Neuropathic facial pain (NFP) is defined as pain around the mouth or face that arises from a primary lesion or dysfunction of the nervous system. The management of NFP can be frustrating as well as rewarding experience in neurosurgical practice because facial pain is often a difficult problem with a wide variety of potential causes. It is therefore important for neurosurgeons to have a broad understanding of the underpinnings of facial pain syndromes. NFP can be primary (with no recognizable underlying pathology) or secondary, such as following traumatic nerve injury. NFP includes a heterogeneous group of entities and can be broadly considered in two categories: paroxysmal and continuous. Paroxysmal neuropathies such as trigeminal neuralgia (TN) are characterized by short electrical shock-like or sharp pain. Continuous pain often has a burning character and is a common feature of conditions such as postherpetic neuralgia (PHN). NFP can vary in severity and also commonly presents with thermal or mechanical allodynia.

HISTORICAL PERSPECTIVE
One of the earliest known descriptions of paroxysmal facial pain was by the Arab physician Jurjani in the 11th century. He described “a type of pain which affects the teeth on one side and the whole of the jaw on the side which is painful.” The 17th century physician John Locke described the symptoms of TN in the wife of the English ambassador to France. Faced with limited treatment options for the patient’s excruciating pain, the physician opted for eight rounds of cleansing of the gastrointestinal tract, and blood vessels and is summarized in Table 163-1. Treatment must be driven by proper diagnosis and the characteristic features of the pain (Fig. 163-1). Pain due to head or neck neoplasm is best treated by treatment of the lesion. Similarly, psychogenic pain is best managed by treatment of the underlying psychiatric condition. It is important to distinguish nociceptive from neuropathic pain. Nociceptive pain is caused by normal and appropriate neural activity in the setting of local tissue injury (e.g., trauma, malignancy, infection). Nociceptive pain is typically constant and aching and only occasionally paroxysmal. Besides appropriate management of the underlying condition, nociceptive pain is best managed by opioid medications.

In contrast, neuropathic pain results from abnormal or inappropriate neural activity and frequently occurs in the absence of obvious organic pathology. Neuropathic pain is thought to arise from aberrant regeneration or conduction following injury to the nervous system. Neuropathic pain can be paroxysmal or constant and is frequently described as electrical, burning, itching, or crawling. Neuropathic pain is thought to be opioid resistant. Medical treatment of neuropathic pain focuses on reducing abnormal neural activity through the use of various anticonvulsant medications.

Nonsteroidal anti-inflammatory drugs may have a role in the treatment of facial pain with an inflammatory component. Topical applications of salicylates and capsaicin may be used as adjunctive therapy in facial pain syndromes especially in the treatment of PHN.

TRIGEMINAL neuralgia
TN, a neuropathic pain syndrome, is defined by the International Association for the Study of Pain (ISAP) as “a sudden and usually unilateral severe brief stabbing recurrent pain in the distribution of one or more branches of the fifth cranial nerve.” It is an excruciating, short-lasting (<2 minutes), unilateral facial pain that may be spontaneous or triggered by gentle, innocuous stimuli and separated by pain-free intervals of varying duration (Fig. 163-2).

TN is classified as follows:
- **Classic** (also known as primary or idiopathic)
- **Symptomatic** (or secondary)—due to intrinsic brainstem pathology with trigeminal nerve, nuclei, or tract involvement, (e.g., multiple sclerosis or lacunar infarction), or due to extrinsic cerebellopontine angle pathology (e.g., neoplasms or vascular lesions).
elination lead to hyperexcitability of injured afferents, which results in after discharges large enough to result in a non-nociceptive signal being perceived as pain.11 One theory to explain TN is the one proposed by Devor and colleagues,12 called the ignition theory, which can be explained as follows. The triggering of pain in TN may follow innocuous stimuli, a phenomenon that is probably explained by postinjury changes in neuronal function. After nerve injury, there is an increased proportion of A-beta fibers with subthreshold oscillations that ultimately generate ectopic discharges.13-15 These produce a transient depolarization in neighboring passive C neurons in the same ganglion.16 These findings favor a mechanism whereby afferent nociceptors could be stimulated by activity in injured low-threshold mechanoreceptors. It is likely that both central and peripheral changes occur, which would explain why not all patients with a treated compression of the nerve get permanent relief. There are likely Most TN patients (>85%) have classic TN. Diagnosis in typical cases is often straightforward; however, most TN patients suffer from misdiagnosis. Common conditions that mimic TN as well as their presenting features are listed in Table 163-2.

Etiology and Pathophysiology
Considerable progress has been made in elucidating the etiology of TN. In most patients with classic TN, the pain is generated because of compression of the trigeminal nerve most commonly at the root entry zone by an artery or vein. Observations supporting this are summarized in Table 163-3. The plaques of demy-
other factors involved given the rarity of the disease, and there are reports of genetic and familial forms.17,18

Epidemiology
TN is considered a rare condition with the following features:
- Annual incidence of 5.7 per 100,000 in women and 2.5 per
  100,000 in men
- Peak incidence in the 50- to the 60-year-old group, increasing
  with age

A recent study using general practice research databases in the
United Kingdom and very broad diagnostic criteria that may have
allowed inclusion of neuropathic facial pain syndrome other than
TN suggested a higher prevalence of 26 per 100,000.19

Risk Factors
The major risk factor for TN is multiple sclerosis.11 Hyperten-
sion may play a role but is common in the age group at risk.
Familial tendency is rare but has been reported.17,18 Bilateral
involvement is present in only 5% of cases, and sensory deficits
are usually subtle and partial and are associated with either chronic-
ity of the syndrome or a history of prior surgical interven-
tion.20,21 In a retrospective study by Pollock and colleagues,21
patients with bilateral TN were more commonly females (74% versus
58%; P < .1), had a higher rate of “familial” TN (17% versus
4.1%; P < .001), and had a greater increased incidence of
additional cranial nerve dysfunction (17% versus 6.6%; P < .05)
and hypertension (34% versus 19%; P < .05). Early, significant,
and nonsurgical sensory loss, in addition to bilateral involvement,
should trigger a thorough investigation for symptomatic (i.e.,
secondary) TN.

Clinical Features
Diagnostic criteria for classic TN have been described in the
International Classification of Headache Disorders (Table 163-
4). These include paroxysmal attacks of pain, characterized by
intense, sharp, superficial, or stabbing precipitated from trigger
areas or by trigger factors, similar attacks in a patient, absence
of neurological findings, and absence of other demonstrable cause.
However, these criteria have not been validated.22 The most
problematic feature of the diagnostic criteria is a requirement for
absence of sensory deficit in the absence of prior surgical inter-
vention history. There is abundant evidence that subtle clinically
detectable sensory deficits are present in the setting of typical TN
as well as evidence that electrophysiologic abnormalities may

| TABLE 163-2 Common Conditions that Mimic Trigeminal Neuralgia |
|----------------------|---------------------------------------------------------------|
| DIAGNOSIS            | IMPORTANT FEATURES                                           |
| Dental infection or cracked tooth | Well localized to tooth; local swelling and erythema, appropriate findings on dental examination |
| Temporomandibular joint pain | Often bilateral and may radiate around ear and to neck and temples; jaw opening may be limited and can produce an audible click |
| Persistent idiopathic facial pain (previously called atypical facial pain) | Often bilateral and may extend out of trigeminal territory; pain often continuous, mild to moderate in severity, and aching or throbbing in character |
| Migraine             | Often preceded by aura; severe unilateral headache often associated with nausea, photophobia, phonophobia, and neck stiffness |
| Postherpetic neuralgia | History of herpes zoster or vesicular outbreak |
| Temporal arthritis    | Common in elderly people; temporal pain should be constant and often associated with jaw claudication, fever, and weight loss; temporal arteries may be firm, tender, and nonpulsatile on examination |

Adapted from Bennetto L, Patel NK, Fuller G. Trigeminal neuralgia and its management. BMJ. 2007;334:201-205.

| TABLE 163-3 Evidence of Neurovascular Compression as Causative for Trigeminal Neuralgia |
|------------------------------------------|----------------------------------------------------------------------------------------|
| • An aberrant loop of artery, or less commonly vein, is found to be compressing the root entry zone of the trigeminal nerve in 80% to 90% of patients at surgery. |
| • The trigeminal nerve is demyelinated next to the compressing vessel. |
| • Eliminating the compression by surgery provides long-term relief in most patients. |
| • Intraoperative assessments report immediate improvement in trigeminal conduction on decompression. |
| • Sensory function recovers after decompression. |
| • Other causes, such as compression by tumors or the demyelinating plaques of multiple sclerosis, produce similar lesions of the root entry zone of the trigeminal nerve. |

Adapted from Bennetto L, Patel NK, Fuller G. Trigeminal neuralgia and its management. BMJ. 2007;334:201-205.

| TABLE 163-4 Diagnostic Criteria for Classic Trigeminal Neuralgia |
|---------------------------------------------------------------|----------------------------------------------------------------------------------------|
| • Paroxysmal attacks of pain lasting from a fraction of a second to 2 minutes that affect one or more divisions of the trigeminal nerve |
| • Pain the has at least one of the following characteristics: |
| • Intense, sharp, superficial, or stabbing precipitated from trigger areas or by trigger factors. |
| • Attacks that are similar in individual patients |
| • No clinically evident neurological deficit is clinically evident |
| • Not attributed to another disorder |

Adapted from Bennetto L, Patel NK, Fuller G. Trigeminal neuralgia and its management. BMJ. 2007;334:201-205.
antedate detectable sensory loss on examination.23-27 There are other forms of TN that most frequently have been called atypical trigeminal neuralgia and trigeminal neuropathy. Because there are no long-term cohort studies, it is not possible to determine whether these atypical forms are in fact the same condition but further on in the natural history or whether they may represent a distinct condition.

The timing of the attacks and remission periods, as well as the character of the pain, are the distinguishing features for classic TN. Many patients with increased pain severity during the day and only one third of patients will report nocturnal pain resulting in awakening.11 Patients with atypical TN often describe a burning, dull, aching after pain that is persistent with a completely pain-free interval.11

Quality of life in TN can be severely impaired. Because the attacks are usually spontaneous and provoked when eating or talking, this reduces the ability to relax and enjoy social activity. Depression is common, and suicides have been reported.11 Although on routine examination most patients have no sensory deficit, existing minor sensory deficits may be very subtle and may increase in frequency with chronicity of the syndrome. Abnormalities in neurophysiologic testing may identify subclinical deficits.25-27 Patients may exhibit tactile trigger areas within the trigeminal distribution, which will precipitate an attack when stimulated. There are no autonomic features.

**Ancillary Tests**
The diagnosis of TN is purely clinical. However, hematologic and biochemical monitoring is important in patients on drug therapy (see later). Radiologic investigations are important to differentiate between symptomatic and idiopathic TN. Magnetic resonance imaging (MRI) is useful to rule out secondary TN (e.g., neoplasms, cysts, vascular pathologies, multiple sclerosis plaques, lacunar infarctions). MRI does not have sufficient positive or negative predictive value to assess vascular compression as an etiology for the syndrome. Sensory testing is not done routinely, but quantitative sensory testing (QST) and evoked potentials may play an important role in differentiating between symptomatic and idiopathic TN.26-27

**Medical Management**
All patients with TN are initially managed medically. Medical management begins with a comprehensive history and physical examination, including baseline measure of pain and quality of life. Psychological support is important, and patients should be provided information about support groups. Key points in the management of patients with TN are summarized in Table 163-5. Commonly used drugs are carbamazepine, oxcarbazepine, gabapentin, lamotrigine, and baclofen. The evidence for their use is summarized in Table 163-6. Patients should keep pain diaries and change their drug levels to adjust to the changing severity of the pain and tolerability of side effects. Most of the drugs need to be escalated and withdrawn slowly to avoid side effects.

Carbamazepine is the drug of choice, with good evidence to show that this drug is highly effective. Common adverse effects such as drowsiness, dizziness, constipation, ataxia, and syndrome of inappropriate diuretic hormone (NNH, 3; 95% confidence interval, 2 to 4), although most can continue taking the drug.28 Other adverse effects include rashess, leukopenia, and abnormal liver function tests. The efficacy of the drug may diminish with long-term use.29 The pharmacokinetics of the drug also result in numerous drug interactions, and one of special note is that with warfarin. If the patient responds well, a controlled-release preparation can be substituted, and the dose can gradually be reduced. What is less clear is what to do if a patient is intolerant or allergic to carbamazepine, or if the drug is ineffective. In the absence of clear evidence of the effectiveness of other drugs, the choice among other agents can be made on the basis of adverse effects and ease of use.

Oxcarbazepine is a prodrug of carbamazepine with similar efficacy of pain control.30 Although it is of similar efficacy to carbamazepine, it is much better tolerated and results in fewer drug interactions.31 Long-term follow-up has also shown that the drug is safe and gradually loses its efficacy because of either development of tolerance or increase in severity of the disease.32 Lamotrigine and baclofen have been suggested as second-line agents for TN on the basis of small studies. In practice, lamotrigine needs to be titrated over many weeks and has limited value in severe pain. Other drugs to consider are phenytoin, clonazepam, valproate, mezaetine, and topiramate.

Gabapentin is widely used for neuropathic pain, although it lacks evidence in TN. Use of gabapentin therefore relies on the similarities between TN and other neuropathic pain syndromes, rather than their obvious differences.33 A recent randomized controlled trial suggests that gabapentin, combined with repeated topical injections of ropivacain, gives better pain control than gabapentin on its own.34 Familiarity with use of gabapentin in other neuropathic pain syndromes has led many clinicians to choose this as second-line for TN.35 Pregabalin has been licensed for use in neuropathic pain and has been reported to be effective in a cohort series in TN.36 Clonazepam, valproate, and phenytoin are often used. There are no high-quality studies on the use of polypharmacy as often practiced in epilepsy. Topical injections of lidocaine into trigger points can give some temporary relief. Drugs such as tocainide, tizanidine, and pimozone are ineffective or their side-effect profile is severe enough to exclude their use.37,38 The fear, loneliness, and depression associated with TN may require psychological, social, or other nonmedical help. Support groups can help to reduce feelings of isolation and despair and can also provide high-quality information.

**Prognosis**
Untreated, TN becomes gradually more severe with fewer remission periods, but the rate at which this occurs is unpredictable. Spontaneous remission periods of up to 6 months are common, yet the syndrome remains predominantly progressive in nature.39,40 Up to 44% of patients when followed for up to 16 years will fail to get complete pain relief with medical therapy.41

<table>
<thead>
<tr>
<th>TABLE 163-5 Key Points in the Management of Patients with Trigeminal Neuralgia</th>
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<tr>
<td>A comprehensive history and examination, including baseline measure of pain and quality of life, is essential.</td>
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<tr>
<td>Magnetic resonance imaging is used for diagnosis of symptomatic trigeminal neuralgia and evaluation of neurovascular compression.</td>
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<tr>
<td>Medical management starts with carbamazepine and then trial of other drugs.</td>
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<tr>
<td>Refer early for a neurological opinion.</td>
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<tr>
<td>Abative surgery results in some degree of trigeminal nerve injury and gives pain relief for 3 to 5 years. Microvascular decompression offers the longest pain-free period with little sensory loss but risk for mortality.</td>
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<tr>
<td>Psychological support is important and includes the need to provide access to written information.</td>
</tr>
<tr>
<td>Patient is provided details of a support group.</td>
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TABLE 163-6 Drugs Used in the Medical Management of Trigeminal Neuralgia

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<tr>
<th>DRUG</th>
<th>LEVEL OF EVIDENCE</th>
<th>EFFECT</th>
<th>ADVERSE EFFECTS</th>
<th>SUGGESTED DOSE</th>
<th>COMMENT</th>
</tr>
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<tr>
<td>Carbamazepine (the only first-line agent)</td>
<td>Systematic review of four randomized controlled trials (n = 160)</td>
<td>NNT for pain relief is 1.9; 72% of patients had excellent or good response</td>
<td>Drowsiness, ataxia, nausea, constipation (minor); NNT 3.7</td>
<td>100 mg twice daily; increase as necessary by 50-100 mg every 3-4 days; target range 400-1000 mg/day</td>
<td>Dose may need to be adjusted after 3 weeks because of enzyme induction</td>
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<td>Baclofen</td>
<td>One controlled trial compared baclofen with placebo (n = 10)</td>
<td>Seven of 10 patients improved with baclofen; 0 of 10 improved with placebo (P = 0.5)</td>
<td>Drowsiness, hypotonia; avoid abrupt withdrawal</td>
<td>10 mg 3 times daily, increase as necessary by 10 mg/day; target dose 50-60 mg daily</td>
<td>May be useful in patients with multiple sclerosis when its antispasticity effects can be harnessed</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Five uncontrolled studies (n = 123)</td>
<td>Good to excellent pain relief in 40%, any pain relief in 53%</td>
<td>Drowsiness, ataxia, diarrhea (minor); NNT 2.5.</td>
<td>300 mg once daily, increase as necessary by 300 mg every 3 days in divided doses (3 times daily); target dose 900-2400 mg daily</td>
<td>Widely used for trigeminal neuralgia although evidence is weak; evidence base in other types of neuropathic pains much stronger</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>One randomized controlled trial with lamotrigine as add on to carbamazepine or phenytoin (n = 14)</td>
<td>Ten of 13 patients improved on lamotrigine; 8 of 14 improved on placebo; (NS)</td>
<td>Drowsiness, dizziness, constipation, nausea (no different from placebo)</td>
<td>25 mg twice daily; increase by 50 mg weekly; target dose 200-600 mg daily</td>
<td>Probably better tolerated than carbamazepine but needs slow titration; may therefore have a role in the elderly patients or patients with multiple sclerosis who have less severe disease</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Two uncontrolled studies (n = 21)</td>
<td>Pain relief in all 21 patients</td>
<td>Dizziness, fatigue, rash, hyponatremia</td>
<td>300 mg twice daily; increase by 600 mg weekly; target dose 600-2400 mg daily</td>
<td>Evidence weak; structurally similar to carbamazepine although probably better tolerated</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Three uncontrolled studies (n = 30)</td>
<td>About 77% of patients reported some pain relief</td>
<td>Drowsiness, ataxia, dizziness, gum hypertrophy</td>
<td>300 mg a day; dose altered to achieve therapeutic plasma concentration</td>
<td>First drug used in the successful management of trigeminal neuralgia; little evidence but rapid dose titration and once-daily dosing are advantages</td>
</tr>
</tbody>
</table>

NNT, number needed to treat; NS, not statistically significant. Adapted from Bennett L, Patel NK, Fuller G. Trigeminal neuralgia and its management. BMJ. 2007;334:201-205.

SUGGESTED READINGS

NHS Clinical Knowledge Summaries found at <http://www.cks.library.nhs.uk/>.


Full references can be found on Expert Consult @ www.expertconsult.com.
REFERENCES

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