A systematic review of the management of trigeminal neuralgia in patients with multiple sclerosis.

Abbreviation list

AD	Anaesthesia dolorosa
APR	Acute pain relief
AED	Antiepileptic drug
BC	balloon microcompression
BNI	Barrow Neurological Institute
EDSS	Expanded Disability Status Scale
MS	Multiple sclerosis
MRI	Magnetic resonance imaging
MVD	Microvascular decompression
NR	Not reported
NVC	Neurovascular compression
PGR	percutaneous glycerol rhizotomy
PSR	Partial sensory rhizotomy
PwTNMS	Patient with trigeminal neuralgia and multiple sclerosis
SRS	stereotactic radiosurgery procedures
RFT	radiofrequency thermocoagulation
TN	Trigeminal neuralgia
VAS	Visual analogue scale

A systematic review of the management of trigeminal neuralgia in patients with multiple sclerosis.

Joanna. M. Zakrzewska MD *

* Corresponding author

Facial Pain Unit Eastman Dental Hospital,
UCLH NHS Foundation Trust , 256 Gray's Inn Road, London WC1X 8LD,UK
Email: j.zakrzewska@ucl.ac.uk

Jianhua Wu PhD

Dental Translational and Clinical Research Unit

School of Dentistry, University of Leeds, LS2 9LU, UK

Email: J.H.Wu@leeds.ac.uk

Tricia S-L Brathwaite MSc
Oral & Maxillofacial Surgery Department Eastman Dental Hospital,
UCLH NHS Foundation Trust , 256 Gray's Inn Road, London WC1X 8LD,UK
Email triciabrathwaite@gmail.com

ABSTRACT

Background and Objective: Patients with trigeminal neuralgia (TN) and multiple sclerosis (MS) are often treated with medications or a surgical procedure. However, there is little evidence that such treatments result in 50% pain reduction and improvement in quality of life. The aim of this systematic review is to evaluate the clinical effectiveness of treatments in patients with MS and trigeminal neuralgia.
Databases and Data Treatment: We searched Medline, EMBASE, and the Cochrane Collaboration database from inception until October 2016. Two authors independently selected studies for inclusions, data extraction and bias assessment.

Results: All studies were of low quality using the GRADE system. For medical management, ten studies were included of which one was a randomised control trials. Two studies were on the use of misopropol, unique to patients with MS. For surgical therapy, 26 studies with at least 10 patients and a minimum of two-year follow-up were included. All types of surgical procedures are reported and the results are poorer than for TN without MS with 50% having a recurrence by two years. The main complications were sensory loss. Many patients had to undergo further procedures to become pain free and there were no agreed prognostic factors.

Conclusions: There was insufficient evidence to support any one medical therapy and so earlier surgery may be preferable. A patient with TN and MS has therefore to make a decision based on low level evidence beginning with standard drug therapy and then choosing a surgical procedure.

Key words: antiepileptic drugs , multiple sclerosis, neurosurgery , systematic review, trigeminal neuralgia

INTRODUCTION

Unlike many other types of chronic pain, trigeminal neuralgia (TN), a severe unilateral episodic facial pain, can be managed both with medications or a variety of surgical procedures. In the majority of patients the cause remains unknown but Harris [1] in 1950 noted a connection with multiple sclerosis (MS) and early epidemiological studies showed that there was a strong connection with MS ~~with~~ and a 20 fold higher prevalence of TN in this group. [2]

A recent systematic review of pain in MS suggested a prevalence of 3.8% (CI 2.0-6.0%) of TN and this is lower than headaches or neuropathic pain. [3] Another recent review suggested that over 30% of medications used by patients with MS are for pain. [4]

The clinical manifestations of TN in patients with MS are the same as for other forms of TN although there are reports of the attacks having some atypical features in that there is a more prolonged background pain. [5, 6, 7] However Sandell et al.,[7] in their small cohort of 19 suggested that all patients initially have episodic pain and others [8] also showed in their series that background pain was not related to presence or absence of demyelination in the trigeminal area. Mohammadi et al [9] found in their series that over time the pain became more atypical, larger number of divisions ~~was~~ were involved and 6% became bilateral. It is generally thought that MS precedes TN but several series reported TN as a first symptom with intervals of between 10 and five years before another MS symptom. [10 9 11]. No correlation between extent of MS plaques and clinical manifestations have been shown. [12, 13] There is a lack of data as to whether periods of remission occur in patients with MS. Trigeminal reflexes including the blink reflex are abnormal in patients with MS and electrophysiological testing is highly accurate in distinguishing other forms of TN from MS related TN. [6,14] Cruccu et al [15] suggested that the plaques resulting in TN are in the pontine area and result in damage to the primary afferents. The mechanism in MS related TN could be different and not the result of neurovascular compression although both mechanisms may be present in some patients. [14] It has been suggested that in MS

there is increased activity of T-cells leading to increased inflammatory activity in the plaques which makes them more susceptible to ephaptic nerve conduction. [6]

Antiepileptic drugs (AEDs) are the major drugs used for all types of pain in MS. Jawahar et al [16] in a systematic review have showed that for non TN pain this class of drug is effective and although side effects are reported they are demeaned tolerable. It is important to note that currently none of the medications are curative and so they should be used only during periods of relapse and discontinued if surgery has resulted in pain relief.

Two drugs are used more frequently in patients with TN and MS (pwTNMS) than in other TN patients are baclofen and misoprostol . Baclofen is a $GABA_B$ agonist works whereas misoprostol is a prostaglandin-E_1- analogue which may reduce inflammatory activity in the plaques and so result in nerve stabilisation. [6]

The literature suggests that pwTNMS have greater problems with use of medications as they potentiate some of the MS symptoms and so higher more effective doses cannot be used.[17] Ramsaransing et al., [18] reported on six patients with MS whose disability significantly increased when using carbamazepine. Equally, surgical outcomes seem to be less satisfactory than in the other TN patients, possibly because the mechanism is different. However they do offer a period when medications can be withdrawn. It has been suggested that microvascular decompression (MVD) should not be done as the cause of the TN is not compression of the nerve by a vessel but the demyelinating plaques on the trigeminal nerve. However, studies suggest that both can exist [7, 8, 10, 15,19] and a recent study suggests that neurovascular decompression should be actively looked for in all patietns with TN.[14] There is also evidence of demyelination in patients without clinically proven MS [8 ,20] Abhinav et al [8] have demonstrated that these patients can undergo successful partial sensory rhizotomy if no compressive vessels are found.

In a fifty year old fit patient with TN and MS would treatment with medications or a surgical procedure result in 50% pain reduction and improved quality of life? In order to answer this question, a review of the literature on both pharmacological and surgical management of TN in pwTNMS was required. This could provide some

guidance both to clinicians and patients as to the most effective management strategies.

METHODOLOGY

Data sources and search strategy

We performed a database search using Medline (in OvidSP), EMBASE and the Cochrane Collaboration database from their inception date until October 2016. Search terms were related to medical and surgical management of MS-TN patients ~~(for details, see supplemental file 1 table 1~~please see table 1.). Previous searches of surgical treatments for TN were utilised to obtain reports which contained results on pwTNMS. [21] Only articles published in English were included and all abstracts were excluded.

TABLE 1 HERE

Study selection and data extraction

Two reviewers (TB and JZ) independently screened the search results based on title, key words and abstract. 10% of the search results were then reviewed by a third reviewer ECB. All three reviewers met to compare the selection and resolve any differences by consensus.

Of the surgical studies only those having 10 or more pwTNMS and a mean follow up of two years were included. In those which reported mixed cohorts, if the data on pwTNMS could not be extracted they were excluded. The surgical data was graded using the Surgical Trigeminal Neuralgia Score system [22] and if the scores were below 40% these were also rejected.

Reviewers TB and JZ developed and completed the data extraction. Data was extracted into a medical table which compared and contrasted the drugs reported in

the management for pwTNMS and another table was developed for the surgical data. Data were extracted on:

(1) Author, date of publication, journal

(2) Study design and clinical setting

(3) Study population characteristics: basic demographics, TN and MS criteria of the patients, number of patients, number of patients with TN and MS, inclusion and exclusion criteria, study duration, duration of TN, duration of MS, onset order of TN and MS, interval between TN and MS, location of TN.

(4) For drug management studies, the following data were extracted: drug prescribed, daily dosage, pain measure (Visual Analogue Scale), overall drug impact on pain, side effects.

(5) For surgical studies, the follow data were extracted: type of surgery, duration of follow-up, lost to follow up, recurrence rate, recurrence interval, surgical complications.

Data quality and synthesis

~~The quality of the studies was generally poor because a~~All studies were open label and involved very few patients that met the inclusion criteria. The study duration varied significantly and the outcome measures were poorly reported. It was not possible to determine what constituted a 50% pain reduction in the medical trials. There is a high risk of publication bias due to the exclusion of ~~the~~ studies in which the data on pwTNMS could not be extracted in those containing mixed cohorts.

For medical management studies, data synthesis was not possible due to very small sample size. For surgical studies, data were synthesised by the type of surgical procedures.

RESULTS

The initial search identified 540 records, and of these 78 was assessed as shown in Figure 1. Excluding review papers and studies that did not meet the inclusion criteria, 10 medical therapy studies and 26 surgical therapy studies were included in this review. A meta analysis was not possible due to the variability of the studies. All studies yielded a low score on the GRADE system.

Figure 1 HERE

Prevalence of pwTNMS

Table ~~1~~ 2 provides data on prevalence and demographic details of pwTNMS as found in both neurological and neurosurgical settings. The prevalence of TN among pwMS is 4.0%, which is consistent with 3.8% reported in the meta-analysis by Foley et al.,. [3] Women predominate, 60.5%, with the average age of onset of TN being 45.4 years which was significantly lower than that reported in other types of TN which is 50-60 years. Of the 22 studies which reported the timing of TN in relation to MS 10.5% had TN prior to MS and it could be over 10 years before another MS episode was reported. Of the 24 studies reporting location 11% had bilateral symptoms compared to 3% in non MSTN. De Simone [23] case control studies of 15 pwTNMS suggested that the clinical characteristics were the same as in other patients with TN and this was borne out by Cruccu et al.,[15] and several other surgical studies. Cruccu al [15] suggested that MS starts later in those with TN.

Table ~~1~~ 2 HERE

Medical therapies

There were no systematic reviews, two reviews of general pain management in MS. : [50,17] There were 10 studies reported between 1970 and 2003 which included one

RCT [51], one controlled trial [52], two comparing different medications [53, 54] and one comparing an non MS TN group with a TNMS group [55]. The rest were case reports and it was difficult to establish whether they were retrospective or prospective. [6,56, 57, 58] Five studies were from the same institution and no study had more than 18 patients. Only three studies provided details of the type of MS, two studies showed the criteria for diagnosis of TN. [59,52] Only one study used a VAS and recorded both intensity and number of attacks. [52] The majority of studies used a scale of 0-4 or just complete, partial and no response so it was not possible to dichotomize the results. No quality of life measures were used. Additionally, the follow up (from 1 month to 48 months) varied making it impossible to determine how many were lost to follow up or determine recurrence rate.

The main results of the 10 pharmacological interventions including side effects are shown in table ~~2~~3**.**

Table ~~2~~ 3 HERE

Surgical management

There are two ~~poor quality~~ reviews one [60] which reviews of all surgical procedures and Taich et al., [61] which reviews of all stereotactic radiosurgery procedures (SRS). Three studies dealt with multiple procedures of which Mohammadi et al., [9] series treated 96 pwTNMS with 277 surgical procedures. Nine studies did not separate the MS data from their non MS TN so their data could not be used. Only 2 papers provided data on the type of MS. [9 ,10] Table 4 provides ~~E~~extra details of the ~~included~~ selected surgical procedures including details of outcome measures. ~~are found in the supplemental data tables 2 and 3.~~ Table ~~3~~ 5 summarises the outcomes by different surgical procedures and the weighted averages were obtained from the studies with available data.

Tables 4 HERE

Table ~~3~~ 5 HERE

~~Three~~ Two studies [7, ~~8~~,10] reported on outcomes after MVD and one after ~~/posterior fossa~~partial sensory rhizotomy (PSR) [8] in a total of 77 pwTNMS. After MVD ~~the intervention~~, ~~83~~73% of the patients had reported pain relief whereas in the one PSR

study it was 87% and the recurrence rate was ~~32.1~~39%. after MVD and 21.7% after PSR. Numbness occurred in 22/23 patients after PSR and included one with anaesthesia dolorosa compared to numbness only in 2/105 in the MVD group. ~~and i~~Impaired hearing ~~were common complications~~was noted in two patients after MVD. ~~from the procedure~~.

A total of 180 pwTNMS had undergone SRS procedures in six studies. [9, 38,47, 49, 61,62] The average age of 60 years was significantly ~~older~~ higher than those undergone MVD/PSR procedures (52 years). 83.6% of the patients had pain relief after surgery but 51.1% had experienced recurrence during the follow-up period. Facial numbness, sensory loss and paraesthesia were reported in 11.7% of patients. ~~the common complications.~~

Eight studies reported on use of percutaneous glycerol rhizotomy (PGR) in a total of 299 pwTNMS whose average age was 51 years. [9,11,26,38, 42,63,64, 65] The average follow-up was 42 months, 77.3% of the patients had good pain relief after the procedure while 53.4% had recurrences during the follow-up period. Of those patients who experienced a recurrence, the median recurrence time was 20.3 months, which was significantly shorter than those patients undergone SRS procedure (30.4 months).

A total of 74 pwTNMS had undergone balloon microcompression (BC) [9, 37,39,66] and 58 radiofrequency thermocoagulation (RFT) [12, 27, 29, 67] 86.4% of those who had BC and 97.8% of those who had RFT had reported good pain relief. However, those who had BC reported the highest recurrence rate of 67.0% while those who had RFT reported the lowest recurrence rate of 27.5%.

From studies using Kaplan Meier methodology it was possible to determine the probability of recurrence over a period of 5 years (Figure 2). This was the same method as previously used to assess probability of recurrence in non-MS TN.[68] All procedures reported that by two and half years, 50% of pwTNMS were likely to have had a recurrence and those studies which provided comparative data with non MS TN, showed better outcomes for the latter.

The only none destructive procedure was MVD, a major neurosurgical procedure of which there are few studies. Whereas destructive (ablative) procedures, whether at the root entry zone or the Gasserian ganglion level were frequently reported.

Figure 2 HERE

Recommendations for management

Due to the lack of data ~~and poor quality of evidence~~ it is difficult to advise how the presented patient should be managed. No pharmacological treatments can be advised specifically for pwTNMS so the same medical management can be used ~~. Although pain relief was a primary outcome there was a lack of data on quality of life outcomes. Therefore, pwTNMS should be managed medically along the same lines~~ as for non-MS TN ~~using~~ i.e. carbamazepine or oxcarbazepine as first line with second line drugs being lamotrigine, baclofen, gabapentin and pregablin. [69 70] Patients need to be given careful instructions about use of medications i.e. beginning the drugs slowly ~~on~~ with low doses and gradually increasing them and this can be done with the help of ~~. They should be encouraged to keep~~ pain diaries. ~~diaries to evaluate the effect of the drugs.~~ This approach would help to reduce side effects and potential exacerbations of existing MS symptoms. ~~There is a lack of evidence that the side effects are worse in pwTNMS than other patients using AEDs.~~ Monotherapy is encouraged but polytherapy can be introduced to gain better control ~~Single drugs should be used first and then potentially two drugs~~ as Solaro et al.,[71] showed. ~~that carbamazepine could be continued if the dose is reduced and another drug added.~~ Patients need to be aware that flare ups can occur and they need to develop a strategy for how these can be dealt with by increasing the medication for a while. Conversely if a remission is reported in that patients indicate that they have no pain the drugs can be tapered down and stopped until the next flare up. We have shown that support from psychologists and clinical nurse specialists with knowledge of these drugs can be extremely helpful (poster at International Association for the Study of Pain Congress 2016) and Douglas et al.,[72] also showed that patients with MS who had a better biopsychosocial approach to their pain reported better outcomes.

If pain control is poor then surgical options ~~should~~ need to be considered but it is not possible to provide recommendations as to when this should occur nor is there any

data to compare pharmacological versus surgical ~~preferences~~outcomes. Although MVD does give poorer results in pwTNMS and a higher risk of complication there may be a place for it in those few with no plaques on the trigeminal nerve and with clear neurovascular compression(NVC) on MRI although Abhinav et al's [8] study suggested that the other option is to do a partial sensory rhizotomy. There are many more studies reporting other ablative procedures which are relatively easy to perform and carry less risk. They gave similar results in that by 2½ years 50% will have a recurrence. Repeat surgery does increase the risk of sensory changes.

DISCUSSION

TN is common in pwMS. It can occur before MS and many present with classical symptoms [23] but in pwTNMS up to 89% have abnormal trigeminal reflexes as compared to 3% in idiopathic TN.[15] The evidence for pharmacological management of TN is ~~of very poor quality~~based on , open label studies with very small numbers and a high risk of bias. Only the DMKG [52] study group, ~~approached a reasonable standard with clearly~~ defined inclusion criteria and measured outcome measures. It is likely that the studies included a heterogeneous group of patients both from the MS aspect and also TN as criteria used for diagnosis were only provided in one study.[52] Most of the recruited patients had become non responsive to conventional medications but there was no indication as to what proportion they constituted. There was scare data on length of time medications were used for , whether slow escalation occurred or whether drugs were stopped due to remissions. It has been suggested that pwTNMS are more likely to have side effects but in these studies the converse was found ~~The side effects profile was very low~~ and this is not in agreement from other TN literature which shows that most patients have side effects. [73] ~~There is a lack of evidence that the side effects are worse in pwTNMS than other patients using AEDs.~~ Tiredness and ataxia are common side effects and can lead to further disability in patients with MS.

Only oxcarbazepine has not been reported in pwTNMS and there were only two cases of pregablin use. ~~so these should be explored further~~. [74] The data on m~~M~~isoprostol cannot be generalised to other pwTNMS as the studies contained intractable cases with short follow up. ~~has not been reported in non-MS TN and in~~

~~the two small studies patients with intractable TN showed efficacy but the follow up time was short and the results cannot be generalised to other pwTNMS~~.

There is thus an urgent need for RCTs which ~~can take account of the need to~~ avoid use of placebos or active controls. An enhancement withdrawal enriched randomised control trial may be applicable and has been used in other TN trials.[75] More robust outcome measures are needed that measure not only pain relief and reduction of paroxysms but also quality of life and its impact on MS using the EDSS. A more systematic approach to side effects is needed to determine if tolerability is reduced in this group. A natural history of TN in pwTNMS is required to compare with non-MS TN to determine if there are true differences as De Simone et al [23] suggested that there are none. With improved imaging more patients may have MS than previously reported and TN could be the first symptom. It is important to establish if pain increases during relapses of MS or whether it evolves over the course of MS and is linked to type of MS. This could be done using novel methodology such as trials within cohorts.[76]

Within the surgical data there are no RCTs or controlled trials. The majority of data is retrospective ~~and its quality is low when using the surgical trigeminal neuralgia score~~ with a high risk of bias.[22] In a small sub group of pwTNMS who have clear compression Truini et al .,[14] suggest that MVD should be considered although it needs to be noted that at present the results are poorer than in non MS TN so further data is required. Other ablative procedures give poorer outcomes in pwTNMS than those with non MS TN when the same methodology is used [68, 77] but they do provide up to two years pain relief without medication. RCTs comparing the varying ablative procedures should be possible and would provide much needed data. [38]

There is increased evidence that shared decision making increases patients satisfaction but significant challenges arise when the evidence is of low quality , conflicting, unavailable or not relevant to the patient. ~~as has been demonstrated in this review. Among others~~ Epstein & Gramling [78], and Politi et al.,[79] among others ~~put forward some~~ suggestion~~s~~ ~~which include~~ ways of dealing with these problems ~~discussions about uncertainty with the patient ,~~which include exploring values and preferences and engaging in patient centred communication which ~~includes building~~is based on a supportive relationship. Patients, therefore need time and

consultations jointly with physicians and neurosurgeons to determine ~~as to~~ what may be the best option for them at any particular time. In a study in which patients with TN where asked about their preferences for treatment surgical options were preferred to medical ones but ~~again~~ the evidence on which the patients made their decisions ~~these~~ were based ~~were of~~on ~~poor~~ low quality evidence. [80]

CONCLUSIONS

In view of the lack of any high quality evidence it remains impossible to provide a pwTNMS such as the one described here with a definitive treatment plan. Both pharmacological and surgical treatments provide some pain relief but for shorter periods than on other TN patients. More high quality studies are required.

Acknowledgments

Elisabet Cortes Barrera (ECB) , postgraduate MSc student at Eastman Dental Hospital reviewed some of the medical articles. Librarians at Royal Society of Medicine developed the search strategy in conjunction with JZ .

JZ undertook the work at UCL/UCLHT who received a proportion of funding from the Department of Health's NIHR Biomedical Research Centre funding scheme.

Authors contributions : JZ conceived the idea and designed the protocol. TB and JZ independently searched, graded and extracted the data. JW ensured that the analysis was correct. All authors discussed the results, commented on the manuscript and approved the final draft.

Declaration of interest : JZ has a consultancy with Biogen Inc . No funding was obtained for this study.

References

1. Harris W. Rare forms of paroxysmal trigeminal neuralgia, and their relation to disseminated sclerosis. *Br Med J* 1950;2(4687):1015-19.
2. Katusic S, Williams DB, Beard CM, et al. Incidence and clinical features of glossopharyngeal neuralgia, Rochester, Minnesota, 1945-1984. *Neuroepidemiology* 1991;10(5-6):266-75.
3. Foley PL, Vesterinen HM, Laird BJ, et al. Prevalence and natural history of pain in adults with multiple sclerosis: systematic review and meta-analysis. *Pain* 2013;154(5):632-42. doi: S0304-3959(12)00647-1 [pii];10.1016/j.pain.2012.12.002 [doi]
4. Solaro C, Trabucco E, Messmer UM. Pain and multiple sclerosis: pathophysiology and treatment. *Curr Neurol Neurosci Rep* 2013;13(1):320. doi: 10.1007/s11910-012-0320-5 [doi]
5. Jensen TS, Rasmussen P, Reske-Nielsen E. Association of trigeminal neuralgia with multiple sclerosis: clinical and pathological features. *Acta Neurol Scand* 1982;65(3):182-89.
6. Reder AT, Arnason BG. Trigeminal neuralgia in multiple sclerosis relieved by a prostaglandin E analogue. *Neurology* 1995;45(6):1097-100.
7. Sandell T, Eide PK. The effect of microvascular decompression in patients with multiple sclerosis and trigeminal neuralgia. *Neurosurgery* 2010;67(3):749-53. doi: 10.1227/01.NEU.0000375491.81803.5D [doi]
8. Abhinav K, Love S, Kalantzis G, et al. Clinicopathological review of patients with and without multiple sclerosis treated by partial sensory rhizotomy for medically refractory

trigeminal neuralgia: a 12-year retrospective study. *Clin Neurol Neurosurg* 2012;114(4):361-65.

9. Mohammad-Mohammadi A, Recinos PF, Lee JH, et al. Surgical outcomes of trigeminal neuralgia in patients with multiple sclerosis. *Neurosurgery* 2013;73(6):941-50. doi: 10.1227/NEU.0000000000000128 [doi]
10. Broggi G, Ferroli P, Franzini A, et al. Operative findings and outcomes of microvascular decompression for trigeminal neuralgia in 35 patients affected by multiple sclerosis. *Neurosurgery* 2004;55(4):830-38.
11. Linderoth B, Hakanson S. Paroxysmal facial pain in disseminated sclerosis treated by retrogasserian glycerol injection. *Acta Neurol Scand* 1989;80(4):341-46.
12. Kanpolat Y, Berk C, Savas A, et al. Percutaneous controlled radiofrequency rhizotomy in the management of patients with trigeminal neuralgia due to multiple sclerosis. *Acta Neurochir (Wien)* 2000;142(6):685-89.
13. Hooge JP, Redekop WK. Trigeminal neuralgia in multiple sclerosis. *Neurology* 1995;45(7):1294-96.
14. Truini A, Prosperini L, Calistri V, et al. A dual concurrent mechanism explains trigeminal neuralgia in patients with multiple sclerosis. *Neurology* 2016;86(22):2094-9. doi: 10.1212/WNL.0000000000002720 [published Online First: 2016/05/11]
15. Cruccu G, Biasiotta A, Di RS, et al. Trigeminal neuralgia and pain related to multiple sclerosis. *Pain* 2009;143(3):186-91.
16. Jawahar R, Oh U, Yang S, et al. A systematic review of pharmacological pain management in multiple sclerosis. *Drugs* 2013;73(15):1711-22. doi: 10.1007/s40265-013-0125-0 [doi]
17. Solaro C, Uccelli MM. Management of pain in multiple sclerosis: a pharmacological approach. *Nat Rev Neurol* 2011;7(9):519-27. doi: nrneurol.2011.120 [pii];10.1038/nrneurol.2011.120 [doi]

18. Ramsaransing G, Zwanikken C, De KJ. Worsening of symptoms of multiple sclerosis associated with carbamazepine. *BMJ* 2000;320(7242):1113.

19. Eldridge PR, Sinha AK, Javadpour M, et al. Microvascular decompression for trigeminal neuralgia in patients with multiple sclerosis. *Stereotact Funct Neurosurg* 2003;81(1-4):57-64.

20. Love S, Gradidge T, Coakham HB. Trigeminal neuralgia due to multiple sclerosis: ultrastructural findings in trigeminal rhizotomy specimens. *Neuropathol Appl Neurobiol* 2001;27(3):238-44.

21. Zakrzewska JM, Akram H. Neurosurgical interventions for the treatment of classical trigeminal neuralgia. *Cochrane Database Syst Rev* 2011;9:CD007312.

22. Akram H, Mirza B, Kitchen N, et al. Proposal for evaluating the quality of reports of surgical interventions in the treatment of trigeminal neuralgia: the Surgical Trigeminal Neuralgia Score. *Neurosurg Focus* 2013;35(3):E3. doi: 10.3171/2013.6.FOCUS13213 [doi]

23. De Simone R, Marano E, Brescia M, V, et al. A clinical comparison of trigeminal neuralgic pain in patients with and without underlying multiple sclerosis. *Neurol Sci* 2005;26 Suppl 2:s150-s51.

24. Antic B, Peric P. Posterior fossa exploration in treatment of trigeminal neuralgia associated with multiple sclerosis. *Surg Neurol* 2009;71(4):419-23. doi: S0090-3019(08)00434-5 [pii];10.1016/j.surneu.2008.04.033 [doi]

25. Ariai MS, Mallory GW, Pollock BE. Outcomes after microvascular decompression for patients with trigeminal neuralgia and suspected multiple sclerosis. *World Neurosurg* 2014;81(3-4):599-603. doi: S1878-8750(13)01209-6 [pii];10.1016/j.wneu.2013.09.027 [doi]

26. Bender MT, Pradilla G, Batra S, et al. Glycerol rhizotomy and radiofrequency thermocoagulation for trigeminal neuralgia in multiple sclerosis. *J Neurosurg* 2013;118(2):329-36. doi: 10.3171/2012.9.JNS1226 [doi]

27. Berk C, Constantoyannis C, Honey CR. The treatment of trigeminal neuralgia in patients with multiple sclerosis using percutaneous radiofrequency rhizotomy. *Can J Neurol Sci* 2003;30(3):220-23.

28. Brett DC, Ferguson GG, Ebers GC, et al. Percutaneous trigeminal rhizotomy. Treatment of trigeminal neuralgia secondary to multiple sclerosis. *Archives of Neurology* 1982;39(4):219-21.

29. Brisman R. Trigeminal neuralgia and multiple sclerosis. *Arch Neurol* 1987;44(4):379-81.

30. Chakravorty BG. Association of trigeminal neuralgia with multiple sclerosis. *Arch Neurol* 1966;14(1):95-99.

31. Cheng JS, Sanchez-Mejia RO, Limbo M, et al. Management of medically refractory trigeminal neuralgia in patients with multiple sclerosis. *Neurosurg Focus* 2005;18(5):e13. doi: 180513 [pii]

32. Eriksson M, Ben-Menachem E, Andersen O. Epileptic seizures, cranial neuralgias and paroxysmal symptoms in remitting and progressive multiple sclerosis. *Mult Scler* 2002;8(6):495-99.

33. Huang E, Teh BS, Zeck O, et al. Gamma knife radiosurgery for treatment of trigeminal neuralgia in multiple sclerosis patients. *Stereotact Funct Neurosurg* 2002;79(1):44-50. doi: 69503 [doi];69503 [pii]

34. Katusic S, Beard CM, Bergstralh E, et al. Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945-1984. *Ann Neurol* 1990;27(1):89-95.

35. Kondziolka D, Lunsford LD, Bissonette DJ. Long-term results after glycerol rhizotomy for multiple sclerosis-related trigeminal neuralgia. *Can J Neurol Sci* 1994;21(2):137-40.

36. Lummel N, Mehrkens JH, Linn J, et al. Diffusion tensor imaging of the trigeminal nerve in patients with trigeminal neuralgia due to multiple sclerosis. *Neuroradiology* 2015;57(3):259-67. doi: 10.1007/s00234-014-1463-7 [doi]

37. Martin S, Teo M, Suttner N. The effectiveness of percutaneous balloon compression in the treatment of trigeminal neuralgia in patients with multiple sclerosis. *J Neurosurg* 2015;123(6):1507-11. doi: 10.3171/2014.11.JNS14736 [doi]

38. Mathieu D, Effendi K, Blanchard J, et al. Comparative study of Gamma Knife surgery and percutaneous retrogasserian glycerol rhizotomy for trigeminal neuralgia in patients with multiple sclerosis. *J Neurosurg* 2012;117 Suppl:175-80. doi: 10.3171/2012.6.GKS12987 [doi]

39. Montano N, Papacci F, Cioni B, et al. Percutaneous balloon compression for the treatment of trigeminal neuralgia in patients with multiple sclerosis. Analysis of the potentially prognostic factors. *Acta Neurochir (Wien)* 2012;154(5):779-83. doi: 10.1007/s00701-012-1301-9 [doi]

40. Moulin DE, Foley KM, Ebers GC. Pain syndromes in multiple sclerosis. *Neurology* 1988;38(12):1830-34.

41. Osterberg A, Boivie J, Thuomas KA. Central pain in multiple sclerosis--prevalence and clinical characteristics. *Eur J Pain* 2005;9(5):531-42.

42. Pickett GE, Bisnaire D, Ferguson GG. Percutaneous retrogasserian glycerol rhizotomy in the treatment of tic douloureux associated with multiple sclerosis. *Neurosurgery* 2005;56(3):537-45.

43. Putzki N, Pfriem A, Limmroth V, et al. Prevalence of migraine, tension-type headache and trigeminal neuralgia in multiple sclerosis. *Eur J Neurol* 2009;16(2):262-67.

44. Rogers CL, Shetter AG, Ponce FA, et al. Gamma knife radiosurgery for trigeminal neuralgia associated with multiple sclerosis. *J Neurosurg* 2002;97(5 Suppl):529-32.

45. Rushton JG, Olafson RA. Trigeminal neuralgia associated with multiple sclerosis. A case report. *Arch Neurol* 1965;13(4):383-86.

46. Solaro C, Brichetto G, Amato MP, et al. The prevalence of pain in multiple sclerosis: a multicenter cross-sectional study. *Neurology* 2004;63(5):919-21. doi: 63/5/919 [pii]

47. Tuleasca C, Carron R, Resseguier N, et al. Multiple sclerosis-related trigeminal neuralgia: a prospective series of 43 patients treated with gamma knife surgery with more than one year of follow-up. *Stereotact Funct Neurosurg* 2014;92(4):203-10. doi: 000362173 [pii];10.1159/000362173 [doi]

48. Vermote R, Ketelaer P, Carton H. Pain in multiple sclerosis patients. A prospective study using the Mc Gill Pain Questionnaire. *Clin Neurol Neurosurg* 1986;88(2):87-93.

49. Zorro O, Lobato-Polo J, Kano H, et al. Gamma knife radiosurgery for multiple sclerosis-related trigeminal neuralgia. *Neurology* 2009;73(14):1149-54. doi: 73/14/1149 [pii];10.1212/WNL.0b013e3181bacfb4 [doi]

50.De Sante L., Annunziata P. Symptomatic cranial neuralgias in multiple sclerosis: clinical features and treatment. *Clin Neurol Neurosurg* 2012;114(2):101-07. doi: S0303-8467(11)00362-3 [pii];10.1016/j.clineuro.2011.10.044 [doi]

51. Espir MLE, Millac P. Treatment of paroxysmal disorders in multiple sclerosis with carbamazepine (tegretol). *J Neurol Neurosurg Psychiatry* 1970;33:528-31.

52. DMKG group. Misoprostol in the treatment of trigeminal neuralgia associated with multiple sclerosis. *J Neurol* 2003;250(5):542-45.

53. Leandri M, Lundardi G, Inglese M, et al. Lamotrigine in trigeminal neuralgia secondary to multiple sclerosis. *J Neurol* 2000;247(7):556-58.

54. Leandri M. Therapy of trigeminal neuralgia secondary to multiple sclerosis. *Expert Rev Neurother* 2003;3(5):661-71. doi: 10.1586/14737175.3.5.661 [doi]

55. Lunardi G, Leandri M, Albano C, et al. Clinical effectiveness of lamotrigine and plasma levels in essential and symptomatic trigeminal neuralgia. *Neurology* 1997;48:1714-17.

56. Khan OA. Gabapentin relieves trigeminal neuralgia in multiple sclerosis patients. *Neurology* 1998;51:611-14.

57. Solaro C, Lunardi GL, Capello E, et al. An open-label trial of gabapentin treatment of paroxysmal symptoms in multiple sclerosis patients. *Neurology* 1998;51(2):609-11.

58. Solaro C, Uccelli MM, Brichetto G, et al. Topiramate relieves idiopathic and symptomatic trigeminal neuralgia. *J Pain Symptom Manage* 2001;21(5):367-68.

59. Zvartau-Hind M, Din MU, Gilani A, et al. Topiramate relieves refractory trigeminal neuralgia in MS patients. *Neurology* 2000;55(10):1587-88.

60. Montano N, Papacci F, Cioni B, et al. What is the best treatment of drug-resistant trigeminal neuralgia in patients affected by multiple sclerosis? A literature analysis of surgical procedures. *Clin Neurol Neurosurg* 2013;115(5):567-72. doi: S0303-8467(12)00394-0 [pii];10.1016/j.clineuro.2012.07.011 [doi]

61. Taich ZJ, Goetsch SJ, Monaco E, et al. Stereotactic Radiosurgery Treatment of Trigeminal Neuralgia: Clinical Outcomes and Prognostic Factors. *World Neurosurg* 2016;90:604-12. doi: S1878-8750(16)00312-0 [pii];10.1016/j.wneu.2016.02.067 [doi]

62. Weller M, Marshall K, Lovato JF, et al. Single-institution retrospective series of gamma knife radiosurgery in the treatment of multiple sclerosis-related trigeminal neuralgia: factors that predict efficacy. *Stereotact Funct Neurosurg* 2014;92(1):53-58. doi: 000354815 [pii];10.1159/000354815 [doi]

63. Dieckmann G, Bockermann V, Heyer C, et al. Five-and-a-half years' experience with percutaneous retrogasserian glycerol rhizotomy in treatment of trigeminal neuralgia. *Appl Neurophysiol* 1987;50(1-6):401-13.

64. Kondziolka D, Lunsford LD, Bissonette DJ. Long-term results after glycerol rhizotomy for multiple sclerosis- related trigeminal neuralgia. *Can J Neurol Sci* 1994;21(2):137-40.

65. Mallory GW, Atkinson JL, Stien KJ, et al. Outcomes after percutaneous surgery for patients with multiple sclerosis-related trigeminal neuralgia. *Neurosurgery* 2012;71(3):581-86. doi: 10.1227/NEU.0b013e31825e795b [doi]

66. Teo MK, Suttner NJ. Effective management of lower divisional pain in trigeminal neuralgia using balloon traction. *Br J Neurosurg* 2015;29(3):343-46. doi: 10.3109/02688697.2014.990419 [doi]

67. Fraioli B, Esposito V, Guidetti B, et al. Treatment of trigeminal neuralgia by thermocoagulation, glycerolization, and percutaneous compression of the gasserian ganglion and/or retrogasserian rootlets: long-term results and therapeutic protocol. *Neurosurgery* 1989;24(2):239-45.

68. Lopez BC, Hamlyn PJ, Zakrzewska JM. Systematic review of ablative neurosurgical techniques for the treatment of trigeminal neuralgia. *Neurosurgery* 2004;54(4):973-82.

69. Zakrzewska JM, Linskey ME. Trigeminal neuralgia. *Clin Evid (Online)* 2014;pii(1207) doi: 1207 [pii]

70. Zakrzewska JM, Linskey ME. Trigeminal neuralgia. *BMJ* 2015;350:h1238.

71. Solaro C, Messmer UM, Uccelli A, et al. Low-dose gabapentin combined with either lamotrigine or carbamazepine can be useful therapies for trigeminal neuralgia in multiple sclerosis. *Eur Neurol* 2000;44(1):45-48.

72. Douglas C, Wollin JA, Windsor C. Biopsychosocial correlates of adjustment to pain among people with multiple sclerosis. *Clin J Pain* 2008;24(7):559-67. doi: 10.1097/AJP.0b013e318171cdf1 [doi];00002508-200809000-00001 [pii]

73. Besi E, Boniface DR, Cregg R, et al. Comparison of tolerability and adverse symptoms in oxcarbazepine and carbamazepine in the treatment of trigeminal neuralgia and neuralgiform headaches using the Liverpool Adverse Events Profile (AEP). *J Headache Pain* 2015;16:563. doi: 10.1186/s10194-015-0563-z [doi]

74. Solaro C, Boehmker M, Tanganelli P. Pregabalin for treating paroxysmal painful symptoms in multiple sclerosis: a pilot study. *J Neurol* 2009;256(10):1773-74. doi: 10.1007/s00415-009-5203-6 [doi]

75. Zakrzewska JM, Palmer J, Ettlin DA, et al. Novel design for a phase IIa placebo-controlled, double-blind randomized withdrawal study to evaluate the safety and efficacy of CNV1014802 in patients with trigeminal neuralgia. *Trials* 2013;14:402. doi: 1745-6215-14-402 [pii];10.1186/1745-6215-14-402 [doi]

76. Zakrzewska JM, Relton C. Future Directions for Surgical Trial Designs in Trigeminal Neuralgia. *Neurosurg Clin N Am* 2016;27(3):353-63. doi: S1042-3680(16)00023-1 [pii];10.1016/j.nec.2016.02.011 [doi]

77. Tatli M, Satici O, Kanpolat Y, et al. Various surgical modalities for trigeminal neuralgia: literature study of respective long-term outcomes. *Acta Neurochir (Wien)* 2008;150(3):243-55.

78. Epstein RM, Gramling RE. What is shared in shared decision making? Complex decisions when the evidence is unclear. *Med Care Res Rev* 2013;70(1 Suppl):94S-112S. doi: 1077558712459216 [pii];10.1177/1077558712459216 [doi]

79. Politi MC, Lewis CL, Frosch DL. Supporting shared decisions when clinical evidence is low. *Med Care Res Rev* 2013;70(1 Suppl):113S-28S. doi: 1077558712458456 [pii];10.1177/1077558712458456 [doi]

80. Spatz AL, Zakrzewska JM, Kay EJ. Decision analysis of medical and surgical treatments for trigeminal neuralgia: how patient evaluations of benefits and risks affect the utility of treatment decisions. *Pain* 2007;131(3):302-10.

Figure 1 Flow chart of the search process

Figure 2 The probability of a recurrence after a surgical procedure in patients with MS and trigeminal neuralgia.

Legends for tables

Table 1 MS-TN Search Strategy

Table ~~1~~ 2 **Prevalence and demographics of trigeminal neuralgia in patients with MS from neurology and neurosurgery studies.**

Table ~~2~~ 3 Pharmacological trials reporting outcomes for patients with multiple sclerosis and trigeminal neuralgia

Table 4 Details of surgical pwTNMS

Table ~~3~~ 5 Results from surgical interventions for patients with TN and MS

Highlights

Ms. Ref. No.: WNS-17-3306
Title: A systematic review of the management of trigeminal neuralgia in patients with multiple sclerosis.

A systematic review of the management of trigeminal neuralgia in patients with multiple sclerosis.

1. First systematic review of all modalities for management of patients with trigeminal neuralgia and multiple sclerosis shows poor quality of data.
2. A variety of antiepileptic drugs and misoprostol have been used in patients with TNMS but results are poor and significant side effects occur
3. All surgical procedures give patients a mean of two and half years of pain relief and need to be repeated.
4. More higher quality trials are required.

A systematic review of the management of trigeminal neuralgia in patients with multiple sclerosis.

Joanna. M. Zakrzewska MD *

* Corresponding author

Facial Pain Unit Eastman Dental Hospital,
UCLH NHS Foundation Trust , 256 Gray's Inn Road, London WC1X 8LD,UK
Email: j.zakrzewska@ucl.ac.uk

Jianhua Wu PhD

Dental Translational and Clinical Research Unit

School of Dentistry, University of Leeds, LS2 9LU, UK

Email: J.H.Wu@leeds.ac.uk

Tricia S-L Brathwaite MSc
Oral & Maxillofacial Surgery Department Eastman Dental Hospital,
UCLH NHS Foundation Trust , 256 Gray's Inn Road, London WC1X 8LD,UK
Email triciabrathwaite@gmail.com

ABSTRACT

Background and Objective: Patients with trigeminal neuralgia (TN) and multiple sclerosis (MS) are often treated with medications or a surgical procedure. However, there is little evidence that such treatments result in 50% pain reduction and improvement in quality of life. The aim of this systematic review is to evaluate the clinical effectiveness of treatments in patients with MS and trigeminal neuralgia.
Databases and Data Treatment: We searched Medline, EMBASE, and the Cochrane Collaboration database from inception until October 2016. Two authors independently selected studies for inclusions, data extraction and bias assessment.

Results: All studies were of low quality using the GRADE system. For medical management, ten studies were included of which one was a randomised control trials. Two studies were on the use of misopropol, unique to patients with MS. For surgical therapy, 26 studies with at least 10 patients and a minimum of two-year follow-up were included. All types of surgical procedures are reported and the results are poorer than for TN without MS with 50% having a recurrence by two years. The main complications were sensory loss. Many patients had to undergo further procedures to become pain free and there were no agreed prognostic factors.

Conclusions: There was insufficient evidence to support any one medical therapy and so earlier surgery may be preferable. A patient with TN and MS has therefore to make a decision based on low level evidence beginning with standard drug therapy and then choosing a surgical procedure.

Key words: antiepileptic drugs , multiple sclerosis, neurosurgery , systematic review, trigeminal neuralgia

INTRODUCTION

Unlike many other types of chronic pain, trigeminal neuralgia (TN), a severe unilateral episodic facial pain, can be managed both with medications or a variety of surgical procedures. In the majority of patients the cause remains unknown but Harris [1] in 1950 noted a connection with multiple sclerosis (MS) and early epidemiological studies showed that there was a strong connection with MS and a 20 fold higher prevalence of TN in this group. [2]

A recent systematic review of pain in MS suggested a prevalence of 3.8% (CI 2.0-6.0%) of TN and this is lower than headaches or neuropathic pain. [3] Another recent review suggested that over 30% of medications used by patients with MS are for pain. [4]

The clinical manifestations of TN in patients with MS are the same as for other forms of TN although there are reports of the attacks having some atypical features in that there is a more prolonged background pain. [5, 6, 7] However Sandell et al.,[7] in their small cohort of 19 suggested that all patients initially have episodic pain and others [8] also showed in their series that background pain was not related to presence or absence of demyelination in the trigeminal area. Mohammadi et al [9] found in their series that over time the pain became more atypical, larger number of divisions were involved and 6% became bilateral. It is generally thought that MS precedes TN but several series reported TN as a first symptom with intervals of between 10 and five years before another MS symptom. [10] [9] [11]. No correlation between extent of MS plaques and clinical manifestations have been shown. [12, 13] There is a lack of data as to whether periods of remission occur in patients with MS. Trigeminal reflexes including the blink reflex are abnormal in patients with MS and electrophysiological testing is highly accurate in distinguishing other forms of TN from MS related TN. [6,14] Cruccu et al [15] suggested that the plaques resulting in TN are in the pontine area and result in damage to the primary afferents. The mechanism in MS related TN could be different and not the result of neurovascular compression although both mechanisms may be present in some patients. [14] It has been suggested that in MS

there is increased activity of T-cells leading to increased inflammatory activity in the plaques which makes them more susceptible to ephaptic nerve conduction. [6]

Antiepileptic drugs (AEDs) are the major drugs used for all types of pain in MS. Jawahar et al [16] in a systematic review have showed that for non TN pain this class of drug is effective and although side effects are reported they are demeaned tolerable. It is important to note that currently none of the medications are curative and so they should be used only during periods of relapse and discontinued if surgery has resulted in pain relief.

Two drugs are used more frequently in patients with TN and MS (pwTNMS) than in other TN patients are baclofen and misoprostol . Baclofen is a $GABA_B$ agonist works whereas misoprostol is a prostaglandin-E_1- analogue which may reduce inflammatory activity in the plaques and so result in nerve stabilisation. [6]

The literature suggests that pwTNMS have greater problems with use of medications as they potentiate some of the MS symptoms and so higher more effective doses cannot be used.[17] Ramsaransing et al., [18] reported on six patients with MS whose disability significantly increased when using carbamazepine. Equally, surgical outcomes seem to be less satisfactory than in the other TN patients, possibly because the mechanism is different. However they do offer a period when medications can be withdrawn. It has been suggested that microvascular decompression (MVD) should not be done as the cause of the TN is not compression of the nerve by a vessel but the demyelinating plaques on the trigeminal nerve. However, studies suggest that both can exist [7, 8, 10, 15,19] and a recent study suggests that neurovascular decompression should be actively looked for in all patietns with TN.[14] There is also evidence of demyelination in patients without clinically proven MS [8 ,20] Abhinav et al [8] have demonstrated that these patients can undergo successful partial sensory rhizotomy if no compressive vessels are found.

In a fifty year old fit patient with TN and MS would treatment with medications or a surgical procedure result in 50% pain reduction and improved quality of life? In order to answer this question, a review of the literature on both pharmacological and surgical management of TN in pwTNMS was required. This could provide some

guidance both to clinicians and patients as to the most effective management strategies.

METHODOLOGY

Data sources and search strategy

We performed a database search using Medline (in OvidSP), EMBASE and the Cochrane Collaboration database from their inception date until October 2016. Search terms were related to medical and surgical management of MS-TN patients please see table 1.). Previous searches of surgical treatments for TN were utilised to obtain reports which contained results on pwTNMS. [21] Only articles published in English were included and all abstracts were excluded.

TABLE 1 HERE

Study selection and data extraction

Two reviewers (TB and JZ) independently screened the search results based on title, key words and abstract. 10% of the search results were then reviewed by a third reviewer ECB. All three reviewers met to compare the selection and resolve any differences by consensus.

Of the surgical studies only those having 10 or more pwTNMS and a mean follow up of two years were included. In those which reported mixed cohorts, if the data on pwTNMS could not be extracted they were excluded. The surgical data was graded using the Surgical Trigeminal Neuralgia Score system [22] and if the scores were below 40% these were also rejected.

Reviewers TB and JZ developed and completed the data extraction. Data was extracted into a medical table which compared and contrasted the drugs reported in the management for pwTNMS and another table was developed for the surgical data. Data were extracted on:

(1) Author, date of publication, journal

(2) Study design and clinical setting

(3) Study population characteristics: basic demographics, TN and MS criteria of the patients, number of patients, number of patients with TN and MS, inclusion and exclusion criteria, study duration, duration of TN, duration of MS, onset order of TN and MS, interval between TN and MS, location of TN.

(4) For drug management studies, the following data were extracted: drug prescribed, daily dosage, pain measure (Visual Analogue Scale), overall drug impact on pain, side effects.

(5) For surgical studies, the follow data were extracted: type of surgery, duration of follow-up, lost to follow up, recurrence rate, recurrence interval, surgical complications.

Data quality and synthesis

All studies were open label and involved very few patients that met the inclusion criteria. The study duration varied significantly and the outcome measures were poorly reported. It was not possible to determine what constituted a 50% pain reduction in the medical trials. There is a high risk of publication bias due to the exclusion of studies in which the data on pwTNMS could not be extracted in those containing mixed cohorts.

For medical management studies, data synthesis was not possible due to very small sample size. For surgical studies, data were synthesised by the type of surgical procedures.

RESULTS

The initial search identified 540 records, and of these 78 was assessed as shown in Figure 1. Excluding review papers and studies that did not meet the inclusion criteria, 10 medical therapy studies and 26 surgical therapy studies were included in this review. A meta analysis was not possible due to the variability of the studies. All studies yielded a low score on the GRADE system.

Figure 1 HERE

Prevalence of pwTNMS

Table 2 provides data on prevalence and demographic details of pwTNMS as found in both neurological and neurosurgical settings. The prevalence of TN among pwMS is 4.0%, which is consistent with 3.8% reported in the meta-analysis by Foley et al.,.[3] Women predominate, 60.5%, with the average age of onset of TN being 45.4 years which was significantly lower than that reported in other types of TN which is 50-60 years. Of the 22 studies which reported the timing of TN in relation to MS 10.5% had TN prior to MS and it could be over 10 years before another MS episode was reported. Of the 24 studies reporting location 11% had bilateral symptoms compared to 3% in non MSTN. De Simone [23] case control studies of 15 pwTNMS suggested that the clinical characteristics were the same as in other patients with TN and this was borne out by Cruccu et al.,[15] and several other surgical studies. Cruccu al [15] suggested that MS starts later in those with TN.

Table 2 HERE

Medical therapies

There were no systematic reviews, two reviews of general pain management in MS. : [50,17] There were 10 studies reported between 1970 and 2003 which included one RCT [51], one controlled trial [52], two comparing different medications [53, 54] and one

comparing an non MS TN group with a TNMS group [55]. The rest were case reports and it was difficult to establish whether they were retrospective or prospective. [6,56, 57, 58] Five studies were from the same institution and no study had more than 18 patients. Only three studies provided details of the type of MS, two studies showed the criteria for diagnosis of TN. [59,52] Only one study used a VAS and recorded both intensity and number of attacks. [52] The majority of studies used a scale of 0-4 or just complete, partial and no response so it was not possible to dichotomize the results. No quality of life measures were used. Additionally, the follow up (from 1 month to 48 months) varied making it impossible to determine how many were lost to follow up or determine recurrence rate.

The main results of the 10 pharmacological interventions including side effects are shown in table 3**.**

Table 3 HERE

Surgical management

There are two reviews one [60] which reviews of all surgical procedures and Taich et al., [61] which reviews of all stereotactic radiosurgery procedures (SRS). Three studies dealt with multiple procedures of which Mohammadi et al., [9] series treated 96 pwTNMS with 277 surgical procedures. Nine studies did not separate the MS data from their non MS TN so their data could not be used. Only 2 papers provided data on the type of MS. [9 ,10] Table 4 provides extra details of the selected surgical procedures including details of outcome measures. Table 5 summarises the outcomes by different surgical procedures and the weighted averages were obtained from the studies with available data.

Tables 4 HERE

Table 5 HERE

Two studies [7, ,10] reported on outcomes after MVD and one after partial sensory rhizotomy (PSR) [8] in a total of 77 pwTNMS. After MVD , 73% of the patients had reported pain relief whereas in the one PSR study it was 87% and the recurrence rate was 39%. after MVD and 21.7% after PSR. Numbness occurred in 22/23 patients after PSR and included one with anaesthesia dolorosa compared to

numbness only in 2/105 in the MVD group. Impaired hearing was noted in two patients after MVD..

A total of 180 pwTNMS had undergone SRS procedures in six studies. [9, 38,47, 49, 61,62] The average age of 60 years was significantly higher than those undergone MVD/PSR procedures (52 years). 83.6% of the patients had pain relief after surgery but 51.1% had experienced recurrence during the follow-up period. Facial numbness, sensory loss and paraesthesia were reported in 11.7% of patients. Eight studies reported on use of percutaneous glycerol rhizotomy (PGR) in a total of 299 pwTNMS whose average age was 51 years. [9,11,26,38, 42,63,64, 65] The average follow-up was 42 months, 77.3% of the patients had good pain relief after the procedure while 53.4% had recurrences during the follow-up period. Of those patients who experienced a recurrence, the median recurrence time was 20.3 months, which was significantly shorter than those patients undergone SRS procedure (30.4 months).

A total of 74 pwTNMS had undergone balloon microcompression (BC) [9, 37,39,66] and 58 radiofrequency thermocoagulation (RFT) [12, 27, 29, 67] 86.4% of those who had BC and 97.8% of those who had RFT had reported good pain relief. However, those who had BC reported the highest recurrence rate of 67.0% while those who had RFT reported the lowest recurrence rate of 27.5%.

From studies using Kaplan Meier methodology it was possible to determine the probability of recurrence over a period of 5 years (Figure 2). This was the same method as previously used to assess probability of recurrence in non-MS TN.[68] All procedures reported that by two and half years, 50% of pwTNMS were likely to have had a recurrence and those studies which provided comparative data with non MS TN, showed better outcomes for the latter.

The only none destructive procedure was MVD, a major neurosurgical procedure of which there are few studies. Whereas destructive (ablative) procedures, whether at the root entry zone or the Gasserian ganglion level were frequently reported.

Figure 2 HERE

Recommendations for management

Due to the lack of data it is difficult to advise how the presented patient should be managed. No pharmacological treatments can be advised specifically for pwTNMS so the same medical management can be used as for non-MS TN i.e. carbamazepine or oxcarbazepine as first line with second line drugs being lamotrigine, baclofen, gabapentin and pregablin. [69 70] Patients need to be given careful instructions about use of medications i.e. beginning the drugs slowly with low doses and gradually increasing them and this can be done with the help of pain diaries. This approach would help to reduce side effects and potential exacerbations of existing MS symptoms. Monotherapy is encouraged but polytherapy can be introduced to gain better control as Solaro et al.,[71] showed. Patients need to be aware that flare ups can occur and they need to develop a strategy for how these can be dealt with by increasing the medication for a while. Conversely if a remission is reported in that patients indicate that they have no pain the drugs can be tapered down and stopped until the next flare up. We have shown that support from psychologists and clinical nurse specialists with knowledge of these drugs can be extremely helpful (poster at International Association for the Study of Pain Congress 2016) and Douglas et al.,[72] also showed that patients with MS who had a better biopsychosocial approach to their pain reported better outcomes.

If pain control is poor then surgical options need to be considered but it is not possible to provide recommendations as to when this should occur nor is there any data to compare pharmacological versus surgical outcomes. Although MVD does give poorer results in pwTNMS and a higher risk of complication there may be a place for it in those few with no plaques on the trigeminal nerve and with clear neurovascular compression(NVC) on MRI although Abhinav et al's [8] study suggested that the other option is to do a partial sensory rhizotomy. There are many more studies reporting other ablative procedures which are relatively easy to perform and carry less risk. They gave similar results in that by 2½ years 50% will have a recurrence. Repeat surgery does increase the risk of sensory changes.

DISCUSSION

TN is common in pwMS. It can occur before MS and many present with classical symptoms [23] but in pwTNMS up to 89% have abnormal trigeminal reflexes as compared to 3% in idiopathic TN.[15] The evidence for pharmacological management of TN is based on , open label studies with very small numbers and a high risk of bias. Only the DMKG [52] study group, defined inclusion criteria and measured outcome measures. It is likely that the studies included a heterogeneous group of patients both from the MS aspect and also TN as criteria used for diagnosis were only provided in one study.[52] Most of the recruited patients had become non responsive to conventional medications but there was no indication as to what proportion they constituted. There was scare data on length of time medications were used for , whether slow escalation occurred or whether drugs were stopped due to remissions. It has been suggested that pwTNMS are more likely to have side effects but in these studies the converse was found and this is not in agreement from other TN literature which shows that most patients have side effects. [73] Tiredness and ataxia are common side effects and can lead to further disability in patients with MS.

Only oxcarbazepine has not been reported in pwTNMS and there were only two cases of pregablin use.. [74] The data on misoprostol cannot be generalised to other pwTNMS as the studies contained intractable cases with short follow up. .

There is thus an urgent need for RCTs which avoid use of placebos or active controls. An enhancement withdrawal enriched randomised control trial may be applicable and has been used in other TN trials.[75] More robust outcome measures are needed that measure not only pain relief and reduction of paroxysms but also quality of life and its impact on MS using the EDSS. A more systematic approach to side effects is needed to determine if tolerability is reduced in this group. A natural history of TN in pwTNMS is required to compare with non-MS TN to determine if there are true differences as De Simone et al [23] suggested that there are none. With improved imaging more patients may have MS than previously reported and TN could be the first symptom. It is important to establish if pain increases during relapses of MS or whether it evolves over the course of MS and is linked to type of MS. This could be done using novel methodology such as trials within cohorts.[76]

Within the surgical data there are no RCTs or controlled trials. The majority of data is retrospective with a high risk of bias.[22] In a small sub group of pwTNMS who have clear compression Truini et al ., [14] suggest that MVD should be considered although it needs to be noted that at present the results are poorer than in non MS TN so further data is required. Other ablative procedures give poorer outcomes in pwTNMS than those with non MS TN when the same methodology is used [68, 77] but they do provide up to two years pain relief without medication. RCTs comparing the varying ablative procedures should be possible and would provide much needed data. [38]

There is increased evidence that shared decision making increases patients satisfaction but significant challenges arise when the evidence is of low quality , conflicting, unavailable or not relevant to the patient. Epstein & Gramling [78], and Politi et al.,[79] among others suggestion ways of dealing with these problems which include exploring values and preferences and engaging in patient centred communication which is based on a supportive relationship. Patients, therefore need time and consultations jointly with physicians and neurosurgeons to determine what may be the best option for them at any particular time. In a study in which patients with TN where asked about their preferences for treatment surgical options were preferred to medical ones but the evidence on which the patients made their decisions were based on low quality evidence. [80]

CONCLUSIONS

In view of the lack of any high quality evidence it remains impossible to provide a pwTNMS such as the one described here with a definitive treatment plan. Both pharmacological and surgical treatments provide some pain relief but for shorter periods than on other TN patients. More high quality studies are required.

Acknowledgments

Elisabet Cortes Barrera (ECB) , postgraduate MSc student at Eastman Dental Hospital reviewed some of the medical articles. Librarians at Royal Society of Medicine developed the search strategy in conjunction with JZ .

JZ undertook the work at UCL/UCLHT who received a proportion of funding from the Department of Health's NIHR Biomedical Research Centre funding scheme.

Authors contributions : JZ conceived the idea and designed the protocol. TB and JZ independently searched, graded and extracted the data. JW ensured that the analysis was correct. All authors discussed the results, commented on the manuscript and approved the final draft.

Declaration of interest : JZ has a consultancy with Biogen Inc . No funding was obtained for this study.

References

1. Harris W. Rare forms of paroxysmal trigeminal neuralgia, and their relation to disseminated sclerosis. *Br Med J* 1950;2(4687):1015-19.
2. Katusic S, Williams DB, Beard CM, et al. Incidence and clinical features of glossopharyngeal neuralgia, Rochester, Minnesota, 1945-1984. *Neuroepidemiology* 1991;10(5-6):266-75.
3. Foley PL, Vesterinen HM, Laird BJ, et al. Prevalence and natural history of pain in adults with multiple sclerosis: systematic review and meta-analysis. *Pain* 2013;154(5):632-42. doi: S0304-3959(12)00647-1 [pii];10.1016/j.pain.2012.12.002 [doi]
4. Solaro C, Trabucco E, Messmer UM. Pain and multiple sclerosis: pathophysiology and treatment. *Curr Neurol Neurosci Rep* 2013;13(1):320. doi: 10.1007/s11910-012-0320-5 [doi]
5. Jensen TS, Rasmussen P, Reske-Nielsen E. Association of trigeminal neuralgia with multiple sclerosis: clinical and pathological features. *Acta Neurol Scand* 1982;65(3):182-89.
6. Reder AT, Arnason BG. Trigeminal neuralgia in multiple sclerosis relieved by a prostaglandin E analogue. *Neurology* 1995;45(6):1097-100.
7. Sandell T, Eide PK. The effect of microvascular decompression in patients with multiple sclerosis and trigeminal neuralgia. *Neurosurgery* 2010;67(3):749-53. doi: 10.1227/01.NEU.0000375491.81803.5D [doi]
8. Abhinav K, Love S, Kalantzis G, et al. Clinicopathological review of patients with and without multiple sclerosis treated by partial sensory rhizotomy for medically refractory

trigeminal neuralgia: a 12-year retrospective study. *Clin Neurol Neurosurg* 2012;114(4):361-65.

9. Mohammad-Mohammadi A, Recinos PF, Lee JH, et al. Surgical outcomes of trigeminal neuralgia in patients with multiple sclerosis. *Neurosurgery* 2013;73(6):941-50. doi: 10.1227/NEU.0000000000000128 [doi]
10. Broggi G, Ferroli P, Franzini A, et al. Operative findings and outcomes of microvascular decompression for trigeminal neuralgia in 35 patients affected by multiple sclerosis. *Neurosurgery* 2004;55(4):830-38.
11. Linderoth B, Hakanson S. Paroxysmal facial pain in disseminated sclerosis treated by retrogasserian glycerol injection. *Acta Neurol Scand* 1989;80(4):341-46.
12. Kanpolat Y, Berk C, Savas A, et al. Percutaneous controlled radiofrequency rhizotomy in the management of patients with trigeminal neuralgia due to multiple sclerosis. *Acta Neurochir (Wien)* 2000;142(6):685-89.
13. Hooge JP, Redekop WK. Trigeminal neuralgia in multiple sclerosis. *Neurology* 1995;45(7):1294-96.
14. Truini A, Prosperini L, Calistri V, et al. A dual concurrent mechanism explains trigeminal neuralgia in patients with multiple sclerosis. *Neurology* 2016;86(22):2094-9. doi: 10.1212/WNL.0000000000002720 [published Online First: 2016/05/11]
15. Cruccu G, Biasiotta A, Di RS, et al. Trigeminal neuralgia and pain related to multiple sclerosis. *Pain* 2009;143(3):186-91.
16. Jawahar R, Oh U, Yang S, et al. A systematic review of pharmacological pain management in multiple sclerosis. *Drugs* 2013;73(15):1711-22. doi: 10.1007/s40265-013-0125-0 [doi]
17. Solaro C, Uccelli MM. Management of pain in multiple sclerosis: a pharmacological approach. *Nat Rev Neurol* 2011;7(9):519-27. doi: nrneurol.2011.120 [pii];10.1038/nrneurol.2011.120 [doi]

18. Ramsaransing G, Zwanikken C, De KJ. Worsening of symptoms of multiple sclerosis associated with carbamazepine. *BMJ* 2000;320(7242):1113.

19. Eldridge PR, Sinha AK, Javadpour M, et al. Microvascular decompression for trigeminal neuralgia in patients with multiple sclerosis. *Stereotact Funct Neurosurg* 2003;81(1-4):57-64.

20. Love S, Gradidge T, Coakham HB. Trigeminal neuralgia due to multiple sclerosis: ultrastructural findings in trigeminal rhizotomy specimens. *Neuropathol Appl Neurobiol* 2001;27(3):238-44.

21. Zakrzewska JM, Akram H. Neurosurgical interventions for the treatment of classical trigeminal neuralgia. *Cochrane Database Syst Rev* 2011;9:CD007312.

22. Akram H, Mirza B, Kitchen N, et al. Proposal for evaluating the quality of reports of surgical interventions in the treatment of trigeminal neuralgia: the Surgical Trigeminal Neuralgia Score. *Neurosurg Focus* 2013;35(3):E3. doi: 10.3171/2013.6.FOCUS13213 [doi]

23. De Simone R, Marano E, Brescia M, V, et al. A clinical comparison of trigeminal neuralgic pain in patients with and without underlying multiple sclerosis. *Neurol Sci* 2005;26 Suppl 2:s150-s51.

24. Antic B, Peric P. Posterior fossa exploration in treatment of trigeminal neuralgia associated with multiple sclerosis. *Surg Neurol* 2009;71(4):419-23. doi: S0090-3019(08)00434-5 [pii];10.1016/j.surneu.2008.04.033 [doi]

25. Ariai MS, Mallory GW, Pollock BE. Outcomes after microvascular decompression for patients with trigeminal neuralgia and suspected multiple sclerosis. *World Neurosurg* 2014;81(3-4):599-603. doi: S1878-8750(13)01209-6 [pii];10.1016/j.wneu.2013.09.027 [doi]

26. Bender MT, Pradilla G, Batra S, et al. Glycerol rhizotomy and radiofrequency thermocoagulation for trigeminal neuralgia in multiple sclerosis. *J Neurosurg* 2013;118(2):329-36. doi: 10.3171/2012.9.JNS1226 [doi]

27. Berk C, Constantoyannis C, Honey CR. The treatment of trigeminal neuralgia in patients with multiple sclerosis using percutaneous radiofrequency rhizotomy. *Can J Neurol Sci* 2003;30(3):220-23.

28. Brett DC, Ferguson GG, Ebers GC, et al. Percutaneous trigeminal rhizotomy. Treatment of trigeminal neuralgia secondary to multiple sclerosis. *Archives of Neurology* 1982;39(4):219-21.

29. Brisman R. Trigeminal neuralgia and multiple sclerosis. *Arch Neurol* 1987;44(4):379-81.

30. Chakravorty BG. Association of trigeminal neuralgia with multiple sclerosis. *Arch Neurol* 1966;14(1):95-99.

31. Cheng JS, Sanchez-Mejia RO, Limbo M, et al. Management of medically refractory trigeminal neuralgia in patients with multiple sclerosis. *Neurosurg Focus* 2005;18(5):e13. doi: 180513 [pii]

32. Eriksson M, Ben-Menachem E, Andersen O. Epileptic seizures, cranial neuralgias and paroxysmal symptoms in remitting and progressive multiple sclerosis. *Mult Scler* 2002;8(6):495-99.

33. Huang E, Teh BS, Zeck O, et al. Gamma knife radiosurgery for treatment of trigeminal neuralgia in multiple sclerosis patients. *Stereotact Funct Neurosurg* 2002;79(1):44-50. doi: 69503 [doi];69503 [pii]

34. Katusic S, Beard CM, Bergstralh E, et al. Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945-1984. *Ann Neurol* 1990;27(1):89-95.

35. Kondziolka D, Lunsford LD, Bissonette DJ. Long-term results after glycerol rhizotomy for multiple sclerosis-related trigeminal neuralgia. *Can J Neurol Sci* 1994;21(2):137-40.

36. Lummel N, Mehrkens JH, Linn J, et al. Diffusion tensor imaging of the trigeminal nerve in patients with trigeminal neuralgia due to multiple sclerosis. *Neuroradiology* 2015;57(3):259-67. doi: 10.1007/s00234-014-1463-7 [doi]

37. Martin S, Teo M, Suttner N. The effectiveness of percutaneous balloon compression in the treatment of trigeminal neuralgia in patients with multiple sclerosis. *J Neurosurg* 2015;123(6):1507-11. doi: 10.3171/2014.11.JNS14736 [doi]

38. Mathieu D, Effendi K, Blanchard J, et al. Comparative study of Gamma Knife surgery and percutaneous retrogasserian glycerol rhizotomy for trigeminal neuralgia in patients with multiple sclerosis. *J Neurosurg* 2012;117 Suppl:175-80. doi: 10.3171/2012.6.GKS12987 [doi]

39. Montano N, Papacci F, Cioni B, et al. Percutaneous balloon compression for the treatment of trigeminal neuralgia in patients with multiple sclerosis. Analysis of the potentially prognostic factors. *Acta Neurochir (Wien)* 2012;154(5):779-83. doi: 10.1007/s00701-012-1301-9 [doi]

40. Moulin DE, Foley KM, Ebers GC. Pain syndromes in multiple sclerosis. *Neurology* 1988;38(12):1830-34.

41. Osterberg A, Boivie J, Thuomas KA. Central pain in multiple sclerosis--prevalence and clinical characteristics. *Eur J Pain* 2005;9(5):531-42.

42. Pickett GE, Bisnaire D, Ferguson GG. Percutaneous retrogasserian glycerol rhizotomy in the treatment of tic douloureux associated with multiple sclerosis. *Neurosurgery* 2005;56(3):537-45.

43. Putzki N, Pfriem A, Limmroth V, et al. Prevalence of migraine, tension-type headache and trigeminal neuralgia in multiple sclerosis. *Eur J Neurol* 2009;16(2):262-67.

44. Rogers CL, Shetter AG, Ponce FA, et al. Gamma knife radiosurgery for trigeminal neuralgia associated with multiple sclerosis. *J Neurosurg* 2002;97(5 Suppl):529-32.

45. Rushton JG, Olafson RA. Trigeminal neuralgia associated with multiple sclerosis. A case report. *Arch Neurol* 1965;13(4):383-86.

46. Solaro C, Brichetto G, Amato MP, et al. The prevalence of pain in multiple sclerosis: a multicenter cross-sectional study. *Neurology* 2004;63(5):919-21. doi: 63/5/919 [pii]

47. Tuleasca C, Carron R, Resseguier N, et al. Multiple sclerosis-related trigeminal neuralgia: a prospective series of 43 patients treated with gamma knife surgery with more than one year of follow-up. *Stereotact Funct Neurosurg* 2014;92(4):203-10. doi: 000362173 [pii];10.1159/000362173 [doi]

48. Vermote R, Ketelaer P, Carton H. Pain in multiple sclerosis patients. A prospective study using the Mc Gill Pain Questionnaire. *Clin Neurol Neurosurg* 1986;88(2):87-93.

49. Zorro O, Lobato-Polo J, Kano H, et al. Gamma knife radiosurgery for multiple sclerosis-related trigeminal neuralgia. *Neurology* 2009;73(14):1149-54. doi: 73/14/1149 [pii];10.1212/WNL.0b013e3181bacfb4 [doi]

50.De Sante L., Annunziata P. Symptomatic cranial neuralgias in multiple sclerosis: clinical features and treatment. *Clin Neurol Neurosurg* 2012;114(2):101-07. doi: S0303-8467(11)00362-3 [pii];10.1016/j.clineuro.2011.10.044 [doi]

51. Espir MLE, Millac P. Treatment of paroxysmal disorders in multiple sclerosis with carbamazepine (tegretol). *J Neurol Neurosurg Psychiatry* 1970;33:528-31.

52. DMKG group. Misoprostol in the treatment of trigeminal neuralgia associated with multiple sclerosis. *J Neurol* 2003;250(5):542-45.

53. Leandri M, Lundardi G, Inglese M, et al. Lamotrigine in trigeminal neuralgia secondary to multiple sclerosis. *J Neurol* 2000;247(7):556-58.

54. Leandri M. Therapy of trigeminal neuralgia secondary to multiple sclerosis. *Expert Rev Neurother* 2003;3(5):661-71. doi: 10.1586/14737175.3.5.661 [doi]

55. Lunardi G, Leandri M, Albano C, et al. Clinical effectiveness of lamotrigine and plasma levels in essential and symptomatic trigeminal neuralgia. *Neurology* 1997;48:1714-17.

56. Khan OA. Gabapentin relieves trigeminal neuralgia in multiple sclerosis patients. *Neurology* 1998;51:611-14.

57. Solaro C, Lunardi GL, Capello E, et al. An open-label trial of gabapentin treatment of paroxysmal symptoms in multiple sclerosis patients. *Neurology* 1998;51(2):609-11.

58. Solaro C, Uccelli MM, Brichetto G, et al. Topiramate relieves idiopathic and symptomatic trigeminal neuralgia. *J Pain Symptom Manage* 2001;21(5):367-68.

59. Zvartau-Hind M, Din MU, Gilani A, et al. Topiramate relieves refractory trigeminal neuralgia in MS patients. *Neurology* 2000;55(10):1587-88.

60. Montano N, Papacci F, Cioni B, et al. What is the best treatment of drug-resistant trigeminal neuralgia in patients affected by multiple sclerosis? A literature analysis of surgical procedures. *Clin Neurol Neurosurg* 2013;115(5):567-72. doi: S0303-8467(12)00394-0 [pii];10.1016/j.clineuro.2012.07.011 [doi]

61. Taich ZJ, Goetsch SJ, Monaco E, et al. Stereotactic Radiosurgery Treatment of Trigeminal Neuralgia: Clinical Outcomes and Prognostic Factors. *World Neurosurg* 2016;90:604-12. doi: S1878-8750(16)00312-0 [pii];10.1016/j.wneu.2016.02.067 [doi]

62. Weller M, Marshall K, Lovato JF, et al. Single-institution retrospective series of gamma knife radiosurgery in the treatment of multiple sclerosis-related trigeminal neuralgia: factors that predict efficacy. *Stereotact Funct Neurosurg* 2014;92(1):53-58. doi: 000354815 [pii];10.1159/000354815 [doi]

63. Dieckmann G, Bockermann V, Heyer C, et al. Five-and-a-half years' experience with percutaneous retrogasserian glycerol rhizotomy in treatment of trigeminal neuralgia. *Appl Neurophysiol* 1987;50(1-6):401-13.

64. Kondziolka D, Lunsford LD, Bissonette DJ. Long-term results after glycerol rhizotomy for multiple sclerosis- related trigeminal neuralgia. *Can J Neurol Sci* 1994;21(2):137-40.

65. Mallory GW, Atkinson JL, Stien KJ, et al. Outcomes after percutaneous surgery for patients with multiple sclerosis-related trigeminal neuralgia. *Neurosurgery* 2012;71(3):581-86. doi: 10.1227/NEU.0b013e31825e795b [doi]

66. Teo MK, Suttner NJ. Effective management of lower divisional pain in trigeminal neuralgia using balloon traction. *Br J Neurosurg* 2015;29(3):343-46. doi: 10.3109/02688697.2014.990419 [doi]

67. Fraioli B, Esposito V, Guidetti B, et al. Treatment of trigeminal neuralgia by thermocoagulation, glycerolization, and percutaneous compression of the gasserian ganglion and/or retrogasserian rootlets: long-term results and therapeutic protocol. *Neurosurgery* 1989;24(2):239-45.

68. Lopez BC, Hamlyn PJ, Zakrzewska JM. Systematic review of ablative neurosurgical techniques for the treatment of trigeminal neuralgia. *Neurosurgery* 2004;54(4):973-82.

69. Zakrzewska JM, Linskey ME. Trigeminal neuralgia. *Clin Evid (Online)* 2014;pii(1207) doi: 1207 [pii]

70. Zakrzewska JM, Linskey ME. Trigeminal neuralgia. *BMJ* 2015;350:h1238.

71. Solaro C, Messmer UM, Uccelli A, et al. Low-dose gabapentin combined with either lamotrigine or carbamazepine can be useful therapies for trigeminal neuralgia in multiple sclerosis. *Eur Neurol* 2000;44(1):45-48.

72. Douglas C, Wollin JA, Windsor C. Biopsychosocial correlates of adjustment to pain among people with multiple sclerosis. *Clin J Pain* 2008;24(7):559-67. doi: 10.1097/AJP.0b013e318171cdf1 [doi];00002508-200809000-00001 [pii]

73. Besi E, Boniface DR, Cregg R, et al. Comparison of tolerability and adverse symptoms in oxcarbazepine and carbamazepine in the treatment of trigeminal neuralgia and neuralgiform headaches using the Liverpool Adverse Events Profile (AEP). *J Headache Pain* 2015;16:563. doi: 10.1186/s10194-015-0563-z [doi]

74. Solaro C, Boehmker M, Tanganelli P. Pregabalin for treating paroxysmal painful symptoms in multiple sclerosis: a pilot study. *J Neurol* 2009;256(10):1773-74. doi: 10.1007/s00415-009-5203-6 [doi]

75. Zakrzewska JM, Palmer J, Ettlin DA, et al. Novel design for a phase IIa placebo-controlled, double-blind randomized withdrawal study to evaluate the safety and efficacy of CNV1014802 in patients with trigeminal neuralgia. *Trials* 2013;14:402. doi: 1745-6215-14-402 [pii];10.1186/1745-6215-14-402 [doi]

76. Zakrzewska JM, Relton C. Future Directions for Surgical Trial Designs in Trigeminal Neuralgia. *Neurosurg Clin N Am* 2016;27(3):353-63. doi: S1042-3680(16)00023-1 [pii];10.1016/j.nec.2016.02.011 [doi]

77. Tatli M, Satici O, Kanpolat Y, et al. Various surgical modalities for trigeminal neuralgia: literature study of respective long-term outcomes. *Acta Neurochir (Wien)* 2008;150(3):243-55.

78. Epstein RM, Gramling RE. What is shared in shared decision making? Complex decisions when the evidence is unclear. *Med Care Res Rev* 2013;70(1 Suppl):94S-112S. doi: 1077558712459216 [pii];10.1177/1077558712459216 [doi]

79. Politi MC, Lewis CL, Frosch DL. Supporting shared decisions when clinical evidence is low. *Med Care Res Rev* 2013;70(1 Suppl):113S-28S. doi: 1077558712458456 [pii];10.1177/1077558712458456 [doi]

80. Spatz AL, Zakrzewska JM, Kay EJ. Decision analysis of medical and surgical treatments for trigeminal neuralgia: how patient evaluations of benefits and risks affect the utility of treatment decisions. *Pain* 2007;131(3):302-10.

Figure 1 Flow chart of the search process

Figure 2 The probability of a recurrence after a surgical procedure in patients with MS and trigeminal neuralgia.

Legends for tables

Table 1 MS-TN Search Strategy

Table 2 **Prevalence and demographics of trigeminal neuralgia in patients with MS from neurology and neurosurgery studies.**

Table 3 Pharmacological trials reporting outcomes for patients with multiple sclerosis and trigeminal neuralgia

Table 4 Details of surgical pwTNMS

Table 5 Results from surgical interventions for patients with TN and MS

Table 1 MS-TN Search Strategy

MEDLINE SEARCH	No. of RESULTS
1. Multiple Sclerosis.mp.or exp Multiple Sclerosis/	63615
2. MS.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	240108
3. disseminated sclerosis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	613
4. encephalomyelitis disseminata.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol	64

	supplementary concept word, rare disease supplementary concept word, unique identifier]	
5.	1 OR 2 OR 3 OR 4	275154
6.	Trigeminal Neuralgia/	5957
7.	trigemin* neuralg*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	7075
8.	(tic doloureux or TN).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	9144
9.	TGN.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word,	2157

	protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	
10.	facial pain.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	7341
11.	prosopalgia.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	16
12.	fothergill's disease.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	2

13. 6 or 7 or 8 or 9 or 10 or 11 or 12	24122
14. 5 and 13	540

Table(s)

Click here to download Table(s): Table 2 TNMS prevalence resubmission.docx

Table 2 Prevalence and demographics of trigeminal neuralgia in patients with MS from neurology and neurosurgery studies.

First Author year	TN& MS	Clinical setting and overall number	TN & MS %	Male	Female	Age onset TN mean*	Number TN first	Mean interval between MS and TN in years	Bilateral
Abhinav[8] 2012	23	neurosurgery		6	17	50±11	0		0
Antic[24] 2009	8	neurosurgery		6	2	41			
Ariai[25] 2013	10	neurosurgery 350	3	5	5	49			
Bender[26] 2013	63	neurosurgery 822	8	46	29	52	12	NR	9
Berk[27] 2003	13	neurosurgery 86	15	3	10	49	2	NR	
Brett[28] 1982	8	neurosurgery		6	2	53	0		0
Brisman[29] 1987	16	neurosurgery 219	7	3	13	45			5
Broggi[10] 2004	35	neurosurgery		16	19	45	2	NR	3
Chakravorty[30] 1966	10	neurology 124	8	4	6	51	0		0
Cheng[31] 2005	11	neurosurgery		2	9	59±7			3
Cruccu[15] 2009	50	MS neuropathic pain 139		18	32	43±11	15	10	4
de Simone[23] 2005	15	neurology case control 13 MS				43±10.5			0
Eldridge[19] 2003	9	neurosurgery 469	2	3	6	47	0		0
Eriksson[32] 2002	5	neurology MS 255	2						
Hooge[13] 1995	35	MS clinic 1882	2	11	24	51	5	11.8	5
Huang[33] 2002	7	neurosurgery 50		1	6	46	0		0
Jensen[5] 1982	22	neurology 900	2	10	12	50	3	12	7
Kanpolat[12] 2000	17	neurosurgery 1672	1	11	6	42	2	NR	1
Katusic[34] 1990	3	neurology 75	4	0	3		0		
Kondziolka[35] 1994	53	neurosurgery 594	9	18	35	56 (median)			2
Linderoth[11] 1989	23	neurosurgery 300	8	9	14	48	2	5-10 (range)	4
Lummel[36] 2014	12	neuroradiology		3	9	46	5	15	0
Martin[37] 2015	17	neurosurgery 80	15	4	13	53	0		
Mathieu[38] 2012	45	neurosurgery		21	24	52	0		0
Mohammad[9] 2013	96	neurosurgery		38	58	50 (median)	10	10 (median)	10
Montano[39] 2012	21	neurosurgery		10	11	47	6	13.8	0
Moulin[40] 1988	7	neurology MS 159	4						
Osterberg[41] 2005	18	neurology MS 429	5	5	13	49	1	19	2
Pickett[42] 2005	53	neurosurgery MS clinic 277	19			50	0		
Putzki[43] 2009	31	MS clinic 675	6			41-80 (range)			
Rogers[44] 2002	15	neurosurgery 240	6	5	10				
Rushton[45] 1965	35	neurology 1735	2	13	22				4
Solaro[46] 2004	36	neurology MS 364	2	7	29	48			
Tuleasca[47] 2014	43	neurosurgery 723	8	23	20	54			2
Vermote[48] 1986	3	neurology MS 83	3.6						
Zorro[49] 2009	37	neurosurgery 729	5	10	27	54	0		11
TOTAL	**905**			**317**	**486**	**49**	**65**		**72**

*mean±sd is reported if available.

Table(s)

Click here to download Table(s): Table 3 Pharmacological trials.docx

Table 3 Pharmacological trials reporting outcomes for patients with multiple sclerosis and trigeminal neuralgia

1st Author Year	Study duration (Month)	Drug	Daily dosage mg/day	No. patients	Mean/median age	Type of MS	Duration MS years	Duration TN years	Mean/Median follow up months	Outcome measure	Overall impact	No side effects	Side effects
Espir 1970 [50]	48	Carbamazepine	760	5	NR	NR	NR	3.33	NR	good/ poor pain relief	4 good response , 2 recurred	1	NR
Leandri 2000 * [52]	2	Carbamazepine	400-800	18	51.5	NR	14.7	7.1		0-4 intensity activity evoked pain pt score	post treat mean 1.7	16	Drowsiness
		Lamotrigine	75-400								post treat mean 0.2	1	skin rash
Lunardi 1997 * [54]	6	Lamotrigine	25-400					NR		0-4 intensity activity evoked pain patient and clinician score			
		idiopathic TN		15	68	NR			5.5		baseline mean score 2 post treatment 11 patients score 0	1	Skin rash
		TNMS		5	54	NR	2.5		5		baseline mean score 2 post treatement score 0	NR	
Khan 1998 [55]	1	Gabapentin	900-2400	7	39.2	NR	9.7	3.6	12	complete or partial relief	6 complete pain relief, 1 partial	NR	
Solaro 1998 * [56]	3	Gabapentin	600-1200	6	NR	NR	NR	NR	5.6	0-4 intensity activity evoked pain pt and clinician score	5 complete pain relief, 1 partial	2	tiredness, nausea
Zvartau-Hind 2000 [53]	9	Topiramate	50-300	6	36.6	NR	7.5	3.8	6-9	complete , partial pain relief	5 pain free	0	NR

Solaro 2001* [57]	NR	Topiramate	200	2	58, 39	NR	32, 9	15,1		0-4 intensity activity evoked pain pt score	baseline mean score 2 post treatment score 0	0	0
Solaro 2000 * [16]	2	Carbamazepine &	400	6	52	3 RR	8.8	3.36	NR	0-4 intensity activity evoked pain pt score	baseline mean score 1.5 post treatment 0.2	0	0
		Gabapentin	850			3 SP							
		Lamotrigine &	150	5	49.6	1 RR	6.4	2.89	NR	0-4 intensity activity evoked pain pt score	baseline mean score 1.8 post treatment score 0	1	Mild imbalance
		Gabapentin	780			4 SP							
Reder 1995 [6]	NR	Misoprostol	0.3-0.8ug	7	47	4 RR,1CP, 2 unknown	23	NR	NR	complete , partial or no pain relief	4 complete pain relief , 2 partial ,1 nil	NR	mild not specified
DMKG 2003 [51]	1	Misoprostol	0.6ug for 14 days	18	50.3	8 RR,3PP,5SP, 2 unknown	12.2	1.27	1	50% decrease number attacks & pain intensity	9 effective pain relief , 5 no relief , 4 spontaneous remission ,4 recurrences	4	Severe menorrhagia withdrew trial , diarrhoea, GI discomfort

* authors at same institution

NR not reported RR remitting remission, PP primary progressive, SP secondary progressive CP chronic progressive

Table(s)

Click here to download Table(s): Table 4 Details of surgical pwTNMS.docx

Table 4 Details of surgical pwTNMS

	1st Author Year	TN Diagnostic Criteria	Affected Side			TN Division	Outcome Measurement	Operative Technique	KM use	Comments
			Left	Right	Bilateral					
	MVD									
1	Broggi 2004 [10]	NR	12	20	3	19 one division	Excellent- pain relief w/o meds; Good- pain relief w/ intermittent low dose meds: cbz<600mg; Fair- pain relief with high dose meds cbz > 600mg; Poor- drug-resistant recurrence or intolerance to anti-neuralgic therapy EDSS score done	Teflon or fibrillar oxidised cellulose Veins coagulated	Yes	Independent Evaluator
2	Sandell 2010 [7]	Burchiel Classification *	11	8	0	4 one division	Visual analgue scale VAS pain relief - no pain and no medication significant improvement when pain score 0-3		No	
	PSR									
3	Abhinav 2012 [8]	Typical and Atypical with no definition	9	14	0	NR	no or mild pain, moderate , no relief	PSR: 5 MS had decompression	No	
	GKS									
4	Zorro 2009 [48]	NR			11	13 one division	BNI	majority: 1 isocentre 4mm median dose 80GY	Yes	Independent Assessor

5	Mathieu 2012 [37]	Typical episodic; Atypical background pain; Constant pain	12	15		13 one division	BNI	80-90 GY one isocentre	No	Independent Observer
6	Weller 2013 [63]	NR		NR		18 one division	BNI: pre and post treatment failure if BNI IV or V	90Gy using one 4mm collimeter	Yes	Telephone Interview
7	Mohammad-Mohammadi 2013 [9]	Typical TN , Atypical constant pain between			4	54 one division	NR	75-86 Gy one isocentre	Yes	
8	Tuleasca 2014 [46]	Type 1 and type 11 as per Burchiel classification	22	21	2	22 one division	BNI, Burchiel, Regis	4 mm single isocentre median dose 85Gy	Yes	Independent Observer Telephone Interview
9	Taich 2016 [59]	NR	NR	NR	NR	NR	BNI	4mm iso dose 85-90 GY	No	
	PRGR									
10	Dieckmann 1987 [60]	NR	NR	NR	NR	NR	NR	cisternography 0.15-0.4 ml glycerol	No	Data not separated
11	Linderoth 1989 [34]	NR			4	NR	pain free, incomplete pain relief with meds	cisternography 0.20- 0.30ml glycerol	No	
12	Kondziolka 1994 [65]	NR			7	21 one division	Excellent- no meds , good pain control with meds, Poor- inadequate control with meds	cisternography 0.15- 0.30ml glycerol	No	
13	Pickett 2005 [41]	NR	33	16	4	21 one division	complete pain relief with or without meds; partial pain reduction- anything less than pre-op	no cisternography 0.05- - 0.4ml till mild sensory loss	Yes	Telephone Follow up

14	Mathieu 2012 [37]	Typical and Atypical constant	9	9		9 one division	BNI	cisternography, 0.6ml (0.4-1.0) glycerol	No	
15	Mallory 2012 [66]	Classical atypical if constant pain	24	43		29 one division	Excellent- pt remained pain free > 1 mth, no meds; Good- pain free > 1 month with meds; Poor- no relief or return within a month	cisternography, 0.4ml (0.25-0,6) glycerol	Yes	
16	Mohammad-Mohammadi 2013 [9]	Typical TN , Atypical constant pain between	NR	NR	NR	NR	NR	0.5 ml glycerol	Yes	
17	Bender 2013 [24]	provided some data			3	6 one division	Pain relief no meds, pain relief with meds; Partial relief, no relief without meds	fluroscopy only 0.3-0.4ml glycerol	Yes	
	BC									
18	Montano 2012 [38]	Typical/ Atypical		NR		8 one division	BNI	time of compression 2-12 min pear - like 6 elliptical	Yes	KM divided into prognostic factors, no overall KM
19	Mohammad-Mohammadi 2013 [9]	Typical TN , Atypical constant pain between		NR		NR	NR	compression time 1 minute for repeat added 30 sec	Yes	
20	Martin 2015 [36]	NR		NR		NR	Excellent- Pain free, off meds; Satisfactory occasional pain + or - meds, poor dyseasthesia; Recurrence	NR	No	

21	Teo 2015 [67]	NR		NR		NR	Pain relief no meds, Occ pain with or without meds; Poor, moderate or severe dyseasthesia; Fail-no relief, pain recurrence	Pear shape 0.5ml compression 3-4 mins	Yes
	RFT								
22	Brisman 1987 [27]	NR		NR		NR	NR	NR	Yes
23	Fraioli 1989 [69]	NR		NR		NR	NR	Sweet technique nil else reported	No
24	Kanpolat 2000 [12]	NR			1	8 one division	complete pain free no meds, partial some meds	60-70C for one minute five times varied till sensory change	Yes
25	Berk 2003 [25]	classical and provided criteria	4	6	3	12 one division	NR		
	RFT GR								
26	Bender 2013 [24]	NR			6	23 one division	Pain relief no meds, pain relief with meds; Partial relief, no relief without meds	fluroscopy only 0.3-0.4ml glycerol 60C for 60 sec	Yes

Outcome measures: EDSS -Expanded Disability Status Scale ;BNI- Barrow Neurological Institute 1- no pain II occasional pain not requiring medication,III some pain controlled with medication ,IV some pain , not controlled by medication, V severe pain; meds - medication; Regis 1 no TN no meds,IIno pain with meds,IIIa pain improved with meds, IIIb pain improved on meds, III pain frequency reduction >90%, IV pain frequency reduction 50-90%, V no pain reduction, VI pain worsening Burchiel I pain free no meds, II pain free on meds,IIIa pain improved no meds, IIIB pain improved on meds, IV pain not improved

Table(s)

Click here to download Table(s): Table 5 surgical interventions.docx

Table 5 Results from surgical interventions for patients with TN and MS

	1st author year	Study duration yrs	No. patients	Mean/median age yrs	Mean/Median follow up months (range)	Lost to follow up	APR rate %	Probability of a recurrence at yearly intervals					Recurrence rate%	median time to recurrence months	Complications
								1	2	3	4	5			
	MVD														
1	Broggi 2004 [10]	8	35	52	44 (6-108)	2	100	45	42	38	38	30	39	13.5	permanent facial palsy 1
2	Sandell 2010 [7]	8	19	53	65	4	47						NR	NR	bacterial meningitis1, facial numbness 2, dizziness1, impaired hearing 2
Total	**Average MVD**	**8**	**54**	**105**	**54.5**	**6**	**73.5**	**45**	**42**	**38**	**38**	**30**	**39**	**13.5**	
	PSR														
3	Abhinav 2012 [8]	12	23	50	33 (24-80)	NR	87						21.7		numbness 22, AD1
	SRS														
4	Zorro 2009 [48]	12	37	59		0	97	82.6	NR	73.9	NR	54	37.8	74.5	facial numbness 2
5	Mathieu 2012 [37]	5	27	59	39	NR	81.4	NR	NR	NR	NR	NR	51.9	26.5	sensory loss and paraesthesia 6
6	Weller 2013 [63]	8	35	62	39 (3-97)	2	82	57	57	52	52	52	40.7	9.6	facial disturbance 13
7	Mohammad-Mohammadi 2013 [9]	16	24	NR	67 (2-192)	NR	50	27	18	14	NR	5	67	23	0
8	Tuleasca 2014 [46]	18	43	NR	53.8 (12-157.1)	2	90.7	71.8	53.6	43.1	NR	38	61.5	16	numbness 4
9	Taich 2016 [59]	12	14	NR	24	NR	92	NR	NR	NR	NR	NR	NR	NR	NR as mixed series
Total	**Average SRS**	**12.1**	**180**	**60.1**	**46.7**	**4**	**83.6**	**63.2**	**46.4**	**48.5**	**52**	**40.1**	**51.1**	**30.4**	
	PGR														
10	Dieckmann 1987 [60]	5.5	21	NR	24	13	88.2	NR	NR	NR	NR	NR	40	NR	Not separated
11	Linderoth	11	23	NR	43.5	0	91	64	N	N	N	16	61	26	NR

	1989 [34]							R	R	R					
12	Kondziolka 1994 [65]	11	56	35	36 (6-122)	24	59	NR	NR	NR	NR	NR	30	17	herpes simplex10, severe numbness 1, moderate sensory change 5, mild sensory change 12
13	Pickett 2005 [41]	19	53	55	81 (2-151)	NR	91	50	40	38	28	25	59	17	dec corneal reflex 7; no corneal reflex 2, parasthesia 3 ; herpes simplex 1, meningitis 2, masticatory weakness 4
14	Mathieu 2012 [37]	5	18	56.5	38	NR	100	NR	NR	NR	NR	NR	38.9	17	sensory changes 11, no corneal reflex 2
15	Mallory 2012 [66]	13	67	60.5	28.3	NR	75	46	38	30	25	20	54	NR	numbness 35, no corneal reflex 2
16	Mohammad-Mohammadi 2013 [9]	16	39	NR	NR	NR	70	45	35	29	NR	15	69	28	no corneal reflex 1, temporary numbness 4, severe numbness 1
17	Bender 2013 [24]	12	22	53	25	2	68	60	21	21	18	18	87	20	no corneal reflex 2, mild sensory change 5, herpes simplex 2
Total	**Average PGR BC**	**12.8**	**299**	**51.4**	**42.1**	**39**	**77.3**	**50.4**	**35.9**	**31.0**	**25.0**	**19.7**	**53.4**	**20.3**	
18	Montano 2012 [38]	11	21	52	51.57	NR	81	16	10	8	6	3	57	15	mild hypoesthesia 2
19	Mohammad-Mohammadi 2013 [9]	16	19	NR	NR	NR	95	71	57	36		21	61	29	temp numbness 11, severe numbness 1, dec corneal reflex 1, masticatory weakness 2
20	Martin. 2015 [36]	10	17	58.5	43.1	0	82	NR	11	NR	NR	NR	86	15.5	meningitis 2, dysesthesia 2,cheek haemtoma 3
21	Teo 2015 [67]	10	17	NR	28.7	NR	88	63	27	21	NR	NR	NR	15.5	Not separated
Total	**Average BC RFT**	**11.8**	**74**	**54.9**	**41.9**	**0**	**86.4**	**48.4**	**26.2**	**21.2**	**6**	**11.6**	**67.0**	**18.8**	
22	Brisman 1987 [27]	10	10	50	NR	NR	100	92	50	25	NR	NR	25	NR	numbness 2

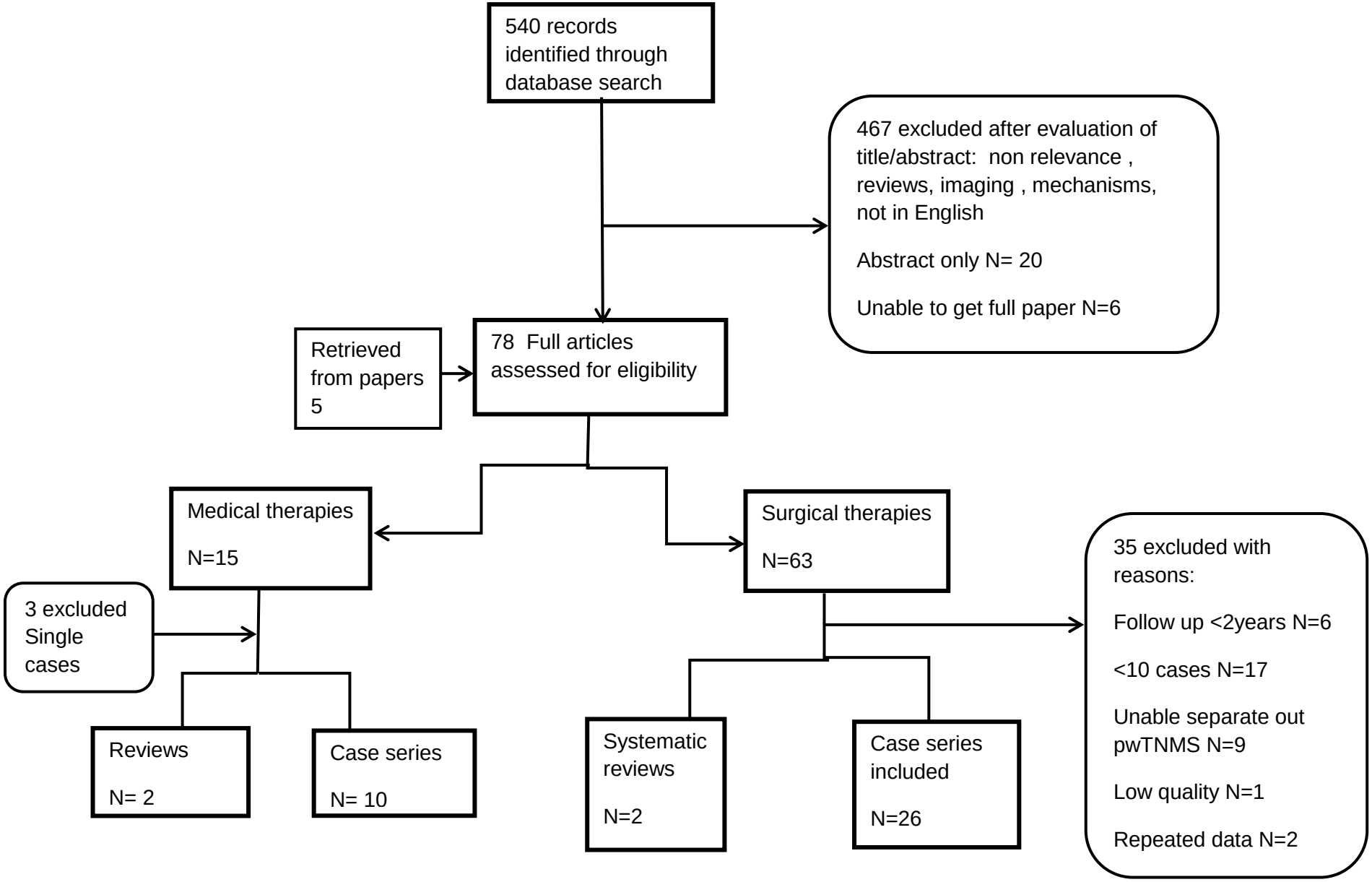
23	Fraioli 1989 [69]	NR	18	NR	69.6	NR	100	NR	NR	NR	NR	NR	11	NR	Analgesia 7, anaesthesia 11
24	Kanpolat 2000 [12]	25	17	45	60 (6-141)	0	94.1	NR	NR	NR	NR	14	29.4	25	hyperalgesia and hypoesthesia 13
25	Berk 2003 [25]	4	13	54	52	NR	NR	NR	NR	NR	NR	NR	50	30	numbness number not specified
Total	**Average RFT RFT/PGR**	**14.4**	**58**	**49.2**	**61.4**	**0**	**97.8**	**92**	**50**	**25**		**14**	**27.5**	**27.2**	
26	Bender 2013 [24]	12	46	58	25	13	72	70	50	35	20	20	64	26	no corneal reflex 1; anaesthesia 1;mild sensory loss 17;masticatory weakness 1

Legend : APR; acute pain relief MVD ;microvascular decompression PSR; partial sensory rhizotomy SRS; stereotactic radiosurgery BC; balloon microcompression PGR; percutaneous glycerol rhizotomy RFT; radiofrequency thermocoagulation AD; anaesthesia dolorosa NR ; not reported temp : temporary dec : decreased

Figure(s)

Click here to download Figure(s): Figure 1 Flow of papers TNMS.docx

Figure 1 Flow chart of the search process



Figure(s)

Click here to download Figure(s): Figure 2 Surgical outcomes TNMS.pptx