either abstracts or full texts, the conflicts will be discussed and solved. When no consensus is reached, a third reviewer will be included. Research results will be published in full, and the selection process will be described in a flowchart, as indicated by PRISMA. Article authors will also be consulted for further information, when necessary, up to three times over 6 weeks, during the study selection process.

Chart 1. Search strategy – Medline via PubMed (search made on October 24, 2021, and updated on June 4, 2022)

Search	Keyword	Records found
#1	"Trigeminal Neuralgia"[Mesh] OR (Neuralgia, Trigeminal) OR (Trigeminal Neuralgias) OR (Tic Doloureux) OR (Fothergill Disease) OR (Disease, Fothergill) OR (Trifacial Neuralgia) OR (Neuralgia, Trifacial) OR (Trifacial Neuralgias) OR (Tic Douloureux) OR (Epileptiform Neuralgia) OR (Epileptiform Neuralgias) OR (Neuralgia, Epileptiform) OR (Secondary Trigeminal Neuralgia) OR (Neuralgia, Secondary Trigeminal) OR (Secondary Trigeminal Neuralgias) OR (Trigeminal Neuralgia, Secondary) OR (Trigeminal Neuralgia, Idiopathic) OR (Idiopathic Trigeminal Neuralgia) OR (Idiopathic Trigeminal Neuralgias) OR (Neuralgia, Idiopathic Trigeminal)	9,970 results
#2	"therapy" [Subheading] OR (treatment) OR (disease management)	12,601,137 results
#3	"Musculoskeletal Manipulations"[Mesh] OR (Manipulations, Musculoskeletal) OR (Manipulation Therapy) OR (Manipulative Therapies) OR (Manipulative Therapy) OR (Therapies, Manipulative) OR (Therapy, Manipulative) OR (Therapy, Manipulation) OR (Manipulation Therapies) OR (Therapies, Manipulation) OR (Reflexology) OR (Bodywork) OR (Bodyworks) OR (Rolfing) OR (Craniosacral Massage) OR (Massage, Craniosacral) OR (Manual Therapies) OR (Manual Therapy) OR (Therapies, Manual) OR (Therapy, Manual)	64,999 results
#4	"Acupuncture Therapy"[Mesh] OR (Acupuncture Treatment) OR (Acupuncture TreatmentS) OR (Treatment, Acupuncture) OR (Therapy, Acupuncture) OR (Pharmacoacupuncture Treatment) OR (Treatment, Pharmacoacupuncture) OR (Pharmacoacupuncture Therapy) OR (Therapy, Pharmacoacupuncture) OR (Acupotomy) OR (Acupotomies)	34,908 results
#5	"Exercise Therapy"[Mesh] OR (Remedial Exercise) OR (Exercise, Remedial) OR (Exercises, Remedial) OR (Remedial Exercises) OR (Therapy, Exercise) OR (Exercise Therapies) OR (Therapies, Exercise) OR (Rehabilitation Exercise) OR (Exercise, Rehabilitation) OR (Exercises, Rehabilitation) OR (Rehabilitation Exercises)	172,692 results
#6	"Mind-Body Therapies"[Mesh] OR (Mind Body Therapies) OR (Mind-Body Therapy) OR (Therapies, Mind-Body) OR (Therapy, Mind-Body) OR (Mind-Body Medicine) OR (Mind Body Medicine)	50,866 results
#7	"Relaxation Therapy"[Mesh] OR (Therapy, Relaxation) OR (Therapeutic Relaxation) OR (Relaxation, Therapeutic) OR (Relaxation Techniques) OR (Relaxation Technique) OR (Technique, Relaxation) OR (Techniques, Relaxation) OR (Relaxation Technics) OR (Relaxation Technic) OR (Technic, Relaxation) OR (Nature Therapy) OR (Nature Therapies) OR (Therapy, Nature) OR (Ecotherapy) OR (Ecotherapies)	134,147 results
#8	"Behavior Therapy"[Mesh] OR (Behavior Therapies) OR (Therapy, Conditioning) OR (Conditioning Therapy) OR (Conditioning Therapies) OR (Therapy, Behavior) OR (Behavior Treatment) OR (Treatment, Behavior) OR (Behavior Modification) OR (Behavior Modifications) OR (Modification, Behavior)	377,678 results
#9	"Physical Therapy Modalities"[Mesh] OR (Modalities, Physical Therapy) OR (Modality, Physical Therapy) OR (Physical Therapy Modality) OR (Physiotherapy (Techniques)) OR (Physiotherapies (Techniques)) OR (Physical Therapy Techniques) OR (Physical Therapy Technique) OR (Techniques, Physical Therapy) OR (Group Physiotherapy) OR (Group Physiotherapies) OR (Physiotherapies, Group) OR (Physiotherapy, Group) OR (Physical Therapy) OR (Physical Therapies) OR (Therapy, Physical) OR (Neurological Physiotherapy) OR (Neurological Physiotherapy) OR (Physiotherapy, Neurological) OR (Neurophysiotherapy)	402,249 results
#10	"Mindfulness"[Mesh]	5,397 results
#11	"Drug Therapy"[Mesh] OR (Therapy, Drug) OR (Drug Therapies) OR (Therapies, Drug) OR (Chemotherapy) OR (Chemotherapies) OR (Pharmacotherapy) OR (Pharmacotherapies)	3,797,223 results
#12	"Low-Level Light Therapy"[Mesh] OR (Light Therapies, Low-Level) OR (Light Therapy, Low-Level) OR (Low Level Light Therapy) OR (Low-Level Light Therapies) OR (Therapies, Low-Level Light) OR (Therapy, Low-Level Light) OR (Photobiomodulation Therapy) OR (Photobiomodulation Therapies) OR (Therapies, Photobiomodulation) OR (Therapy, Photobiomodulation) OR (LLLT) OR (Laser Therapy, Low-Level) OR (Laser Therapies, Low-Level) OR (Laser Therapy, Low Level) OR (Low-Level Laser Therapies) OR (Laser Irradiation, Low-Power) OR (Irradiation, Low-Power Laser) OR (Laser Irradiation, Low Power) OR (Low-Power Laser Therapy) OR (Low Power Laser Therapy) OR (Laser Therapy, Low-Power) OR (Laser Therapies, Low-Power) OR (Laser Therapy, Low Power) OR (Low-Power Laser Therapies) OR (Low-Level Laser Therapy) OR (Low Level Laser Therapy) OR (Low-Power Laser Irradiation) OR (Low Power Laser Irradiation) OR (Laser Biostimulation) OR (Biostimulation, Laser) OR (Laser Phototherapy) OR (Phototherapy, Laser)	14,252 results
#13	"Botulinum Toxins"[Mesh] OR (Toxins, Botulinum) OR (Botulinum Neurotoxins) OR (Neurotoxins, Botulinum) OR (Botulinum Toxin) OR (Toxin, Botulinum) OR (Clostridium botulinum Toxins) OR (Toxins, Clostridium botulinum) OR (Botulinum Neurotoxin) OR (Neurotoxin, Botulinum) OR (Botulin)	24,304 results
#14	"Placebo Effect"[Mesh] OR (Effect, Placebo) OR (Placebo Response) OR (Response, Placebo)	123,401 results
#15	"systematic review"[Publication Type] OR "systematic reviews as topic"[MesH] OR "systematic review" OR "meta-analysis" OR "meta-analysis as topic"[MesH] OR "meta-analysis" OR "network meta-analysis"[MesH] OR "network meta-analysis")	383,494 results
# 16	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	12,758,299 results
#17	#1 AND #16	7,411 results
#18	#17 AND #15	171 results

Data extraction

Two or more independent reviewers will extract the data from included reviews with a data extraction tool developed by the reviewers (Chart 2). The data will encompass specific details on the title, author(s), year of publication, country of origin, objective of the review, number of studies, number of participants, number of databases researched, name of databases researched, date intervals in the databases researched, date of the last research update, population/sample size, age, sex, TN classification, intervention type, dose, frequency, and duration, the instrument used to assess treatment results, type of comparator, primary outcome, secondary outcome, 95% confidence intervals (CI), risk ratios (RR), risk difference (RD), number needed to treat for benefit (NNTB), number needed to treat for harm (NNTH), mean differences, standardized mean difference, study limitations, AMSTAR-2, risk of bias, and certainty of evidence (GRADE). The tool developed to extract data will be modified and revised as necessary throughout the process of extracting data from each source of evidence. Modifications will be described in detail in the overview.

Chart 2. Data extraction instrument

Systematic review identification:	
Title:	
Author(s):	
Year of publication:	
Country of origin:	
Objective of the review:	
Number of studies:	
Number of participants:	
Number of databases researched:	
Name of databases researched:	
Date intervals in the databases researched:	
Date of the last research update:	
POPULATION	**COMPARISON**
Population/sample size:	Type of comparator:
Age:	Dose:
Sex:	Frequency:
Trigeminal neuralgia classification:	Duration:
INTERVENTION	**OUTCOME**
Type:	Primary outcome:
Dose:	Secondary outcome:
Frequency:	
Duration:	
Instrument used to assess treatment results:	
STATISTICAL SUMMARIES	**ADDITIONAL INFORMATION**
95% confidence intervals (CI):	Limitations:
Risk ratios (RR):	AMSTAR-2:
Risk difference (RD):	Risk of bias:
Number needed to treat for benefit (NNTB):	Certainty of evidence (GRADE):
Number needed to treat for harm (NNTH):	
Mean differences:	
Standardized mean difference:	

Methodological quality assessment of included reviews

The methodological quality of the systematic reviews will be assessed with AMSTAR-2. This instrument has 16 items that comprehensively assess the quality of systematic reviews and together judge the reliability of their results[20].

Two independent reviewers will assess the items and judge the reliability of each review sample independently and in duplicate. Discrepancies will be solved by consensus or resorting to a third author.

Risk of bias

Assessments of risk of bias will not be repeated or updated; instead, the assessments present in the systematic reviews will be reported.

Certainty of evidence of included reviews

When available, the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[21] will be reported; it judges the certainty of each basic comparison for primary results. GRADE uses five approaches (risk of bias, inconsistencies, imprecision, indirect evidence, and publication bias) to assess the certainty of the body of evidence for each result. GRADE judgments indicate the following degrees of certainty in systematic review conclusions: high – certainty that the true effect is close to the estimated effect; moderate – moderately certain of the estimated effect, as the true effect is probably close to the estimated effect, though it may be substantially different; low – certainty of the estimated effect is limited, as the true effect may be substantially different from the estimated effect; very low – little certainty of the estimated effect, as the true effect is probably substantially different from the estimated effect.

Result measures

Results will be considered when outcomes are assessed with validated clinical and/or instrumental protocols that assess nonsurgical intervention effects, encompassing measurements of the pain (defined as pain intensity, measured in a continuous self-report scale, such as a visual analog scale [VAS], numerical classification scale [NCS], or brief pain inventory [BPI]), masticatory function and mandibular function (measured with protocols, such as the Orofacial Myofunctional Evaluation Protocol with Scores-extended [OMES-E] or MBGR protocol), and health-related quality of life (measured with a validated tool, such as the Medical Outcome Study 36-Item Short Form (SF-36) or Oral Health Impact Profile (OHIP-14).

Data synthesis

Data will be analyzed to meet the research objectives, characterizing study methodologies and identifying similarities and differences between them.

Primary and secondary outcomes will be presented in decreasing order of certainty of evidence (i.e., from high to very low evidence). The certainty of intervention effect is expected to be judged according to GRADE rating in most cases.

Neither statistical data synthesis nor any informal indirect comparisons will be made regarding the evidence presented in two or more reviews of different interventions that share a common comparator.

Effect sizes will be converted whenever possible into common scales to facilitate interpretation (e.g., pain intensity measures in continuous scales will be converted into a common 0-100 scale).

If available, effects will be presented in dichotomous outcomes, such as relative risks and risk differences, with the 95% CI, which can be converted into NNTB and NNTH. Comparisons will be limited to data available in the included reviews.

Extracted data will be presented in a flowchart, tables, and narrative summary, with a discussion that will clearly describe the results, free from any informal indirect comparisons.

DISCUSSION

The objective of this overview is to answer the research question, gathering evidence on the effectiveness of nonsurgical treatments for people with TN. This will be the first overview addressing the proposed topic and objective. This process aims to map the general body of evidence and thus identify where systematic reviews and primary research are needed. Previously publishing this overview protocol will help batter plan the study and publicize the research to the scientific community.

This overview will provide synthesized information on nonsurgical treatments using interventions either alone or complementary to TN pain treatment. It will also investigate their effects on the masticatory function, mandibular function, and quality of life of people who suffer from this pathology.

The strength in publicizing this overview protocol for systematic reviews is in making known a clear and reproducible procedure. The paper will be useful to patients and health policymakers, as TN is not yet recognized as a disabling disease and TN patients are not covered by occupational insurance. Because it is an overview, the methodological quality of the studies will be assessed, and their certainty of evidence and risk of bias will be reported. This information will help professionals in both clinical practice and academic settings, providing scientific evidence to aid decision-making and pave the way for future research.

FINAL CONSIDERATIONS

This overview protocol for systematic reviews was developed according to Chapter V (Overview) in the Cochrane Handbook for Systematic Reviews of Interventions (second edition)[22] and the PRISMA guidelines for this type of study; hence, it is ready to be carried out. This instrument will synthesize the current evidence on the topic, aiding decision-making and health policymaking and identifying existing gaps for future research.

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