Orofacial Neuropathic Pain and Neuralgia in Older Adults

PHUU HAN
HERMAN OSTROW SCHOOL OF DENTISTRY OF USC
phuuhan@usc.edu
Disclosure Information
Orofacial Neuropathic Pain and Neuralgia in Older Adults
Phuu Han

Continuing Medical Education committee members and those involved in the planning of this CME Event have no financial relationships to disclose.

Phuu Han

I have no financial relationships to disclose

- and

I will discuss off label use and/or investigational use of the following medications in my presentation.

Tricyclic antidepressants, Clonazepam, Oxcarbazepine, Lamotrigine, Gabapentin, Pregablin and Topiramate.
Orofacial Neuropathic Pain

Common Neuropathic Orofacial Pain

Trigeminal Neuralgia
Herpes Zoster and Post-Herpetic Neuralgia
Burning Mouth Syndrome (BMS)

Trigeminal Neuralgia - Epidemiology

- Annual incidence 4 – 13 per 100,000 people
- Most frequently seen neuralgias in the elderly
- Peak age of onset 50 - 60 years and incidence increase with age
- Male : Female – 1 : 1.7
- Most commonly involved V2 and/or V3 division
- V1 division is involved in <5% of patient
Trigeminal Neuralgia - Classic

A. At least three attacks of unilateral facial pain fulfilling criteria B and C

B. Occuring in one or more divisions of the trigeminal nerve, with no radiation beyond the trigeminal distribution

C. Pain has at least three of the following characteristics:
   1. recurring in paroxysmal attacks lasting for a fraction of a second to 2 minutes
   2. severe intensity
   3. electric shock-like, shooting, stabbing or sharp in quality
   4. precipitated by innocuous stimuli to the affected side of the face

C. No clinically evident neurological deficit

D. No better accounted for by another ICHD-3 diagnosis

Trigeminal Neuralgia - Classic

- Classical trigeminal neuralgia, purely paroxysmal
- Classical trigeminal neuralgia with concomitant persistent facial pain
  (Atypical trigeminal neuralgia; trigeminal neuralgia type 2)
  
  A. Recurrent attacks of unilateral facial pain fulfilling criteria for 13.1.1 Classical trigeminal neuralgia
  
  B. Persistent facial pain of moderate intensity in the affected area
  
  C. Not better accounted for by another ICHD-3 diagnosis.
Trigeminal Neuralgia - Classic

- Usually unilateral but it may rarely occur bilaterally.
- Following a painful paroxysm there is usually a refractory period during which pain cannot be triggered.
- In some cases a paroxysm may be triggered from somatosensory stimuli outside the trigeminal area, such as a limb, or by other sensory stimulation such as bright lights, loud noises or tastes.
- The pain often evokes spasm of the muscle of the face on the affected side (tic douloureux).
- Many, possibly most (80 – 90%), patients with this condition have compression of the trigeminal root by tortuous or aberrant vessels.
- Classical trigeminal neuralgia is usually responsive, at least initially, to pharmacotherapy.
Painful trigeminal neuropathy attributed to MS Plaque

A. Head and/or facial pain with the characteristics of Classical trigeminal neuralgia with or without concomitant persistent facial pain, but not necessarily unilateral

B. Multiple sclerosis (MS) has been diagnosed

C. An MS plaque affecting the trigeminal nerve root has been demonstrated by MRI or by routine electrophysiological studies (blink reflex or trigeminal evoked potentials) indicating impairment of the affected trigeminal nerve(s)

D. Not better accounted for by another ICHD-3 diagnosis.

Painful trigeminal neuropathy attributed to space-occupying lesion

A. Unilateral head and/or facial pain with the characteristics of Classical trigeminal neuralgia with or without concomitant persistent facial pain and fulfilling criterion C

B. A space-occupying lesion, and contact between the lesion and the affected trigeminal nerve, have been demonstrated by imaging

C. Pain has developed after contact occurred between the lesion and the trigeminal nerve, or led to its discovery

D. Not better accounted for by another ICHD-3 diagnosis. E.g. Acoustic neuroma, meningioma, epidermoid cyst, aneurysm or AV malformation

Trigeminal Neuralgia

Secondary/Symptomatic

- There may be **sensory impairment** in the distribution of the appropriate trigeminal division.
- Symptomatic trigeminal neuralgia may not demonstrate refractory period after a paroxysm.
- May not respond to pharmacologic treatment.

Pretrigeminal neuralgia

- Pretrigeminal neuralgia → unnecessary dental procedures

Trigeminal Neuralgia – Clinical Examination

- History
- Clinical examination – Cranial nerve examination
- Characteristics of symptomatic TN
  - presence of sensory deficit
  - age of onset
  - first division involvement
  - bilateral involvement
  - unresponsiveness to treatment
  - abnormal blink reflexes
- Additional examination – CT, MRI, MRA (up to 15% of patients with TN), Evoked potential
- Treatment – Pharmacologic, Botulinum Toxin Injection, Surgical (Peripheral or central)
## Trigeminal Neuralgia – Pharmacological Treatment

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Initial Dosage (mg)</th>
<th>Target Dose (mg/day)</th>
<th>Dose Increase (Titration)</th>
<th>Schedule (times/day)</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>100-200</td>
<td>1200</td>
<td>100-200 mg/2 days</td>
<td>3 – 4 times</td>
<td>A</td>
</tr>
<tr>
<td>Carbamazepine-CR</td>
<td>200 – 400</td>
<td>1200</td>
<td>Transfer from regular format</td>
<td>2 times</td>
<td>A</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>150 - 300</td>
<td>1200 – 2400</td>
<td>300 – 600 mg/week</td>
<td>3 times</td>
<td>B</td>
</tr>
<tr>
<td>Baclofen</td>
<td>5 – 15</td>
<td>30 - 60</td>
<td>5 mg/3 days</td>
<td>3 times</td>
<td>A/C</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>25</td>
<td>400 – 600</td>
<td>25 – 60 mg/week</td>
<td>1 – 2 times</td>
<td>A/C</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.25 – 0.5</td>
<td>1 – 4</td>
<td>0.25 mg/week</td>
<td>Bedtime</td>
<td>C</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>300</td>
<td>900 – 2400</td>
<td>300 mg/1 – 2 days</td>
<td>2 – 3 times</td>
<td>B</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>150</td>
<td>300 – 600</td>
<td>50 mg/ 2 – 3 days</td>
<td>2 – 3 times</td>
<td>C</td>
</tr>
<tr>
<td>Topiramate</td>
<td>25</td>
<td>100</td>
<td>25 mg/ week</td>
<td>2 times</td>
<td>C</td>
</tr>
</tbody>
</table>
Trigeminal Neuralgia - Treatment
Trigeminal Neuralgia - Treatment

http://www.seattlecca.org
Case - Trigeminal Neuralgia
Acute Herpes Zoster (Shingle): Epidemiology

- Caused by VZV
- 30% lifetime risk of developing zoster
- Affects adults older than 50 years
- Severity and incidence increase with age (age related decline in cell-mediated immunity)
- Risks: immunosuppression, advanced age, malignancy, chronic kidney or lung disease, HIV infection etc
- 50% of patients over age 85 years will have an episode of herpes zoster
Painful Trigeminal Neuropathy Attributed to Acute Herpes Zoster

A. Unilateral head/or facial pain lasting <3 months and fulfilling criterion C

B. Either or both of the following:
   1. herpetic eruption has occurred in the territory of a trigeminal nerve branch or branches
   2. varicella zoster virus DNA has been detected in the CSF by PCR

C. Evidence of causation demonstrated by both of the following:
   1. pain preceded the herpetic eruption by < 7 days
   2. pain is located in the distribution of the same trigeminal nerve branch or branches

D. No better accounted for by another ICHD-3 diagnosis

Painful Trigeminal Neuropathy Attributed to Acute Herpes Zoster

- Affects the trigeminal ganglion in 10–15% of cases.
- Ophthalmic division being singled out in some 80% of patients. (Only intra-oral lesions can also occur)
- Rarely, pain is not followed by an eruption or rash (zoster sine herpete).
- Burning, stabbing/shooting, tingling or aching, and accompanied by cutaneous allodynia.
- Herpes zoster is common in immunocompromised patients.

Painful Trigeminal Neuropathy Attributed to Acute Herpes Zoster

• CN V1 dermatome, ipsilateral forehead, and upper eyelid. When lesions are found in the CN V1 dermatome.

• Presence of orbital edema is an ophthalmologic emergency.

• Nasociliary branch involvement, with vesicles at the tip of the nose, can indicate that eye involvement is present (the Hutchinson rule). A slit-lamp examination is done to identify corneal findings.

• Ophthalmic herpes may be associated with IIIrd, IVth and VIth cranial nerve palsies.

• Signs of meningeal irritation and meningitis must be excluded.

Painless Trigeminal Neuropathy Attributed to Acute Herpes Zoster

- CN V2 – Ipsilateral cheek, the lower eyelid, side of the nose, upper eyelid, upper teeth, mucous membrane of the nose, nasopharynx, the tonsils and the palate.
- CN V3 - involvement include the side of the head, the external ear and external auditory canal, the lower lip, and a portion of the oral mucosa.
- Only the oral mucous membrane can involved with no cutaneous manifestations.
- Early pre-eruptive herpetic pain can stimulate a severe toothache and result in unnecessary oral surgical or dental treatment.

Am Fam Physician. 2008 May 1;77(9):1307-1309
Facial Neuropathy Caused by Acute Herpes Zoster

- Burning and itching pain of the affected areas and may be extremely bothersome.
- Pale or light purple scars or skin changes may be present.
- Herpes zoster oticus (Ramsay Hunt syndrome)
- CN VII – Facial Palsy
- CN IX, X and XI, (XII) – Jugular foramen syndrome or Vernet’s syndrome

http://emedicine.medscape.com/article/1132465
http://www.biomedcentral.com/1756-0500/6/337
<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Effects Observed in Controlled Trials</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonimmunocompromised persons</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acyclovir (e.g., Zovirax)</td>
<td>800 mg orally five times daily for 7–10 days</td>
<td>Reduced time to last new-lesion formation, loss of vesicles, full crusting, cessation of viral shedding, reduced severity of acute pain(^{10-12})</td>
<td>Malaise</td>
</tr>
<tr>
<td>Famciclovir (e.g., Famvir)</td>
<td>500 mg orally three times daily for 7 days</td>
<td>Reduced time to last new-lesion formation, loss of vesicles, full crusting, cessation of viral shedding, cessation of pain(^{13,14})</td>
<td>Headache, nausea</td>
</tr>
<tr>
<td>Valacyclovir (e.g., Valtrex)</td>
<td>1 g orally three times daily for 7 days</td>
<td>Reduced time to last new-lesion formation, loss of vesicles, full crusting, cessation of pain(^{15,16})</td>
<td>Headache, nausea</td>
</tr>
<tr>
<td>Brivudin (e.g., Zostex, Helpin)*</td>
<td>125 mg orally once daily for 7 days</td>
<td>Reduced time to last new-lesion formation, full crusting, cessation of pain(^{17})</td>
<td>Headache, nausea; contraindicated in persons receiving fluorouracil or other fluoropyrimidines</td>
</tr>
<tr>
<td><strong>Immunocompromised persons</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acyclovir (e.g., Zovirax)</td>
<td>10 mg/kg intravenously every 8 hr for 7–10 days</td>
<td>Reduced time to last new-lesion formation, full crusting, cessation of viral shedding, cessation of pain, reduced cutaneous dissemination, reduced visceral herpes zoster(^{18,19})</td>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>Foscarnet (e.g., Foscavir) for acyclovir-resistant VZV†</td>
<td>40 mg/kg intravenously every 8 hr until lesions are healed</td>
<td></td>
<td>Not reported</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Dose Adjustment</th>
<th>Maximum Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opioid and nonopioid analgesics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodeone</td>
<td>5 mg every 4 hr as needed</td>
<td>Increase by 5 mg four times daily every 2 days as tolerated</td>
<td>None specified, but should not exceed 120 mg daily except in consultation with a pain specialist</td>
<td>Drowsiness, dizziness, constipation, nausea, vomiting</td>
</tr>
<tr>
<td>Tramadol</td>
<td>50 mg once or twice daily</td>
<td>Increase by 50–100 mg daily in divided doses every 2 days as tolerated</td>
<td>400 mg daily; 300 mg daily if patient is &gt;75 years of age</td>
<td>Drowsiness, dizziness, constipation, nausea, vomiting</td>
</tr>
<tr>
<td><strong>Glucocorticoids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>60 mg daily for 7 days, then decrease to 30 mg daily for 7 days, then decrease to 15 mg daily for 7 days</td>
<td>None</td>
<td>60 mg daily</td>
<td>Gastrointestinal distress, nausea, vomiting, mood changes, edema, glucose intolerance, increased blood pressure</td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>300 mg at bedtime or 100–300 mg three times daily</td>
<td>Increase by 100–300 mg three times daily every 2 days as tolerated</td>
<td>3600 mg daily</td>
<td>Drowsiness, dizziness, ataxia, peripheral edema</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>75 mg at bedtime or 75 mg twice daily</td>
<td>Increase by 75 mg twice daily every 3 days as tolerated</td>
<td>600 mg daily</td>
<td>Drowsiness, dizziness, ataxia, peripheral edema</td>
</tr>
<tr>
<td><strong>Tricyclic antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>25 mg at bedtime</td>
<td>Increase by 25 mg daily every 2–3 days as tolerated</td>
<td>150 mg daily</td>
<td>Drowsiness, dry mouth, blurred vision, weight gain, urinary retention</td>
</tr>
<tr>
<td><strong>Topical therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lidocaine patch (5%)</td>
<td>One patch, applied to intact skin only, for up to 12 hr per day</td>
<td>None</td>
<td>One patch for up to 12 hr per day</td>
<td>Local irritation; if systemic, absorption can cause drowsiness, dizziness</td>
</tr>
</tbody>
</table>

Post-herpetic Trigeminal Neuropathy

A. Unilateral head/or facial pain persisting or recurring for 3 months and fulfilling criterion C

B. History of acute herpes zoster affecting a trigeminal nerve branch or branches

C. Evidence of causation demonstrated by both of the following:
   1. pain developed in temporal relation to the acute herpes zoster
   2. pain is located in the distribution of the same trigeminal nerve branch or branches

D. No better accounted for by another ICHD-3 diagnosis

Post-Herpetic Neuralgia (PHN)

A. Damage to the nervous system
   1) Deafferentation
   2) Peripheral and/or central sensitization
   3) Myelin destruction
   4) Inflammation
   5) Signalling errors in the brain

B. As many as 20% (9-34%) of patients with Singles develop PHN

C. More prevalent in elderly >60 years of age

D. PHN incidence: Risks: older age, greater acute pain, greater rash severity, ophthalmic location of rash
<table>
<thead>
<tr>
<th>Agent</th>
<th>Average Effective Dose in Clinical Trials</th>
<th>Starting Dose</th>
<th>Dose Adjustment</th>
<th>Number Needed to Treat (95% CI)</th>
<th>Side Effects</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topical treatments</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lidocaine patch</td>
<td>5%; up to 3 patches/day</td>
<td>Maximum of 3 patches/day for a maximum of 12 hr</td>
<td></td>
<td>2.0 (1.4–3.3)¹⁰</td>
<td>Local erythema</td>
<td></td>
</tr>
<tr>
<td>Capsaicin cream</td>
<td>0.075%; 4 applications/day</td>
<td>NA</td>
<td></td>
<td>3.3 (2.3–5.8)¹⁰</td>
<td>Pain on application, local erythema, rash</td>
<td>Avoid eyes and nose</td>
</tr>
<tr>
<td>Capsaicin patch</td>
<td>8%; application time of 30–90 min</td>
<td>NA</td>
<td></td>
<td>11.0 (6.1–62.0)¹²</td>
<td>Pain on application, local erythema, rash; systemic adverse events in ≤5% of study participants;‡</td>
<td></td>
</tr>
<tr>
<td><strong>Oral treatments</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>2572 mg/day</td>
<td>100 mg 3 times daily</td>
<td>Increase each of the 3 daily doses by 100–300 mg every 3–7 days as tolerated; maximum dose is 1800 mg/day, but unlicensed dose of up to 3600 mg/day is used by some clinicians</td>
<td>4.4 (3.3–6.1)¹⁰</td>
<td>Sedation, dizziness, peripheral edema</td>
<td>Avoid in patients with renal insufficiency</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>398 mg/day</td>
<td>50–75 mg twice daily</td>
<td>Increase to 300 mg daily after 3–7 days, then by an additional 150 mg daily every 3–7 days as tolerated, to a maximum dose of 600 mg daily</td>
<td>4.2 (3.4–5.4)²⁰,³³</td>
<td>Same as with gabapentin</td>
<td>Same as with gabapentin</td>
</tr>
<tr>
<td>Tricyclic antidepressants (off-label use)</td>
<td>Amitriptyline, 95 mg/day; or nortriptyline, 122 mg/day</td>
<td>10–25 mg at bedtime</td>
<td>Increase by 10–25 mg every 3–7 days as tolerated to 75–150 mg/day with caution as side effects permit; if blood level of active drug and its metabolite is &gt;100 ng/mL, continue dose adjustment very cautiously</td>
<td>2.6 (2.1–3.5)¹⁰</td>
<td>Sedation, dry mouth, blurred vision, weight gain, urinary retention</td>
<td>Avoid in patients with cardiac disease, glaucoma, or seizure disorder; avoid concomitant use of tramadol</td>
</tr>
<tr>
<td>Morphine and oxycodone</td>
<td>Morphine, 90 mg/day; oxycodone, 45 mg/day</td>
<td>5–15 mg every 4 hr as needed</td>
<td>After 1–2 wk, convert total daily dose to long-acting opioid and continue short-acting formulation as rescue medication</td>
<td>Morphine, 2.8 (2.0–4.6)¹⁰; oxycodone, 2.5 (1.7–4.4)¹⁰</td>
<td>Nausea, vomiting, constipation, drowsiness, dizzi- ness, mood change, disorientation</td>
<td>There is risk of abuse and uncertainty over long-term effectiveness and safety§</td>
</tr>
<tr>
<td>Tramadol</td>
<td>298 mg/day</td>
<td>50 mg every 4–6 hr</td>
<td>Increase by 50–100 mg/day in divided doses every 3–7 days as tolerated, to maximum dose of 400 mg/day (300 mg/day in patients &gt;75 yr of age)</td>
<td>4.8 (2.6–27.0)¹⁰</td>
<td>Nausea, vomiting, constipation, drowsiness, dizzi- ness, seizures</td>
<td>Same as with morphine and oxycodone; also, avoid concomitant use of SSRIs, SSNRIIs, tricyclic antidepressants</td>
</tr>
</tbody>
</table>

Suggested therapeutic ladder for treatment of post-herpetic neuralgia

Prevention of Post-Herpetic Neuralgia

Vaccination

- Childhood varicella vaccine
- VZ vaccines – FDA approved for individuals >= 50 years of age
  ◦ Life attenuated vaccine
  ◦ >14 times more potent than varicella vaccine
  ◦ Subcutaneously as a single dose
  ◦ Activates specific T-cell production
  ◦ Prevents viral reactivation
  ◦ Reduced the overall incidence of shingles by 51% and the incidence of PHN by 67%.
  ◦ The efficacy (reduction in risk of herpes zoster) was higher in the younger age group (60-69 years; vaccine efficacy was 64%) than in the older age group (older than 70 years; vaccine efficacy was 38%).

http://www.cdc.gov/vaccines/vpd-vac/shingles/hcp-vaccination.htm
Case - Post-Herpetic Neuralgia

- 55 YO female patient
  - Pain on the lower left posterior gingiva
  - Constant burning pain started after cleaning
  - Still painful for more than one month
  - Good dentition, good hygiene
Burning Mouth Syndrome (BMS)

- Burning sensation of the oral mucosa in the absence of clinically apparent mucosal alterations.
- Positive sensory symptoms: burning pain, dysgeusia, dysestheisa, dry mouth
- Negative sensory symptoms: loss of taste and paresthesia
- Affects the tongue (tip and lateral borders, anterior two third), lips, hard and soft palate, alveolar ridges
- Common in Female of 5th to 7th decades with female : male ratio of 3:1 to 16:1
- Around menopause (3 years before and 12 years after the onset of menopause)
- Prevalence: 0.7 – 7% of general population, up to 12 – 18% in post menopausal women

Burning Mouth Syndrome

A. Oral pain fulfilling criteria B and C
B. Recurring daily for >2 hours per day for >3 months
C. Pain has both of the following characteristics:
   1. burning quality
   2. felt superficially in the oral mucosa
D. Oral mucosa is of normal appearance and clinical examination including sensory testing is normal
E. Not better accounted for by another ICHD-3 diagnosis.

Burning Mouth Syndrome

International Association for the Study of Pain (IASP)

“Burning pain of the tongue or other oral mucous membrane persisting for at least four months and associated with normal oral mucosa and normal laboratory findings.”

• Burning sensation of the tongue or other oral mucosa
• Usually bilateral
• Associated with dysgeusia, dry mouth and denture intolerance

Classification and subtypes

• Three types according to clinical oral pain pattern
  • **Type 1 (35%)**: pain free waking, burning sensation develop in late morning and gradually increasing in severity during the day, reaching peak intensity by evening, usually linked to systemic disorders such as nutritional deficiency, diabetes mellitus
  • **Type 2 (55%)**: continuous symptom throughout the day, difficult to sleep, usually associated with psychological disorders
  • **Type 3 (10%)**: intermittent symptoms with pain free periods during the day, associated with allergic reactions

Classification and subtypes

- Scala et al.
  - Primary (essential or idiopathic with no organic cause)
  - Secondary (local, systemic or psychological factors)

- Three types according to pathophysiology of primary burning mouth
  - Small diameter fiber neuropathy (50 – 65%)
  - Subclinical lingual, mandibular or trigeminal system pathology (20 – 25%)
  - Central pain related to hypofunction of dopaminergic neurons in basal ganglia (20 – 40%)

Burning Mouth Syndrome

- Altered structure and function in the hippocampus and medial prefrontal cortex in patients with burning mouth syndrome
- 9 healthy control and 9 Clinical Type 1 BMS patients
- Record pain, anxiety and depression ratings
- Measured gray matter volume (GMV), white matter and resting state functional MRI
- Patients had increased GMV and lower FA in the hippocampus (Hc), and decreased GMV in the medial prefrontal cortex (mPFC).
- rsfMRI revealed altered connectivity patterns in different states of pain/burning
- mPFC-Hc connectivity was higher in BMS patients than control subjects for the afternoon but not the morning session.
- Evidence supporting aberrant structure and function in the medial prefrontal cortex and Hippocampus, and implicate a circuit involving these brain structures in regulating mood and depressive symptoms in BMS.

Burning Mouth Syndrome

Causes of burning mouth:
- Local oral causes
  - Candidiasis
  - Lichen planus
  - Herpetic infections
  - Parafuncional habits
- Systemic causes
  - ACE inhibitors
  - Drug reaction/alergy
  - Sjogren's syndrome
  - Nutritional deficiencies
  - Haematological causes

Psychological Factors

Burning Mouth Syndrome

<table>
<thead>
<tr>
<th>Diagnostic Test Used as Part of the BMS Diagnostic Process</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete blood cell count (CBC)</strong></td>
</tr>
<tr>
<td>This common blood test provides a count of each type of blood cell in a given volume of blood. The CBC measures the amount of hemoglobin, the percentage of blood that's composed of red blood cells (hematocrit), the number and kinds of white blood cells, and the number of platelets. This blood test may reveal a wide variety of conditions, including infections and anemia, which can indicate nutritional deficiencies.</td>
</tr>
<tr>
<td><strong>Other blood tests</strong></td>
</tr>
<tr>
<td>Because nutritional deficiencies are one cause of a burning mouth, running a test on the blood levels of iron, zinc, folate (vitamin B-9), thiamin (vitamin B-1), riboflavin (vitamin B-2), pyridoxine (vitamin B-6) and cobalamin (vitamin B-12) is important. Also, because diabetes causes neuropathic pain, a check may be done of the fasting blood sugar level.</td>
</tr>
<tr>
<td><strong>Allergy tests</strong></td>
</tr>
<tr>
<td>While it is not common, occasionally, testing to see if the patient may be allergic to certain foods, additives or even substances in dentures can be ordered through an allergist.</td>
</tr>
<tr>
<td><strong>Oral swab culture or cytologic smear</strong></td>
</tr>
<tr>
<td>If a fungal infection is suspected, a small tissue sample (biopsy) or an oral swab of the mouth for culture and examination may be ordered.</td>
</tr>
<tr>
<td><strong>Tongue tissue biopsy</strong></td>
</tr>
<tr>
<td>With the recent suggestion that small nerve fibers are depleted in the affected area, some special tests may be ordered when a biopsy is taken.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medications (class of drug)</th>
<th>Common dosage range</th>
<th>Prescription</th>
<th>Mechanisms of action; FDA approval status</th>
<th>Evidence basis for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nortriptyline (TCA)</td>
<td>10–75 mg/day</td>
<td>10 mg h.s.; increase dosage by 10 mg q4–7d until oral burning is relieved or side effects occur.</td>
<td>TCAs inhibit the activity of such diverse agents as histamine, 5-hydroxytryptamine, and acetylcholine. This drug is approved for use of the symptoms of depression, but is used off-label for neuropathic pain.</td>
<td>No published evidence for it in BMS, but it is used commonly for neuropathic pain.</td>
</tr>
<tr>
<td>Oral clonazepam (benzodiazepine)</td>
<td>0.25–2 mg/day</td>
<td>0.25 mg h.s.; increase dosage by 0.25 mg q4–7d until oral burning is relieved or side effects occur; as dosage increases, medication is taken as full dose or in three divided doses.</td>
<td>Mechanism is unknown, although it is believed to enhance the activity of GABA, the major inhibitory neurotransmitter in the CNS. This agent is approved by the FDA for seizures and for panic disorders. It is used off-label for neuropathic pain and BMS in particular.</td>
<td>Open clinical trials show some efficacy for BMS. No RBCT study (not exception below) is available.</td>
</tr>
<tr>
<td>Topical clonazepam (benzodiazepine)</td>
<td>1-mg tablet t.i.d., after meals</td>
<td>Let tablet dissolve and hold fluid in mouth in area of most intense burning for 3 minutes and then expectorate.</td>
<td>Same as for oral clonazepam</td>
<td>RBCT is available showing this approach is helpful in many BMS patients and is better than placebo.</td>
</tr>
<tr>
<td>Gabapentin (anticonvulsant)</td>
<td>300–2400 mg/day</td>
<td>100 mg h.s.; increase dosage by 100 mg q4–7d until oral burning is relieved or side effects occur; as dosage increases, taken in three divided doses</td>
<td>Anticonvulsant action is unknown; gabapentin is known to prevent seizures as do other marketed anticonvulsants. This drug is FDA approved for partial seizures and for PHN pain.</td>
<td>Case-report data suggests this agent may be helpful in some patients. No RBCT study performed.</td>
</tr>
<tr>
<td>Pregabalin (anticonvulsant)</td>
<td>100 mg p.o. t.i.d.</td>
<td>100 mg p.o. t.i.d.</td>
<td>This is a new drug that is being suggested for use in neuropathic pain patients. Its mechanism of action is thought to be similar to gabapentin. It is approved by the FDA as an adjunctive agent in adult patients with partial onset seizures and for PHN and diabetic neuropathy.</td>
<td>No data for BMS is yet available, but it should work similarly to gabapentin and is thought to have better pharmacokinetics. No RBCT study performed.</td>
</tr>
<tr>
<td>Topical lidocaine (anesthetic)</td>
<td>Viscous gel 2%</td>
<td>5mL q.i.d.; rinse for 2 minutes then expectorate</td>
<td>This agent is a sodium channel blocking agent and provides analgesic effects when applied topically. It is FDA approved as a topical anesthetic agent but its use is specified as an aid for minor surgeries or skin abrasions.</td>
<td>No data for BMS is yet available. No RBCT study performed.</td>
</tr>
<tr>
<td>Medications (class of drug)</td>
<td>Common dosage range</td>
<td>Prescription</td>
<td>Mechanisms of action; FDA approval status</td>
<td>Evidence basis for use</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>---------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Alpha-lipoic acid (antioxidant)</td>
<td>200mg t.i.d.</td>
<td>200mg t.i.d. for 2 months in association with gastroprotective</td>
<td>This agent is not a drug and it is described as an antioxidant. It is not regulated by the FDA and therefore requires no prescription because it is consider a nutritional supplement. The mechanism is unknown. The antidepressant and pain-inhibitory actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS. This agent is approved by the FDA for major depression and for treatment of diabetic neuropathic pain.</td>
<td>RBCT shows that this agent is helpful for BMS.</td>
</tr>
<tr>
<td>Duloxetine (serotonin, norepinephrine reuptake inhibitor)</td>
<td>60mg p.o. qd</td>
<td>Start with 30mg for 1 week then increase to 60mg qd</td>
<td>Mechanism is unknown. The antidepressant and pain-inhibitory actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS. This agent is approved by the FDA for major depression and for treatment of diabetic neuropathic pain.</td>
<td>No RBCT study performed so no data specific to BMS is available.</td>
</tr>
<tr>
<td>Tramadol (analgesic, non-narcotic)</td>
<td>50mg taken up to 4/day</td>
<td>50mg in the evening is the starting dose, if needed the dose can be increased up to 4 tablets per day or more (depending on side effects).</td>
<td>While it is classified as a nonopioid medication, most consider tramadol as an opioid because it does bind to opioid receptors. It also inhibits reuptake of norepinephrine and serotonin similar to TCAs. It is FDA approved for moderate to severe pain relief.</td>
<td>One RBCT study showed that tramadol was ineffective for BMS.</td>
</tr>
<tr>
<td>Hydrocodone (narcotic analgesic)</td>
<td>5mg/500mg</td>
<td>One tablet q6h</td>
<td>Used primarily for chronic pain control. It is FDA approved for moderate to severe pain relief.</td>
<td>No RBCT study performed so no data specific to BMS is available.</td>
</tr>
<tr>
<td>Olanzapine (atypical antipsychotic agent)</td>
<td>5mg/day</td>
<td>5mg once a day</td>
<td>Antipsychotics decrease unusually high levels of brain activity. This drug is FDA approved for schizophrenia.</td>
<td>Obviously this is a powerful pain-relieving agent.</td>
</tr>
<tr>
<td>Amisulpride (atypical antipsychotic agent)</td>
<td>50mg/day</td>
<td>50-mg tablets up to t.i.d.; maximum dose not to exceed 400mg/day</td>
<td>Same as for olanzapine, but not available in the United States.</td>
<td>Only a single case report has reported it is helpful for BMS. No RBCT study performed to date.</td>
</tr>
</tbody>
</table>

Burning Mouth Syndrome

- Cognitive behavior therapy (one/week for 12 – 15 weeks)
- Alpha-lipoic acid (600mg/day) more effective if combine with psychotherapy
- Clonazepam (0.25 to 0.5mg topical or systemic once a day to three times daily)

Notes
- Systemic clonazepam should not be use in older patients with fall risks
- Very long duration of action

The main characteristics of the most common chronic non-dental pains and their management

<table>
<thead>
<tr>
<th>Post traumatic trigeminal neuropathy</th>
<th>Burning mouth syndrome</th>
<th>Temporomandibular disorders</th>
<th>Trigeminal neuralgia</th>
<th>Persistent idiopathic facial pain</th>
<th>Trigeminal post herpetic neuralgia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td>becoming increasingly common</td>
<td>rare</td>
<td>common</td>
<td>rare</td>
<td>rare</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>3-6 months of traumatic event</td>
<td>slow</td>
<td>sometimes starts abruptly</td>
<td>memenabr, sudden</td>
<td>slow post herpetic zoster</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>continuous with minor fluctuations, some have intermittent episodes</td>
<td>continuous</td>
<td>often constant</td>
<td>intermittent seconds to minutes</td>
<td>constant</td>
</tr>
<tr>
<td><strong>Periodicity</strong></td>
<td>constant</td>
<td>can vary throughout the day</td>
<td>fluctuations often worse in evening</td>
<td>refractory periods, many attacks a day periods of complete remission weeks, months</td>
<td>constant</td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td>distribution of a nerve branch, tooth or tooth bearing area</td>
<td>tongue, lips, palate</td>
<td>masseter, temporals, around TMJ area, retromolar area</td>
<td>V2, V3 most common intracranial and extra oral</td>
<td>non anatomical, gradually gets larger</td>
</tr>
<tr>
<td><strong>Radiation</strong></td>
<td>nil</td>
<td>all parts of the oral mucosa</td>
<td>may radiate to neck</td>
<td>only within trigeminal distribution</td>
<td>can spread over whole face, head, upper oral</td>
</tr>
<tr>
<td><strong>Character</strong></td>
<td>dull burning, tingling, pins and needles at times sharp</td>
<td>burning, stinging, sore</td>
<td>aching, heavy, deep, can be sharp</td>
<td>sharp, shooting, lightening may be a dull ache, burning after pain</td>
<td>dull, nagging, can be sharp</td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td>moderate to severe</td>
<td>mild to severe</td>
<td>variable, moderate to severe</td>
<td>moderate to severe</td>
<td>moderate to severe</td>
</tr>
<tr>
<td><strong>Aggravating factors</strong></td>
<td>touch</td>
<td>sometimes certain food,</td>
<td>prolonged chewing, opening wide, jaw movements</td>
<td>light touch, eating, some attacks are spontaneous</td>
<td>light touch, eating, some attacks are spontaneous</td>
</tr>
<tr>
<td><strong>Associated factors</strong></td>
<td>may be altered sensation, reduced quality of life, altered taste, dry mouth, depression, anxiety, poor quality of life</td>
<td>clenching, bruxism, may have clicking of TMJ, locking, reduced opening, headaches, migraines</td>
<td>very rare autonomic features, fear of pain return, depression, poor quality of life</td>
<td>often other chronic pain, significant life events, vulnerable personalites</td>
<td>may be altered sensation, skin changes</td>
</tr>
<tr>
<td><strong>Examination</strong></td>
<td>allodynia, hyperesthesia</td>
<td>nil, sometimes geographic tongue</td>
<td>palpation of muscles/joint induces same pain, unassisted reduced opening, clicking uncommonly evidence of frictional keratitis in cheeks, attrition of teeth</td>
<td>may trigger attack on touch, very rare sensory changes</td>
<td>nil, allodynia, hyperesthesia, hyperesthesia</td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td>drugs for neuropathic pain may benefit from CBT</td>
<td>neuropathic drugs, clozapine, CBT</td>
<td>education, physiotherapy, psychology, anti-inflammavory drugs</td>
<td>carbamazepine, oxcarbazepine, neurosurgical procedures</td>
<td>CBT, antidepressant drugs</td>
</tr>
<tr>
<td><strong>CBT</strong></td>
<td>cognitive behaviour therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Thank you!

phuuhan@usc.edu