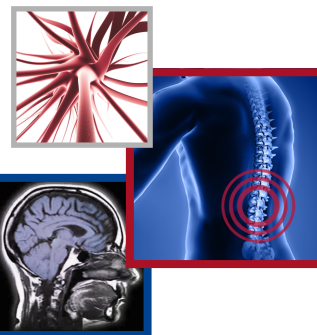


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The journeys of patients with trigeminal neuralgia on a background of multiple sclerosis

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Practice points

- Trigeminal neuralgia (TN) in patients with a background of multiple sclerosis (MS) can be challenging to manage due to co-existing chronic pain and polypharmacy.
- Patients require frequent changes of their pharmacological therapies, including the introduction of polytherapy to manage their TN.
- Many patients will continue to experience refractory pain, and require surgical input to manage their pain.
- The surgical input of choice, is often an ablative procedure, with increased risk of postoperative complications, mainly sensory changes.
- Patients with TN and MS often require more frequent ablative procedures to control their TN than patients with primary TN.
- Patients with TN and MS, often suffer from high levels of anxiety and depression, which would benefit from pain psychology input.
- Long-term follow-up shows that patients global impression of change, shows overall improvement in their management of TN when using a holistic personalized care pathway.
- These patients benefit from a multidisciplinary approach in enabling them to optimally live well with their pain.

Aim: Multiple sclerosis (MS) is well recognized as a secondary cause for trigeminal neuralgia (TN). In this case series, we detail the management of all the patients with TN and MS (pwTNMS) presenting to a specialist unit. **Materials & methods:** A prospective patient database was used to extract key clinical data on pharmacological, psychometric and surgical management of 20 pwTNMS. **Results:** 65% of pwTNMS underwent surgical interventions for management of their pain. 12/20 achieved remission periods, through surgery and/or medication. Significant improvement was noted on the global impression of change illustrated by a $p < 0.001$. **Conclusion:** pwTNMS require a multifaceted approach combining polypharmacy, surgical interventions and psychological support. Developing self-management skills is crucial if patients are to live well with pain.

Lay abstract: **Aim:** Multiple sclerosis (MS) is understood to be the leading secondary cause for the development of trigeminal neuralgia (TN). Very little is known about how this group of patients are managed, in terms of the medication and surgical treatments used. In this study we follow the journey of all the patients with TN and MS (pwTNMS) presenting to the same multidisciplinary (several specialists) unit, detailing their management and impact on the quality of life. **Materials & methods:** Data were collected on 20 pwTNMS on what types of medication and surgical treatments were undertaken to try and manage their pain. **Results:** A total of 65% of pwTNMS underwent one or more surgical treatments for management of their pain. Twelve patients achieved periods of being pain free, through surgery and/or medication. There was significant improvement noted on the global impression of change in pain. Pain catastrophizing scores remained high, suggesting many patients remained fearful and worried regarding their pain. **Conclusion:** TN in patients with MS can be very challenging to manage, often necessitating a more complex approach to treatment involving a combination of medication, surgery and psychological support, to

achieve better management of their pain. Multiple medications are often used in an attempt to reduce adverse drug side effects. Patients, are likely to undergo frequent surgical procedures. A multidisciplinary approach encouraging self-management is crucial if patients are to live well with their pain and improve prognosis.

First draft submitted: 7 January 2021; Accepted for publication: 29 April 2021; Published online: 9 June 2021

Keywords: ablative procedures • multiple sclerosis • pain management • refractory pain • trigeminal neuralgia

Multiple sclerosis (MS) is a chronic inflammatory disease causing widespread progressive demyelination of the CNS.

Major comorbidities reported in relation to MS include anxiety, depression, cerebro- and cardiovascular-diseases and certain autoimmune disorders such as diabetes, thyroid disease and inflammatory bowel disease. Interestingly, pain as a symptom in MS, is reported in up to 75% of patients [1], and yet reviews based on MS comorbidities have failed to recognize pain, as a significant comorbidity in this cohort of patients [2]. Paroxysmal pain symptoms in patients with MS can cause significant impact and increase anxiety and depression. In patients with MS trigeminal neuralgia (TN) is the most widely recognized neuropathic pain syndrome with a prevalence range from 1.9 to 6.3% [3]. TN, can increase the prevalence of anxiety, depressive and sleep disorder in affected patients [4] and anecdotal pain reports further support this observation, leading to a strong research initiative into how TN on a background of MS could be contributing to these major comorbidities [5]. Furthermore, there continues to be emerging evidence, regarding the role of chronic pain and especially TN, in suicide [6].

Patients with TN and MS (pwTNMS), are thought to develop TN as a result of demyelinating lesions in close proximity to the trigeminal nerve which can be visualized on contrast enhanced MRI in up to 63% of patients [7].

MS is associated with a 15-fold higher prevalence of TN than the general population. In most cases, TN appears after an established diagnosis of MS. Laakso *et al.* [7], reported that on an average, TN is diagnosed 12.9 years after a diagnosis of MS, however, in a systematic review up to 11% can have TN up to 10 years before a diagnosis of MS is made [8].

The clinical presentation of TN has a similar form to that seen in the primary form of the condition; however it is appreciated that there are features of prolonged background pain, with some presenting atypically and increased number of bilateral presentations [8–10].

There is little published data on the challenges faced by pwTNMS specifically and in particular regarding their quality of life and management of their condition. This patient cohort is often more complex given the natural progression of MS, leading to increased disability and pain. It is becoming increasingly recognized that this patient population can become medically refractory to treatment and, increasingly require surgical intervention for pain management [11]; thus, an optimal management strategy remains to be decided which includes managing patient expectations. A multidisciplinary care pathway for these patients has been proposed which is the same as for classical TN [12]. This pathway has been shown to result in significant improvement in global impression of change [13]. It includes support from clinical nurse specialists [14] and psychology support to help patients live well with pain and uncertainly [15].

To date, there have been no studies to document outcomes over a long period of time in pwTNMS who are managed by a multidisciplinary team rather than only neurologists who rarely include psychological therapies. A multidisciplinary approach inclusive of psychological therapies is important given that patients with MS are at higher risk of depression and anxiety than a control group of non-MS patients [2].

This paper follows the journeys of the patients identified in an earlier publication [16] in which pwTNMS were phenotyped in detail, at a single specialist unit as part of managing their TN. We present the pharmacological, surgical and psychological sequelae of this group of patients with regards to managing their TN on a background on MS. The follow-up period spans 10 years, between 2009 and 2019. Patients were encouraged to develop their personal care plans based on shared decision making.

Through this series, we endeavor to add to the growing body of evidence surrounding the challenges in managing pwTNMS, and the need for a multidisciplinary approach in managing their TN, on a background of MS.

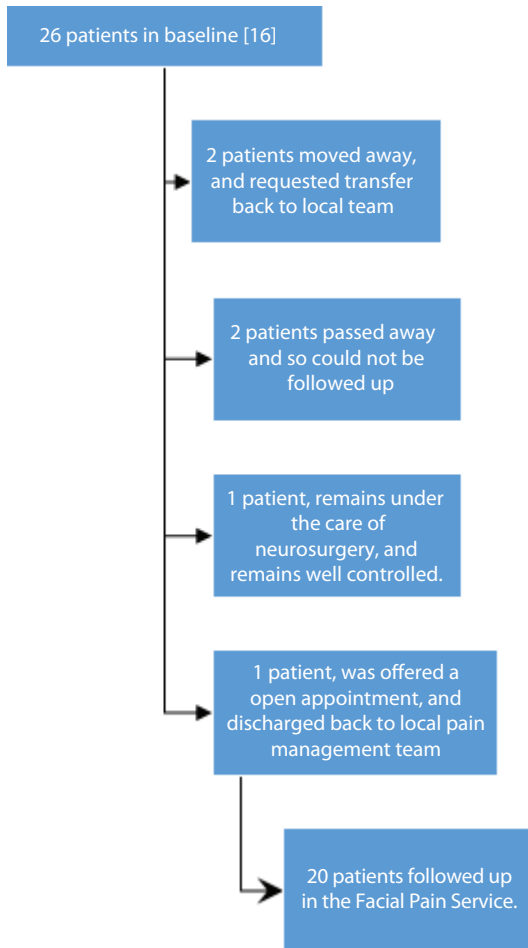


Figure 1. Flow chart of patients from the original dataset who were followed up.

Materials & methods

Participants

All patients included were part of the original study, whereby they fulfilled the diagnostic criteria for TN and MS. Patients with no or only one follow-up appointment were excluded as shown in Figure 1. A number of different reasons are noted for loss to follow-up including patients moving away, dying and remaining under the care of the Neurosurgery team.

Data collection

A prospective Excel database was used to record extracted data from the paper-based patient hospital notes (K Godazandeh and K Patel). The second appointment onwards of each patient with a minimum interval of 6 months between each appointment was used. The same clinician, JM Zakrzewska, managed all the patients. Data collection was performed by a medical student and trainee in oral medicine and facial pain, and any concerns were discussed by the team. Patients did not attend on regular basis.

All patients were telephoned in the period of March–July 2020 by the specialty trainee K Patel and in order to obtain a current snapshot of their pain status and their global impression of change since first entering the service and their current medication.

All the data were analyzed and discussed with an experienced statistician (J Wu), to confirm how best to present the data collected, and if any statistical methods could be used to ascertain the significance of the data.

Measures

Patient data consisted of medical notes, letters, telephone scripts and self-reported questionnaires from the second follow-up onwards (time frame 2009–2019). Detailed data gathered regarding pharmacological input included

Table 1. Demographics and outcomes.

	n	Mean (SD)	Range
Age at 1 September 2020	20	69	55–92
Gender			
Male	6		
Female	14		
First MS diagnosis			
Relapsing-remitting	7		
Primary progressive	6		
Secondary progressive	2		
Benign	3		
Unknown	2		
Duration of trigeminal neuralgia from first attack to first visit		7.65 years	0–21 years
Duration of trigeminal neuralgia from first attack to 2020		13.85 years	4–31 years
Duration of follow-up		6.53 years	2.62–12.51 years
Recorded patient appointments per patient		5.8	2–15
Remission(s) undergone	14		
≥4 remissions experienced in course of follow-up	9		
With drugs	8		
With and/or without drugs	4		
No drugs	2		
Final recorded drug regime			
Monotherapy	8		
Polytherapy	8		
Drug-free	4		
Changes to medical therapy			
No changes	4		
Frequent changes (over ≥2 visits)	12		
Medications withdrawn (average per patient)	48 (3)		0–6
Medications added (average per patient)	31 (1.9)		0–6
Final recorded pain status	20		
In pain	8		
Intermittent pain	7		
No pain	5		

SD: Standard deviation.

medications, polypharmacy and effectiveness of the medication used to manage the TN. Data regarding any surgical input, and effectiveness of any procedures were recorded.

Questionnaires utilized included those in the original study, namely pain catastrophizing scale, hospital anxiety and depression scale and brief pain inventory (BPI). BPI calculations were separated into impact on daily function and facial pain impact. Adverse events profile was included to record side effects from the medications.

The patient global impression of change was scored a range of 1 to 7, where a score of 1 indicating that their pain had ‘very much improved’, a score of 4 implied ‘no improvement’ and a score of 7 indicated their pain had become ‘very much worsened’.

The data were entered on an Excel spreadsheet in the same manner as the baseline study. A remission is defined as a period of no pain report for at least 3 months whether on or off medications.

Results

Demographics

These are shown in Table 1. All but two patients were diagnosed with TN after their MS. Changes to the type of MS diagnoses were made, with three becoming secondary progressive.

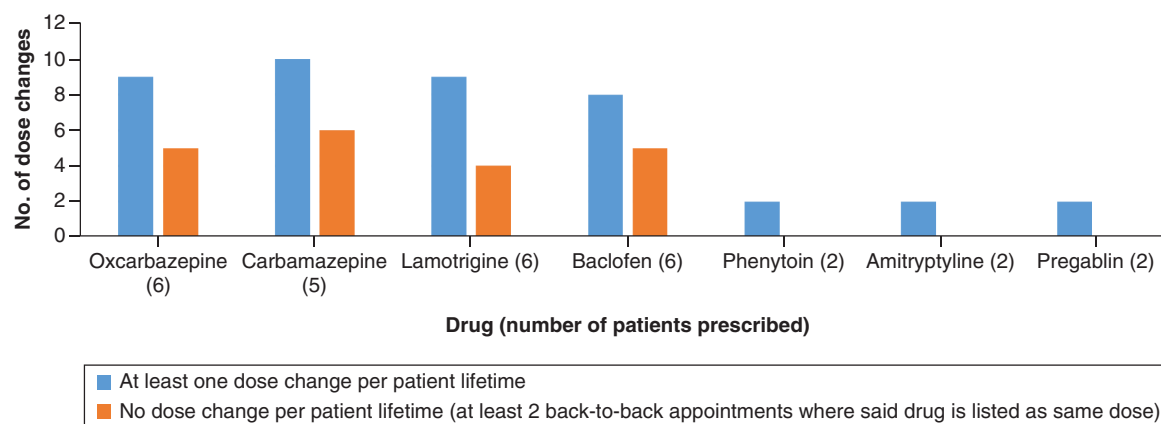


Figure 2. Comparing common drugs and their changes.

Table 2. Surgical procedures undergone by patients with trigeminal neuralgia and multiple sclerosis and their outcomes.

Procedure	n	Mean period of pain relief	Repeated (n)	Current drug status	Current pain status
Glycerol rhizotomy	7	16.6 months	3 repeat glycerol rhizotomies 1 RFT	4 on medication 3 off medication	3 pain free 4 improved pain
RFT	3	9 months in 1 patient	1 repeated	3 on medication	3 in pain But 1 numbness
Stereotactic radiosurgery	2		0 repeated	1 off medication 1 on medication	1 pain free but numbness 1 in pain
Microvascular decompression	1	Pain free 4–6 weeks	0 repeated	1 on medication	Improved pain

RFT: Radiofrequency thermocoagulation.

Drugs

As seen in Figure 2, oxcarbazepine, lamotrigine and baclofen were all independently used by six patients, either with or without other medications. Carbamazepine was used by five patients and phenytoin by two. Baclofen was most commonly started but also frequently discontinued. Carbamazepine was most frequently lowered in dosage, with the dosage of this drug remaining the same for less than half of reported dosage adjustments. Both oxcarbazepine and lamotrigine had their dosages increased and decreased roughly the same number of times. However, lamotrigine was frequently stopped. Polypharmacy was common as seen in Table 1.

Surgery

Not all patients who had been followed up over a significant period (>5 years) had undergone a surgical procedure for their TN pain. Thirteen (65%) of the follow-up participants received one or more surgical procedures for their TN. In total, nine (69%) are female.

Compared with the group as a whole, the average age of surgical patients was the same (68 years). However, these patients have a smaller average interval in between appointments (1.38 vs 2.01 years). The number of total appointments surgical patients have, compared with the group as a whole is roughly the same. Of the nine patients who had four or more remissions, six were surgical patients. The procedures they underwent and outcomes are shown in Table 2.

Despite surgery, nine (69.2%) patients remain on medication for management of their TN. Overall, five patients underwent a repeat ablative procedure of the management of their pain. On an average, the repeat procedure was carried out 21.4 months later due to the pain in relation to TN recurring.

The patient who had a repeat radiofrequency thermocoagulation has been left with significant numbness as a result of the procedure and is still in pain and on medication.

Remission

Fourteen (70%) of the patients had at some stage gone into remission, and nine of these patients experienced four or more remissions. There is insufficient data to determine the average remission period. Eight patients had gone

Table 3. Psychometric outcomes.

	n	Mean (SD)	Range
HAD-A: first, last visit	9	6.33 (3.39), 6.44 (5.05)	
p-value of t-test		0.455	
HAD-D: first visit, last visit	8	8.38 (5.97), 8.5 (6.46)	
p-value of t-test		0.275	
PCS	12	34.6	0–52
Global Impression Scores	20	2	
p-value of t-test		<0.001	

HAD: Hospital anxiety and depression; HAD- A: Hospital Anxiety and Depression – Anxiety score; HAD- D: Hospital Anxiety and Depression – Depression score; PCS: Pain catastrophizing scale.

remissions but continued with drugs, four had at some stage stopped drugs but at other times stayed on drugs and two patients were using no drugs.

The majority of patients were more likely to have remission periods between their first or second appointment rather than later. Five patients had complete remission with no relapse, whereas other patients had periods of remissions and relapses, with no particular pattern.

Impact of pain

On assessment hospital anxiety and depression (HAD) score, it was evident across the cohort, that scores remained high at sequential visits, where this data were available. Sequential visits ranged from 3 month intervals to annual review. The average length between the first and last visits of HAD-A and HAD-D scores were 4.89 and 4.75 visits, respectively, with a range of 0–12 for both HAD-A and HAD-D (with zero visits between denoting no visits in between the first and last). This equates to over 24 months as the average interval between both HAD scores, given the minimum interval of 6 months between appointments were used. Of the 20 patients in this case series, we were able to obtain sequential HAD scores from 14 patients.

On an average, mild levels of anxiety with an average score of 6.33 was noted, with a standard deviation (SD) of 3.39 at the first visit. Comparing this with the last visit, the average anxiety score reported was 6.44 (SD: 5.05). A *t*-test performed on the reported anxiety score resulted in a p-value of 0.455, indicating no significant difference.

Similarly, average depression scores reported for the first and last visit were 8.38 (SD: 5.97) and 8.5 (SD: 6.46). A *t*-test performed on the reported scores gave a p-value of 0.275, indicating no significant difference in the scores.

Pain catastrophizing scores remained high across visits where these data were available on 12 patients, again at sequential visits, with a range of 0–52, and an average of 34.6, indicating that catastrophizing about pain remained consistent in this cohort of patients (Table 3).

Too few BPI questionnaires were completed in order to make a comparison between first and last visit.

Global impression of change scores were obtained from all of the 20 patients included in this patient series. The scores showed that on the whole, pain was better controlled either following surgery or on medication, with an average global impression score of 2, which indicates improvement. A *t*-test was performed, and a p-value < 0.001 suggests an overall improvement in their pain with time.

Discussion

Following this small cohort of pwTNMS for a mean 6.5 years demonstrates that it is possible to achieve a global improvement of their TN, including remission periods, using a mixture of drugs and surgical procedures. Not all patients experience progressive worsening of symptoms.

When looking at drug regimes, carbamazepine overall appeared to be the drug which most often required lowering. While it was difficult to consistently score the adverse effects of the drugs used, qualitative analysis of the patient notes suggests that the dose was often lowered due to side effects.

A review in 2019 [17], also echoed the relatively poor tolerability of sodium channel blockers such as carbamazepine. In this cohort, sixteen patients were managed on multiple medications to improve pain control and reduce side effects. Frequent changes were needed to find the best combination for each patient, and this was helped by regular assessment of side effects. Physicians need to be flexible about using a range of drugs either as monotherapy or polytherapy.

A recent multicenter study in Italy featuring 298 pwTNMS [18] managed by neurologists found the most frequent first-line treatments were carbamazepine and oxcarbazepine. There seems to be some consensus among centers on using carbamazepine as a first line, but there appears to be substantial variability surrounding which surgical techniques to use in managing this cohort of patients. On an average, 30% of patients underwent a surgical procedure with the most common being stereotactic radiosurgery followed by microvascular decompression. These variations could be due to varied access to the procedures. A comparative study in 2012 [19] found that both stereotactic surgery and percutaneous rhizotomies are satisfactory methods for management of pwTNMS, however, highlighted that although stereotactic radiosurgery carried less morbidity, it was associated with a period of delay before pain relief was achieved. The care pathway followed by this group of patients is in line with the recently published guidelines by the European Academy of Neurology [20].

Comparatively, in this cohort, a higher proportion of patients underwent a surgical procedure as management of the TN. The higher use of surgery among this cohort could be because our patients attend a joint clinic between a physician and neurosurgeon, and are offered the option of a surgical procedure earlier compared with other centers. However, we also found that these procedures needed to be repeated.

The anxiety, low mood and persistent catastrophizing noted in these patients highlight the impact that TN on a background of MS has on quality of life. There are many reports which highlight that anxiety is high in MS as measured on the 'HAD scale' and the level of anxiety is the same as in a reported study in 949 patients with MS although our depression score is slightly higher but still not at a level requiring therapy [21]. Therefore, consistently assessing the impact of pain would facilitate the identification of support needed for these patients who in addition to their TN, may require provision for their mood and widespread pain as a result of the MS. Access to a pain management program run by psychologists, physiotherapists and clinical nurse specialists offer support and help in dealing with mood, fear, isolation and uncertainty which remain high as shown by our outcome measures.

Ferraro *et al.* [18] noted that the level of disability had a significant impact on outcomes. The level of disability was assessed on the 'expanded disability status scale'. This study did not use this scale which may have been helpful when attempting to compare patients from other reports.

We found that the majority of outcome measures used in this study were not sensitive to change, and this could have been affected by the ever changing natural progression of MS in the background, or inability to use the outcome measures at the same time points in disease progression. Patients did not always complete the whole questionnaires, possibly due to questionnaire fatigue and so it was impossible to determine scores given the missing data.

In the initial assessment, BPI (scored 0–10) for pain interference were a mean of 4.7 for general daily activities and 5.64 for facial interferences [16]. These measures often only capture the mood and pain of the patient at a set time point of 1 week, and this can be very readily influenced by how the patient's pain has been in the few days leading up to their appointment. We also know that few of these measures have been psychometrically tested in this population [22]. Comparatively, a global summary of improvement in their pain is more reflective of the patient's perspective on how well they feel their pain is managed overall. Thus, the global impression of change provided the most statistically significant results in this cohort and was administered over the telephone. It was possible to contact all the patients at the same time point in 2020.

Although frequent changes of medication were required as well as repeated surgery, patients expressed their appreciation of being followed up by a multidisciplinary team, as well as being given a wide range of choices and help with shared decision making. Each patient had their personal care plan which in some instances included multiple attendances whereas others were able to manage their pain with minimal input but were grateful for the option to be followed up when necessary. This is reflected in the 100% response to the review call. Many had accessed the services of our dedicated clinical nurse specialist who is an independent prescriber and thus, could contact general medical practitioners (GPs) to ensure medications were appropriately dispensed and provide education [14]. Psychological support is crucial as low mood, anxiety and poor sleep are common in patients diagnosed with TN [4,16]. Patients were offered psychological support to facilitate them living well with pain as reported by our unit [15].

Patients with MS find it hard to travel either due to distance or disability, and this is reflected in the variability of outpatient visits. It seems that a telephone/video review is a feasible alternative as expressed by many of the patients who were contacted this way, especially as this was during the COVID pandemic.

Although remission periods do occur, it is important to recognize that many of these patients will rely on long-term use of medication, and often undergo multiple surgical interventions to maintain pain control as seen in this cohort.

Conclusion

pwTNMS face many challenges in achieving pain control in relation to their condition. For the patient, it is about achieving pain reduction, both in relation to the TN, and the widespread chronic neuropathic pain on a background of physical disability. For the clinician, it is about achieving pain control, taking into consideration the physical disability, polypharmacy and potential side effects of any treatments offered and administered. This patient series, highlights the need for a multidisciplinary approach to managing these patients, with patient's choice at the very center of each consultation. Enabling the patient to be well informed with regards to their options in relation to pharmacological and surgical options via joint discussions with physicians and neurosurgeons, they are empowered to make the right decision for their individual care. The challenges with managing refractory and recurrent pain in pwTNMS highlight the need to develop self-management strategies that can address patient expectations, and facilitate pain management in this group of patients with complex pain management needs.

Acknowledgments

The authors thank the patients and AcaMedics, the medical student research group at UCL, who assigned the student to the project.

Informed consent disclosure

The authors state that informed consent has been obtained from all participants. Institutional approval was not required as the data were gathered within the scope of a service review under the Quality and Safety Department at UCLH NHS Foundation Trust.

Financial & competing interests disclosure

JM Zakrzewska undertook the work at UCL/UCLHT who received a proportion of funding from the Department of Health's NIHR Biomedical Research Center funding scheme. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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