Review Article

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Efficacy of medications in adult patients with trigeminal neuralgia compared to placebo intervention: a systematic review with meta-analyses

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Background: Trigeminal neuralgia (TN) is characterized by brief, unilateral, sharp, stabbing, and shooting pain of the fifth cranial nerve. The objective of this systematic review with meta-analysis was to determine the effect of medications compared to placebo in adult patients with TN.

Methods: Review authors identified randomized placebo-controlled trials (RCTs) from PubMed, Web of Science, Cochrane, and EMBASE up to February 2021. We assessed the inclusion and exclusion criteria as well as the risk of bias of the studies based on the Cochrane Handbook. A total of 324 unduplicated references were scanned independently and reduced to eight relevant RCTs, with 89 patients included. Medications investigated included oral carbamazepine, subcutaneous sumatriptan, lidocaine (intranasal, 8% spray on the oral mucosa or intravenous), buprenorphine (ganglionic local opioid analgesia), and oral Nav1.7, a selective sodium channel blocker.

Results: Meta-analyses showed that overall patients receiving lidocaine reported a significantly lower post-treatment intensity of pain −3.8 points on a 0–10 scale (95% CI = −4.653 to −2.873; $P < 0.001$). Patients who received lidocaine were 8.62 times more likely to have pain improvement than patients on placebo ($P < 0.001$). In one RCT, patients receiving oral carbamazepine showed a significant improvement in pain intensity of −32% compared to the placebo ($P < 0.001$). In one trial, patients receiving 3 mg subcutaneous sumatriptan had a significantly lower intensity of pain on average −6.1 points on a scale of 0–10 compared to placebo ($P < 0.001$) and a significant improvement in pain intensity of −75% compared to the improvement in the placebo group ($P < 0.001$). Patients who received subcutaneous sumatriptan were 10 times more likely to have pain improvement than those who received placebo ($P = 0.001$) in one study. Due to the unclear/high risk of bias and small sample size, the quality of the evidence for lidocaine in the treatment of TN was low.

Conclusion: Further studies are needed for carbamazepine, sumatriptan, buprenorphine, and oral Nav1.7 sodium channel blockers, as only one study reported outcomes.

Keywords: Carbamazepine; Lidocaine; Meta-Analysis; Systematic Review; Trigeminal Neuralgia; Visual Analog Scale.

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INTRODUCTION

Trigeminal Neuralgia (TN) is defined as recurrent, unilateral, brief, electric shock-like pain affecting one or more divisions of the trigeminal nerve [1]. It may occur due to another diagnosed disorder or develop without an apparent cause [2]. The differential diagnosis of this condition includes but is not limited to toothache, temporomandibular joint disorders (TMD), and a variety of different types of headache disorders. Pain can be triggered by ordinary stimuli such as light touch while eating, shaving, or a breeze to the perioral or intraoral site [3]. Classical TN is a chronic pain disorder described as one of the most severe pains that one can experience [4]. Other types of TN include classical TN with concomitant continuous pain, secondary TN, and idiopathic TN [2].

The exact cause of TN remains unknown [5]. The most prevalent theory of TN etiology is that the root entry zone of the trigeminal nerve is compressed by blood vessels, which causes demyelination of the trigeminal sensory nerve fibers [4,6]. However, it should be noted that a substantial number of patients have magnetic resonance evidence of neurovascular compression without any symptoms [4].

Treatment for TN is typically successful; the anticonvulsant drug carbamazepine is often prescribed, as it has been studied extensively in the literature in controlled trials [7-10]. The number needed to treat (NNT) with carbamazepine to obtain one patient with at least 50% pain relief compared to placebo was 1.7 [11]. When carbamazepine does not prove effective in the management of TN, other anticonvulsants (i.e., gabapentin, oxcarbazepine, phenytoin, lamotrigine, and valproic acid), local anesthetics (such as lidocaine), opioids, sodium channel blockers, and botulinum toxin type A may be considered as second-line treatments [11,12]. Medications may stabilize the cell membrane by interfering with different ion channels to prevent the creation and propagation of an action potential, thereby inhibiting pain signals [13].

The varying mechanisms of action of anticonvulsants include effects on repetitive neuronal firing mechanisms, effects on neuronal networks, effects on neurotransmitter action, and effects on neuronal ionic transport [14]. Several anticonvulsant drugs such as carbamazepine and oxcarbazepine block sodium channels, stabilize the membrane, and therefore prevent action potentials [15]. Other anticonvulsants such as valproic acid may target gamma-aminobutyric acid (GABA) receptors [16]. In comparison, gabapentin and pregabalin are designed to block calcium channels and inhibit the presynaptic release of excitatory neurotransmitters [17].

Local anesthetics bind to voltage-gated sodium channels in the plasma membrane of the nerve, reversibly inhibiting nerve transmission [18]. These sodium channels are anchored in the membrane; when a local anesthetic binds to this channel, the membrane becomes impermeable to sodium (Na), thereby preventing an action potential from being initiated or propagated [18]. The mechanism of action of selective sodium blockers is similar, as sodium channels exist only in peripheral nerves and can be blocked at the resting state, which allows the selective blockade of damaged, overexcited nerves [19].

Opioids imitate the actions of endogenous opioid peptides by interacting with specific opioid receptors, such as μ, δ, and κ [20]. Opioids are mainly inhibitory; when they couple with G-proteins, N-type voltage-operated calcium channels close and calcium-dependent potassium channels open, and the neuron's excitability is reduced due to the hyperpolarization of the membrane [20]. Opioids also regulate the release of nociceptive neurotransmitters, such as substance P, by decreasing intracellular cyclic adenosine monophosphate [20].

Botulinum toxin has also been systematically reviewed for its effectiveness in the treatment of TN [21,22]. Although not within the scope of this review, it is currently under consideration as a treatment modality [22]. The mechanism of action includes extracellular binding of the medication to glycoprotein structures that

are found on terminals of cholinergic nerves, which causes a blockade of intracellular acetylcholine secretion [23].

Other interventions not typically prescribed for TN that have been investigated include triptans (sumatriptan), herbal medications, physical therapy, cannabidiol (CBD), and transcutaneous electrical nerve stimulation (TENS). Although surgical management of TN (microvascular decompression) may be indicated, especially when a patient becomes refractory to medication, these patients are outside the scope of this review. It should be noted that surgical interventions are considered when medication interventions fail and include procedures such as microvascular decompression surgery, percutaneous radiofrequency rhizotomy, stereotactic radiosurgery, and gamma knife surgery [24].

Objective

The aim of this systematic review with meta-analyses was to determine the effect of medications compared to placebo in adult patients with TN, when considering both subjective pain outcomes and secondary pain outcomes.

METHODS

1. Research question

The authors followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [25], and the protocol was registered with PROSPERO (# BLINDED).

The PICOS question is:

- Type of study: Randomized controlled trials (RCTs).
- Population: Adult patients with TN.
- Intervention: Any medications excluding herbals, CBD, TENS, physical therapy, and botulinum toxin; all routes of administration (subcutaneous, intranasal, or nerve block).
- Comparison: Placebo intervention.
- Outcomes: Primary: pain intensity; Secondary: improvement in TN intensity as a percentage; quality of TN pain; effect of the drug on the number of triggers, hyperalgesia, number of paroxysms, time to treatment failure, preference for treatment by the patient, quality of life outcomes, and adverse effects.
- Setting: Orofacial pain clinic or university clinical care center.

2. Inclusion and exclusion criteria

Studies included publications in English of RCTs on the efficacy of medications of all routes of administration in the treatment of TN compared to placebo groups. Excluded manuscripts included those not in English, pilot studies, open label studies, studies with multiple medications, studies using botulinum toxin, reviews, systematic reviews, meta-analyses, editorials, and practice guidelines. In addition, trials that investigated herbal medications, TENS, physical therapy, and CBD were excluded.

3. Search methods for identification of studies

Four electronic databases (Embase, MEDLINE through PubMed, Web of Science, and Cochrane Library) were searched up to 02/07/2021 using the strategies described in Table 1.

4. Data collection and analysis

Two authors (blinded), after removing duplicates, screened all the articles selected by the search strategy listed in Table 1. The titles and abstracts of all the references were reviewed using the inclusion and exclusion criteria. The full article was reviewed by two authors if there was no agreement. If a disagreement arose between the two reviewers after reviewing the full article, the final inclusion was decided by a third author (blinded). Two authors (blinded) scanned the following for any additional relevant references: the bibliography sections of all literature and systematic reviews, meta-analyses, and clinical guidelines from the original search as well as all eligible included trials. The same two authors reviewed any new references using the same criteria. A third reviewer (blinded) made the final

Table 1. Electronic database search strategies

Electronic database	Search strategy
MEDLINE via PubMed (searched up to 3/26/2020); re-run on 2/7/2021 search strategy:	Language: limit to English Species: limit to Humans Article types: limit to Randomized Controlled Trials, Systematic Reviews, Meta-analysis, Practice Guideline ("Anticonvulsants"[Mesh] OR carbamazepine OR oxcarbazepine OR gabapentin OR anticonvulsant* OR "Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR (Non-Steroidal anti-inflammatory) OR (nonsteroidal anti-inflammatory) OR (non-steroidal anti-inflammatory) OR (non-steroidal anti-inflammatory) OR (nonsteroidal anti- inflammatory) OR diclofenac OR ketorolac OR NSAID* OR "Anesthetics, Local"[Mesh] OR (local anesthetic*) OR (local anesthesia) OR lidocaine OR "Receptors, N-Methyl-D-Aspartate"[Mesh] OR NMDA-receptor OR NMDAR OR "N-methyl-D-aspartate receptor" OR ketamine OR esketamine OR "Sodium Channel Blockers"[Mesh] OR (sodium channel blocker*) OR "Nav1.7" OR "Calcitonin Gene-Related Peptide Receptor Antagonists"[Mesh] OR (calcitonin gene-related peptide) OR (calcitonin gene related peptide) OR CGRP) AND (trigeminal neuralgia) AND random*
The Web of Science (searched up to 3/26/2020); re-run on 2/7/2021 search strategy:	TOPIC: carbamazepine OR oxcarbazepine OR gabapentin OR anticonvulsants OR (Non-Steroidal anti-inflammatory) OR (nonsteroidal anti-inflammatory) OR (non-steroidal anti-inflammatory) OR (non-steroidal anti-inflammatory) OR (nonsteroidal anti-inflammatory) OR diclofenac OR ketorolac OR NSAIDs OR (local anesthetic) OR (local anesthesia) OR lidocaine OR NMDA-receptor OR NMDAR OR (N-methyl-D-aspartate receptor) OR ketamine OR esketamine OR (sodium channel blocker) OR (Nav1.7) OR (calcitonin gene-related peptide) OR (calcitonin gene related peptide) OR CGRP AND TOPIC: (trigeminal neuralgia) AND TOPIC: random OR randomly OR randomized Refined by: DOCUMENT TYPES: (ARTICLE OR REVIEW OR PROCEEDINGS PAPER)
COCHRANE (searched up to 3/26/2020); re-run on 2/7/2021 search strategy:	#1 carbamazepine OR oxcarbazepine OR gabapentin #2 (trigeminal neuralgia) #3 random OR randomly OR randomized #4 #1 AND #2 AND #3 #5 (Non-Steroidal anti-inflammatory) OR (nonsteroidal anti-inflammatory) OR (non-steroidal anti-inflammatory) OR (non-steroidal anti-inflammatory) OR (nonsteroidal anti-inflammatory) OR diclofenac OR ketorolac OR NSAIDs OR (local anesthetic) OR (local anesthesia) OR lidocaine OR NMDA-receptor OR NMDAR OR (N-methyl- D-aspartate receptor) OR ketamine OR esketamine OR (sodium channel blocker) OR (Nav1.7) OR (calcitonin gene-related peptide) OR (calcitonin gene related peptide) OR CGRP #6 #5 AND #2 AND #3 #7 #4 OR #6
EMBASE (searched up to 3/26/2020); re-run on 2/7/2021 search strategy:	#1 'anticonvulsant therapy'/exp OR 'anticonvulsant therapy' OR 'carbamazepine'/exp OR 'carbamazepine' OR 'oxcarbazepine'/exp OR 'oxcarbazepine' OR 'gabapentin'/exp OR 'gabapentin' #2 'nonsteroid anti-inflammatory agent' OR 'diclofenac' OR 'ketorolac' #3 'local anesthetic agent' OR 'lidocaine' #4 'n methyl dextro aspartic acid receptor blocking agent' OR 'ketamine' OR 'esketamine' #5 'sodium channel blocking agent' OR 'sodium channel Nav1.7' #6 'calcitonin gene related peptide' #7 'randomized controlled trial' OR 'randomization' OR randomly OR 'random sample' #8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 #9 'trigeminal neuralgia' #10 #7 AND #8 AND #9 #11 #10 AND ('article'/it OR 'review'/it) Note: limits to article and reviews

decision if there was a disagreement after reviewing the full text.

5. Data extraction and management

From the full-text articles of the eligible RCTs, two authors (blinded) independently extracted data using a pilot form including the study design, recruitment period, inclusion/exclusion criteria, sample size per group, demographics of participants, characteristics of the intervention and placebo therapy, as well as outcomes measured and results reported in the studies. A third reviewer (blinded) resolved any disagreements with the data and information extracted by the two authors (blinded).

6. Assessment of risk of bias in the included studies

Two reviewers independently (blinded) assessed the risk of bias for each included RCT, which was then

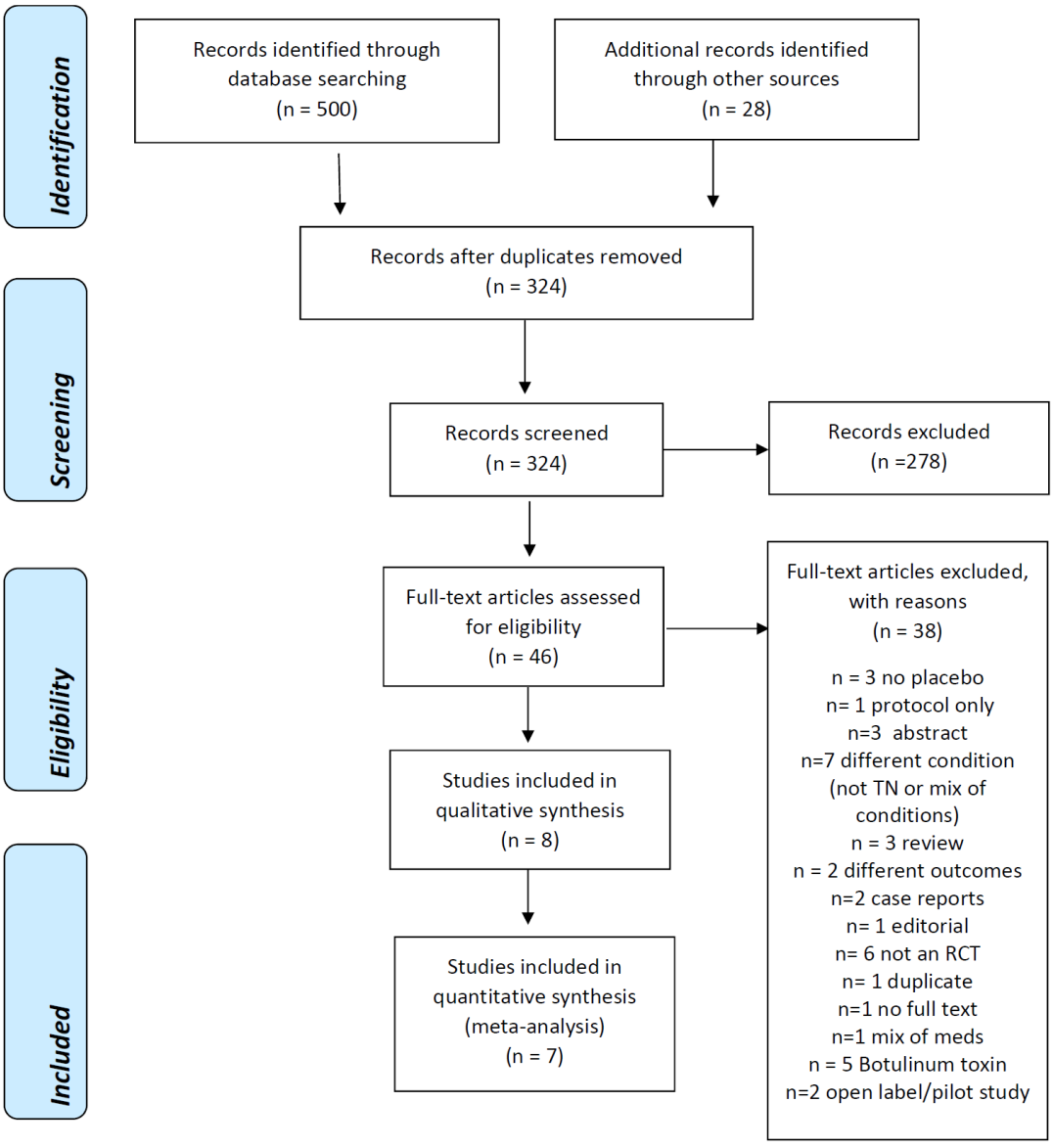

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram. [25] Abbreviations: RCT, Randomized controlled trial; TN, trigeminal neuralgia.

reviewed by a third author (blinded), as part of the extraction process. This approach is in accordance with the method described in the Cochrane Handbook [26].

7. Statistical analyses

Only RCTs on medications for the treatment of TN compared to placebo were included in the meta-analysis. When authors reported medians (m) and interquartile (IQR) ranges = (q1, q3) with q1 = 25% quartile and q3 = 75% quartile, mean and standard deviation (SD) were calculated using the following formulas: mean = (q1 + m + q3)/3; SD = (q3 − q1)/1.35. Pain intensity was reported on a 0 to 10 visual analog scale (VAS) or a 0 to 10 numerical rating scale (NRS).

Regarding pain intensity, treatment effects were expressed as the difference in means (DM) of the change in pain intensity from baseline with 95% confidence intervals (CI). One study reported differences between placebo and 95% CI and was also incorporated in the meta-analysis. Regarding the percentage improvement in TN pain intensity with the intervention, treatment effects were expressed as the difference in means of the change

in pain intensity from baseline with 95% CI. Regarding the number of patients with improved pain/relief, treatment effects were expressed as risk ratios (RRs) with 95% CIs.

All statistical analyses were conducted using Comprehensive Meta-Analysis v3 software (Biostat, Englewood, NJ, USA). Cochran's Q test [27] and the I2 statistic [28] were used to test for heterogeneity. Effect estimates were combined with a random-effects model if there was heterogeneity (Q-test $P < 0.10$), or with the fixed-effect model otherwise.

8. Subgroup and sensitivity analyses

Due to the heterogeneity of the medications, subgroup analyses for each type of medication (carbamazepine, lidocaine, sumatriptan, buprenorphine [opioid], and sodium-channel blocker [BIIB074]) were conducted. Due to the small number of studies, sensitivity analyses for low risk of bias studies could not be conducted, nor a funnel plot to assess for publication bias.

9. Quality of the evidence (GRADE)

Summary of the findings tables and quality of evidence assessment were performed using the software developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group GRADE Profiler (GRADE pro) [29].

RESULTS

1. Results of the search

The initial search strategy through database searching up to 3/26/2020 yielded 500 references and 28 hand-search references identified through other sources. After duplicates were removed, 324 references were scanned and reduced to 46 relevant manuscripts. All 46 manuscripts identified were searched for full-text, and eight manuscripts were relevant for inclusion. The main reasons for exclusion were as follows: no placebo group (n = 3), study protocol (n = 1), proceedings abstract (n = 3), no TN patients or patients with a reported diagnosis of multiple sclerosis (n = 7), a review (n = 3), different outcomes (n = 2), case reports (n = 2), editorial (n = 1), not an RCT (n = 6), duplicate (n = 1), no PDF available through library (n = 1), mix of medications (n = 1), botulinum toxin as intervention (n = 5), and open label and/or pilot study (n = 2).

All four databases were searched again on 02/07/2021. The PRISMA flowchart [25] summarizes the results (Fig. 1).

2. Included studies

A total of eight publications comparing medications to placebo for the treatment of adults with TN were eligible for the qualitative analysis, as shown in Table 2. All articles included in this systematic review were double-blinded [7,8,30-35]. Seven were placebo- controlled crossover studies [7,8,30-34], and one was a placebo-controlled randomized withdrawal phase 2a trial [35].

1) Population

Adult patients with TN were enrolled in the included RCTs. The diagnostic criteria for TN in each study included in this review are presented in Table 3. Some studies [30,32,35] used imaging to ensure that no secondary cause was present for TN (i.e., autonomic symptoms, dental causes, or other neuropathic pain [NP]). Four studies used the International Classification of Headache (ICH) criteria to include or exclude patients into the investigation [30-32,35], while another [34] used the International Association for the Study of Pain (IASP) criteria [36]. The remaining authors did not provide a reference for the TN criteria [7,8,33]. This review included studies that did not distinguish between the different types of TN.

The age of the participants ranged from 20 to 84 years. The number of study subjects ranged from a minimum of nine [8] to 70 participants [7]. Most patients were women. RCTs were conducted in England [7], Japan [30-32], USA [8], Austria [33], Greece [34], and one study was conducted in multiple European countries, the

Table 2. Summary of included studies

Reference	Year/ Country	Study Design/ Sample size	Treatment (Tx)	Tx n	Placebo (P)	P n	Gender (M/F)	Age mean ± SD, (range in y)
Campbell, et al. 1966 [7]	1966, England	DBRPCT Crossover N = 70	Carbamazepine (C) then placebo (P) (C, P, C, P)	36	Lactose Placebo (P) then carbamazepine (n = 34, P, C, P, C)	34	24M/46F	(20 – 84) y
Kanai, et al. 2006a [30]	2006, Japan	DBRPCT Crossover N = 24	3 mg (1 mL) subcutaneous sumatriptan then placebo	12	1 mL Saline placebo then sumatriptan	12	10F/2M	mean 63 y (42 – 80) y
Kanai, et al. 2006b [31]	2006, Japan	DBRPCT Crossover N = 25	Lidocaine 8% then placebo	13	Saline placebo then lidocaine	12	5M/20F	Lidocaine / P: mean 65 y (45 – 77) y P / lidocaine: mean 63 y (44 – 85) y
Niki, et al. 2014 [32]	2014, Japan	DBRPCT Crossover N = 24	Lidocaine 8% then placebo	12	Saline placebo then lidocaine	12	9F/3M	Lidocaine / P: mean age 73 y (66 – 77) y P / Lidocaine: mean age 68 (63 – 80) y
Rockliff and Davis, 1966 [8]	1966, USA	DBRPCT Crossover N = 9	Carbamazepine tablets 200 mg each 3x a day for 3 days then placebo	9	Placebo tablets then carbamazepine	9	1M/8 F	(37 - 81) y
Spacek, et al. 2002 [33]	2002, Austria	DBRPCT Crossover N = 19	0.045 mg buprenorphine then saline	9	Saline then 0.045 mg buprenorphine	10	5F/4M	Buprenorphine: 61.7 ± 12.4 Saline: 64.8 ± 14.8
Stavropoulou, et al. 2014 [34]	2014, Greece	DBRPCT Crossover N = 20	Lidocaine (5 mg per kilogram of body weight) in 250 mL of 5% dextrose solution	20	250 mL of 5% dextrose solution	20	7M/13F	65.20 ± 15.28
Zakrzewska, et al. 2017 [35]	2017, Europe, UK, South Africa	DBRPCT withdrawal phase 2a N = 29	BIIB074 150 mg 3xday for up to 28 days	15	Placebo	14	10M/19F	BIIB074: 52 y (26 – 72) P: 57 y (21 – 74)

Abbreviations: DBRPCT, double-blinded randomized placebo-controlled trial; F, female sex; M, male sex; N, total sample size; n, sample size per group; P, placebo group; Tx, treatment group.

United Kingdom, and South Africa [35]. Centers providing the intervention varied from hospitals [7], university medical schools [8,30-33], one outpatient pain and palliative care center [34], and one study included 25 secondary care centers in different countries [35].

2) Interventions

Medications analyzed in this review included:
- Oral carbamazepine [7,8],
- Subcutaneous sumatriptan [30],
- Lidocaine (intranasal [31], 8% spray on oral mucosa [32], or intravenous [34]),
- Ganglionic local opioid analgesia [33],
- Oral Nav1.7 selective sodium channel blocker [35].

The placebo group included matched placebo tablets, spray, or saline injections. The study duration ranged from two weeks [30-32,34], 10-15 days [33], and 8 weeks [7]. One study did not state this duration [8].

3) Co-interventions

Co-interventions were noted in some of the studies. In one trial [30], five patients were being treated with phenytoin, clonazepam, baclofen, or mexiletine in combi-

Table 3. Diagnosis of TN in included studies

Study	Diagnosis of TN criteria classification
Campbell, et al. 1966 [7]	1. Patients with TN 2. All patients included in the trial were in pain at the time of entry.
Kanai, et al. 2006a [30]	Idiopathic TN: 1. According to the IHC, a paroxysmal, unilateral pain that can be triggered in the anatomical region on the trigeminal nerve, without any sensory or motor focal symptoms in this region. 2. Extensive tests including MRI showed no cause for the TN. 3. Patients had been suffering from the painful paroxysms for ≥ 3 months with a pain intensity > 4 cm according to a 0 to 10 VAS.
Kanai, et al. 2006b [31]	Idiopathic TN: 1. According to the IHC, a paroxysmal, unilateral pain that can be triggered in the anatomical region on the trigeminal nerve, without any sensory or motor focal symptoms in this region. 2. Extensive tests including MRI showed no cause for the TN. 3. Patients had been suffering from the painful paroxysms for ≥ 3 months with a pain intensity > 4 cm according to a 0 to 10 VAS.
Niki, et al. 2014 [32]	Classic TN: 1. The inclusion criteria for the selection of classic TN were based on the definition of the IHC: paroxysmal unilateral pain triggered in the anatomical region of the trigeminal nerve, without any sensory or motor focal symptoms in this region. 2. Extensive tests including MRI showed no cause for the TN. 3. Patients had been suffering from the painful paroxysms for ≥ 3 months with a pain intensity > 4 cm according to a 0 to 10 NRS.
Rockliff and Davis, 1966 [8]	1. Patients with active, typical TN were enrolled. 2. The characteristic paroxysms of jabbing, severe, facial pain sometimes occurred spontaneously or were more often triggered by touch, cold air, chewing or other movements, and stimuli.
Spacek, et al. 2002 [33]	Patients with TN suffering from refractory pain despite a standard treatment with carbamazepine.
Stavropoulou, et al. 2014 [34]	Confirmed diagnosis of TN according to IASP criteria [36].
Zakrzewska, et al. 2017 [35]	Diagnosis of TN was based on the ICHD 2ndedition[54] and 3rdedition(betaversion)[1].

Abbreviations: IASP, International Association for the Study of Pain; ICHD, International Classification of Headache Disorders; IHC, International Headache Classification; MRI, magnetic resonance imaging; NRS, numerical rating scale; TN, trigeminal neuralgia; VAS, visual analog scale.

Table 4. Risk of bias analyses in table form

Study	Random Seq. Generation	Allocation Concealment	Blinding participants/ personnel	Blinding assessors/ statistician	Incomplete Outcome Data	Selective Reporting	Other potential bias	Overall Bias
Campbell, et al. 1966 [7]	-	-	-	?	+	-	-	+
Kanai, et al. 2006a [30]	-	-	-	-	-	-	?	?
Kanai, et al. 2006b [31]	-	-	?	?	-	-	+	+
Niki, et al. 2014 [32]	?	-	-	?	-	-	+	?
Rockliff and Davis, 1966 [8]	?	-	-	-	?	-	?	?
Spacek, et al. 2002 [33]	-	?	?	?	?	-	?	?
Stavropoulou, et al. 2014 [34]	-	-	?	-	?	-	-	?
Zakrzewska, et al. 2017 [35]	-	-	-	?	-	-	+	+

KEY: + = high risk of bias; − = low risk of bias; ? = Unclear risk of bias.

nation with carbamazepine. In other RCTs, it was unclear whether the subjects discontinued other modalities of therapy prior to the interventional therapy [8,32,34]. No co-interventions were reported in the remaining studies

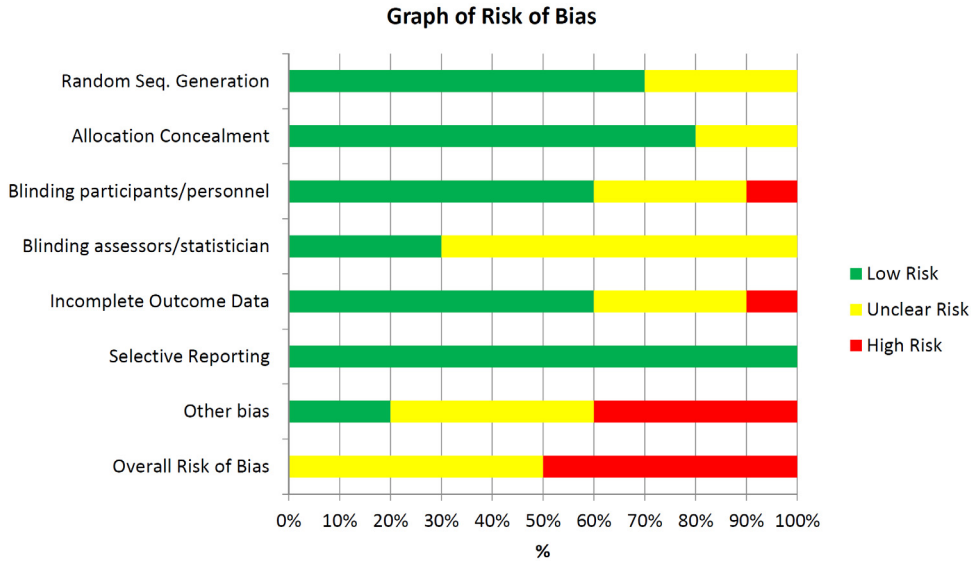

Fig. 2. Summary of the risk of bias of eligible Randomized controlled trials.

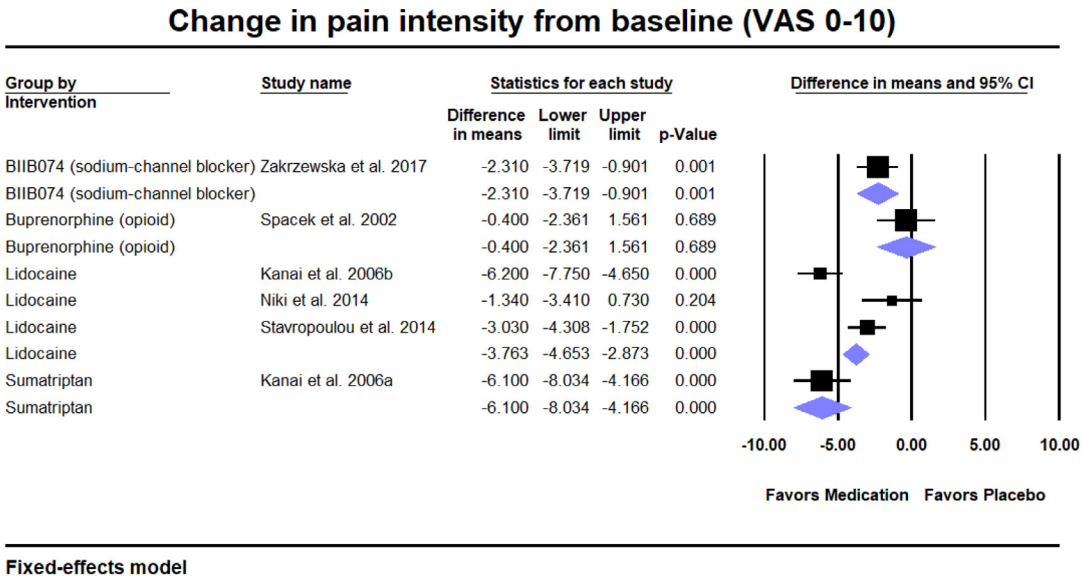

Fig. 3. Results of the meta-analysis comparing medication to placebo intervention for trigeminal neuralgia patients. Differences in average change in VAS pain from baseline (0 to 10). A negative difference of mean change in pain intensity from baseline indicates a favorable improvement in pain intensity in the medication group vs the placebo group. CI, Confidence interval; VAS, visual analog scale.

[7,33,35].

4) Outcomes

The primary outcomes were TN [30,31,33,34] and visual NRS [32,35]. Secondary pain outcomes reported were improvement in TN intensity as a percentage [7,30,34] or quality of TN (rated as improved, unchanged, or temporary relief) [30-32]. Other secondary outcomes reported in the original studies included the effect of the drug on triggering mechanisms and number of triggers becoming inactive [7], number of patients with reduced hyperalgesia [34], percentage reduction in the number of paroxysms daily [7,35], median time to treatment failure [35], and preference for treatment [8]. Improvement in quality of life was rated in one study [35] with the Patient Global Impression of Change, Clinician Global Impression

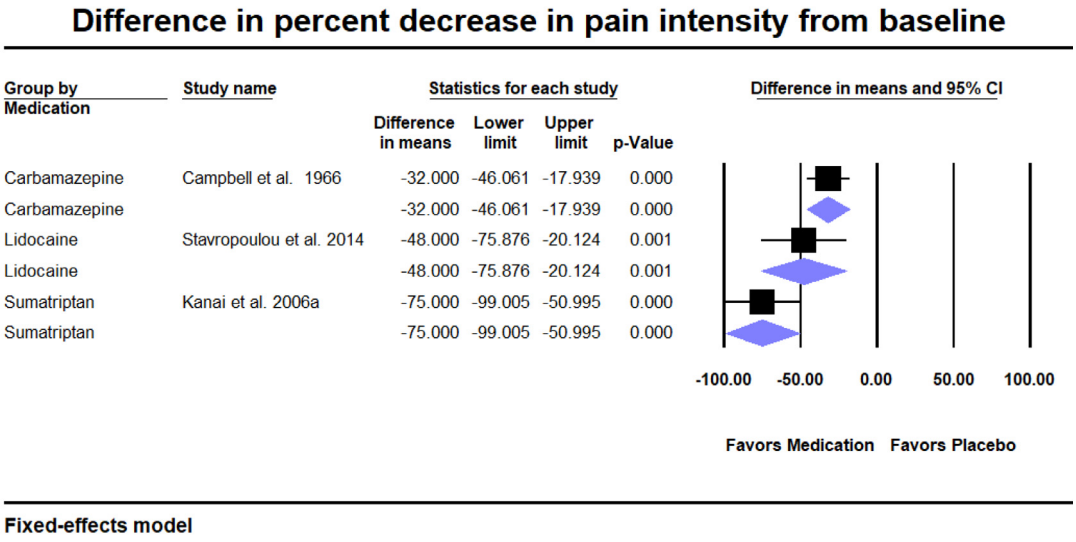

Fig. 4. Results of the meta-analysis comparing medication to placebo intervention for trigeminal neuralgia patients. Differences in average pain percentage improvement from baseline (%). A negative difference of mean percentage decrease in pain intensity from baseline indicates a favorable larger % decrease in the medication group versus the placebo group. CI, Confidence interval.

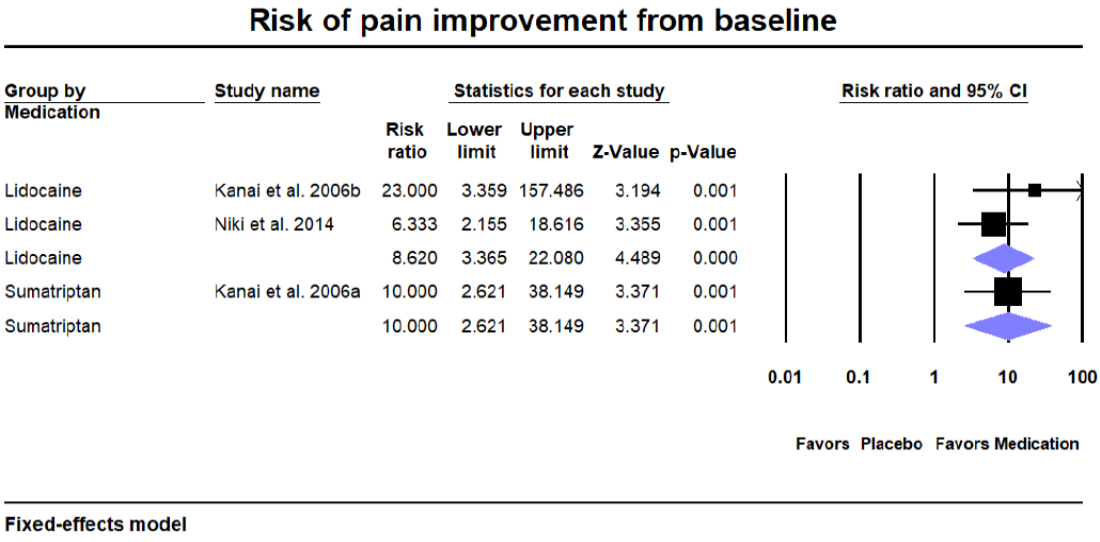

Fig. 5. Results of the meta-analysis comparing medication to placebo intervention for trigeminal neuralgia patients. Risk ratio of pain improvement in intervention versus placebo group. A Risk Ratio > 1 indicates that medication worked better than placebo, with more patients having pain improvement. CI, Confidence interval.

of Change, and the Brief Pain Inventory-Facial.

3. Risk of bias in included studies

The risk of bias assessment is presented in Table 4. In summary, an unclear overall risk of bias was assigned to five studies [8,30,32-34], and a high overall risk of bias was assigned to three studies [7,31,35] (Fig. 2).

4. Meta-analyses

1) Lidocaine vs placebo

Three studies [31,32,34] reported baseline and post-treatment VAS pain scores (0-10) after seven days of treatment. Patients receiving lidocaine reported a significantly lower intensity of pain compared to the placebo group (difference in means = −3.763; 95% CI

Table 5. Adverse events

Study	Interventions, sample size	Adverse effects in INTERVENTION Group	Adverse effects in PLACEBO Group
Campbell, et al. 1966 [7]	Carbazepine (C) (n = 36, C, P, C, P) Placebo (P) (n = 34, P, C, P, C)	50% of patients on Carbazepine experienced at least one side effect • Giddiness: 30% • Unsteadiness and drowsiness: 15% and not necessarily together • Rash: n=1	24% in placebo experienced at least one side effect
Kanai, et al. 2006a [30]	Crossover N = 24 3mg subcutaneous Sumatriptan/P (n = 12) Saline placebo/ sumatriptan (n = 12)	• n = 2 patients, Blood Pressure increased by 15% • n = 5 patients had fatigue • n = 2 patients had nausea	Minimal adverse events and disappeared without drugs within a few hours
Kanai, et al. 2006b [31]	Crossover N = 25 Lidocaine 8% then placebo (n = 13) Saline then lidocaine (n = 12)	• Local irritation; burning, stinging or numbness of the nose and eye (n = 15), • Bitter taste and numbness of the throat (n = 1) • No potential serious side-effects were reported, and none had difficulty in phonation or swallowing. • No substantial changes in arterial pressure or heart rate were detected in any subject of the two treatment groups.	
Rockliff and Davis, 1966 [8]	Crossover N = 9 Carbamazepine tablets 200 mg each 3x a day for 3 days Placebo tablets	Total number of patients with reactions n = 12 mild, 2 severe Number of patients that stopped using drug because of reaction n = 1 • Drowsiness n = 7 mild • Dizziness n = 6 mild • Nausea n = 4 mild, 2 severe • Headache n = 4 mild • Vomiting n = 1 severe • Abdominal cramps n = 1 mild • Dysuria n = 1 mild • Tinnitus n = 1 mild • Vertigo n = 1 mild	No mention of adverse effects in placebo group
Stavropoulou, et al. 2014 [34]	Crossover N = 20 Lidocaine (5 mg per kg) in 250 mL of 5% dextrose solution 250 mL of 5% dextrose solution	• Somnolence n = 13 • Dry mouth n = 5 • Dizziness n = 5 • Headache n = 3 • Feeling flushed n = 2 • Confusion n = 1 • Dysarthria n = 1 • Tinnitus n = 1	• Somnolence n = 1 • Dry mouth n = 2 • Dizziness n = 0 • Headache n = 1 • Feeling flushed n = 0 • Confusion n = 0 • Dysarthria n = 0 • Tinnitus n = 0
Zakrzewska, et al. 2017 [35]	BIIB074 150 mg 3xday for up to 28 days (n = 15) Placebo (n = 14)	4 / 15 (27%) of patients reported 13 treatment emergent adverse events (new events or worsening events from the open-label phase), of which seven were treatment-related	5 / 14 (36%) of patients in the P group reported 17 treatment-emergent adverse events, of which 5 were treatment-related

Abbreviations: C, carbazepine; N, total sample size; n, number of participants; P, placebo group.

= −4.653 to −2.873; P < 0.001; Fig. 3). In one trial [34], patients receiving lidocaine had an improvement in pain of −48% compared to the improvement in the placebo group (95% CI = −75.876% to −20.124%; P = 0.001; Fig. 4). Patients in two studies [31,32] who had lidocaine were 8.62 times more likely to have pain improvement than patients on placebo (95% CI = 3.365 to 22.080; P < 0.001; Fig. 5).

2) Opioids vs placebo

One study [33] reported a non-significant difference in pain improvement from baseline for patients receiving 0.045 mg buprenorphine in 1.5 mL 0.9% NaCl compared with placebo (P = 0.689; Fig. 3).

3) Carbamazepine vs placebo

In one RCT [7], patients receiving carbamazepine

Table 6. GRADE assessment of quality of the evidence [29].

Lidocaine compared to placebo for TN					
Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95%CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Lidocaine (95% CI)
Change in VAS pain from baseline VAS 0 to 10	89 (3 studies)	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision	N/A	N/A	The mean change in VAS pain from baseline in the lidocaine groups was 3.763 lower than in the placebo groups (4.653 to 2.873 lower)
Pain improvement	98 (2 studies)	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision	RR 8.620 (3.365 to 22.080)	82 per 1000	622 patients more per 1000 with improved pain/relief with lidocaine than placebo (from 193 more to 1000 more)

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

[1]All studies at unclear or high risk of bias
[2]Small total sample size (less than 400 patients), small number of studies.

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; N/A, not applicable; RR, risk ratio; TN, trigeminal neuralgia; VAS, visual analog scale.

showed a significant improvement in pain intensity of −32% compared to the improvement in the placebo group (95% Cl = −46.061% to −17.939%; P < 0.001; Fig. 4).

4) Sumatriptan vs placebo

One trial [30] reported significantly lower intensity of pain on an average of 6.1 points on a scale of 0 to 10 for patients receiving 3 mg (1 mL) sumatriptan compared to placebo (95% CI = −8.034 to −4.166; P < 0.001; Fig. 3). This study also demonstrated a significant improvement in pain intensity of −75% compared to the improvement in the placebo group (95% Cl = −99.005 to −50.995; P < 0.001; Fig. 4). Patients who received 3 mg (1mL) sumatriptan were 10 times more likely to have pain improvement than patients who received placebo (95% CI = 2.621 to 38.149; P = 0.001; Fig. 5).

5) Sodium-channel blocker vs placebo

One RCT [35] reported a significantly lower intensity of pain on an average of 2.3 points on a scale of 0 to 10 for patients receiving BIIB074 (95% CI = −3.719 to −0.901; P = 0.001; Fig. 3).

5. Adverse events

Several of the publications reported adverse events including giddiness [7], unsteadiness [7], drowsiness [7,8], rash [7], fatigue [30,35], nausea [8,30], local irritation [31], burning [31], stinging or numbness of the nose and eye [31], bitter taste and numbness in the throat [31], dizziness [8,34,35], headache [8,34,35], vomiting [8,35], abdominal cramps [8], dysuria [8], tinnitus [8,34], vertigo [8], somnolence [34], dry mouth [34], feeling flushed [34], confusion [34], dysarthria [34], nasopharyngitis [35], sleep disorder [35], and tremor [35] (Table 5).

6. Quality of the evidence (GRADE)

In summary, due to the small sample size of participants in each meta-analysis (< 400), risk of bias (unclear/high), and the small number of studies pooled in each meta-analysis (2 or 3 studies), the quality of the evidence was low (Table 6) for lidocaine compared with placebo groups for change in VAS pain from baseline (Fig. 3) and percentage pain improvement (Fig. 5). Other subgroup analyses had only one study and are shown for

visual reference; however, the quality of the evidence (GRADE) was not conducted in only one study.

DISCUSSION

1. Main findings

This systematic review and meta-analysis provides a summary of the efficacy of pharmacologic therapy versus placebo for primary TN. Lidocaine (intranasal [31], 8% spray on oral mucosa [32] or intravenous [34]) was used in three studies and meta-analysis revealed that it significantly reduced pain compared to controls by -3.8 points on a 0 to 10 VAS scale. According to Kelly 2001 [37], the 'minimum clinically significant difference' in a VAS 0 to 10 is 1.2 units (95% CI = 0.9 to 1.5 units). The difference in VAS pain of -3.8 units comparing lidocaine to the placebo group found in this systematic review may be clinically significant. In one trial [34], patients receiving lidocaine (intravenous [34]) showed an improvement in pain of -48% compared to the improvement in the placebo group. Patients in two studies [31,32] who received lidocaine were 8.62 times more likely to have pain improvement than patients on placebo (95% CI = 3.365 to 22.080; P < 0.001; Fig. 5).

Patients who received subcutaneous sumatriptan had an improvement in pain intensity of -75% compared to the improvement in the placebo group [30] (95% Cl = −99.005 to −50.995; P < 0.001; Fig. 4). Patients who received 3 mg (1 mL) sumatriptan were 10 times more likely to have pain improvement than patients who received placebo [30] (95% CI = 2.621 to 38.149; P = 0.001; Fig. 5). Therefore, further studies are required.

Patients receiving oral carbamazepine showed a significant improvement in pain intensity of −32% compared to the improvement in the placebo group (95% Cl = −46.061% to −17.939%; P < 0.001; Fig. 4). Sodium channel blockers reported significantly lower intensity of pain compared to placebo (an average of 2.3 points on a scale of 0 to 10 for patients receiving BIIB074). Opioids had a non-significant difference in pain improvement from baseline for patients receiving 0.045 mg buprenorphine in 1.5 mL 0.9% NaCl compared to placebo. Therefore, further studies are required.

2. Agreements and disagreements with other studies or reviews

1) Carbamazepine

In 2011, Martin et al. [38] reviewed the results of the study by Campbell et al. [7] and found that pain intensity was reduced by 58% in the carbamazepine group compared with 26% in the placebo group. In their meta-analyses, Do et al. [22] found that carbamazepine had a clinically significant pain reduction in patients with TN; however, they also found that patients had hematologic side effects and recommended further studies on new anticonvulsants such as oxcarbazepine. Six reviews of the literature agree that carbamazepine should be a first-line drug therapy for TN, but should be used with caution due to side effects [39-44]. Yang et al. [45] reported that carbamazepine was considered a second-line treatment for TN and cautioned the side effect profile. In this systematic review, we only found one RCT comparing carbamazepine with placebo; thus, further studies are needed.

2) Sumatriptan

Sumatriptan, which can be prescribed for the treatment of migraine headaches with or without aura, as a prophylactic treatment for migraine, and for the treatment of cluster headaches [46], is used "off-label" in the United States of America for the treatment of TN. Sumatriptan is a selective serotonin receptor agonist that functions by vasoconstriction in the basilar artery and blood vessels of the dura mater of the brain [46]. The pain that occurs during migraine is associated with middle cerebral artery dilatation, which results in lower blood flow [46]. In this systematic review, we found one RCT comparing sumatriptan to placebo with favorable results. A possible explanation for the success of sumatriptan in the treatment of TN was explained by Moran and Neligan [47]. The

vasoconstrictive mechanism of sumatriptan may relieve the compressive effects occurring at the root of the affected trigeminal nerve, a common origin of the symptoms that are manifested in TN. Sridharan et al. [48] based on their network meta-analysis, discussed that despite the low quality of the evidence, subcutaneous sumatriptan is a potentially useful drug intervention in patients with refractory TN.

3) Lidocaine

Yang et al. [45] reviewed the results of Niki et al. [32] and agreed that lidocaine was the first-line medication for TN patients. Niki et al. [32] reported that in TN patients experiencing severe intraoral pain, when 8% lidocaine was administered intraorally, prompt analgesia was produced without any serious side effects. However, the authors noted that increases in the blood concentration of lidocaine will affect other important signal transmissions, causing side effects such as excitation and depression of the central nervous system. The authors caution that the dosage should be controlled to avoid these adverse effects. Sridharan et al. [48] in their network meta-analysis suggested that despite the low quality of the evidence, intravenous and intranasal lidocaine reduced pain and may be useful drug interventions in patients with refractory TN. Our study found that lidocaine (intranasal [31], 8% spray on oral mucosa [32], or intravenous [34]) was used in three studies, and meta-analysis revealed that it significantly reduced pain compared to controls by −3.8 points on a 0 to 10 VAS scale. According to Kelly (2001) [37], this difference could be clinically significant; however, further studies are needed to explore the best route of administration and dosage.

4) Sodium channel blocker

Oberman et al. [41] found that CNV1014802, a novel sodium channel blocker that selectively blocks the Nav1.7 sodium channel, showed promising results, but the evaluation period was very short to provide conclusive results. In our study, we found that BIIB074 (Nav1.7-selective, state-dependent sodium-channel blocker) had a significantly lower intensity of pain compared to placebo (an average of 2.3 points on a scale of 0 to 10 for patients receiving BIIB074). According to Kelly 2001 [37], this difference could be clinically significant; however, further studies are needed, as only one study could be found comparing BIIB074 to placebo.

5) Opioids

One study [33] reported a non-significant difference in pain improvement from baseline for patients receiving 0.045 mg buprenorphine in 1.5 mL 0.9% NaCl compared with placebo. Although this study was not successful for TN, buprenorphine has been successfully used for treating neuropathic and chronic pain. In a case report by Induru and Davis [49], buprenorphine was found to be effective in reducing hyperalgesia in neuropathic pain (NP). They hypothesized that buprenorphine may be used with success when pure μ agonists fail to help with pain or in individuals who are intolerant to pure μ agonists. More research is needed in this area to understand whether buprenorphine is effective for TN.

3. Overall completeness and applicability of evidence

Four electronic databases were searched for articles published in English up to February 7, 2021. The review authors manually searched all the reference sections of the included studies, reviews, systematic reviews, and clinical guidelines to identify further studies. The results of this review are applicable to adult patients with TN, ranging from 20 to 84 years; most patients were female. RCTs were conducted in England [7], Japan [30-32], USA [8], Austria [33], Greece[34], and one study was conducted in multiple European countries, the UK, and South Africa [35].

4. Heterogeneity of the review

This systematic review only included RCTs comparing TN medications (excluding Botulinum toxin A per design) with placebo and similar reported outcomes. The primary outcome was pain intensity, and the secondary

outcomes were improvement in pain intensity as a percentage, quality of pain, effect of the drug on the number of triggers, hyperalgesia, number of paroxysms, time to treatment failure, preference for treatment by the patient, quality of life outcomes, and adverse effects. These outcomes were measured subjectively before and at the end of each treatment.

Clinical heterogeneity was found in terms of study design, with mostly crossover trials (seven of the studies), and only one was a withdrawal phase 2a study [35]. Treatment duration ranged from 2 weeks [30-32,34], 10–15 days [33] to 8 weeks [7] for each intervention; however, one study [8] did not state the duration.

Different types of interventions for TN were utilized in the included studies with varied dosages, mechanisms of action, and schedules. In terms of the different routes of administration, studies reported using oral tablets, subcutaneous injections, the intranasal route, oral mucosa spray, the intravenous route, and applied as local analgesia. Additionally, these interventions have different mechanisms of action, as discussed in the introduction of this paper.

The dosages administered for each medication varied. In terms of carbamazepine, one study did not mention the dosages used [7], and another used only 200 mg tablets 3 times a day for 3 days [8], using much less than the current recommended established dosage schedule. Typically, one would take 200 mg a day with an increasing dose of 200 mg in increments of 100 mg every 12 h, with a maximum dosage of 1200 mg per day [50]. In terms of the other medications used in the studies reviewed, they are not considered first-line medical interventions for the management of TN; therefore, no official dosages are established for their utilization to manage such a condition.

5. Implications for research

The implications for research from this meta-analysis include the need to promote further studies with larger sample sizes using different dosages and longer treatment times (versus short follow-up). Most of the research completed in this area spans several years in the past (1966 – 2017), and more recent studies are needed. There is also an ethical dilemma for treating patients with intense pain with a placebo.

6. Implications for clinical practice

Carbamazepine is the first-line therapy for TN. Despite this, our systematic review and meta-analysis revealed no conclusive results for this drug. This may be because only two randomized placebo-controlled studies [7,8] meeting our inclusion criteria were found by reviewing its usage for the treatment of TN. In its application in clinical practice, it is interesting to note that two medications that are not commonly prescribed for TN - lidocaine and sumatriptan - showed promising results.

Lidocaine has long been established as a medication that helps relieve pain as a local anesthetic in dentistry; as the initial amide local anesthetic, lidocaine transformed pain control in the dental field [51]. It is considered safe for most patients, and we found three RCTs with favorable results for its specific treatment for TN [31]. In terms of sumatriptan, there seems to be potential for its use in the treatment of TN, attributed to its mechanism of action involving vasoconstrictive properties [46].

As with all medical treatments, adverse events should be considered when prescribing a medication; several studies have mentioned adverse events in the intervention groups [7,8,30,31,34,35]. Therefore, it should be noted that adverse effects of varying degrees occurred with carbamazepine, sumatriptan, lidocaine, and BIIB074. It has been reported that these medications have documented adverse events when they are utilized for other diseases and disorders [46,52,53]. Lidocaine may cause neuropsychiatric and cardiological side effects [52]. Sumatriptan may produce mild sedative effects, such as sleepiness and fatigue [46]. Carbamazepine is known to cause nausea, dizziness, and drowsiness [53], which is consistent with the findings of this systematic review.

Future research needs to have a more definitive diagnosis of TN. Some of the papers reviewed did not specify which criteria were used for the diagnosis of TN

(such as the ICHD or IASP diagnostic criteria).

In conclusion, due to the bias and small sample size, the quality of the evidence was low for lidocaine in the treatment of TN. Further studies are needed for carbamazepine, sumatriptan, opioids, and sodium channel blockers, as only one study reported their outcomes.

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