



# Persistent Orodontal Pain, Atypical Odontalgia, and Phantom Tooth Pain: When Are They Neuropathic Disorders?

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## ABSTRACT

Patients with unrelenting pain in the teeth, gingival, palatal or alveolar tissues often see multiple dentists and have multiple irreversible procedures performed and still have their pain. Up to one-third of patients attending a chronic facial pain clinic have undergone prior irreversible dental procedures for their pain without success. In these cases, if no local source of infectious, inflammatory, or other pathology can be found, then the differential diagnosis must include a focal neuropathic pain disorder. The common diagnoses given include the terms atypical odontalgia, persistent orodontal pain, or if teeth have been extracted, phantom tooth pain. One possibility is that these pain complaints are due to a neuropathic alteration of the trigeminal nerve. There are several diagnostic procedures that need to be performed in any patient suspected of having a trigeminal neuropathic disorder including (1) cold testing of involved teeth for pulpal nonvitality; (2) a periapical radiograph examining the teeth for apical change; (3) a panoramic radiograph examining for other maxillofacial disease; (4) a thorough head and neck examination also looking for abnormality; (5) a cranial nerve examination including anesthetic testing which documents any increased or decreased nerve trigeminal nerve sensitivity and rules out other neurologic changes outside the trigeminal nerve; and (6) MRI imaging in some cases. Finally, when a nonobvious atypical toothache first presents, direct microscopic examination of the tooth for incomplete tooth fracture is also suggested.

The majority of these patients are women over the age 30 with pain in the posterior teeth/alveolar arch.

Multiple causes exist for sustained neuropathic pain including direct nerve injury (e.g., associated with fracture or surgical treatment), nerve injection injury, nerve compression injury (e.g., implant, osseous growth, neoplastic invasion) and infection-inflammation damage to the nerve itself. Sustained nerve pain is commonly seen in patients with psychiatric impairment. It may be that the unrelenting nature of the pain itself alters the patient's personality.

Treatment includes pharmacologic medications which suppress nerve activity. The common medications used for atypical odontalgia and phantom tooth pain include gabapentin, tricyclics, topical anesthetics, and opioids. A list of these medications is provided in table form. Data suggest that once the patient has failed dental treatment and pain persists, the long-term outcome is less than 25 percent will have complete pain relief with treatment. With earlier treatment, better pain control, and improved nerve activity suppression medications, this should also prevent secondary psychiatric disease from developing and lower the number of inappropriate treatments.



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This article focuses on the diagnosis, etiology, and pharmacologic management of unrelenting pain in the teeth, gingival, palatal, or alveolar tissues that do not respond to the usual and customary dental-medical treatments. One possibility is that these pain complaints represent a neuropathic disorder of the trigeminal nerve.

Patients with this disorder often see multiple dentists, have multiple irreversible procedures performed, and still have the pain in spite of scaling, curettage, antibiotics, NSAIDs, corticosteroids, endodontics, extractions, and even apical and alveolar surgical debridement. One recent case report in 2005 described a patient who had had multiple failed treatments performed because of unrelenting orodental pain.<sup>1</sup>

An article in 2003 described the prevalence of failed invasive therapies in a case series of 120 consecutive patients who attended a hospital center for treatment of their orofacial pain.<sup>2</sup> The report categorized patient self-reports of prior treatment and the success or failure of those treatments. The study reported that 38 out of the 120 (32 percent) patients with chronic oral pain had undergone prior irreversible dental procedures for their pain (e.g., endodontics (30 percent), extractions (27 percent) and apicoectomies (12 percent)). All 38 patients still had pain, and 21 of 38 (55 percent) of the patients reported that these interventions actually exacerbated their pain. This article did not address whether psychiatric illness was co-morbid in this population.

Psychiatric assessment of chronic pain subjects with failed treatment was described in an earlier case series report (21 patients) on atypical facial pain.<sup>3</sup> These patients had a total of 65 irreversible dental and oral surgical treatments

(3 per patient) trying to solve their pain and only one patient reported showing less pain as a result of the treatment. Each of the patients in this report also had a full psychiatric assessment. Based on these data, these authors concluded that failed treatment patients with chronic orodental pain suffered a high degree of psychiatric illnesses. The authors recommended psychiatric assessment before repeated dental and

unexplained persistent dental pain even after the suspected tooth was extracted.<sup>10-13</sup> As such, phantom tooth pain is best described as a syndrome of persistent, unexplained pain at the site of the extracted tooth. While the mechanism is debated, it also is most likely a neuropathic pain process, which is defined by the International Association for the Study of Pain as "pain initiated or caused by a primary lesion, or dysfunction in the nervous system."<sup>14</sup>

These specific changes that occur in the nervous system peripherally and centrally are described later in this article.

**The authors recommended psychiatric assessment before repeated dental and surgical procedures are performed in this population.**

#### *Differential Diagnosis of Chronic Orofacial Pain*

For most persistent orodental pain patients, unless a psychiatric illness is obviously necessitating immediate referral for mental health assessment, the dentist seeing a patient with chronic orodental facial pain would begin by first ruling in or out infection and/or inflammation as a source of the pain. If the teeth and surrounding oral tissues have a healthy appearance and probing of the gingival tissues reveals no obvious pathology, the next consideration is that there is pathology under the site of pain. This can usually be evaluated with periapical dental films and a panoramic film of the jaw. When this is also negative, the dentist must consider further a field disorders (e.g., sinus infection, myofascial pain and temporomandibular joint pain) and any local maxillofacial pathology (e.g., neoplastic disease).

Depending on the situation, sometimes irreversible diagnostic treatments (e.g., root canal or extraction) are performed to see if they will have any beneficial effect. These are labeled diagnostic treatments when they are performed, even though the usual and customary signs of infection or inflammation being not present. If these treatments

surgical procedures are performed in this population. While the need for a psychiatric assessment with a mental health professional is easy to comprehend and implement in the chronic multiple treatment failure patient, it is harder to justify and implement if the patient has not yet failed treatment and presents with a single symptom such as toothache and no obvious behavioral abnormalities. Whether psychological pathoses in this population precedes or is a consequence of chronic pain is unknown.

#### *Definition and Terminology*

Neuropathic orodental pains are not new phenomena. In 1932, Wilson described a group of patients with atypical facial neuralgia and among them were patients who had dental pain of unknown origin.<sup>4</sup> Since then, many others have coined terms for these patients such as idiopathic periodontalgia and atypical odontalgia.<sup>5-9</sup> The term phantom tooth pain, PTP, was applied for the subgroup of these patients who had

**Table 1**

## Three Phases of the Diagnostic Work-up for Suspected Dental Neuropathic Pain

### Phase I: Problem: Pain in a vital tooth

Step 1 **Action:** Progressively perform the following tests:

- (1) Cold testing for pulpal nonvitality
- (2) Periapical radiographic examination for apical change
- (3) A panoramic radiograph looking for other maxillofacial disease
- (4) A thorough head and neck examination looking for other causative diseases
- (5) A cranial nerve examination which assess any sensory alterations

1.1a **Response:** Positive evidence of nonvitality or new periapical lucency would lead to recommendation of immediate endodontics treatment; positive evidence of other disease in the maxillofacial region evident on panoramic radiograph, clinical examination or as a result of a cranial nerve examination would lead to treatment of this other disease or referral to the appropriate specialist.

1.1b **Response:** No evidence of “nonvitality” or other disease in the maxillofacial region. Proceed to phase II.

### Phase II. Problem: Lingering (>3 weeks) pain in a vital tooth without periapical lucency

Step 2.1 **Action:** Remove all fillings, examine under microscope (or loops) for crack. (Note: Most cracks are mesial-distal in direction and U>L; M>P>>A). If the tooth has already been extracted, see step 3.

2.1a **Response:** Positive evidence of crack on close inspection, perform endodontics treatment on tooth and fabricate crown; if a cracked tooth already has endodontic treatment, extract tooth. (Note: Odds of success if definite crack identified is 90 percent, however, 1/10 will still fail to improve.)

2.1b **Response:** No evidence of crack on close inspection, restore tooth and see step 2.2

Step 2.2 **Problem:** Lingering pain in a vital tooth without periapical lucency and no evidence of crack on close inspection with all restorative materials removed; pain continues.

**Action:** Adjust tooth slightly out of occlusion or make a full-arch orthotic device to examine for excessive tooth loading pattern during sleep. This is done by waiting one month and after delivering the appliance and re-examining the orthotic surface for dents or grooves. Make it on the arch that hurts and try unloading most painful teeth. (Note: If, during the removal of the restoration, the tooth was difficult to anesthetize with local anesthetic injection, this indicates a lower prognosis for this being a reversible process and central neuropathic changes are more likely.)

2.2a **Response:** If occlusal splint is positive for tooth loading during sleep and pain reduces, continue using orthotic device for as long as needed and try to adjust device so that the painful area is not in heavy contact. (Note: Because sometimes teeth undergo slow degenerative changes, re-examine, X-ray, and pulp-test at intervals.)

2.2b **Response:** If occlusal splint is negative for evidence of tooth loading and pain continues, discontinue splint use and see step 2.3.

Step 2.3 **Problem:** Persistent pain in a tooth, with or without prior endodontics treatment, or in a tooth site if an extraction was performed. If nonendodontic-treated tooth present, there is no evidence of cracks, tooth is vital to cold test, no periapical lucency evident, occlusal appliance surface shows no bruxism or sustained clenching during sleep.

**Action:** Perform anesthetic test protocol which involves topical, infiltration, and get pain diary (one week).

2.3a **Response:** If topical stops pain, use a neurosensory stent with topical anesthetic as long as needed.

2.3b **Response:** If topical unsuccessful but local helps reduce pain, start medication protocol (see below). Re-examine, radiograph, and pulp-test vital teeth at intervals.

**Phase III: Problem: Lingering pain in a vital tooth, that shows no evidence of nonvitality, cracks or fractures, and radiographic, clinical examination for other pathology is negative. Moreover, it does not respond to occlusal adjustment/occlusal splint treatment, topical or local anesthetics have no effect and patient is not responsive to anticonvulsant medications. Note: Phase III can be initiated earlier if psychosocial issues or neurological signs and symptoms dictate these tests.**

Step 3.1 **Action:** Perform the following tests:

- (1) MRI of brain
- (2) Psychological consultation

3.1a **Response:** Positive evidence of CNS lesion or positive report psychiatric impairment that could explain the symptoms would lead to treatment of this other disease by referral to the appropriate specialist.

3.1b **Response:** No evidence of “nonvitality” or other disease in the maxillofacial region. Return to phase I and reassess, or if pain is substantial, referral to a medical or dental pain specialist for pain management.



fail to help, before performing a second diagnostic treatment on a second tooth or oral tissue site, the possibility that the patient has a neuropathic basis to their pain must be considered.

There are three phases of diagnostic testing that may be needed in a patient suspected of having a persistent orodental pain that might have converted into a neuropathic disorder (Table 1). Phase 1 is a baseline work-up for all patients that would likely include: (1) cold testing for pulpal nonvitality; (2) periapical radiographic examination for apical change; (3) a panoramic radiograph looking for other maxillofacial disease; (4) a thorough head and neck examination looking for other potentially causative diseases; and (5) a cranial nerve examination which documents any altered sensory alterations (especially the trigeminal nerve). Phase 2 is for those patients who have no obvious causation found with the above baseline examination protocol.

This involves three additional steps that should be taken to assess the patient who has a suspected orodental neuropathic pain disorder (Table 1). These three steps include microscopic inspection of the tooth with all restorations removed, occlusal adjustment/orthotic device use, and anesthetic testing of the intraoral pain site. While the first step of the process is the most expensive and the last step (anesthetic testing) is the least expensive, anesthetic testing cannot be considered as a definitive test. In contrast, if a crack in the tooth is identified after removing all restorations, this is definitive. Phase 3 is considered when the above three procedures fail to identify a cause of a treatment method. This phase involves ordering an MRI examination to screen for central or peripheral pathology, and, if clinical history is suggestive of any psychopathology or a mood disorder (e.g., depression, anxiety), a

behavioral assessment by a trained psychologist is needed. These last two tests are especially indicated if the pain does not respond to treatment.

An index of suspicion for all deadly diseases, including cancer, should elevate when dental professionals are dealing with any patient with a history of prior cancer, when dealing with a patient with exposure to risk factors (e.g., smoking) or when the pain disorder is not within the expected sites or age group of the commonly affected.

**CT imaging of the tooth may not pick up the partial tooth fracture which leaves direct microscopic examination of the tooth for cracks as the best method.**

The common site and age of first presentation for atypical odontalgia was described in a study on atypical odontalgia patients. In a study, 74 percent of the sufferers were women in their 40s at initial onset, and the pain was usually present in posterior teeth/alveolar arch with molar teeth affected 58.8 percent of the time, premolars 26.8 percent, canines 4.2 percent, and incisors 12 percent.<sup>15</sup> In another study that evaluated 120 subjects complaining of atypical odontalgia, they had 80.8 percent of women between the ages of 23 and 60 years, with a mean age of  $43 \pm 13.9$  years<sup>16</sup> (Table 1).

#### *Other Trigeminal Neuropathic Pains*

While this article focuses on orodental neuropathic pains (atypical gingival pain, atypical odontalgia, and phantom tooth pain), there are several trigeminal pains that have a neuropathic basis to

the pain. For example, burning mouth syndrome is now thought to have clear neuropathic pain causation. In addition, some patients with chronic temporomandibular joint pain develop a persistent, anti-inflammatory medication-resistant TMJ pain, which may be neuropathic.

Sensitization of the auriculotemporal nerve may account for the reason some patients have sustained unchanging pain even after direct corticosteroid injection into the joint itself. In general, NSAIDs and corticosteroid injections do not strongly suppress neuropathic pain. Proof of auriculotemporal nerve change was provided in recent study that used quantitative sensory testing on 72 patients (44 who had arthralgia and 28 who had chronic myalgia) and 22 health controls.<sup>17,18</sup> Testing of nerve response threshold was achieved with electrical stimulation applied bilaterally in three trigeminal nerve sites (cheek, temple, and chin). By comparing the affected side threshold to the control (nonaffected) side, they found the electrical detection threshold ratio for the three sites, which did not vary from the expected value of 1 in the controls.

However, the patients with arthralgia the mean ratio obtained for the stimulation at the temple region site was significantly lower compared to the other sites and this was not so for the cheek or chin sites. These data suggest that the auriculotemporal nerve which innervates both the TMJ and also the temple was sensitized and had a lower threshold.

#### *Microscopic Inspection of Teeth With Persistent Oro dental Pain*

Incomplete tooth fracture is a rational alternative explanation for persistent toothache without definitive evidence of dental-pulpal disease, such as a periapical radiolucency.

Incompletely fractured teeth will show evidence of vitality (responsiveness) to thermal and electrical pulp testing. Unfortunately, both the partially fractured tooth and the neuropathically sensitized tooth will show increased sensitivity to testing (e.g., palpation, percussion, cold, and electrical stimulation). Of course this theory can be tested by performing what has been termed a diagnostic root canal or diagnostic extraction. If the root canal or extraction abruptly stops the pain, then the pulpal tissues were the source of the pain, and hopefully any fractures will be confirmed, and if salvageable, neutralized by a full-crown restoration after the root canal. If these procedures do not stop the pain, the possibility of a neuropathic change in the nerve supplying the area is elevated. Since an irreversible procedure is not the first choice of the diagnostic process, it is necessary to discuss alternative methods for diagnosis beyond pulp testing and periapical imaging. These methods include computerized tomography and microscopic examination for tooth cracks. Unfortunately, CT imaging of the tooth may not pick up the partial tooth fracture which leaves direct microscopic examination of the tooth for cracks as the best method.

One recent study assessed the value of direct visual examination of 46 chronically painful teeth in 32 patients after removal of all restorations was performed for evidence of an incomplete fracture.<sup>19</sup> They found evidence of incomplete tooth fracture in one or more teeth from 29 of the 32 patients. While this study suggests that if one looks hard enough, 90 percent of teeth with persistent pain will have a incomplete tooth fracture as the underlying cause. This finding is not consistent with the literature since the long-term outcomes for patients seeking care in a chronic orofacial pain clinic suggests that less 25

percent have complete relief with irreversible dental and oral surgical treatment (see section on prognosis below). Clearly, additional data on this method of diagnosis (direct visualization using an operating microscope) and the long-term results needs more research, but in the meantime, this method should be considered to confirm the presence of a structural abnormality of the tooth before a diagnostic root canal or diagnostic extraction is performed.

**If there are neuropathic changes that result in persistent tooth site pain, this is commonly called phantom tooth pain.**

#### *Evidence for True Hyperalgesia in Phantom Tooth Pain*

When tooth pain becomes persistent and root canal treatment is unsuccessful in stopping the pain, the treating dentist commonly elects to extract the tooth, hoping that the pain symptoms will stop. If the tooth is the source of the pain and extrapulpal trigeminal neuropathic changes have not occurred, then the pain should stop. If there are neuropathic changes that result in persistent tooth site pain, this is commonly called phantom tooth pain. Eide and Rabben were the first to conduct quantitative sensory testing in the trigeminal region on symptomatic continuous neuropathic pain cases.<sup>20</sup> Specifically, they reported on eight cases with spontaneous onset continuous trigeminal neuropathic pain. Moreover, four of these had unsuccessful endodontic treatment or extraction for their pain. They determined the threshold for mechanosensory detection and

first pain threshold detection using von Frey filaments applied to the painful facial skin area. They compared the pain patient results with a similar test performed on the contralateral nonpainful side. They reported that in the group of eight spontaneous onset trigeminal neuropathic pain cases, they found no difference between sides for tactile threshold using von Frey filaments. Of course, it should be noted there were no control (nonpain) subjects, these cases were a mixture of probable atypical odontalgia and phantom tooth pain cases and the mechanosensory testing was performed at an extraoral facial skin site. In one study, the authors performed threshold level measurements for light touch sensation using an intraoral site in clearly defined group of phantom tooth pain subjects. They did this using a case-control experimental on 10 phantom tooth pain patients (mean age 56, range 32-71, nine females) and 10 controls.<sup>21</sup> They found the phantom tooth pain complaints were predominantly reported in the upper jaw (ratio 8:2) with the majority in the molar region (ratio 5:3). In addition, phantom tooth pain subjects showed significantly lower threshold levels for light touch sensations on the affected side. While limited in quantity, the above data suggests that PTP subjects demonstrate measurable mechanical hyperalgesia, and among all tests performed, mechanical pain threshold was significantly altered on both sides with the greatest change being on the pain side.

#### *Etiology and Co-morbid Psychological Diseases*

There are case reports of sustained neuropathic pain after direct traumatic (e.g., fracture or surgical) injury, nerve injection injury, implant compression injury, osseous growth compression



**Table 2**

## Medications Used for Trigeminal Neuropathic Pain

| Medication/Dosage   | Action   | Rating/Efficacy  | Issues to consider with use of this drug   |
|---|--|--|--|
| <p>Sodium channel-blocking medications:</p> <ul style="list-style-type: none"> <li>■ Benzocaine 20%</li> <li>■ Lidoderm Patch 5%</li> <li>■ EMLA cream</li> </ul> <p>(all three are applied topically to area of pain)</p>  | <p>MOA: Blocks nerve transmission along the axon by blocking sodium channels</p>   | <p>First-line tx for chronic trigeminal neuropathic pain</p> | <ul style="list-style-type: none"> <li>■ All three are FDA-approved as an aid for minor surgical procedures but benzocaine and EMLA are used off-label for neuropathic pain. Lidoderm Patch is approved for allodynia and chronic pain associated with postherpetic neuralgia.</li> </ul>  |
| <p>Mild anticonvulsant medications:</p> <ul style="list-style-type: none"> <li>■ Gabapentin (Adults: 300 mg; 3-5/day) (range: 1800-3600 mg/day, daily doses &gt;1800 mg do not generally show benefit)</li> <li>■ Pregabalin (Adults: 50 mg; 3/day)</li> </ul>              | <ul style="list-style-type: none"> <li>■ MOA: Not known, for gabapentin but has properties in common with anticonvulsants</li> <li>■ MOA: Pregabalin binds to subunit of voltage-gated Ca<sup>+</sup> channels in CNS and inhibits excitatory neurotransmitter release</li> </ul>  | <p>First-line tx for chronic neuropathic pain</p>            | <ul style="list-style-type: none"> <li>■ FDA-approved as an adjunctive medication for epilepsy. Gabapentin is frequently used for neuropathic pain but this is an off-label use of this medication.</li> <li>■ Pregabalin is FDA-approved for both diabetic neuropathic pain and postherpetic neuralgia. Both medications yield infrequent and benign side effects at high doses, but total dosage must be lower in individuals with renal compromise. There is generally no necessity to monitor blood levels and no significant drug/drug interactions.</li> </ul> |
| <p>Tricyclic antidepressants</p> <ul style="list-style-type: none"> <li>■ Amitriptyline (Adults: 50-150 mg/day at bedtime or in divided doses; maximum suggested dose is 300 mg/day)</li> <li>■ Nortriptyline (Adults: 10-25 mg; 3-4 times/day up to 150 mg/day)</li> </ul> | <ul style="list-style-type: none"> <li>■ MOA: Inhibits paroxysmal neuronal activity; blocks sodium and calcium channels; decreases sensitivity of adrenergic receptors on injured nerve sprouts; blocks the reuptake of norepinephrine and serotonin</li> </ul>  | <p>First-line medication for neuropathic pain</p>            | <ul style="list-style-type: none"> <li>■ FDA approves of TCAs for depression. Amitriptyline and nortriptyline are also used off-label commonly for chronic neuropathic pain in temporomandibular dysfunction (TMD); for CDH and postherpetic neuralgia, traumatic nerve injury, diabetic neuropathy, tension-type headaches, migraine prophylaxis and fibromyalgia. They generally have a high side effect profile with sedation, dry mouth, constipation, urinary retention, weight gain being common.</li> </ul>   |
| <p>Nonopioid analgesics</p> <ul style="list-style-type: none"> <li>■ Acetaminophen (Adults: 325-650 mg every 4-6 hours or 1000 mg 3-4 times/day)</li> <li>■ Tramadol (Adults: 50-100 mg every 4-6 hours, not to exceed 400 mg/day)</li> </ul>                               | <ul style="list-style-type: none"> <li>■ MOA (Acetaminophen): Inhibits the synthesis of prostaglandins in the CNS and peripherally blocks pain impulse generation in axons</li> <li>■ MOA (Tramadol): Binds to <math>\mu</math>-opiate receptors in CNS and inhibits reuptake of norepinephrine and serotonin</li> </ul> | <p>Second-line medication for neuropathic pain</p>           | <ul style="list-style-type: none"> <li>■ FDA approves acetaminophen for treatment of mild-to-moderate pain and fever.</li> <li>■ FDA approves tramadol for relief of moderate to moderately-severe pain.</li> </ul>  |

| NNT   | NNH   |
|---|---|
| <ul style="list-style-type: none"> <li>■ Lidocaine patch 5% has a 4.4 NNT for PHN</li> </ul>  | <ul style="list-style-type: none"> <li>■ NNH: All three medications would likely have a high NNH with essentially no major systemic adverse effects</li> </ul>                                |
| <ul style="list-style-type: none"> <li>■ NNT for gabapentin use in various neuropathic pain conditions at high doses (2400 mg/day) was 3.8</li> <li>■ NNT for pregabalin use in treating PHN and DN at dose ranging from 150 to 600 mg/day was 4.2</li> </ul> | <ul style="list-style-type: none"> <li>■ NNH for withdrawal for gabapentin is 26.1</li> <li>■ NNH for pregabalin was 11.7 indicating a higher high withdrawal rate than gabapentin</li> </ul> |
| <ul style="list-style-type: none"> <li>■ NNT ranges from 2 to 3</li> </ul>  | <ul style="list-style-type: none"> <li>■ NNH is not known for neuropathic pain</li> </ul>   |
| <ul style="list-style-type: none"> <li>■ NNT for less potent opioid medication (tramadol) is 3.9</li> </ul>   | <ul style="list-style-type: none"> <li>■ NNH for tramadol use in neuropathic pain is not known</li> </ul>   |

(Table continues on Page 606)

injury, neoplastic perineural invasion injury, and infection damage to the nerve itself such as with a trigeminal herpes zoster and herpes simplex infection.<sup>22</sup> Neuropathic pain also can be caused by diabetic-related neural injury and altered sympathetic nervous system-related neuropathy. Medications and other chemical toxins as well can cause neuropathic pain along with idiopathic neuropathies. All branches of the trigeminal nerve can be involved including the lingual, inferior alveolar, mental nerve, auriculotemporal and infraorbital nerves.<sup>23</sup>

Regardless of the cause or which nerve branch is damaged, neuropathic pain and psychiatric impairment are common co-morbid problems.<sup>24</sup> The fact that two problems are associated strongly, does not prove that one is the cause of the other.

In fact, pretreatment depression or anxiety as a psychological characteristic does not dictate that the individual to become a neuropathic pain sufferer in the future. An alternate explanation for the strong association between psychological disturbance and neuropathic pain is that the unrelenting nature of the pain itself alters the patient's personality.

Another recent study examined the relative contribution of catastrophic thinking (i.e., rumination, magnification, helplessness) to the pain experience in 80 neuropathic pain patients.<sup>25</sup>

Those individuals who scored higher on a measure of catastrophic thinking also rated their pain as more intense, and rated themselves to be more disabled due to their pain. Catastrophizing thinking predicted pain-related disability over and above the variance accounted for by pain severity and combined, these data suggest that unrelenting pain without highly effective treatment methods may induce helplessness in patients and shift them to express more psychopathology and mood disorders.

### *Mechanism of Neuropathic Sensitization Conversion*

The mechanisms that turn a normal sensory signal into neuropathic pain occur because of multiple alterations e.g., the type and number of sodium channels on an affected nerve. These alterations increase the nerve's sensitivity. The sensitivity of some nerves can be increased to such a degree that they will fire with no obvious physical stimulus. The various mechanisms responsible for these changes include spontaneous ectopic discharge of peripheral nerves, sensitization of sensory nerves from altered receptors, and an increased excitatory neurotransmitter release. Cross-excitation of these nerves occurs after demyelination. Sometimes the sympathetic nervous system can stimulate the sensory system directly after sustained pain causes the sensory system to start upregulating sympathetic neurotransmitter (i.e., adrenergic) receptors. With any peripheral nerve injury or substantial pain nerve activity, the spinal cord undergoes reorganization. An alteration in the descending modulatory nerves also develops that increases the excitability of spinal and trigeminal neurons and with loss of interneurons after injury, there is a reduction of inhibitory activity. Finally, the brain itself can and does change and these supraspinal influences are potent amplifiers and even generators of pain.<sup>26-29</sup>

### **Medications for Chronic Trigeminal Neuropathy**

There still exists no clear choice as to the best medication for the treatment of neuropathic pain. This is due to the large number of pharmacologic medications that can be used to treat both pain symptoms and the co-morbid diseases. There are no neuropathic-activity suppressing medications that affect only the damaged, sensitized nerves without having a powerful effect on normal sensory nerve systems. This



**Table 2**

**Medications Used for Trigeminal Neuropathic Pain (continued)**

| Medication/Dosage   | Action  | Rating/Efficacy  | Issues to consider with use of this drug  |
|---|---|--|---|
| <p>Atypical antidepressants</p> <ul style="list-style-type: none"> <li>■ Venlafaxine (Adults: 75 mg/day, tid and taken with food; maximum dose is up to 225-375 mg/day)</li> <li>■ Duloxetine (Adults: 20 mg bid. Maximum dose is 60 mg/day)</li> </ul> | <p>■ MOA: Both medications are serotonin and norepinephrine reuptake inhibitors (SNRIs)</p>                               | <p>Second-line medication for neuropathic pain</p>   | <ul style="list-style-type: none"> <li>■ FDA has approved venlafaxine for major depression; generalized anxiety disorder (GAD), social anxiety disorder (social phobia); panic disorder.</li> <li>■ Duloxetine is FDA-approved for depression and diabetic neuropathy. In general, SNRIs have fewer anticholinergic properties than TCAs. Adverse effect profile is similar to that of SSRIs and blood pressure must be monitored regularly.</li> </ul> |
| <p>Moderate and strong opioids:</p> <ul style="list-style-type: none"> <li>■ Oxycodone</li> <li>■ Hydrocodone</li> <li>■ Morphine</li> </ul> <p>(These medications have a variable dose for chronic pain use and they have titrated to effect.)</p>     | <p>■ MOA: Agonist for opioid receptors</p>  | <p>Third-line medication for neuropathic pain</p>  | <ul style="list-style-type: none"> <li>■ FDA has approved opioids for pain. Oral long-term treatment with opioids. More relevant in chronic pain, has only been tested using placebo-controlled designs in peripheral neuropathic pain conditions and was found superior to placebo in patients with postherpetic neuralgia, phantom limb pain, and painful diabetic neuropathy.</li> </ul>   |
| <p>Moderate anticonvulsant medications:</p> <ul style="list-style-type: none"> <li>■ Valproic acid (Adults-migraine): 500 mg/day for 7 days; then increase to 1000 mg/day</li> </ul>  | <p>■ MOA: Increase GABA neurotransmission</p>   | <p>Third-line medication for neuropathic pain, but first-line medication for CDH</p>                       | <ul style="list-style-type: none"> <li>■ FDA approves of valproic acid for treatment of seizures and bipolar disorder and for migraine prophylaxis. It is off-label when used for neuropathic pain. This medication needs frequent hematologic, hepatic, and blood level monitoring, and it has multiple drug-drug interactions.</li> </ul>   |
| <p>Strong anticonvulsant medications:</p> <ul style="list-style-type: none"> <li>■ Carbamazepine (Adults: 400-1200 mg/day using divided dose [bid])</li> </ul>  | <p>■ MOA: Depresses thalamic activity and temporal stimulation by limiting influx of sodium ions across cell membrane</p> | <p>Third-line tx for chronic neuropathic pain but is a first-line tx for episodic trigeminal neuralgia</p> | <ul style="list-style-type: none"> <li>■ FDA approves of carbamazepine for treatment of seizures and bipolar disorder and trigeminal neuralgia. It is off-label when used for neuropathic pain and this medication is not commonly used for sustained neuropathic pain. This medication needs frequent hematologic, hepatic, and blood level monitoring, and it has multiple medication-medication interactions.</li> </ul>                             |
| <p>Benzodiazepines</p> <ul style="list-style-type: none"> <li>■ Clonazepam (Adults: 0.25-3 mg/day in two divided doses)</li> </ul>  | <p>■ MOA: This medication binds to the GABA receptor and function as an anti-convulsant and anxiolytic</p>                | <p>Third-line medication for neuropathic pain but first-line medication for BMS</p>                        | <ul style="list-style-type: none"> <li>■ FDA-approved for general anesthesia sedation and analgesia. It is off-label when used for neuropathic pain, anxiety. Clonazepam also may be useful in managing the co-morbid anxiety that may amplify pain symptoms. It is thought to act by potentiating inhibitory GABA transmission, but its analgesic effects may be more related to its anti-anxiety and anti-spasticity properties.</li> </ul>           |

| NNT  | NNH   |
|--|---|
| <ul style="list-style-type: none"> <li>■ NNT for duloxetine for DN was 4.1 (at 60mg/d and 120mg/d)</li> <li>■ NNT for venlafaxine for painful polyneuropathies is 4.0</li> </ul> | <ul style="list-style-type: none"> <li>■ NNH for SNRIs used in neuropathic pain is not known</li> </ul>                                   |
| <ul style="list-style-type: none"> <li>■ NNT for P.O. opioids when used for chronic pain is 2.5 to 3.0</li> </ul>  | <ul style="list-style-type: none"> <li>■ NNH for tramadol was 9.0 and was very low (nonsignificant) for oxycodone and morphine</li> </ul> |
| <ul style="list-style-type: none"> <li>■ NNT is not known for neuropathic pain</li> </ul>  | <ul style="list-style-type: none"> <li>■ NNH is not known for neuropathic pain but will be much higher than gabapentin</li> </ul>         |
| <ul style="list-style-type: none"> <li>■ NNT for trigeminal neuralgia of 1.7</li> <li>■ NNT for painful diabetic neuropathy was 2.3</li> </ul>                                   | <ul style="list-style-type: none"> <li>■ NNH for neuropathic pains is 21.7</li> </ul>   |
| <ul style="list-style-type: none"> <li>■ NNT for clonazepam as a neuropathic medication is not known</li> </ul>  | <ul style="list-style-type: none"> <li>■ NNH for clonazepam as a neuropathic medication is not known</li> </ul>                           |

(Table continues on Page 608)

means that high side effects are likely to be associated with these medications. Direct medication-to-medication trials are not commonly performed, and therefore it is difficult to compare medications for relative efficacy. It is common to use two numbers calculated from randomized blinded-controlled clinical trials to help rate and compare drugs. The first is the number needed to treat, NNT, which is defined as the number of patients needed to treat with a certain medication to obtain one patient with a defined degree of pain relief (usually 50 percent).<sup>30,31</sup> The second one is the number needed to harm, NNH. This is defined as the number of patients that need to be treated for one patient to drop out due to an adverse effect. The characteristic of a good medication is one that has a low NNT and a high NNH. Several meta-analyses of medication trials have reported these two numbers for medications commonly used in the management of neuropathic pain.<sup>32-39</sup>

Using the above meta-analysis information, plus the NNT and NNH calculations, this paper has ranked neuropathic suppressing medications as first-, second-, third-, or fourth-line medications (Table 2). Using these rankings, the first and safest approach for persistent neuropathic orodental pain is to apply topical anesthetics (a first-line medication) for a prolonged time to attempt to suppress nociceptive activity and reverse the neuropathic changes. Usually these medications are applied to the focal pain site using a tissue-covering oral stent as a holding device. The most common topical anesthetic medication is benzocaine 20 percent in orobase paste. This agent is very helpful controlling the patient's pain.<sup>40</sup> Two other first-line oral medications that might be added to the treatment protocol would be either a tricyclic antidepressant type medication (e.g., nortriptyline) and/or a mild anticon-

vulsant type medication (gabapentin or pregabalin). If adequate control is not achieved with these two agents and the topical anesthetics, another second-line medication would be an atypical antidepressant (e.g., duloxetine).

This medication is used if the tricyclic antidepressant/anticonvulsant combination does not work or the side effects are not acceptable to the patient. In all situations, the above medications would be supplemented with a non-opioid analgesic for breakthrough pain (another second line medication). In some cases, a moderate or strong opioid (third-line medication) is used if the nonopioid analgesic is not adequate. In some select neuropathic pain conditions (e.g., trigeminal neuralgia, CDH, BMS) individual neuropathic medications that would be third- or fourth-line medications for orodental pain might be first-line medications, these medications are not the focus of this review article but are included in the table for completeness. Finally, in cases where the patient has substantial comorbid depression a fourth-line neuropathic pain medication, such as an SSRI, would be used as part of the treatment protocol.

As a general rule, the clinician also must try to avoid polypharmacy, which sometimes is impossible in the treatment of chronic pain. Theoretically, the use of a single medication that is directed toward the responsible pain receptor is preferred over a combination of medications that are nonspecific for the condition being treated. Likewise, the use of multiple medications with different mechanisms of action should increase effectiveness for conditions where more than one receptor needs to be targeted. The clinician's goal should be to alleviate pain and distress while keeping medications to a minimum effective dose. This article has not covered the nonpharmacologic methods used to treat pain (e.g., behavioral and



**Table 2**

**Medications Used for Trigeminal Neuropathic Pain (continued)**

| Medication/Dosage  | Action   | Rating/Efficacy                              | Issues to consider with use of this drug  |
|--|--|--|---|
| Antidepressants - Serotonin selection reuptake inhibitors:<br>■ Fluoxetine<br>■ Paroxetine<br>■ Sertraline<br>■ Citalopram (variable dosing, tritrate to effect) | ■ MOA: All SSRIs act via potentiation of the serotonin system pathways | Fourth-line medications for neuropathic pain | ■ FDA has approved SSRIs for major depression. They are used off-label for pain. Overall these medications have been very disappointing for pain but useful for managing the co-morbid symptoms of depression |

physical medicine methods) but without question a comprehensive approach to assessment and treatment of pain is paramount (Table 2).

**Long-term Prognosis for Atypical Odontology and Phantom Tooth Pain**

All patients with a neuropathic pain disorder ask about the future in that they wish to know: (1) How long with the pain last? and (2) Will it go away with time? In addition, when they are having irreversible treatments, they usually want to know the odds of the treatment working. Extensive data on the prevalence of how often irreversible dental treatments (e.g., endodontics and extractions) completely solve a patient with persistent orofacial pain without pretreatment evidence of nonvitality and or periapical lucency is based only on retrospective analysis of cases. While such reports are valuable because they are retrospective studies on complex “chronic pain” patients, they make it difficult to reliably predict the future for an individual patient. There are only two studies that examine the long-term prognosis of patients suffering facial pain that does not fit with the traditional diagnostic criteria and which

does not respond to dental treatment was examined in a recent study. One recent article described the long-term results of a cohort of 74 patients suffering chronic idiopathic facial pain who were seen a minimum of nine to 19 years prior.<sup>41</sup> Of the 74, 13 had died and 16 did not wish to participate. Of the 45 remaining study participants 10 (22 percent) were free of orofacial pain. In a subset of 14 of these patients who had undergone multiple extractions (7.1 per patient), only 3 (21.4 percent) reported permanent pain relief, which is no higher than the rate seen in non-extraction cases.

Overall, these authors reported a very low success rate for the invasive dental treatments that were performed and suggested they may be contraindicated in patients suffering from idiopathic orofacial pain.

These data were consistent with a prior study on persistent facial pain.<sup>42</sup> This study followed up 109 consecutive patients seen in a dental school pain clinic. The patients had between four to nine years of time from their first visit to the follow-up and of the 109, 85 percent responded to the questionnaire. The data suggested only 27 percent of the patients experienced total disap-

pearance of pain. These two studies suggest that between 21 percent and 27 percent of patients who have chronic orofacial pain will have pain relief with time. It may also suggest that the treatments provided in the late 1980s and early 1990s were not highly effective. Based on these data, assuming no obvious dental infection or cracked tooth is identified, the odds of pain stopping in a atypical odontalgia case or in a phantom tooth pain case (after failed root canal therapy or extraction has not stopped the pain) is 25 percent for full-pain remission in five-plus years.

Moreover, the odds of a positive psychiatric diagnosis being made (e.g., anxiety, depression, somatization) in a failed treatment atypical odontalgia or phantom tooth pain case is 67 percent. It seems logical to hope that with a logical plan, a more defined diagnosis and with some of the newer medications and methods of treatment that the percent of patients having full remission will increase and more patients overall will feel better managed. Hopefully with earlier treatment and pain control with the best neuropathic suppressing medications (Table 2) this should also prevent secondary psychiatric disease from developing. ■■■■

| NNT   | NNH  |
|---|--|
| <p>■ NNT for SSRIs for neuropathic pain is almost 7</p> | <p>■ NNH for SSRI as a neuropathic medication is not known</p> |

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