BJA
British Journal of Anaesthesia

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Journal:	*British Journal of Anaesthesia*
Manuscript ID	Draft
Article Type:	Review article
Date Submitted by the Author:	n/a
Complete List of Authors:	Moore, David; Beaumont Hospital , Anaesthesia Chong, Mun Seng; University College London Hospitals NHS Foundation Trust National Hospital for Neurology and Neurosurgery, Pain Management Shetty, Ashish; University College London Hospitals NHS Foundation Trust National Hospital for Neurology and Neurosurgery, Pain Management Zakrzewska, Joanna; UCLH, Pain Management Centre
Keywords:	HUMANS, TRIGEMINAL NEURALGIA, ACUTE PAIN, DRUG THERAPY, TREATMENT OUTCOMES, SYSTEMATIC REVIEW

A Systematic Review of Rescue Analgesic Strategies in Acute Exacerbations of Primary Trigeminal Neuralgia

D.Moore[1], M.Chong [2], A. Shetty [3], J. M. Zakrzewska [4]

Corresponding Author

J.M. Zakrzewska [4]
Consultant in Facial Pain
University College London Hospital
London, UK
j.zakrzewska@ucl.ac.uk

Co-Authors
D.Moore [1]
Consultant in Anaesthesia and Pain Medicine, Department of Anaesthesia,
Beaumont Hospital, Dublin 9, Ireland.
davidmoore@beaumont.ie
+ 353 86 3134927

M Chong [2]
Consultant Neurologist
University College London Hospital
London, UK
schong@nhs.net

A. Shetty [3]
Consultant in Pain Medicine
University College London Hospital
London, UK
ashish.shetty@uclh.nhs.uk

Word count: 5,176
(excluding title page, abstract, references, figures and tables)

References: 67

SUMMARY (ABSTRACT)

Background

Trigeminal neuralgia (TN) can have a significant impact an a patients wellbeing and quality of life. Limited data exists for treatments that improve TN pain acutely, within 24 hours of administration. This systematic review aims to identify effective treatments that acutely relieve TN exacerbations.

Methods

We searched Medline and Cochrane Central Register of Controlled Trials (CENTRAL) for relevant English language publications. The reference list for all articles was searched for other relevant publications.

All studies that satisfied the following PICO criteria were included:
Population - Adults with acute exacerbation of primary TN symptoms.
Intervention - Any medication or intervention with the primary goal of pain relief within 24 hours.
Comparator - Usual medical care, placebo, sham or active treatment.
Outcome - More than 50% reduction in pain intensity within 24 hours of administration.

Results

Out of 431 studies, 17 studies were identified that reported immediate results of acute treatment in TN. The evidence suggests that the following interventions may be beneficial: local anaesthetic, mainly lidocaine (ophthalmic, nasal or oral mucosa, trigger point injection, intravenous infusion, nerve block); anticonvulsant: phenytoin or fosphenytoin (intravenous infusion); serotonin agonist, sumatriptan (subcutaneous injection, nasal). Other referenced interventions with very limited evidence are: NMDA antagonist (magnesium sulphate infusion); botulinum toxin (trigger point injection).

Conclusions

A number of treatment options exist that may provide fast and safe relief of TN. Future studies should report on outcomes within 24 hours to build on our knowledge of the acute analgesic effects of TN treatments.

Keywords

Humans, Trigeminal neuralgia, Acute pain, Drug therapy, Treatment outcome, Systematic review

INTRODUCTION

Trigeminal neuralgia (TN) is a painful condition that is associated with sudden, lancinating, unilateral pain attacks in the distribution of the trigeminal nerve branches. The attacks last from a few seconds up to 2 minutes and are often associated with typical triggers (e.g. brushing teeth, talking, eating). There is generally no pain between attacks. [1] Primary or classical TN can be due to compression of the trigeminal nerve by a blood vessel. Secondary TN is due to compression by a tumour or due to demyelination of the nerve (e.g. multiple sclerosis) [2].

The annual incidence of TN is reported as 4.7-28.9 per 100,000 person years.[3,4] The age of onset is 53-60 and it is more common in women (female:male ratio is 1.5-1.9:1).[5,6] TN can be a disabling condition and many patients often report moderate to severe episodes of pain with associated functional, occupational and emotional impairment and disability.[7] In a study by Tolle et al of TN patients established on pharmacological treatment, 48% reported severe episodes of pain over a 24 hour period and 78% report at least one visit to their primary care physician over a 4 week period. These patients missed on average 3.9 work days per month due to pain and 34% had reduced hours or were unemployed due to the pain.[8]

Most treatment options in TN are symptomatic and aim to reduce the severity and frequency of attacks in the future. There is limited evidence on interventions that offer rescue analgesia in the acute phase of an exacerbation or attack. First line treatment is carbamazepine or oxcarbazepine.[9] This is a very effective treatment option with large numbers reporting pain relief on initiation of treatment (98%).[5] However, it is associated with many side effects that limit its tolerability and 27% may have to stop or reduce the drug dose.[5] Also, they must be titrated to effective levels over the course of days to weeks to avoid serious side effects, making them ineffective as acute analgesics.

If pharmacological therapy fails or is not tolerated, interventional options include Gasserian ganglion rhizotomy and microvascular decompression. Such interventional options require image guidance, skilled staff and/or operating theatre access which limit their utility as rescue options in the acute phase.

Data from Hospital Episodes Statistics (HES) in England show that not all patients admitted to hospital with acute TN undergo a surgical procedure. Patients in the UK and USA report the prevalent use of opioid analgesics from which it is inferred that the pain intensity is high. [7,10] The management of these cases is challenging and can have serious socioeconomic and health care utilisation implications, not to mention the negative impact on the patient.

The objective of our systematic review is to identify therapeutic strategies or interventions that effectively reduce the severity or terminate an acute exacerbation of TN. We will grade the evidence and offer recommendations that will support the care of these patients in the outpatient clinic, emergency department or in the primary care setting.

METHODS

Our review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[11] We employed a PICO approach to define our study inclusion criteria. The *Population* of interest was adults (>18 year old) with primary TN as per the International Classification of Headache Disorders (ICHD 2013) and/or International Association for the Study of Pain (IASP) definition, with an acute exacerbation of symptoms. [1, 12] The *intervention* was the administration of any medication or interventional treatment with the primary goal of acute pain relief within 24 hours. The *comparator (or control group)* may be usual medical care, placebo, sham, or active treatment. Due to the limited available evidence from randomised control trials (RCT), we reviewed all relevant studies (i.e. case reports, case series, observational studies and RCTs). The primary *outcome* measure we were interested in was pain intensity, and we deemed an effective treatment would give more than 50% pain relief within 24 hours of administration. Other important outcomes we searched for included frequency of attacks, adverse effects of treatment, medication usage, health care utilisation, quality of life measures, and patient satisfaction scores.

Studies that reported on the use of interventions that require surgical theatre access or image-guidance were excluded. Such interventions are not practical options in the pursuit of acute pain relief. Studies of medications that require days to weeks to titrate to effect were also excluded (e.g. carbamazepine, lamotrigine).

We performed a literature search for effective analgesic options in an acute TN exacerbation. We searched Medline and Cochrane Central Register of Controlled Trials (CENTRAL) for [“trigeminal neuralgia” OR “facial/trigeminal nerve pain” OR “tic doloreux”] AND [“acute pain” OR “emergency” OR “refractory”]. We only included full publications in English. The reference list for all included papers were searched for other suitable papers. The literature was reviewed by two authors independently (DMM and JMZ) and agreement on study inclusion was sought. If there was a disagreement on study inclusion, a third author (MSC) made the final decision. A PRISMA flow diagram of our search results is included below (Figure 1).

After pooling the search results, we removed duplicates. We reviewed the abstracts and selected studies that may meet inclusion criteria. We retrieved the full article for these studies and extracted data for inclusion in the review. We graded the level of evidence using the American Academy of Neurology (AAN) classification scheme (Table 1).[13]

Class I	A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
Class II	A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a-e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
Class III	All other controlled trials (including well-defined natural history controls or patients serving as their own controls) in a representative populations, where outcome is independently assessed, or independently derived by objective outcome measurement.
Class IV	Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

Table 1: American Academy of Neurology (AAN) classification scheme requirements for therapeutic questions.

We used the Cochrane Collaborations risk of bias tool to rate the level of bias in the included RCTs.[14] As per the Cochrane groups recommendation, all other studies were deemed to be at "high" risk of bias. Finally, we used the GRADE summary of evidence tool to rate the quality of evidence and accordingly grade our recommendations.[15]

RESULTS

A total of 17 studies met our inclusion criteria (Figure 1).

FIGURE 1 HERE

All studies investigated the effect of a pharmacological intervention, and the results are detailed below under each drug group heading. Table 2 gives an overview of the interventions and the results from each study. Figure 2 indicates the level of bias in the included RCTs. Not all the drugs mentioned in this review are available in all countries.

Table 2: Evidence for acute analgesic treatments in Trigeminal Neuralgia

Author, Year	Drug	Study	Diagnosis	Population	N	Dosage	Route	Outcome measure(s)	Efficacy within 24 hours	Side effects (n)	Level of Evidence	Risk of bias
Zavon, 1991	Proparacaine	Case report	Not specified	Classical TN Presenting for cataract surgery	1	0.50%	Eye drops	Incidental reduction of TN pain	Alleviation of pain	Not specified	IV	High
Spaziante, 1992	Proparacaine	Prospective observational	Not specified	Classical TN All divisions	25	0.5% (? 2 drops)	Eye drops	50% reduction of analgesics	15 pts > 50% reduction (8 stopped all analgesics) - not clear at which time point over a one month period	Nil	IV	High
Kanai, 2006	Lidocaine	RCT cross-over double-blind	ICHD	Classical TN Division: V2 Intensity on VAS > 4/10	25	Active: 8% 0.2ml, Control:0.2ml saline	Nasal spray	VAS (15 mins post-intervention), GIC (4-point scale), use of medications	Active: VAS 8.0 to 1.5, Control: 7.9 to 7.6, Duration: 4.3 hrs	Local irritation (stinging, burning numbness) (15), bitter taste or numb throat (1)	II	Unclear
Niki, 2014	Lidocaine	RCT cross-over double-blind	ICHD	Classical TN Division: V2, V3 Intensity on VAS > 4/10	24	Active: 8% 0.2m, Control: saline 0.2ml	Oral mucosa (trigger point) - applied via patients finger	NRS, GIC (4-point scale)	Active: NRS 5 to 1, Control: 5 no (change), Duration: 2.8 hrs	Numbness (active [9], control [3]), bitterness (1)	II	Unclear
Baykal, 2010	Lidocaine	Retrospective observational	Not specified	Classical TN Division: V2, V3	13	5ml 2% (100mg)	"Blind" injection of 2nd or 3rd division via mandibular notch	VAS	Complete relief 1-2 mins post-injection	Hypoesthesia (4), dizzyness (3), Ptosis (1), insufficient block (1)	IV	High
Galer, 1993	Lidocaine	Retrospective observational	Not specified	TN with concomitant persistent facial pain	6	5mg/kg/hr	IV infusion over 60-90 minutes	VPR, VAS, PRS 1 hr post-infusion	5 pts > 70% reduction in VAS or VPR, 1 pt 30-70% reduction	Not specified	IV	High
Stavropoulou, 2014	Lidocaine	RCT cross-over double-blind	IASP	Classical TN All divisions DN4 Score > 4 VAS > 3/10	20	5mg/kg	IV infusion over 60 minutes	VAS, Allodynia, Hyperalgesia	VAS: (active) 76% reduction, (control) 40.1% reduction; at 24 hours, (active) 52% redcution (control) 4% increase, decrease in evoked pain	Mild somnolense (33%), 3 patients dropped out	II	Low
Chaudhry, 2014	Lidocaine	Case report	Not specified	TN with concomitant persistent facial pain Division: V2	1	60mg/hr for 4 hrs, 120mg/hr for next 20 hrs, followed by 60mg/hr for next 48 hrs	IV infusion for 72 hrs	VPR	VPR: 10 to 0 after 1st hr infusion	Not specified	IV	High
Arai, 2013	Lidocaine + Magnesium Sulfate	Retrospective observational	Not specified	Classical TN Division: V2	9	Lidocaine 100mg and MgSO4 1.2g	IV infusion over 60 minutes	NRS	NRS: 7 to 4	Mild dizziness (2)	IV	High

Author, Year	Drug	Study	Diagnosis	Population	N	Dosage	Route	Outcome measure(s)	Efficacy within 24 hours	Side effects (n)	Level of Evidence	Risk of bias
Soleimanpour, 2014	Magnesium Sulfate	Case report	Not specified	Classical TN - acute presentation	1	50mg/kg	IV infusion over 30 minutes	VAS	VAS: 10 to 2 (30 mins post-infusion)	Nil	IV	High
Tate, 2011	Phenytoin	Case report	Not specified	Classical TN - acute presentation	1	15mg/kg	IV infusion in 2 divided doses 4 hrs apart	NRS	NRS: 10 to 2 after 1st infusion and 1 after 2nd infusion	Nil	IV	High
Cheshire, 2001	Fosphenytoin	Case series	Not specified	Classical TN - acute presentation, carbamazepine no longer effective	3	14 (11-18) mg/kg (PE) over 20-180 minutes	IV infusion	Pain relief (not quantified)	Immediate pain relief post-infusion	Mild and transient dizziness, tinnitus, ataxia	IV	High
Vargas, 2015	Fosphenytoin	Case report	Not specified	Classical TN - acute presentation Division: V2 + V3	1	15mg/kg	IV infusion over 30 minutes	VAS	VAS: 10 to 2	Not specified	IV	High
Zuniga, 2008	Botulinum toxin	Prospective observational	Not specified	Classical TN All divisions	12	20-50 units	SC trigger zones	VAS (8 weeks)	10 pts: relief “after some minutes”, 1 pt: VAS 10 to 0 in 24 hrs	Transient facial asymetry (1)	IV	High
Kanai, 2006	Sumatriptan	RCT cross-over double-blind	ICHD	Classical TN All divisions Intensity on VAS > 4/10	24	Active: 3mg (1ml) Control:1ml saline	SC	VAS (15 mins post-intervention), GIC (4-point scale)	Active: Vas 8.3 to 2.4, Control: 8.5 to 8.1, Duration: 7.9 hrs	Mild hypertension (2), fatigue (5), nausea (2)	II	Unclear
Kanai, 2006	Sumatriptan	Prospective observational, placebo control, partially blinded	ICHD	Classical TN All divisions	15	3mg (1ml) SC followed by 50mg orally twice daily for one week	SC saline, then SC sumatriptan, followed by oral one day later	VAS (15 mins post-intervention)	VAS decreased by 4.0 (resting), 4.7 (touching face), 4.6 (talking)	Fatigue (4), nausea (2)	IV	High
Shimohata, 2009	Sumatriptan	Case series	ICHD	Classical TN All divisions	3	20mg	Nasal spray	VAS	VAS: 8 to 2 (30 mins)	Nil	IV	High

DN4, douleur neuropathique 4 questionnaire; GIC, global impression of change; IASP, International Association for the Study of Pain; ICHD, International Classification of Headache Disorders; IV, intravenous; MgSO4, magnesium sulphate; N, number of study patients; NRS, numerical rating scale; PE, phenytoin equivalents; PRS, pain relief scale; RCT, randomised controlled trial; SC, subcutaneous; TN, trigeminal neuralgia; V2, second division of trigeminal nerve; V3, third division of trigeminal nerve; VAS, visual analogue scale; VPR, verbal pain rating.

Local anaesthetic

Ophthalmic

In 1992, a prospective observational study assessed the impact of 0.5% proparacaine eye drops on 25 patients.[16] This study was inspired by a letter published by Zavon et al which reported the unintended relief of TN in a patient presenting for cataract surgery and a second patient with symptoms resistant to carbamazepine, both of whom received 0.5% proparacaine eye drops.[17] All participants in the observational study were managed as TN cases, but the diagnostic criteria are not clear. Patients with incomplete pain relief on standard treatment or awaiting surgery were included. A positive outcome was more than 50% reduction in analgesic medications. This was reported in 15 of the 25 patients, with 8 patients stopping all medications. Positive response was not limited to those with first division symptoms. The duration of follow-up was for "at least a month", but the exact time frame for each patient was not documented. Also, the time to onset of pain relief in the 15 patients is not reported. No adverse events were reported.

A subsequent RCT in 47 patients with TN (primary and secondary cases) rejected the long-term benefit of 0.5% proparacaine eye drops.[18] However, the first patient report was recorded at 3 days, so no acute pain reduction within the first 24 hours was assessed.

Nasal

Kanai et al published a double-blind cross-over RCT in 25 patients with second division trigeminal neuralgia.[19] Patients were randomised to receive two sprays of lidocaine 8% (0.2ml, 16mg, n=13) or two sprays of saline solution (0.2ml, n=12) in the ipsilateral nostril to the pain. After 7 days, the groups crossed over to receive the alternative treatment. Patients remained supine with their head in a neutral position for 30 minutes during observation, presumably to establish a sphenopalatine ganglion (SPG) block.

The primary outcome was pain score (VAS) on stimulation of a trigger zone. VAS in the lidocaine group reduced from 8.0 to 1.5, while the saline group reported a non-significant reduction from 7.9 to 7.6. Ten patients (40%) in the lidocaine group reported complete pain relief at 15 minutes. This positive effect of lidocaine persisted for a median of 4.3 hours. Fifteen patients (60%) in the lidocaine group reported minor adverse side-effects which included stinging, burning or numbness of the nose and eye (n=15) and bitter taste and numbness of the throat (n=1).

Oral

The same Japanese group as above conducted a study of lidocaine use in patients with primarily oral mucosa trigger points.[20] They used a similar methodology to the previous study.[19] They recruited 24 patients with TN in the maxillary and/or mandibular branches. A dose of 0.2ml of lidocaine spray (8%) was applied to the patients finger and rubbed into the trigger zone of the oral mucosa (n=12). Alternatively, the patient rubbed 0.2ml of saline into the painful zone (n=12). NRS in the lidocaine group reduced from 5 down to 1. NRS in the saline group did not change from 5. Eleven patients (46%) were pain free following lidocaine application. Only one patient in the saline group reported complete pain relief. The median duration of pain relief was 2.8 hours (0.3, 3) in the lidocaine group.

Intravenous Infusion

Galer et al reported on the use of lidocaine infusions in the management of neuropathic pain in 111 patients in a retrospective cohort study.[21] Six of these patients were diagnosed with trigeminal neuralgia. The patients described their pain as "near constant lancinating pain" which may indicate that they had classical trigeminal neuralgia with concomitant persistent facial pain (type 2 TN). The patients received a 5mg/kg/hr infusion of lidocaine for 60-90 minutes. At one hour post infusion, one patient reported partial relief (30-70% reduction in pain score) and 5 patients reported

excellent relief (more than 70% reduction in pain scores). The authors did not mention adverse side effects.

Chaudhry et al reported a case of lidocaine infusion relieving intractable TN symptoms from a verbal pain rating of 10/10 down to 0/10 after the first hour of infusion. The patient was on an infusion over a 72-hour period, running at 60-120mg/hr.[22]

Stavropoulou et al designed a cross-over double-blind RCT to assess the role of lidocaine infusion in trigeminal neuralgia.[23] The study included patients with TN as per IASP criteria, and only patients who had a Douleur Neuropathique 4 Questionnaire (DN4) score equal to or greater than 4 (out of a maximum 10). The majority of patients had hyperalgesia and allodynia (thermal and mechanical) on examination. Each patient received four infusions (each infusion two days apart), two active and two control, allocated at random. The active infusion was lidocaine 5mg/kg in 250 mL of 5% dextrose solution given over one hour. The control infusion was 250 mL of 5% dextrose solution. At one hour post infusion, the overall reduction in pain score (VAS) was 76.4% for the active group versus 40.1% for the control group. At 24 hours, pain scores reduced by 52% for the active group versus a 4% increase in pain score for the control group. The active group also reported decreased hyperalgesia and allodynia. Somnolence was the most common side effect reported in 33% of the active infusions.

Nerve block

Baykal et al reported on the use of blind injection of the mandibular and maxillary branches of the trigeminal nerve at the level of the lateral pterygoid plate or the pterygopalatine fossa, respectively.[24] Their study included 13 patients presenting with TN symptoms, the severity of which is not clearly documented. They performed a weekly injection with 5ml 2% lidocaine over a 5-week period (6 injections). The patients were “completely pain free in 1-2 minutes” post injection. However, they did not report on baseline or post-intervention pain scores. They used this 5-week period to establish or titrate the carbamazepine dose. After this one patient remained pain free for one month, another two pain free for 6 months, and the remaining 10 patients were pain free for at least 12 months. Side effects were hypoesthesia (n=4), dizziness (n=3), ptosis (n=1) and incomplete block (n=1).

N-Methyl D-Aspartate (NMDA) Antagonists

A case report details the use of a magnesium sulphate infusion to control an acute exacerbation of TN.[25] A 65 year-old man presented to the emergency department with a VAS score of 10/10 and received 30mg/kg of magnesium sulfate in 100ml saline, infused over 30 minutes. His pain score dropped to 2/10 at 30 minutes post-infusion. He did not report any adverse effects. He was monitored for 4 hours and was then discharged from the emergency department.

Arai et al retrospectively reported the outcomes of 9 patients with TN intractable to conventional treatment who were treated with a combined infusion of lidocaine and magnesium sulphate.[26] Each patient received 100mg lidocaine mixed with 1.2g magnesium sulphate infused over one hour. The mean NRS for the patients reduced from 7 down to 4 following the infusion. It is not clear how soon after the infusion the pain score was recorded. Two patients reported mild dizziness post infusion.

Anti-convulsants

The intravenous anti-convulsants reported to be effective in the literature are phenytoin and its prodrug fosphenytoin. A case report of a 77 year-old man with intractable TN supports the use of intravenous phenytoin.[27] Following admission to the emergency department, he received a phenytoin infusion of 15mg/kg in two divided doses each infused over 30 minutes. His pain score

dropped from 10/10 down to 1/10 following the infusions. This pain relief persisted for up to 3 days. No adverse effects were reported. Vargas et al published a case report of a 53 year old man who presented to the emergency department with intractable TN symptoms.[28] He received 15mg/kg of fosphenytoin over 30 minutes. His pain score (VAS) reduced from 10/10 to 2/10 immediately following the infusion. No adverse effects were reported. The pain relief was maintained at follow up 20 days later.

Cheshire reports a case series of three patients with intractable TN who responded to a fosphenytoin infusion.[29] All three patients were previously controlled on carbamazepine, but subsequently developed an acute, unremitting phase of TN attacks that compromised their ability to eat or drink. The fosphenytoin was diluted to 5-10mg phenytoin sodium equivalents (PE)/ml in 5% dextrose with 0.45% saline. During infusion, the patients were monitored with ECG and non-invasive blood pressure observations. The first patient received 18mg/kg PE of fosphenytoin over 20 minutes. This gave immediate pain relief which lasted 2 days. She opted for a MVD. The second and third patient received an incremental dosing schedule of 100mg every 10 minutes up to a maximum of 10 doses in order to limit the required dose. Patient 2 received good pain relief after 11mg/kg dose and this was maintained for 20 hours. The patient subsequently had a trigeminal ganglion balloon compression. The third patient had 14mg/kg infused in increments as above over 3 hours, with immediate pain relief. This lasted for 2 days. This patient also opted for trigeminal ganglion balloon compression. All patients reported transient adverse effects including mild dizziness, tinnitus and ataxia.

Serotonin agonists

Kanai et al reported on the use of subcutaneous sumatriptan in triggered TN attacks.[30] They used a similar methodology to the previously mentioned studies.[19,20,31] Patients received either subcutaneous sumatriptan 3mg in 1ml (n=12) or 1ml of subcutaneous saline (n=12). Sumatriptan decreased VAS from 8.3 down to 2.4. There was no significant decrease in the saline group with 8.5 down to 8.1. Twelve patients (50%) were pain free following sumatriptan. The positive effect of sumatriptan lasted for a median of 7.9 hours (range of 1-20 hours). The reported adverse effects in the sumatriptan group included mild elevation in blood pressure (n=2), fatigue (n=5) and nausea (n=2).

A further study by the same group in patients (n=15) with at least a one month exacerbation of TN symptoms, demonstrated a significant decrease in VAS pain scores while resting (4.0), touching (4.7) and talking (4.6) in those who received subcutaneous sumatriptan (3mg in 1ml).[32] They maintained these positive improvements with a 1 week course of oral sumatriptan 50mg twice daily.

Nasal sumatriptan (20mg) was effective in a case series of 3 patients with refractory TN reducing the mean VAS from 8 to 2 within 30 minutes.[33] No adverse effects were reported.

Botulinum toxin

Zuniga et al reported on the use of botulinum toxin (BTx) injections in the trigger zones of patients with primary trigeminal neuralgia.[34] The 12 patients were assessed weekly for 8 weeks in an open label study. The patients received 20-50 units in total to individual trigger points. The authors reported that 10 of the patients (83%) experienced pain relief “after some minutes” of the injection. They also noted faster onset of pain relief with higher doses. However, precise details about pain scores or number of paroxysms within the first 24 hours are not reported. They give details of one female patient who had a pain score (VAS) of 10 and 30-40 painful paroxysms per day. She received 40 units into a left frontotemporal trigger point, and 5 units each into a zygomatic and buccal trigger point. At 24 hours her pain score was 0 and she had no painful paroxysms. This level of pain relief persisted for 70 days. The same group published a RCT on BTx in primary

trigeminal neuralgia.[35] In the article, they refer to unpublished observations of TN pain that "almost remitted at the time of injection". Other reports on BTx use in TN do not record the acute response.

DISCUSSION

Quality of evidence

The overall quality of evidence for effective acute analgesia in TN exacerbations is very low. A number of reasons may exist for this. TN is a rare condition and the number of patients required to adequately power a RCT makes such a project very difficult. Also, the majority of TN patients respond well to conventional treatment with carbamazepine. The patient group of interest in this review are a small subset of TN patients. TN is associated with painful paroxysms that may remit for long periods of time. In observational studies it can be difficult to determine if the remission is due to treatment or simply the natural course of the condition. As such, the review includes small RCTs, observational studies and case series/reports. In addition, many of the included studies did not specifically look at acute (emergency department or outpatient clinic) presentations, and some specifically triggered attacks to judge the acute effect of treatment,[19,20,30,32] while others included patients with intractable symptoms with conventional management.[16,18,26,34] However, all included studies reported on the degree of acute relief of TN pain within 24 hours.

Very few studies in TN report outcomes within the first 24 hours of starting treatment. The earliest time point in many studies was 7 days post intervention and so were excluded. While the ultimate goal of therapy should be to reduce the intensity and frequency of TN attacks, patients would also value a therapeutic strategy that provides a fast resolution of symptoms.

Local anaesthetic

The primary agent used in the included trials was lidocaine. Like all local anaesthetic agents, it is a voltage-gated sodium channel blocker and its effect in TN is most likely due to its inhibition of the triggering mechanism in the ignition hypothesis, proposed by Devor et al.[36] It's therapeutic effect in the trials that involved local application (e.g. nasal or oral mucosa) is certainly due to blockade of the peripheral nerve sodium channels. In higher systemic doses, it can demonstrate a neuromodulatory effect by reducing C-fibre transduction of pain signals and inhibition of ectopic discharges from damaged neurons without impacting on normal sensory function.[37,38] This would account for its effect in the intravenous infusion studies. While it has a shorter duration of action than other local anaesthetics, it is preferred due to it better safety profile in terms of cardiac and neurological toxicity.

The effect of 0.5% proparacaine eye drops in TN is equivocal. It may have an effect that is lost after a few hours but further studies are required to establish this. This is the case in nasal and oral mucosal lidocaine which gave a median of 4.3 and 2.8 hours of pain relief, respectively. The method of application used in applying the lidocaine to the oral mucosa (spray on the patients finger) was unusual,[20] and in patients with mucosal trigger zones it could be sprayed directly but using a lower concentration e.g 5%.

The studies investigating the effects of intravenous lidocaine included primarily trigeminal neuralgia patients with concomitant persistent facial pain (type 2 TN). The dose of 5mg/kg infused over one hour is recognised to be effective and safe in other neuropathic pain states.[39] The study by Stavropoulou et al used the DN4 (score > 4) to select patients with trigeminal neuropathic pain. However, the DN4 is not specific enough for TN and may actually select out patients with concomitant persistent facial pain (type 2 TN).[40] As such, the role of IV lidocaine in classical primary TN (type 1) is not clear. Matharu et al reported on the use of lidocaine infusions (1.3-3.3

mg/kg/hr) in SUNCT, considered by some as TN with autonomic features.[41] The SUNCT symptoms were significantly relieved by the infusion, but recurred soon after discontinuation.

A number of studies have investigated the utility of trigger point or distal nerve branch injection of local anaesthetic in TN patients. These included continuous infusion of bupivacaine around the peripheral nerve branches,[42] ropivacaine to trigeminal trigger points either alone or in combination with gabapentin,[43] peripheral nerve injection of lidocaine versus streptomycin plus lidocaine,[44,45] peripheral and proximal nerve blocks with high concentration lidocaine,[46] and tetracaine +/- bupivacaine peripheral nerve injection.[47,48] While these trials reported variable long-term outcomes, none of them reported acute outcomes within the first 24 hours. The Baykal paper reported on the use of more proximal nerve blocks to achieve acute pain relief while titrating carbamazepine.[24] These blocks should be done with image-guidance and contrast screening for vascular up-take.

Local anaesthetic injection to trigger points offers effective but transient relief of symptoms (less than 24 hours). Indeed, all the local anaesthetic interventions included in this review have a limited duration of action (2-24 hours). However, this may be valuable to the patient during a period of drug titration or waiting for a more definitive treatment to be established. Importantly, the risk profile of the interventions is low, as is the cost of the medications used. Many can be performed by dental practitioners who in the UK use 1- 2% lidocaine . Lidocaine infusions on the other hand require a nurse monitored bed for the duration of the infusion which adds to the treatment cost.

NMDA Antagonists

NMDA receptor activation is a key step in central sensitisation and NMDA antagonists may improve the associated symptoms.[49] Central sensitisation is not believed to be a significant part of classical trigeminal neuralgia.[36] The typical clinical features of central sensitisation are allodynia and hyperalgeia. These may be observed in trigeminal neuropathies, type 2 TN or persistent idiopathic facial pain, but should not be present in classic primary TN.

Magnesium sulfate (MgSO4) is a natural NMDA receptor blocker and a magnesium ion resides in the receptors central pore in normal physiological states. During periods of intense nociceptive input, the Mg ion is displaced, and the NMDA receptor can facilitate calcium influx, potentiating the nociceptive signal at the dorsal horn level in the spinal cord - one element of central sensitisation.

The included case report and case series offer very weak evidence for the use of MgSO4 in managing the acute pain of TN. In the case series, the 9 patients received 100mg lidocaine (less than 2mg/kg) combined with MgSO4 1.2g (approximately 20mg/kg over one hour). The case report dose was 30mg/kg infused over 30 minutes. The advantage of MgSO4 infusion is that it is cheap with minimal side effects. It has proven efficacy in the management of other neuropathic pain conditions like post-herpetic neuralgia and neuropathic back and leg pain.[50,51]

Other NDMA receptor blockers have been trialled in small case series of facial pain patients. Patients with chronic facial pain received various sub-anaesthetic doses of ketamine.[52] Of the 7 patients, only 3 reported transient pain relief (1-3 days) with doses of 0.4-1.8mg/kg of ketamine. All patients had pain secondary to traumatic trigeminal nerve injury rather than TN. A study of dextromethorphan (NMDA antagonist) in facial neuralgias included three patients with primary TN .[53] While acute pain relief was not reported, the patients pain control over a 14-day period was worse on the oral dextromethorphan compared to oral lorazepam (active control).

Anticonvulsants

Treatment algorithms for TN contain many anti-convulsant agents including carbamazepine, oxcarbazepine, lamotrigine, and gabapentin.[9,54] However, many of these agents are not available in intravenous form and their oral administration requires a period of cautious titration. This makes them unsuitable for the management of acute TN attacks.

The exception to the above is phenytoin, or its prodrug fosphenytoin, which is a commonly used intravenous anti-convulsant. Both drugs have been used successfully in the acute control of TN attacks. The evidence is weak, based on case reports and a small case series. Phenytoin is a use-dependent antagonist of voltage-gated sodium channels. It selectively blocks sodium channels that are opened repeatedly, a property which makes it an effective anticonvulsant.[55] It also blocks voltage-gated calcium channels. These pharmacodynamic properties help to explain how it may inhibit the triggering and amplification steps in the ignition hypothesis. Fosphenytoin is a phenytoin prodrug with a better side-effect profile.[56] The loading dose for both drugs is 15-18mg/kg over 30 minutes. Similar to lidocaine infusions, the patient requires a nurse-monitored bed during the infusion. Adverse effects include dizziness and ataxia, hypotension and rarely heart block.

The onset of pain relief in the included cases was immediate post-infusion and lasted for 1-3 days on average. This allowed the patients to consider more definitive treatment options.

Serotonin agonists

Sumatriptan is the most commonly used triptan and is a serotonin (5-hydroxytriptamine, 5-HT) agonist, specifically 5-HT 1B and 1D receptors.[57] It may be administered orally, intranasally, subcutaneously or rectally. It is a first line rescue agent in migraine treatment and it is most effective when given subcutaneously at a dose of 6mg.[58] It may also have a role in the acute management of TN attacks.

Its mechanism of action in the termination of migraine attacks is believed to be direct vasoconstriction of dilated meningeal blood vessels, inhibition of release of vasodilatory peptides from trigeminal sensory neurons, and a reduction in pain transmission in the trigeminal dorsal horn in the pons.[59-61] Sumatriptan may exert its analgesic effect in TN by reducing pain transmission in the pons. As a vasoconstrictor, it may also reduce the mechanical compression of the trigeminal nerve root by a vascular loop.

While the use of the subcutaneous route is more effective in migraine management, and was the chosen route in the included studies, it is more expensive than the oral option. The nasal route is a more attractive option in a patient with acute TN symptoms who cannot take oral medication or wants to avoid injections. Sumatriptan is generally well tolerated but may be associated with moderate increases in blood pressure. It should be used with caution in hypertensive patients or those with coronary artery disease.

Botulinum toxin

Botulinum toxin is indicated as a prophylactic treatment in the management of refractory chronic migraine,[62,63] and a growing number of observational and RCT studies support its use in refractory primary TN.[64] However, there is limited data on its acute analgesic effect. The included studies were not designed to investigate the acute analgesic effect of botulinum toxin in this patient group, but remark on the early onset of pain relief.

The mechanism of action of botulinum toxin in painful conditions like chronic migraine or TN is believed to be inhibition of neuropeptide release (e.g. CGRP and substance P) from peripheral sensory nerve endings.[65] This may limit peripheral sensitisation and could account for a role in reducing neural triggering in TN. However, in comparison to other treatment options, botulinum toxin is more expensive with the National Institute of Health and Care Excellence (NICE) estimating each treatment for chronic migraine may cost £349.40. A mixture of botulinum toxin and

lidocaine into trigger points to manage acute exacerbations in specific cases could be trialed. The botulinum toxin prolongs the acute effect of the lidocaine. and we have had a number of positive results with this approach. As such, while the evidence is still weak for acute exacerbations, a case-by-case basis could be considered in experienced specialist centres.

Algorithm for acute management

If a patient presents with an acute exacerbation of their facial pain, it is important to confirm that this is consistent with primary TN .[66] If the pain is different in quality or character to their usual TN pain, or if they report red flag symptoms, a clinical history, examination +/- investigations are warranted to rule out a secondary cause.

However, if the patient has a diagnosis of primary TN and this episode is consistent with previous attacks, then it is appropriate to treat without further investigations. The GRADE summary of evidence table gives an indication of how the data was graded (*Supplementary table 1)*. It is recommended to start with the intervention with the highest evidence, and lowest cost and side effects (Figure 3). Most of the interventions are associated with immediate relief (within one hour of completing the therapy). Therefore, it is appropriate to move swiftly through the algorithm if a treatment has not been successful.

FIGURE 3 HERE

Most of the interventions give less than 24 hours of pain relief, so a more definitive care plan needs to be put in place according to current guidelines.[9,67] This may involve starting or titrating medications, or planning surgical interventions. The case series by Cheshire describes this process well with the acute management of 3 patients with fosphenytoin infusion while simultaneously planning more definitive management plans.[29] Some of the studies count the early discontinuation or reduction of prophylactic medications (e.g. carbamazepine) as a positive outcome measure, and the Japanese studies even discontinued these medications 12 hours before intervention.[19,20,30] Abrupt discontinuation of a well tolerated medication is not generally recommended and in an acute exacerbation increasing the dose of these medications to achieve better long term control is the preferred option.

CONCLUSION

TN is associated with periods of moderate to severe flare-up that can have a detrimental impact on an individual's personal and professional life. Many current treatment strategies are aimed at long-term symptom control and fail to give acute pain control (within 24 hours). This may lead to work absence or hospital admission. Weak evidence exists to support the use of lidocaine, sumatriptan, phenytoin/fosphentoin, botulinum toxin and MgSO4 as acute rescue analgesics. Future studies of interventions in TN should consider recording the first point of onset of analgesia as well as the duration of effect. It may be necessary to look at N of one trials to get over some of the difficulties of designing RCTs of acute management.

CONTRIBUTORSHIP

D.M.M. : systematic literature search and review, study inclusion, data extraction, manuscript preparation and revision; J.M.Z. : systematic literature search and review, study inclusion, data extraction, manuscript preparation and revision; M.S.C. : data retrieval, adjudication on study inclusion, manuscript preparation and revision; A.S. : data retrieval, manuscript preparation and revision.

ACKNOWLEDGEMENTS

None

DECLARATION OF INTERESTS

J.M.Z. has a consultancy with Biogen.

FUNDING

J.M.Z. undertook this work at University College London and University College London Hospital Trust who received a proportion of funding from the Department of Health's National Institute for Health Research (NIHR) Biomedical Research Centre funding scheme.

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FIGURES

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Flow Diagram details the literature search. Out of 452 potentially relevant studies, 17 studies t investigate or reference the efficacy of an analgesic therapy within 24 hours of administration for trigeminal neuralgia.

Figure 2: Risk of bias summary - review authors' judgements about each risk of bias item for the included randomised control trials.

Figure 3: Evidence-based treatment algorithm for the management of acute exacerbations of trigeminal neuralgia. Management of acute exacerbations should proceed in parallel with a more definitive long term management plan. The quality of evidence is included after each intervention. The ***moderate*** and ***high*** quality evidence receives a “should consider” recommendation. The **very low** and **low** quality evidence are options the clinician “may consider” if interventions with higher quality evidence are contraindicated or not available. * Sumatriptan injection pens in the UK contain 6mg in 1ml, and we have recommended this for convenience as opposed to the 3mg used by the Japanese group. ** these concentrations may not be available in all countries 2-5% more common.

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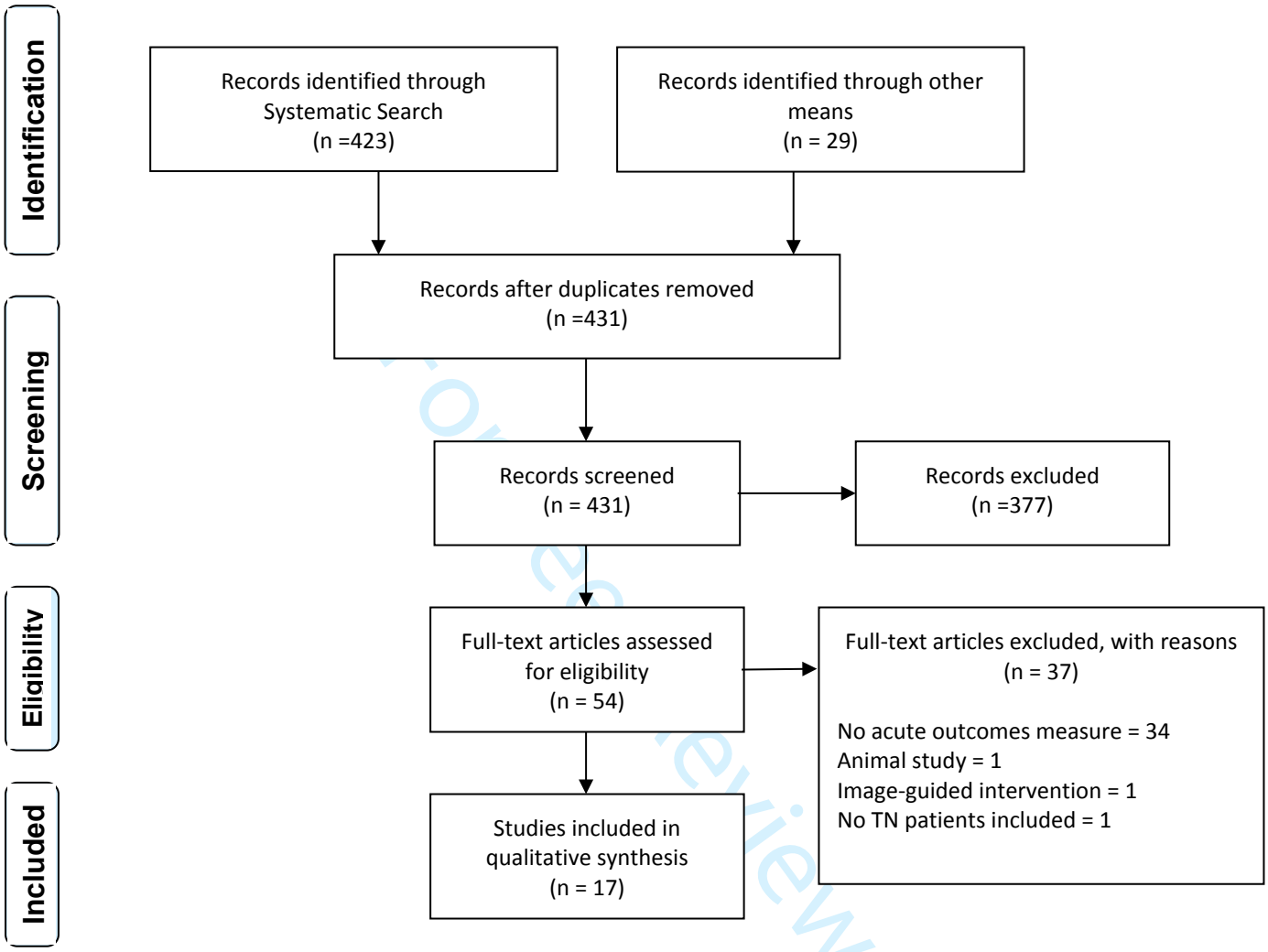

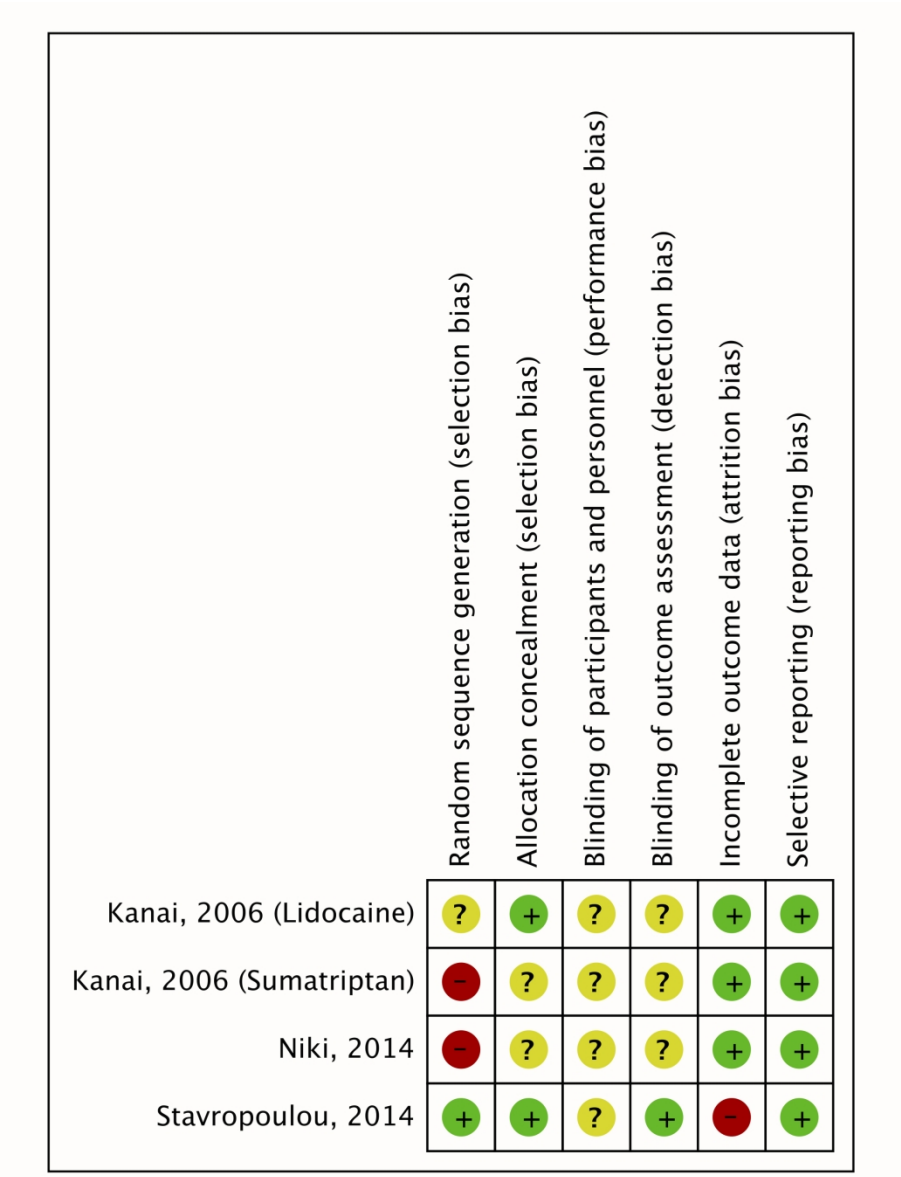

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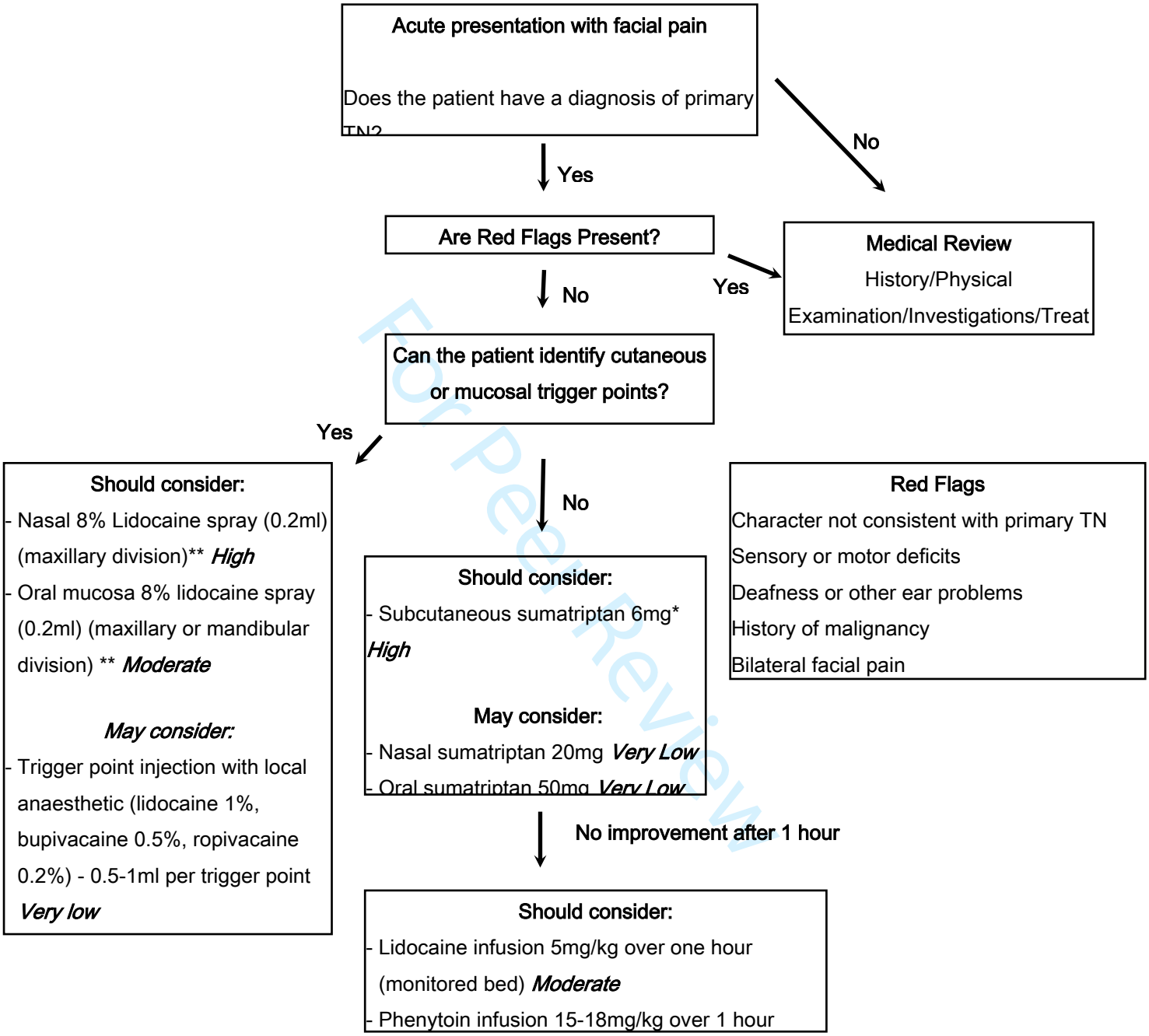
Figure 3



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