

New classification and diagnostic grading for practice and research

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ABSTRACT

Trigeminal neuralgia (TN) is an exemplary condition of neuropathic facial pain. However, formally classifying TN as neuropathic pain based on the grading system of the International Association for the Study of Pain is complicated by the requirement of objective signs confirming an underlying lesion or disease of the somatosensory system. The latest version of the International Classification of Headache Disorders created similar difficulties by abandoning the term symptomatic TN for manifestations caused by major neurologic disease, such as tumors or multiple sclerosis. These diagnostic challenges hinder the triage of TN patients for therapy and clinical trials, and hamper the design of treatment guidelines. In response to these shortcomings, we have developed a classification of TN that aligns with the nosology of other neurologic disorders and neuropathic pain. We propose 3 diagnostic categories. Classical TN requires demonstration of morphologic changes in the trigeminal nerve root from vascular compression. Secondary TN is due to an identifiable underlying neurologic disease. TN of unknown etiology is labeled idiopathic. Diagnostic certainty is graded possible when pain paroxysms occur in the distribution of the trigeminal nerve branches. Triggered paroxysms permit the designation of clinically established TN and probable neuropathic pain. Imaging and neurophysiologic tests that establish the etiology of classical or secondary TN determine definite neuropathic pain. *Neurology*® 2016;87:220-228

GLOSSARY

DTI = diffusion tensor imaging; **ICHD** = International Classification of Headache Disorders; **MS** = multiple sclerosis; **TN** = trigeminal neuralgia.

The diagnosis of trigeminal neuralgia (TN) critically depends on a patient's description of pathognomonic pain attacks.¹ Unequivocal definition of the characteristic features of TN is therefore mandatory. Diagnostic criteria must encompass variants of the clinical phenotype and incorporate the etiology of TN. However, existing criteria are plagued by terminologic inconsistencies that compromise the communication among patients, physicians, and researchers (appendix e-1 on the *Neurology*® Web site at Neurology.org). Two recently published diagnostic guidelines have inadvertently made the classification of TN harder.^{2,3}

Although TN is a prototype of neuropathic pain, typical TN does not fit the grading system for the diagnosis of neuropathic pain. For a definite diagnosis, the grading system requires objective signs or tests that reveal an underlying lesion or disease of the nervous system.² This requirement is suitable for secondary forms of TN, but cannot be applied to classical TN, the most common form of the neuralgia.^{4,5} Conversely, the most recent edition of the International Classification of Headache Disorders (ICHD) no longer lists symptomatic or secondary

Supplemental data
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TN as a diagnostic category,³ leaving a widely used designation for TN that is caused by a major neurologic disease without defined criteria. Recognizing these shortcomings, we developed a new classification of TN that accommodates the needs of clinical practice and research, matches the grading system for neuropathic pain, and corresponds to the common nosology of neurologic disorders. Treatment recommendations are beyond the scope of this article, but we anticipate that they will become more specific following widespread use of the proposed classification.

METHODS With endorsements from the Neuropathic Pain Special Interest Group of the International Association for the Study of Pain and the Scientific Panel Pain of the European Academy of Neurology, we convened experts in TN, diagnostic grading, and evidence-based medicine to review existing definitions of TN and develop a new classification and grading system for TN that fits the specific pathophysiology of the disease. The authors represented multiple specialties: neurology, neurosurgery, orofacial pain medicine, clinical pain research, and basic neuroscience. The proposed classification of TN was based on a thorough review of the literature and discussion among the authors (details can be found in appendix e-2).

To align categories of TN with the grading of diagnostic certainty that was introduced for neuropathic pain,² we first defined criteria of possible, clinically, and etiologically established TN.

DIAGNOSTIC GRADING SYSTEM FOR TN **Possible TN.** The minimum requirements for possible TN are pain distribution within the facial or intraoral territory of the trigeminal nerve and a paroxysmal character of pain (figure 1). The examining physician must ascertain that the pain does not extend to the posterior third of the scalp, the back of the ear, or the angle of the mandible, as these territories are innervated by cervical nerves (figure 2). The territory of the mandibular division of the trigeminal nerve reaches to the cranium; a patient with TN in the mandibular branch of the trigeminal nerve may therefore describe pain both in the lower lip and the temple. If the neuralgia involves 2 trigeminal divisions, they should be contiguous; a combination of the maxillary and mandibular divisions is most frequent. TN in the ophthalmic division or the tongue tends to be considered an indication of TN secondary to a major neurologic disease. However, this interpretation has not been adequately scrutinized.^{4,5} It is further important to note that both the affected division of the trigeminal nerve and the side of the face may change over the course of the disease.^{6–8}

Pain qualifying as possible TN must have a paroxysmal character. Abrupt onset and termination of each paroxysm are unmistakable, whereas the actual description of the paroxysms may vary. Typical

characterizations include notions of brief, sudden, stabbing, electric shock–like, and severe pain attacks.⁹ The paroxysms may last up to 2 minutes, but their duration is usually limited to a few seconds. Frequency of the pain attacks may range from 1 to over 50 a day.^{10,11} Refuting earlier assumptions,⁷ a recent study in 200 patients with classical TN did not find evidence supporting an increase in frequency or duration of the pain paroxysms with the disease duration.¹² Unlike other forms of neuropathic pain, TN enters into periods of complete remission in up to 63% of patients.¹¹ These periods may last from weeks to years.^{11,13}

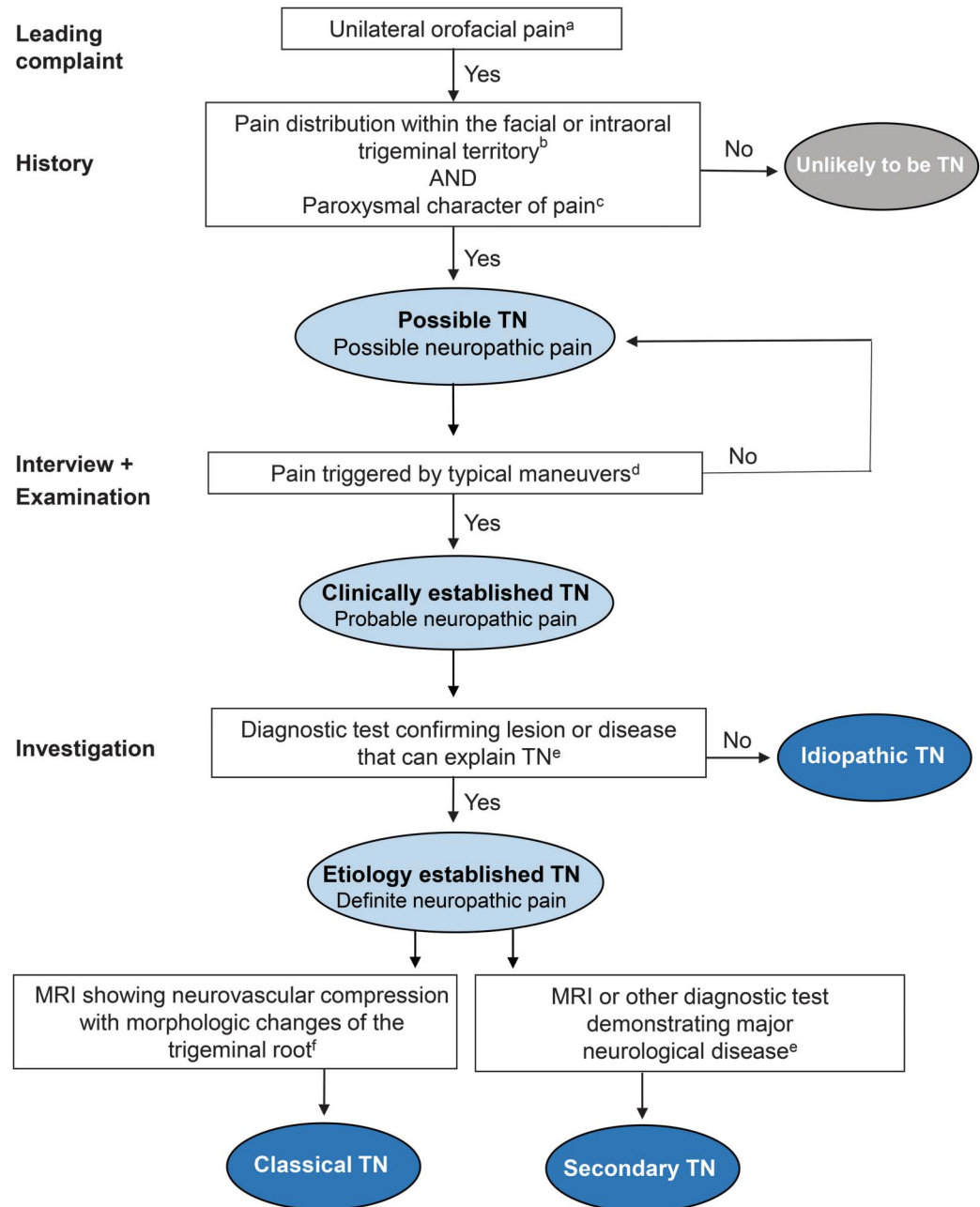
Painful symptoms associated with TN are virtually always unilateral. Bilateral TN is very rare except for TN caused by multiple sclerosis (MS). Occasional reports of bilateral classical TN reflect successive episodes of unilateral pain switching the side of the face rather than pain occurring simultaneously on both sides.^{14,15} A meta-analysis did not reveal any report of truly bilateral TN in 234 patients with classical TN.⁴ We reviewed studies of MS associated with TN and identified 5 reports describing 24 out of 252 patients (~10%) with bilateral TN.^{16–20}

Previous definitions of TN emphasized a stereotypic character of the pain. Stereotypy, however, is not a unique feature of TN. A uniform pain character occurs in other conditions of neuropathic and non-neuropathic pain and should not be considered a defining diagnostic criterion. In addition, it is not uncommon for TN to change its sensory quality over the course of the disease.^{6–8}

Clinically established TN. While pain paroxysms may occur spontaneously, patients with exclusively spontaneous attacks are virtually unknown. In the few studies that examined trigger stimuli or maneuvers in classical TN, evoked pain was reported in 99% of the patients.^{11,21–23} Therefore we propose that triggered pain qualifies as criterion supporting the diagnosis of clinically established TN (figure 1). The rare patients without triggered attacks would remain at the level of possible TN.

Stimulus-evoked pain is one of the most striking features of TN, with high diagnostic value.²⁴ In most patients, pain is triggered by innocuous mechanical stimuli within the trigeminal territory, including the oral cavity. Subtlety of the trigger maneuvers is another unique sign of TN. The stimulus may simply be light touch or a whiff of air. More complex maneuvers involve both tactile stimuli and facial movement, e.g., shaving, application of makeup, brushing teeth, eating, or drinking. Movement alone, e.g., smiling or talking, may suffice to provoke a pain attack. The location of the evoked pain may differ from the site of the stimulation and the pain can be

Figure 1 New classification and diagnostic grading system for trigeminal neuralgia (TN)

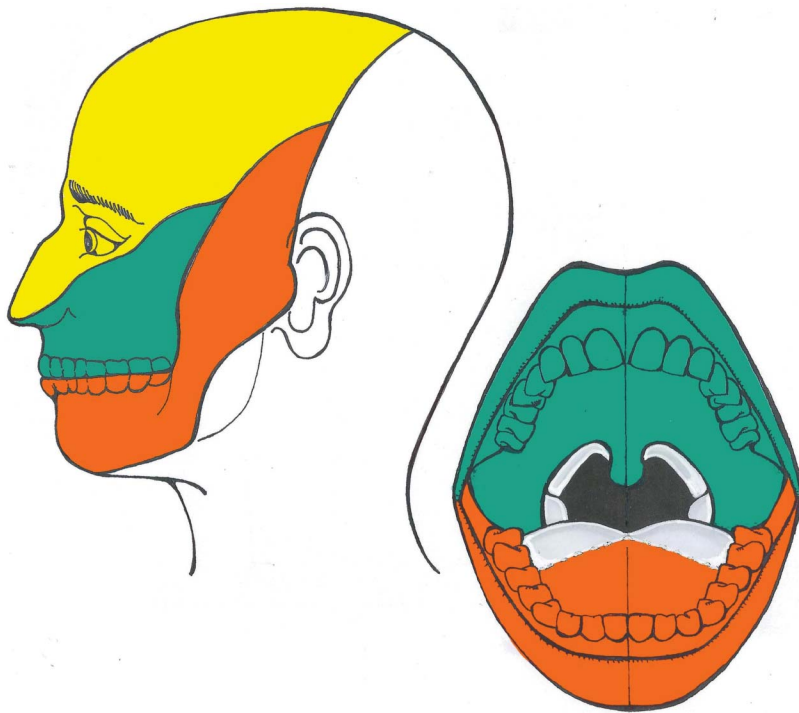


^aTN is typically a unilateral condition. Few patients develop TN on both sides of the face over the course of a disease, e.g., in multiple sclerosis, but they virtually never present with simultaneous bilateral pain. ^bThe pain strictly follows the distribution of the trigeminal nerve branches. It does not extend to the posterior third of the scalp, the posterior part of the external ear, or the angle of the mandible (figure 2). ^cParoxysmal pain is the main complaint, but it may be accompanied by continuous pain. ^dTrigger maneuvers include innocuous mechanical stimuli, facial or oral movements, or complex activities such as shaving or applying make-up. Confined trigger zones and a common combination with brisk muscle contractions (tics) help distinguish triggered TN from allodynia in other conditions of neuropathic pain. Trigger maneuvers may be tested by the examiner. ^eMRI readily identifies major neurologic diseases, such as tumors of the cerebellopontine angle or multiple sclerosis. Other investigations may include the neurophysiologic recording of trigeminal reflexes and trigeminal evoked potentials, which become necessary in patients who cannot undergo MRI. ^fAdvanced MRI techniques are capable of demonstrating neurovascular compression with morphologic changes of the trigeminal nerve root.

felt as radiating. Stimulus-evoked pain is usually reported by the patient. It may also be tested by the examiner, who should pay attention to the typical tic, an involuntary facial movement in reaction to the pain.

The triggered pain paroxysms of TN resemble allodynia in other conditions of neuropathic pain, but there are important differences. The term allodynia was originally coined to describe the abnormal painful response to gentle stroking of the skin in

Figure 2 Innervation territories of the trigeminal nerve



Facial and intraoral territories of innervation of the 3 trigeminal branches (ophthalmic, maxillary, and mandibular). The white areas are innervated by cervical nerves. The light gray areas in the back of tongue and throat are innervated by the glossopharyngeal nerve.

postherpetic neuralgia.²⁵ TN is also often elicited by normally painless mechanical stimuli, or a combination of external stimuli and orofacial movements. But unlike allodynia, trigger zones and pain sensation may be dissociated, a phenomenon that has been interpreted as a sign of cross-excitation between somatosensory afferents.^{26,27} A refractory period of several seconds or minutes during which a second pain paroxysm cannot be provoked is another specific feature of TN; refractory periods do not occur with any forms of mechanical allodynia.²⁸ The TN trigger zones are most often found in the central portion of the face, around nose and mouth, such as the nasolabial fold, and in most patients, trigger zones are small, even punctate.²⁹ These phenotypic differences clearly distinguish triggered pain in TN. Because triggered pain paroxysms are such a unique somatosensory phenomenon, they provide evidence of probable neuropathic pain (figure 1).

Few authors suggest that sensory deficits are detectable on bedside examination of patients with classical TN,¹¹ and absence of a sensory deficit is one criterion for the diagnosis of classical TN in the International Classification of Headache Disorders–3-beta.² However, subtle sensory abnormalities are often found upon quantitative sensory testing.^{21,30} Clinical deficits of discriminatory sensory functions are highly suspicious of TN caused by a major

underlying disease. They occurred in 25 out of 67 patients (37%) with TN secondary to tumors or MS.⁴ Consequently, if sensory deficits are found during a routine clinical examination, they should always be followed up with additional investigations under the assumption of secondary TN. It is important to note that the reverse conclusion is not true: absence of a sensory deficit does not rule out secondary TN.

The diagnosis of clinically established TN should prompt treatment implementation and allow enrollment of a patient into a clinical trial. Additional information about the underlying etiology and definite evidence of neuropathic pain may be preferred for pathophysiologic studies.

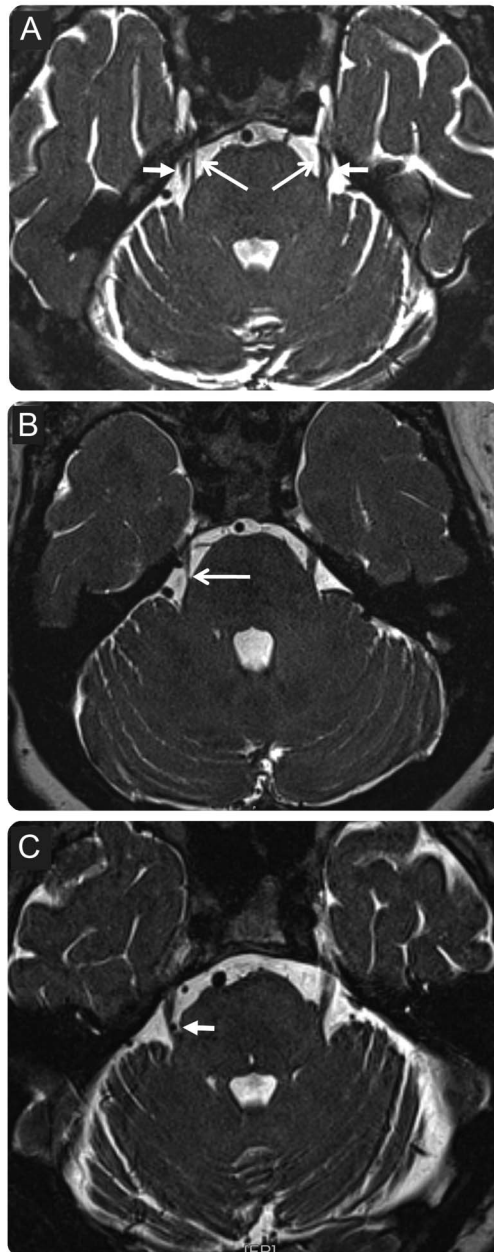
Does treatment response support the diagnosis of TN?

Frequency-dependent sodium channel blockers that increase the refractory period of action potentials are currently the most effective treatment of TN.^{31,32} Carbamazepine and oxcarbazepine, the first-line recommended medications in many clinical guidelines, reduce pain in approximately 90% of patients.^{4,5} A positive response to these drugs, possibly as a single application of a small dose, might therefore be regarded an operant criterion of TN. However, no standardized criteria or generally accepted rules exist for the definition of satisfactory pain relief (e.g., complete vs partial suppression of pain paroxysms). In addition, it would not be possible to apply a treatment-related criterion to those patients who do not tolerate the side effects of carbamazepine or oxcarbazepine. Therefore, we decided against the inclusion of treatment response as diagnostic criterion of TN.

Etiologically established TN. This level of diagnostic certainty, based on identification of a cause for the TN, corresponds to 2 categories: classical and secondary TN are defined by an underlying cause. Both diagnostic entities qualify as definite neuropathic pain.² However, in a relatively small proportion of patients with clinically established TN, even the most advanced diagnostic investigations fail to show a cause.^{33–35} This condition is categorized as idiopathic TN (figure 1).

Classical TN. Classical TN is defined as a specific category of TN in which MRI demonstrates vascular compression with morphologic changes of the trigeminal nerve root (figure 3). Because of its sensitivity to detect pathologic processes involving brainstem and cranial nerves running through the base of the skull, MRI is widely seen as the method of choice to examine the trigeminal nerve and root. MRI may reveal neurovascular contact of the trigeminal nerve root, but the frequency of blood vessel contact with asymptomatic trigeminal nerve roots cautions against the implementation of contact alone as a diagnostic

Figure 3 Neurovascular compression of the trigeminal root



3D constructive interference in steady state MRI shows axial sections at the level of trigeminal nerve root entry into the pons. (A) Bilateral neurovascular contact without morphologic changes of the root in a patient with left trigeminal neuralgia (TN). Nerve (long arrows) and blood vessel (short arrows) appear hypointense surrounded by hyperintense CSF. Contact is seen at the root entry zone as well as mid-cisternal segment. (B, C) Morphologic changes exceeding mere neurovascular contact of the trigeminal nerve root are compatible with the diagnosis of classical TN. (B) Root atrophy in a patient with right TN. (C) Indentation and dislocation of the root in a patient with right TN (short arrow).

criterion. In a recent meta-analysis of 9 high-quality blinded and controlled studies, neurovascular contact was found in 471 out of 531 symptomatic nerves (89%) and 244 of 681 asymptomatic nerves (36%),

indicating high sensitivity but poor specificity.³⁵ Several authors have instead emphasized the importance of physical impact of the blood vessel on the nerve.^{36,37} Nerve dislocation or atrophy raised the specificity to 97%. Two prospective studies have corroborated these results.^{38,39} Location of the neurovascular contact also appears to be relevant. Compression of the trigeminal nerve root at its entry into the brainstem increased specificity and positive predictive value to 100%, with high interobserver consistency.³⁵ The degree of morphologic root changes is therapeutically relevant. Long-term outcome after surgical revision of mere neurovascular contact is uncertain compared to the decompression of dislocated, distorted, or flattened nerve roots.^{37,40,41} Flattening and atrophy appear to be particularly sensitive signs of clinically relevant compression.^{36,41} Advanced MRI techniques further allow for visualization of structural changes within the root that are highly suggestive of physical alteration and provide high predictive value for pain relief after decompression.³⁸ However, it is important to acknowledge that all cited studies relied on a clinical diagnosis of TN before MRI. MRI is a valuable diagnostic tool only if preceded by an evaluation of symptoms and signs that indicate probable TN.

Reliable detection of neurovascular compression requires the use of specific imaging techniques with 3D reconstruction. Several methods improve the depiction of the trigeminal nerve root and adjacent blood vessels in the posterior fossa. Typical imaging paradigms include sequences for 3D T2-weighted MRI, e.g., driven equilibrium or constructive interference in steady state, for a detailed examination of cisternal and cavernous nerve segments (figure 3), 3D time-of-flight magnetic resonance angiography for the visualization of arteries, and 3D T1-weighted MRI with gadolinium or phase-contrast MRI for the visualization of veins.^{33,38,42} Diffusion tensor imaging (DTI) and fiber tractography detect abnormalities of the trigeminal nerve root that normalize following decompression or radiosurgery.^{43,44} DTI may become an essential diagnostic test for TN in the near future. However, so far too few studies have been conducted with sufficient stringency to derive diagnostic criteria with sensitivity/specificity. Most investigations involved group analyses only, and some yielded conflicting results. Pending additional evaluation, these imaging tools may in the future allow predicting the outcome of neurosurgical treatment.⁴⁴

Secondary TN. Diagnosis of secondary TN relies on the demonstration of a major neurologic disease that causes the neuralgia. A tumor at the cerebellopontine angle or MS causes TN in 15% of patients.^{4,5} Tumors leading to TN are mostly benign and typically

compress the root near its entry into the pons. The compression induces focal demyelination and is thought to trigger paroxysmal ectopic discharges. Malignant tumors are more likely to infiltrate the nerve and lead to axonal degeneration. If malignant tumors cause trigeminal pain, it usually does not resemble the pain attacks experienced in TN. TN occurs in 2%–5% of patients with MS; conversely, MS is detected in 2%–14% of patients with TN.^{45,46} The development of pain paroxysms has variably been explained with the presence of demyelinating plaques in the pons or increased susceptibility of the trigeminal nerve root to neurovascular compression.^{46–50}

While MRI is the most useful investigation in the search of underlying etiology, imaging is not possible in some cases, e.g., patients with metal implants such as cardiac pacemakers. Recording of the trigeminal reflexes is an established alternative assessment of trigeminal nerve function.⁵¹ The reflexes can be elicited from all branches of the trigeminal nerve. Reflex abnormalities achieve a sensitivity of 94% and specificity of 87% to identify secondary TN, comparable to the diagnostic accuracy of MRI.⁴⁵ Trigeminal reflex recording is particularly helpful in rare cases of TN secondary to neuropathy (appendix e-2). Various evoked potentials after electrical or thermal stimuli have been studied in TN. In contrast to the trigeminal reflexes, evoked potentials may be altered even in idiopathic or classical TN: we found them abnormal in 103 out of 209 patients, thus yielding a sensitivity of 50% (appendix e-2). However, their specificity in revealing secondary TN (64%) is low.^{5,52,53}

TN with continuous pain. Some patients with TN experience pain between attacks. This pain is continuous or near-continuous and qualitatively different from the paroxysmal pain. It is not associated with any other cause for facial pain. Common descriptions include dull, burning, or tingling. Its distribution coincides with that of the paroxysmal pain, and fluctuations in intensity as well as periods of remission and recurrence parallel those of the paroxysmal pain, thus

demonstrating a close relationship between the two.^{11,54,55} It is known by several designations, including atypical TN and TN type 2 (appendix e-1), but we prefer the term TN with continuous pain, because it directly highlights the defining feature, is easy to communicate, and is least prone to misinterpretation.

Occasionally patients with severe TN may describe their paroxysms as continuous pain, so that differentiating the exact characteristics of their pain becomes difficult. If movement is one of the pain-triggering factors, pain may be suppressed when patients hold completely still for a few minutes, allowing for a better distinction of pain features that match the defining criteria of TN.⁵⁶

Continuous pain is not related to etiology. It occurs in idiopathic, classical, or secondary TN. Whether the continuity of pain results from progressive root damage or a secondary central mechanism is unclear.^{53,55} Several authors have suggested that continuous pain is associated with poorer outcome after surgical intervention,^{6,37,57,58} but this conclusion is controversial.⁴¹ There is, however, compelling evidence that continuous and paroxysmal pain may improve independently after microvascular decompression, suggesting that the mechanisms responsible for the 2 pain components are distinct.^{8,36,58}

DISCUSSION We have developed a new definition and diagnostic classification for TN (table), one that integrates an evaluation of diagnostic certainty based on criteria equivalent to those applied for neuropathic pain in general.² The added assessment of diagnostic certainty will be helpful for treatment decisions. Diagnostic requirements for idiopathic, classical, and secondary TN are based on a thorough review of clinical and etiologic features of TN.

Even after MRI or other investigation, the etiology of TN remains unclear (idiopathic) in approximately 11% of patients.^{33–35} Classical TN, caused by neurovascular compression, is the most frequent form of TN with defined etiology. Morphologic changes indicative of compression rather than mere vascular contact of the trigeminal root markedly increase the specificity of the diagnosis. Therapeutic relevance of these stricter criteria is supported by improved outcome of microvascular surgery in patients with clear signs of morphologic root alterations.³⁵ MRI is the investigation of choice to detect trigeminal nerve compression. 3D reconstructions delineate the anatomic setting with high levels of sensitivity and specificity that help avoid unnecessary posterior fossa exploration. In about 15% of patients with TN, MRI reveals a major neurologic disease such as a benign tumor or MS.⁴ Secondary TN is a well-established term for the designation of these manifestations of neuralgia and should be maintained.

Table	Definition and classification of trigeminal neuralgia (TN)
Definition	TN is orofacial pain restricted to one or more divisions of the trigeminal nerve. With the exception of TN caused by multiple sclerosis, the pain affects one side of the face. It is abrupt in onset and typically lasts only a few seconds (2 minutes at maximum). Patients may report their pain as arising spontaneously but these pain paroxysms can always be triggered by innocuous mechanical stimuli or movements. Patients usually do not experience pain between paroxysms. If they do report additional continuous pain, in the same distribution and in the same periods as the paroxysmal pain, they are considered to have TN with continuous pain.
Classification	TN is classified in 3 etiologic categories. Idiopathic TN occurs without apparent cause. Classical TN is caused by vascular compression of the trigeminal nerve root. Secondary TN is the consequence of a major neurologic disease, e.g., a tumor of the cerebellopontine angle or multiple sclerosis. Either phenotype (with purely paroxysmal pain or with additional continuous pain) may occur with any of the 3 categories.

The diagnostic grading system of neuropathic pain is difficult to administer in TN, because it emphasizes the value of pathologic findings, which are absent in idiopathic TN. However, patient description of trigger zones or demonstration of trigger maneuvers in the physical examination is sufficiently specific to clinically establish TN and diagnose probable neuropathic pain. Additional investigations, primarily MRI, that reveal the etiology of classical or secondary TN fulfill the requirements for a diagnosis of definite neuropathic pain.²

Evaluation and treatment of TN regularly involve clinicians in diverse fields of medicine, including neurology, neuroradiology, neurosurgery, dentistry, maxillofacial surgery, and specialists in pain medicine. A classification system for TN must account for common differential diagnoses in these disciplines. The likelihood that patients with classical TN, whose pain is insufficiently relieved by medication, or patients with secondary TN will require invasive treatment highlights the importance of diagnostic certainty. The ICHD does not differentiate levels of evidence and in its most recent edition³ dismisses the widely accepted diagnostic label of secondary TN. Instead, ICHD-3 favors painful trigeminal neuropathy as a diagnostic label for TN that is caused by a major neurologic disease. However, this category also includes conditions that are distinct from TN and present with different pain phenotypes; for example, trigeminal pain caused by acute herpes zoster. Secondary TN is a well-established and widely accepted designation that should be maintained to avoid confusion.

The proposed new classification provides defined criteria that offer diagnostic accuracy with the added value of a grading system for neuropathic pain (appendix e-3). The classification is designed for intuitive implementation in diagnostic decisions and treatment guidelines. We encourage clinicians and academics to begin using the classification, which will be reflected in the upcoming revision of the WHO's ICD.^{59,60}

AUTHOR CONTRIBUTIONS

All authors complied with the International Committee of Medical Journal Editors criteria for authorship. This article is a review, in which all authors participated in the study concept, preliminary drafting, critical revision, and final approval.

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