Post Traumatic Neuropathic Pain

Oral Surgery
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Early intervention is suggested to be important in patients with pain to prevent development of chronicity.[3]

Macfarlane GJ. The epidemiology of chron
pain. *PAIN* 2016;157:2158–9.

Thus, psychosocial factors have been shown to have a strong association with the development and persistence of orofacial pain[13,44] and common comorbidities in chronic pain conditions. In light of reports of increasing prevalence of psychosocial factors such as stress, depression, and anxiety in the general population, especially in young adults and adolescents,[46] it is reasonable to assume that this trend may also be reflected as an increase in the prevalence of orofacial pain.

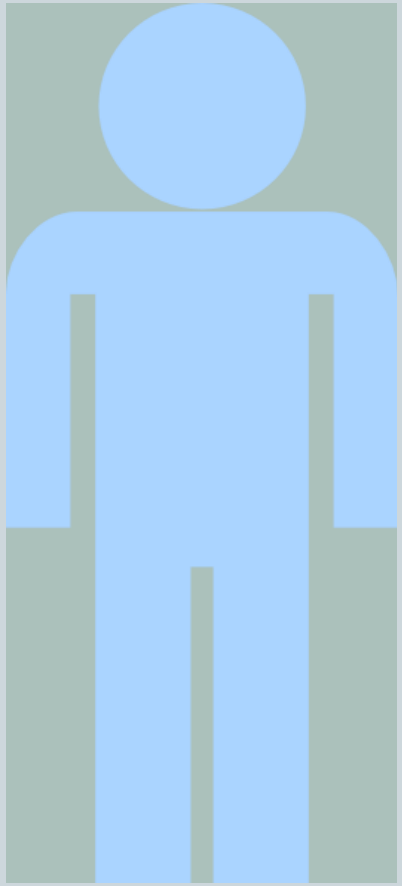
13 Fillingim RB, Slade GD, Greenspan JD, Dubner R, Maixner W, Bair E, Ohrbach R. Long-term changes in biopsychosocial characteristics related to temporomandibular disorder: findings from the OPPERA study. *PAIN* 2018;159:2403–13.

44. Slade GD, Ohrbach R, Greenspan JD, Fillingim RB, Bair E, Sanders AE, Dubner R, Diatchenko L, Meloto CB, Smith S, Maixner W. Painful temporomandibular disorder: decade of discovery from OPPERA studies. *J Dent Res* 2016;95:1084–92.

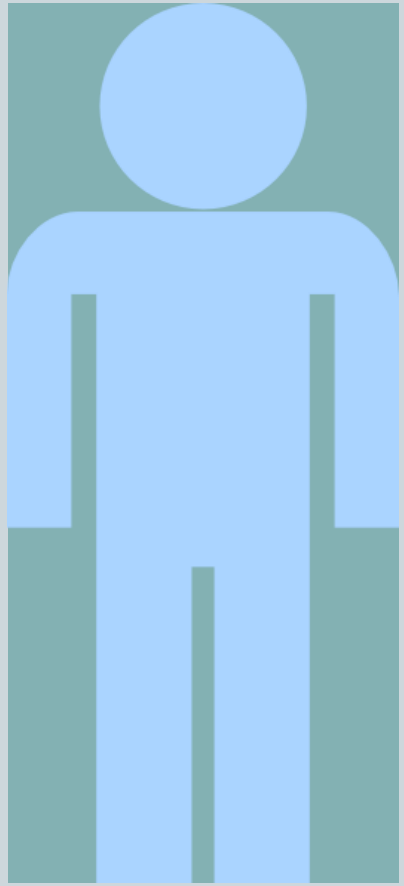
46. Twenge JM, Cooper AB, Joiner TE, Duffy ME, Binau SG. Age, period, and cohort trends in mood disorder indicators and suicide-related outcomes in a nationally representative dataset, 2005-2017. *J Abnorm Psychol* 2019;128:185–99.

Overview

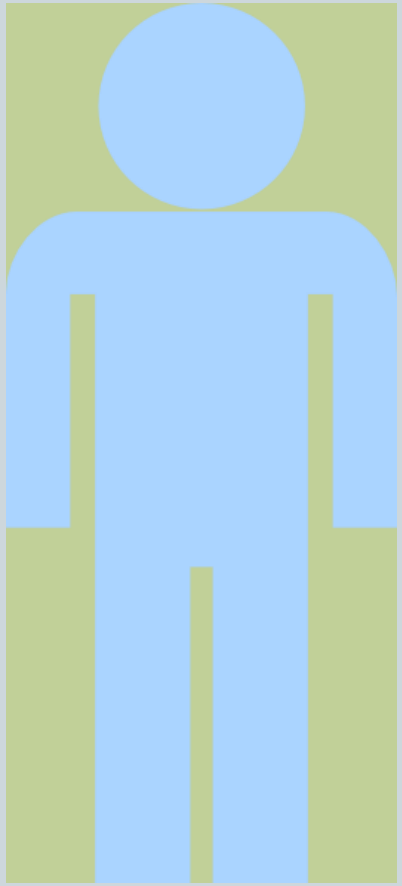
Neuropathic pain
Definitions &
Diagnosis



Neuropathic pain
Classification &
Trigeminal presentation



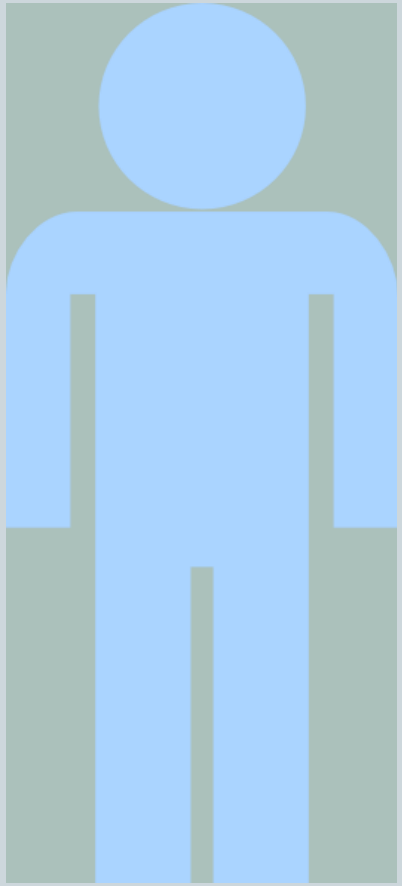
Neuropathic pain
prevention of
nerve injuries



Prognosis and
outcome &
management

Overview

Neuropathic pain
Definitions &
Diagnosis



Neuropathic pain
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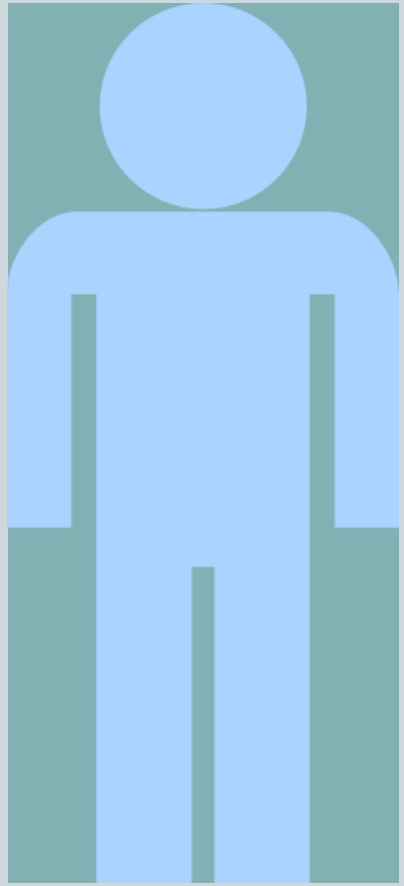

Neuropathic pain
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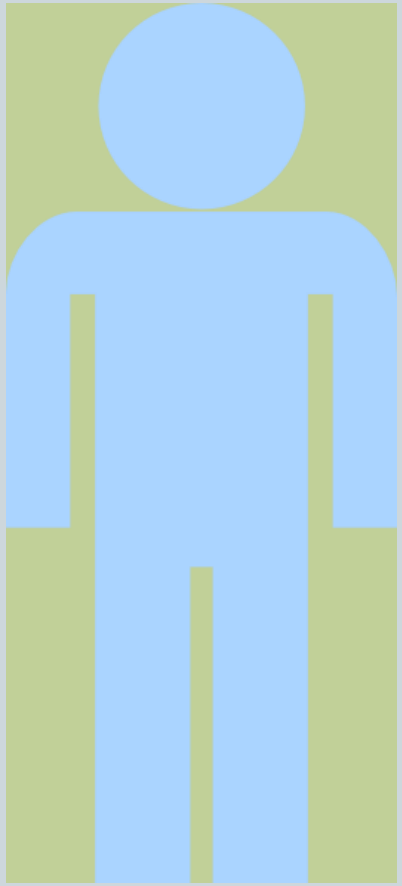
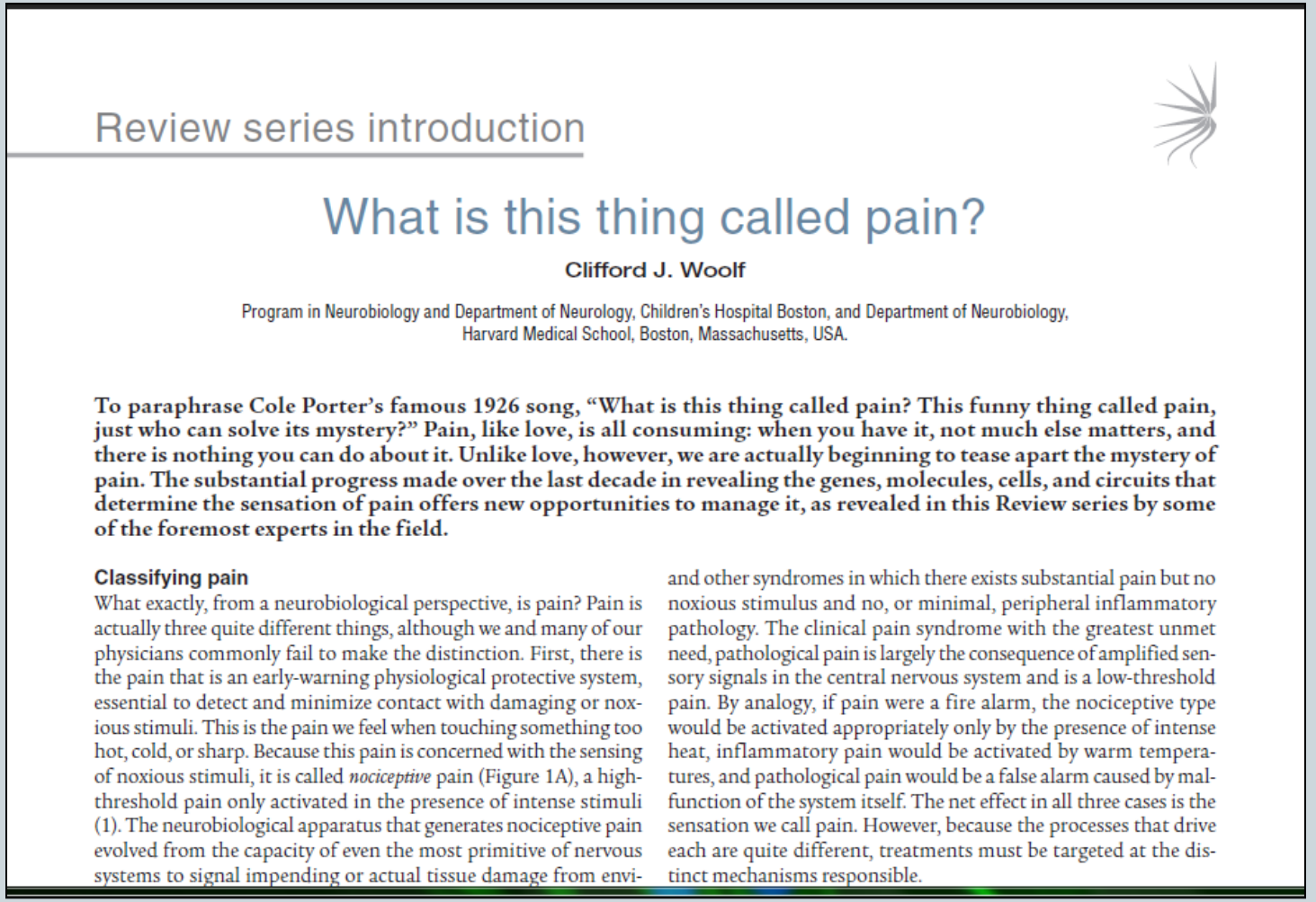


Prognosis and
outcome &
management

Definitions Mechanistic and Temporal Types of Pain……



Review series introduction

What is this thing called pain?

Clifford J. Woolf

Program in Neurobiology and Department of Neurology, Children's Hospital Boston, and Department of Neurobiology, Harvard Medical School, Boston, Massachusetts, USA.

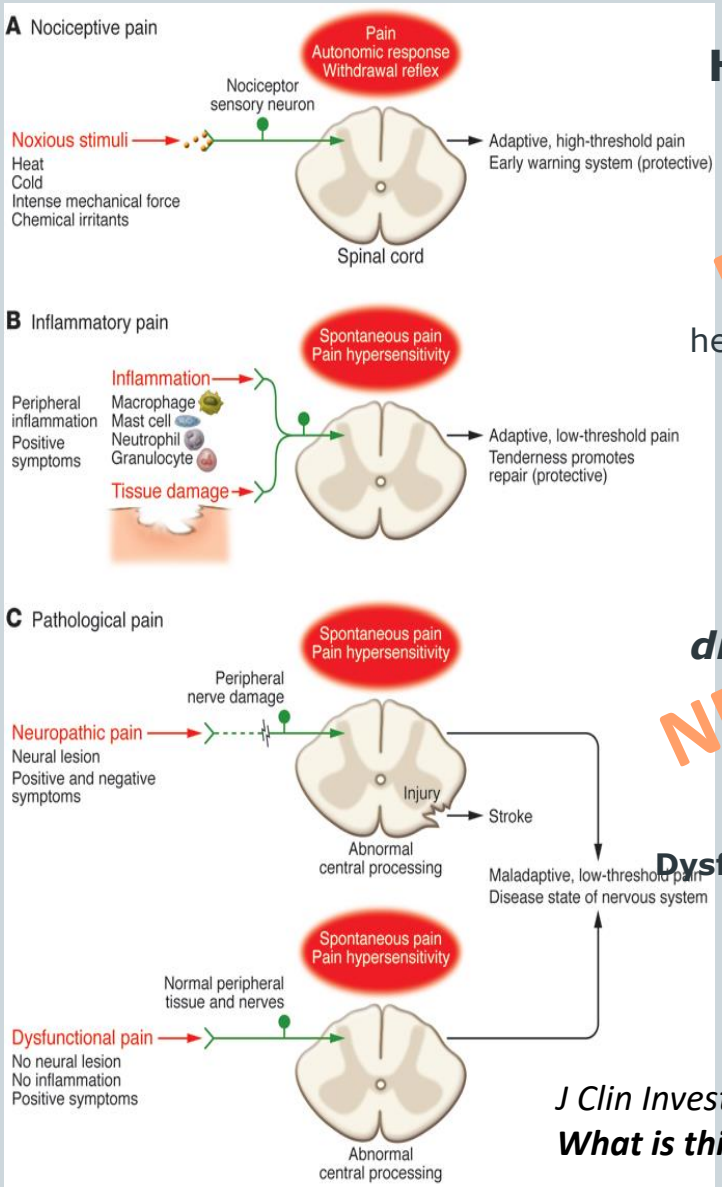
To paraphrase Cole Porter's famous 1926 song, "What is this thing called pain? This funny thing called pain, just who can solve its mystery?" Pain, like love, is all consuming: when you have it, not much else matters, and there is nothing you can do about it. Unlike love, however, we are actually beginning to tease apart the mystery of pain. The substantial progress made over the last decade in revealing the genes, molecules, cells, and circuits that determine the sensation of pain offers new opportunities to manage it, as revealed in this Review series by some of the foremost experts in the field.

Classifying pain

What exactly, from a neurobiological perspective, is pain? Pain is actually three quite different things, although we and many of our physicians commonly fail to make the distinction. First, there is the pain that is an early-warning physiological protective system, essential to detect and minimize contact with damaging or noxious stimuli. This is the pain we feel when touching something too hot, cold, or sharp. Because this pain is concerned with the sensing of noxious stimuli, it is called *nociceptive* pain (Figure 1A), a high-threshold pain only activated in the presence of intense stimuli (1). The neurobiological apparatus that generates nociceptive pain evolved from the capacity of even the most primitive of nervous systems to signal impending or actual tissue damage from envi-

and other syndromes in which there exists substantial pain but no noxious stimulus and no, or minimal, peripheral inflammatory pathology. The clinical pain syndrome with the greatest unmet need, pathological pain is largely the consequence of amplified sensory signals in the central nervous system and is a low-threshold pain. By analogy, if pain were a fire alarm, the nociceptive type would be activated appropriately only by the presence of intense heat, inflammatory pain would be activated by warm temperatures, and pathological pain would be a false alarm caused by malfunction of the system itself. The net effect in all three cases is the sensation we call pain. However, because the processes that drive each are quite different, treatments must be targeted at the distinct mechanisms responsible.

Types of pain –mechanistic and duration



Healthy acute pain

Nociceptive
healthy feeling pain 'pain'

NOCICEPTIVE

Inflammatory pain
healthy short lived after insult

Chronic pain = disease of neuromatrix

NEUROPATHIC

Neuropathic pain
Associated with nerve lesion

Dysfunctional or centralised pain
Unknown cause

NOCIPLASTIC

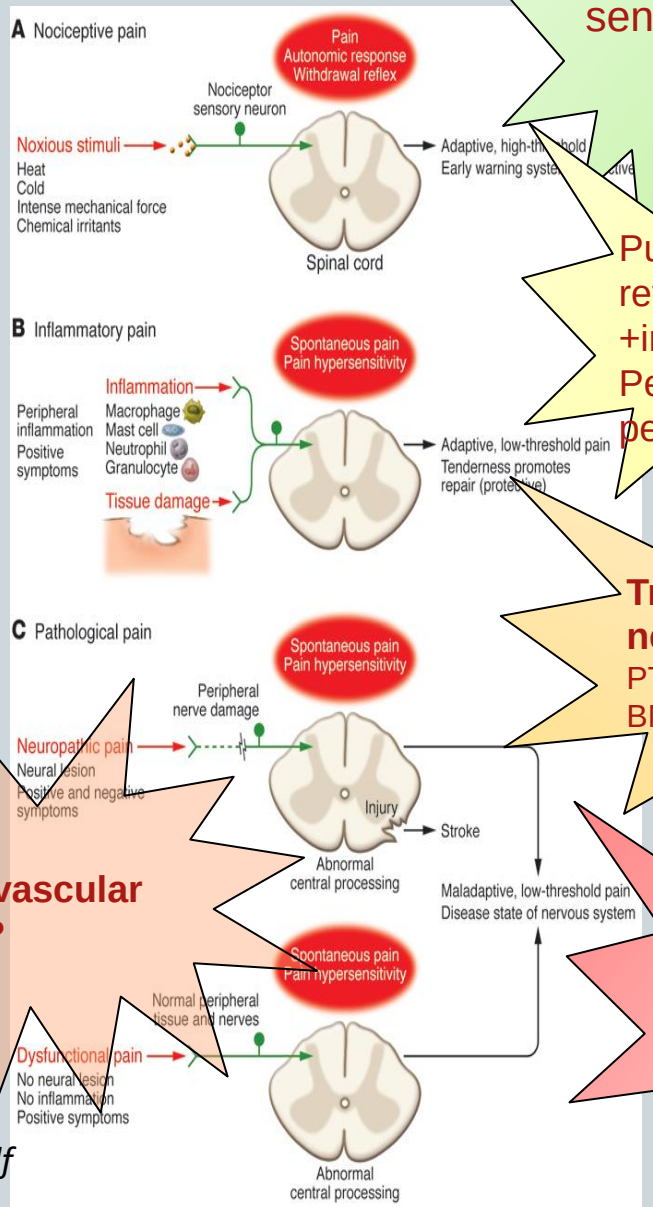
?? Neurovascular pain??

Dentine sensitivity

Pulpitis reversible +irreversible
Periapical periodontitis

Trigeminal neuropathic pain
PTN, CPSP, 2y TN, BMS, PDAP/ PHN

Fibromyalgia
PIFP
TMD
arthromyalgia
?



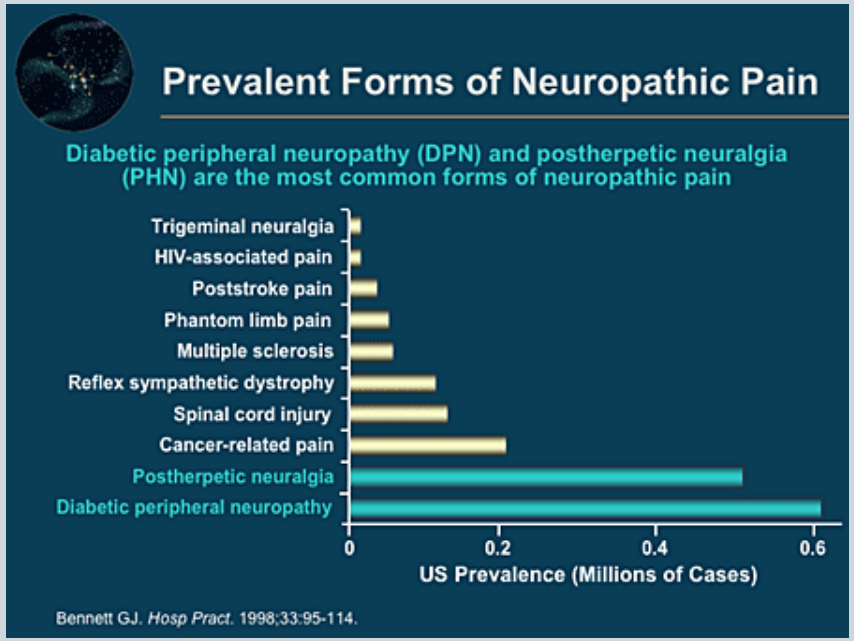
J Clin Invest. 2010 Nov 1; 120(11): 3742–3744.
What is this thing called pain? *Clifford J. Woolf*

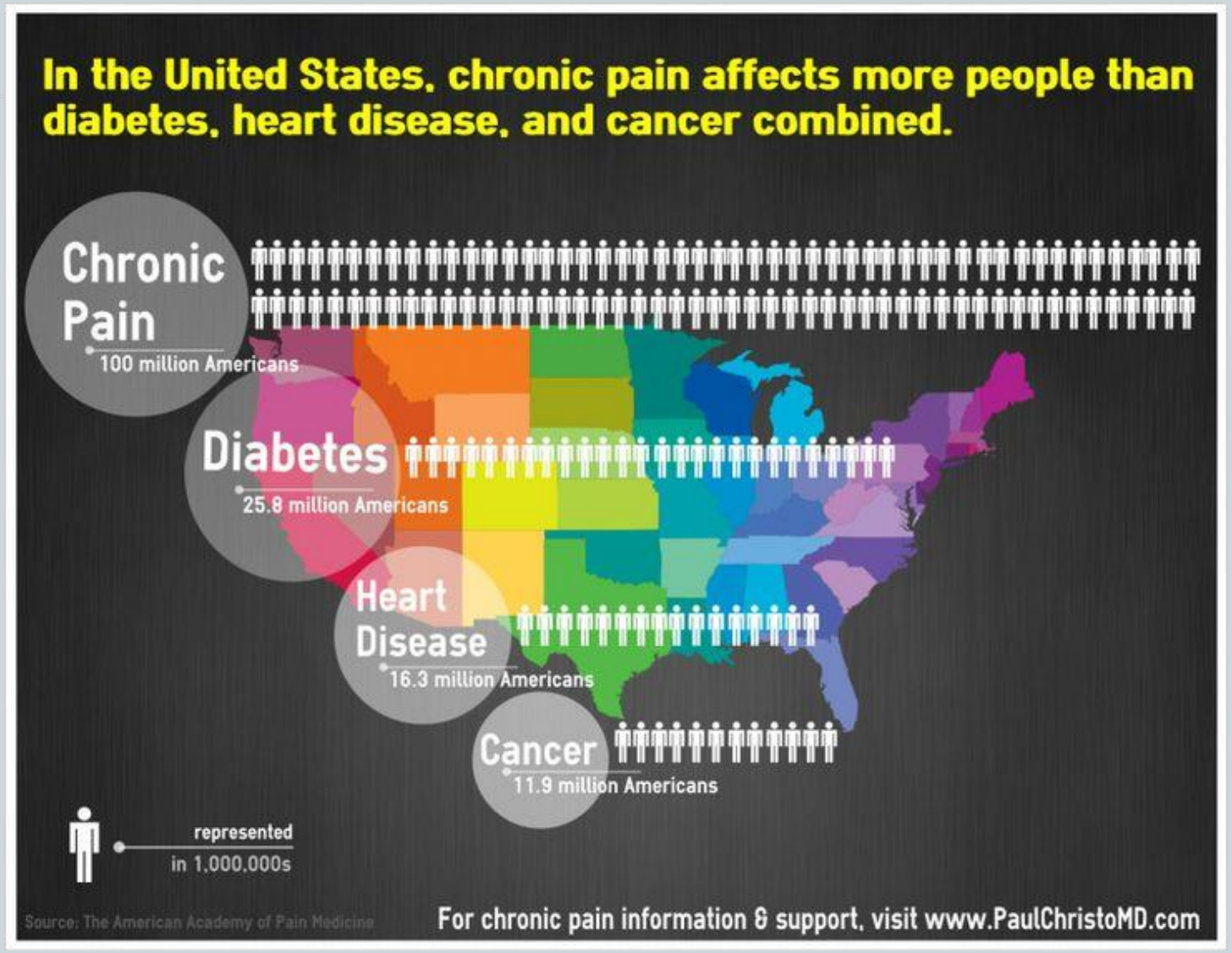
Prevalence of chronic pain

About 1 in 3 Americans experience chronic pain.

Of those, 1 in 5 experience neuropathic pain.

A 2014 study estimated that as many as 10 percent of Americans experience some form of neuropathic pain.





O. van Hecke, Sophie K. Austin, Rafi A. Khan, B.H. Smith, N. Torrance,Neuropathic pain in the general population: A systematic review of epidemiological studies, PAIN®, Volume 155, Issue 4,2014,Pages 654-662,SSN 0304-3959 https://doi.org/10.1016/j.pain.2013.11.013

Prevalence/ Incidence of OFP diagnoses

Common things happen commonly

Toothache Prevalence estimates for 5 case definitions identified were: 'toothache' 7-32%, 'pain in teeth with hot, cold or sweet things' **25-38%, 'pain and discomfort needing medication or treatment' 7-9%, 'pain or discomfort in the mouth, teeth or gums' 19-66%, and 'oral and facial pain'40-44%.** Pau AK, Croucher R, Marcenes W Prevalence estimates and associated factors for dental pain: a review. Oral Health Prev Dent.2003;1(3):209-20

Tension type headache Episodic TTH,occurring on fewer than 15 days per month, is reported by more than **70% of some populations.** http://www.who.int/mediacentre/factsheets/fs277/en/

Migraines 22.7% in the National Health and Nutrition Examination Survey, 16.6% of adults 18 or older reported having migraine or other severe headaches in the last 3 months in the 2011 National Health Interview Survey. In contrast, the AMPP study found an overall prevalence of migraine of 11.7% and probable migraine of 4.5%, for a total of 16.2%. Smitherman TA, Burch R, Sheikh H, Loder E.The prevalence, impact, and treatment of migraine and severe headaches in the United States: a review of statistics from national surveillance studies. Headache. 2013 Mar;53(3):427-36. doi: 10.1111/head.12074. Epub 2013 Mar 7.

Pain from TMD Males / Females **6.7% / 12.4%** Johansson et al2002

Post traumatic Painful neuropathic pain/ Chronic post surgical V pain

0.01-20% of patients undergoing third molar surgery/ **1:14-54k** post LA block / ? Post Implants

PDAP 1.6% -5%

Burning Mouth Syndrome prevalence 0.1% [**Incidence over 55 years (3.7%), 11 men (1.6%) and 42 women (5.5%)]** Bergdahl M Bergdahl J Burning mouth syndrome: prevalence and associated factors. J Oral Pathol Med. 1999 Sep;28(8):350-4.

Non traumatic secondary neuropathy???

Trigeminal neuralgia General population **0.1% and 0.3%,** although studies carried out in primary care settings suggest that it may be much higher, around 12% per 100,000 persons per year http://www.iasp-pain.org/files/Content/ContentFolders/GlobalYearAgainstPain2/20132014OrofacialPain/FactSheets/Trigeminal_Neuralgia.pdf

Fayaz et al 2016; Renton 2015; Nixdorf & Moano-Filho 2011;Kohorst etal 2015;Mueller et al 2015

Prevalence/ Incidence of OFP diagnoses

Neuropathic pain is rare but preventable in many cases

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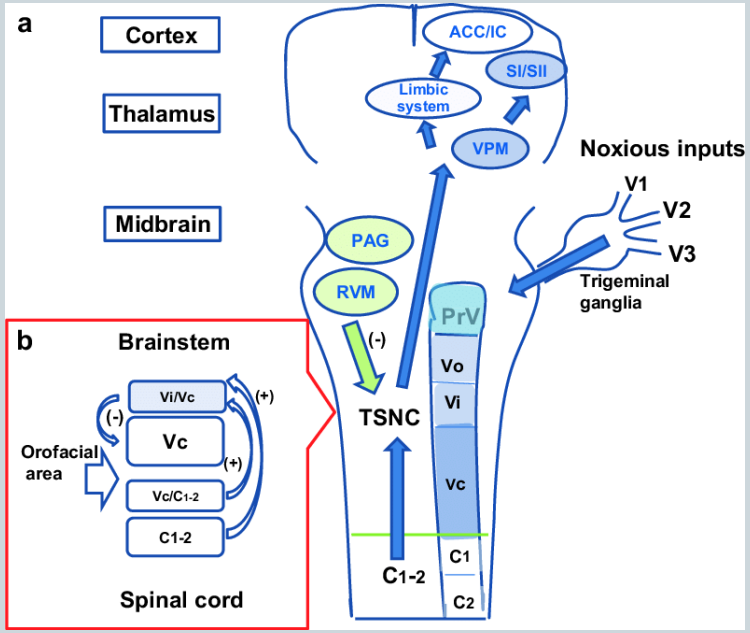
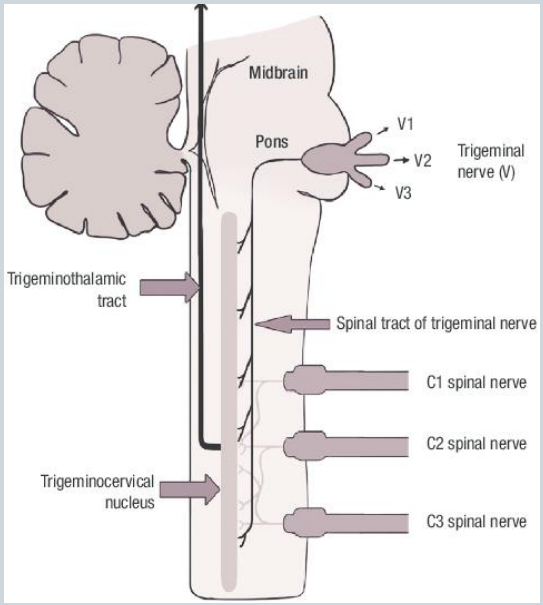
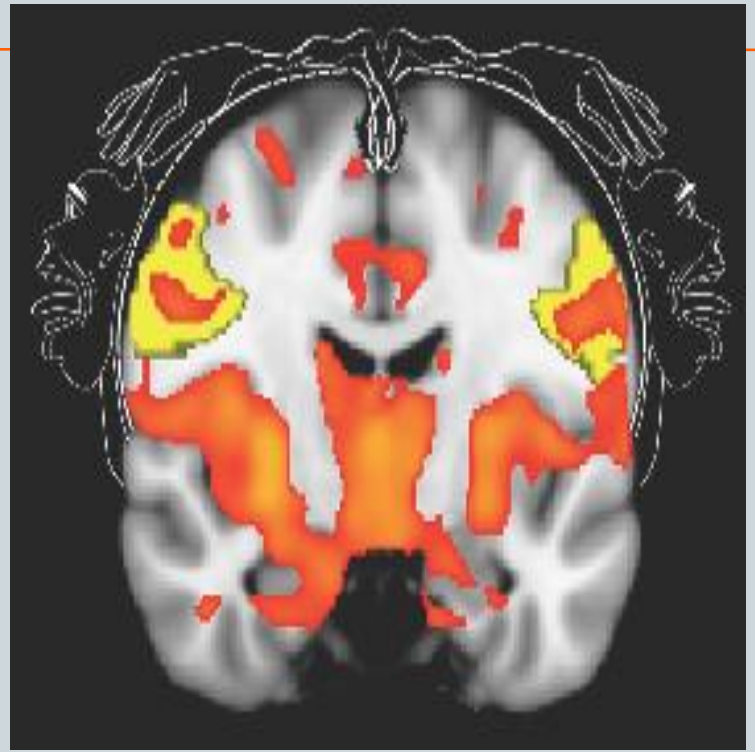
The problem complexity of the Trigeminal nerve

- 50% Homunculus – sensory cortex
- Substantial Limbic component in V pain
- Trigemino-cervical complex
- Significant Autonomic input- Vagus
- Trigemino-vascular complex







On a Pain Scale of 1 to 10, Trigeminal Neuralgia Can Feel Like 11

Significantly higher affective component to trigeminal pain

- Noxious stimuli experienced by the head and facial region are detected and conveyed to the central nervous system (CNS) by sensory neurons located in the trigeminal (TG) ganglia, whereas noxious stimuli affecting extracranial regions are sensed and relayed to the CNS via primary sensory neurons residing in the dorsal root ganglia (DRG)

- Humans generally rank head and facial pain as much more severe and emotionally draining than body pain. For example, two of the arguably most severe chronic pain conditions are trigeminal neuralgia and cluster headaches1–3 .

- Craniofacial pain sensation is qualitatively different from bodily nociception as shown in human experiments, where repeated application of noxious heat to the face induces sensitization, yet similar stimulation applied to the hand induced habituation4 .

- Fear induced by pain in human subjects was rated higher for face than for extremities, despite comparable ratings of the pain intensity5 .
- fMRI studies further revealed that face pain resulted in higher levels of amygdala activation compared to the same intensity stimulation applied to the hand6 .

1. Waldman, SD. Atlas of common pain syndromes. Elsevier Health Sciences; 2011. 2. Zakrzewska JM, Wu J, Williams MM, Phillips N, Pavitt SH. Evaluating the impact of trigeminal neuralgia. Pain. 2017 3. Smith JG, et al. The psychosocial and affective burden of posttraumatic neuropathy following injuries to the trigeminal nerve. Journal of orofacial pain. 2013; 27:293–303. [PubMed: 24171179] 4. Schmidt K, Schunke O, Forkmann K, Bingel U. Enhanced Short-Term Sensitization of Facial Compared With Limb Heat Pain. The Journal of Pain. 2015; 16:781–790. [PubMed: 26043953] 5. Schmidt K, et al. The differential effect of trigeminal vs. peripheral pain stimulation on visual processing and memory encoding is influenced by pain-related fear. NeuroImage. 2016; 134:386– 395. [PubMed: 27015710] Moulton EA, et al. Capsaicin-induced thermal hyperalgesia and sensitization in the human trigeminal nociceptive pathway: An fMRI study. NeuroImage. 2007; 35:1586–1600. [PubMed: 17407825]

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A craniofacial-specific monosynaptic circuit enables heightened affective pain

Erica Rodriguez[1], **Katsuyasu Sakurai**[1], **Jennie Xu**[1], **Yong Chen**[2], **Koji Toda**[3], **Shengli Zhao**[1], **Bao-Xia Han**[1], **David Ryu**[1], **Henry Yin**[3], **Wolfgang Liedtke**[2], and **Fan Wang**[1,*]

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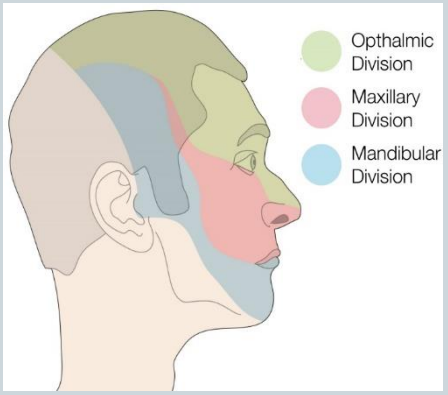
Abstract

Humans often rank craniofacial pain as more severe than body pain. Evidence suggests that a stimulus of the same intensity induces stronger pain in the face than the body. However, the underlying neural circuitry for the differential processing of facial versus bodily pain remains unknown. Interestingly, the lateral parabrachial nucleus (PB_L), a critical node in the affective pain circuit, is activated more strongly by noxious stimulation of the face than the hindpaw. Using a novel activity-dependent technology called CANE developed in our lab, we identified and selectively labeled noxious stimuli-activated PB_L neurons, and performed comprehensive anatomical input-output mapping. Surprisingly, a hitherto uncharacterized monosynaptic connection between cranial sensory neurons and the PB_L-nociceptive neurons was uncovered. Optogenetic activation of this monosynaptic craniofacial-to-PB_L projection induced robust escape/avoidance behaviors and stress calls, whereas optogenetic silencing specifically reduced facial nociception. The monosynaptic circuit revealed here provides a neural substrate for heightened

The problem of the significant burden of Trigeminal Pain

- V is the great protector
- Sensory Feedback for all craniofacial functions
  - Eyes
  - Part Meninges
  - Nose
    - Airway
  - Face
    - Expression and communication
  - Mouth
    - Breathing
    - Speaking
    - Eating



Underpins our own identity and pleasurable experiences in life

Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology
ELSEVIER
Volume 123, Issue 1, January 2017, Pages 58-66

Oral medicine

The impact of chronic orofacial pain on daily life: the vulnerable patient and disruptive pain

Yaron Haviv DMD, PhD [a], Avraham Zini DMD, PhD, MPH [b], Yoni Etzioni DMD [c], Valeri Klitinich DMD [a], Alex Dobriyan DMD, MHA [d, e], Yair Sharav DMD, MS [a], Rafael Benoliel BDS, LDS, RCS [f], Galit Almoznino DMD, MSc, MHA [a, g]

JOURNAL OF ORAL REHABILITATION

REVIEW | Open Access

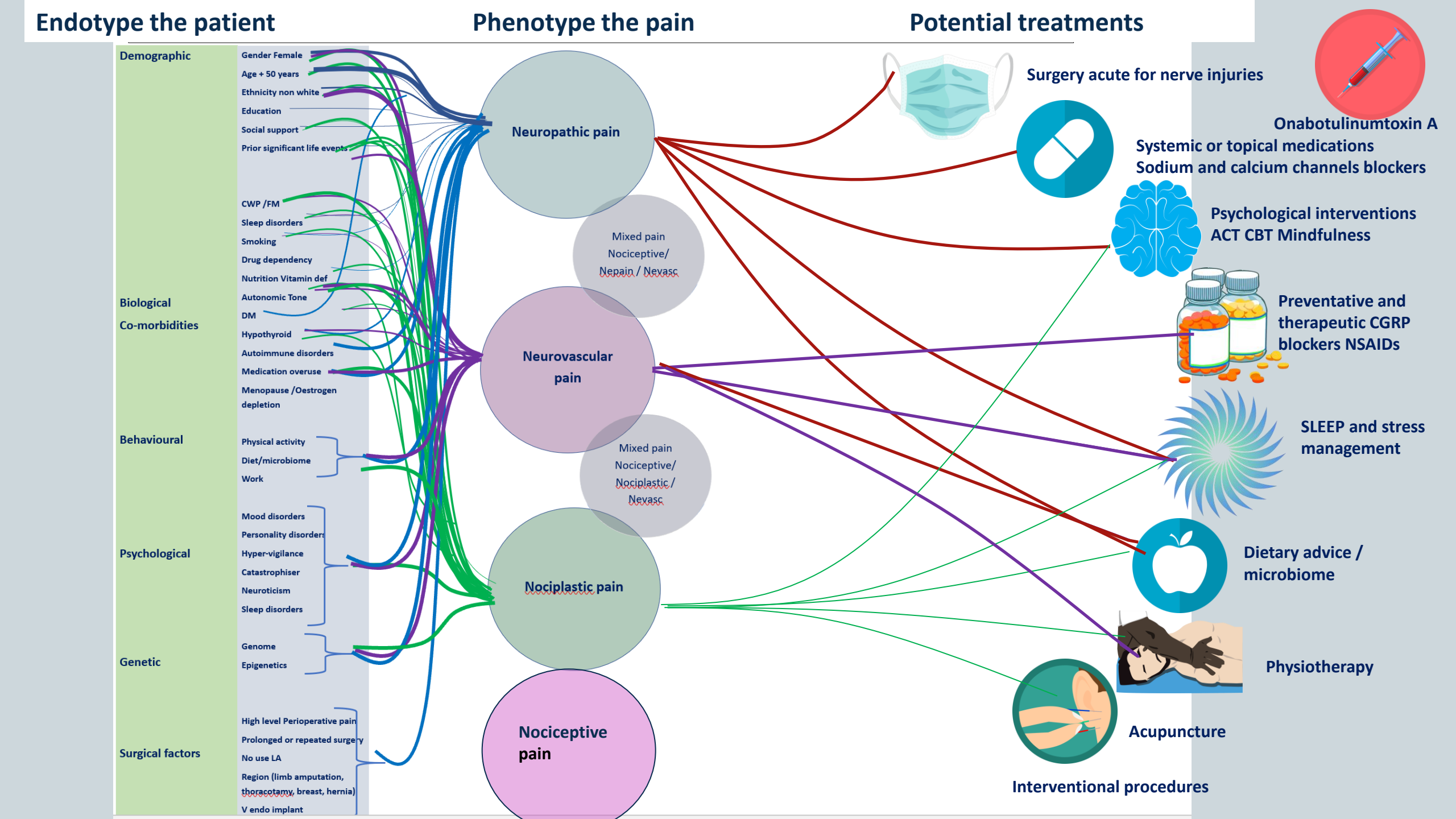
The impact of oro-facial pain conditions on oral health-related quality of life: A systematic review

Ibrahim Oghli, Thomas List, Naichuan Su, Birgitta Häggman-Henrikson

First published: 16 May 2020 | https://doi.org/10.1111/joor.12994 | Citations: 1

Scandinavian Center for Orofacial Neurosciences: http://www.sconresearch.eu/
The peer review history for this article is available at https://publons.com/publon/10.1111/joor.12994

How do we optimise treating our patients?


Endotype the patient
Phenotype the pain
Potential treatments
Demographic
Gender Female
Age + 50 years
Ethnicity non white
Education
Social support
Prior significant life events
Biological
Co-morbidities
CWP /FM
Sleep disorders
Smoking
Drug dependency
Nutrition Vitamin def
Autonomic Tone
DM
Hypothyroid
Autoimmune disorders
Medication overuse
Menopause /Oestrogen depletion
Behavioural
Physical activity
Diet/microbiome
Work
Psychological
Mood disorders
Personality disorders
Hyper-vigilance
Catastrophiser
Neuroticism
Sleep disorders
Genetic
Genome
Epigenetics
Surgical factors
High level Perioperative pain
Prolonged or repeated surgery
No use LA
Region (limb amputation, thoracotamy, breast, hernia)
V endo implant
Neuropathic pain
Mixed pain Nociceptive/ Nepain / Nevasc
Neurovascular pain
Mixed pain Nociceptive/ Nociplastic / Nevasc
Nociplastic pain
Nociceptive pain
Surgery acute for nerve injuries
Onabotulinumtoxin A
Systemic or topical medications
Sodium and calcium channels blockers
Psychological interventions
ACT CBT Mindfulness
Preventative and therapeutic CGRP blockers NSAIDs
SLEEP and stress management
Dietary advice / microbiome
Physiotherapy
Acupuncture
Interventional procedures

Correct diagnosis involves…….

Phenotyping the pain

- Site
- Onset
- Pain characteristics
- Radiation
- Associated factors
- Timing Frequency Duration
- Exacerbating and relieving factors
- Severity
- Quantitative sensory testing
- Endogenous pain (CPM offset)
- Response to Pharmacologic challenge

Correct treatment planning involves……..

Endotyping the patient

Demographics
Age, gender, ethnicity, social, education

Culture, Religion, Beliefs, Previous significant life events

Psychological
Mood disorders, personality disorders

Lifestyle
Diet, exercise, smoking, alcohol, caffiene

Comorbid pain conditions

Sleep disorders

Microbiome

Endogenous pain (CPM offset)
HRV

Medicine sensitivity

Endotype the patient

Phenotype the pain

Potential treatments

Demographic
- Gender Female
- Age + 50 years
- Ethnicity non white
- Education
- Social support
- Prior significant life events

Biological Co-morbidities
- CWP /FM
- Sleep disorders
- Smoking
- Drug dependency
- Nutrition Vitamin def
- Autonomic Tone
- DM
- Hypothyroid
- Autoimmune disorders
- Medication overuse
- Menopause /Oestrogen depletion

Behavioural
- Physical activity
- Diet/microbiome
- Work

Psychological
- Mood disorders
- Personality disorders
- Hyper-vigilance
- Catastrophiser
- Neuroticism
- Sleep disorders

Genetic
- Genome
- Epigenetics

Surgical factors
- High level Perioperative pain
- Prolonged or repeated surgery
- No use LA
- Region (limb amputation, thoracotomy, breast, hernia)
- V endo implant

Neuropathic pain

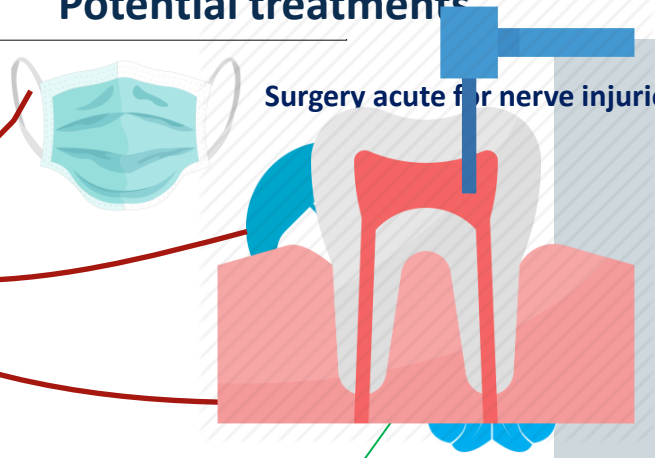
Mixed pain Nociceptive/ Nepain / Nevasc

Neurovascular pain

Mixed pain Nociceptive/ Nociplastic Nevasc

Nociplastic pain

Dental Nociceptive pain



Restorative Care

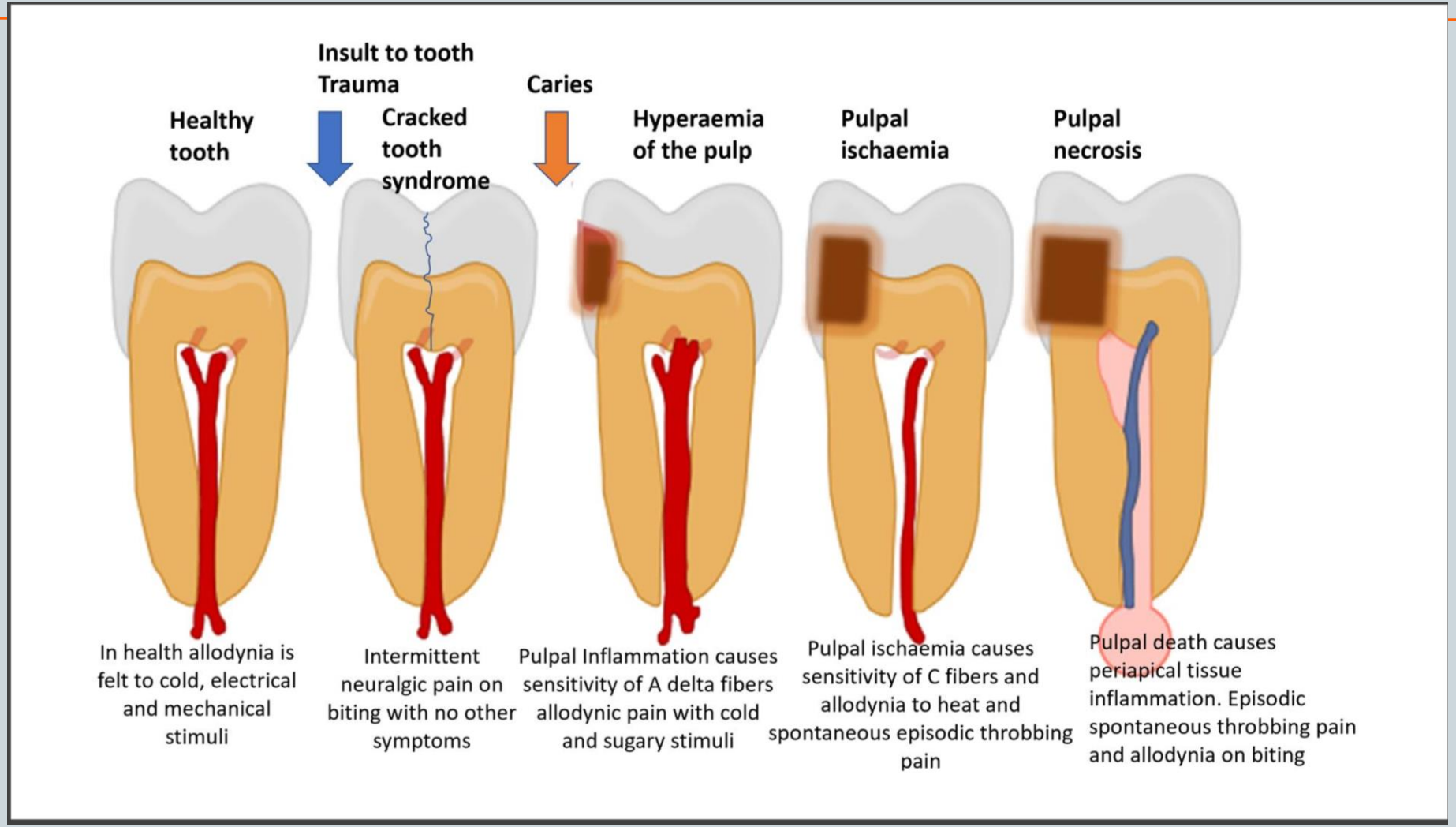
Analgesics and antibiotics

SLEEP and stress management

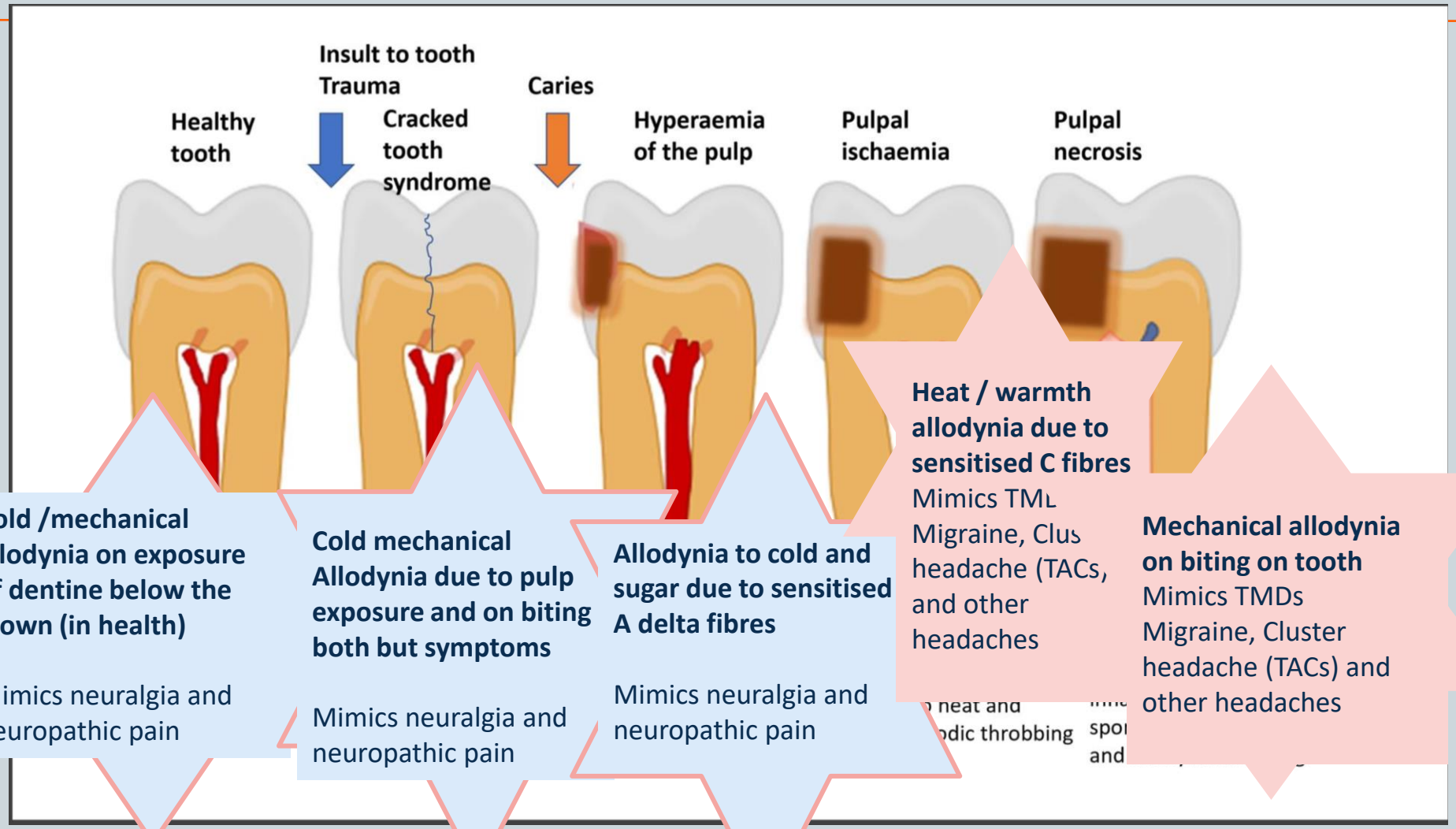
Dietary advice / microbiome

Root canal

Differential Diagnosis Toothache



Differential Diagnosis Toothache



So how do we differentiate between Nociceptive and Neuropathic pain?

What is neuropathic pain?

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Neuropathic pain

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Author contributions

Colloca L, Ludman T, Bouhassira D, Baron R, Dickenson AH, Yarnitsky D, Freeman R, Truini A, Attal N, Finnerup NB, Eccleston C, Kalso E, Bennett DL, Dworkin RH, Raja SN. Neuropathic pain. Nat Rev Dis Primers. 2017 Feb 16;3:17002. doi: 10.1038/nrdp.2017.2. PMID: 28205574; PMCID: PMC5371025.

Definition and Prevalence of neuropathic pain

Neuropathic pain (NP) is a pain caused by damage or disease affecting the somatosensory system.

Peripheral nervous system disorders include diseases of the spinal nerve roots, dorsal root ganglia, and peripheral nerves
(outside brain or spinal column).

Classical examples include;
Diabetic neuropathy
Polyneuropathies
Postherpetic neuralgia
Trigeminal neuralgia
Post traumatic neuropathy

- NP is estimated to afflict as much as **7%–8% of the general population in Europe.**
- An American study showed that **1/3 of patients affected by malignancies suffered from NP** or a mix of NP and nociceptive pain.
- The Canadian Pain Society developed treatment guidelines of CPNP and **estimated a 2%–3% prevalence**.
- GMP applied DN4 questionnaire to 58,480 rural Italian primary care patients 0.82%, mean age 69 years
  - Diabetes (*n* = 179)
  - herpes zoster (*n* = 142)
  - trigeminal neuralgia (*n* = 41)
  - trauma (*n*= 27),
  - nerve entrapment (*n* = 27)
  - systemic diseases (*n* = 11), and unknown causes (*n* = 21) were the etiological determinants of CPNP in our study

Buono M et al Postherpetic neuralgia, diabetic neuropathy, and trigeminal neuralgia – Chronic peripheral neuropathic pain in 58,480 rural Italian primary care patients. J Family Med Prim Care. 2017 Jan-Mar; 6(1): 110–114

C. Pérez, M.V. Ribera, R. Gálvez, J.A. Micó, C. Barutell, I. Failde, I. Sánchez-Magro, A. Stern. High prevalence of confirmed, but also of potential and believed, neuropathic pain in pain clinics European Journal of Pain Volume17, Issue3 March 2013 Pages 347-356. https://doi.org/10.1002/j.1532-2149.2012.00204.x

Definitions – do not confuse nomenclature

Neuropathic pain (IASP)

Pain caused by a lesion or disease of the somatosensory nervous system.

Neuropathy (IASP)

A disturbance of function or pathological change in a nerve: in one nerve, mononeuropathy; in several nerves, mononeuropathy multiplex; if diffuse and bilateral, polyneuropathy.

Neuralgia – nerve pain

Note: **Neuritis** (q.v.) is a special case of neuropathy and is now reserved for inflammatory processes affecting nerves.

ICD 2016 Disorders of trigeminal nerve G50- >

Includes disorders of 5th cranial nerve

Clinical Information A disorder characterized by involvement of the trigeminal nerve (fifth cranial nerve).

A non-neoplastic or neoplastic disorder affecting the trigeminal nerve (fifth cranial nerve).

Diseases of the trigeminal nerve or its nuclei, which are located in the pons and medulla. The nerve is composed of three divisions: ophthalmic, maxillary, and mandibular, which provide sensory innervation to structures of the face, sinuses, and portions of the cranial vault. The mandibular nerve also innervates muscles of mastication. Clinical features include loss of facial and intra-oral sensation and weakness of jaw closure. Common conditions affecting the nerve include brain stem ischemia, infratentorial neoplasms, and trigeminal neuralgia

ICHD3 Cranial neuralgias

International Classification of Orofacial pain 2020

Burden of neuropathic pain

About 413 physicians completed a total of 3,956 patient records forms.

Total annual direct health-care costs per patient ranged from €1,939 (Italy) to €3,131 (Spain).

Annual professional caregiver costs ranged from €393 (France) to €1,242 (UK), but this only represented a small proportion of total care because much care is provided by family or friends. Sick leave costs ranged from €5,492 (UK) to €7,098 (France), with 10%–32% patients prevented from working at some point by NP.

Total cost (including **direct and indirect costs**) of NP per patient was €10,313 in France (69% of the total cost), €14,446 in Germany (78%), €9,305 in Italy (69%), €10,597 in Spain (67%), and **€9,685 in the UK (57%).**

Indirect costs (ie, sick leave) constituted the majority of costs in all five countries: €7,098 in France, €11,232 in Germany, €6,382 in Italy, €7,066 in Spain, and **€5,492 in the UK**. In the subgroup analysis, total annual direct costs per patient were highest for neuropathic back pain and radiculopathy, and lowest for fibromyalgia.
Mean WPAI score range was 34.4–56.1; BPI interference was 4.1–4.8; and EQ-5D was 0.57–0.74. The results suggest that a significant proportion of the patient's work time in the previous week was affected by NP, and these are relatively high compared with other diseases such as diabetes, respiratory conditions, and arthritis.

ClinicoEconomics and Outcomes Research

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ORIGINAL RESEARCH

A burden of illness study for neuropathic pain in Europe

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Clinico Economics and Outcomes Research
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Number of times this article has been viewed

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Purpose: Neuropathic pain (NP) is often severe and represents a major humanistic and economic burden. This study aimed at providing insight on this burden across France, Germany, Italy, Spain, and the UK, considering direct and indirect costs, productivity loss, and humanistic impact on patients and their families.

Methods: Physician questionnaires provided data on patients presenting with NP covering demographics, sick leave and retirement, number of consultations, drug treatments, and surgical procedures. Patients provided further demographic and disease-related data and completed the Work Productivity and Activity Impairment (WPAI), the EuroQol 5-Dimension (EQ-5D), and the Brief Pain Inventory (BPI) questionnaires. All health-related direct unitary costs were collected from relevant country-specific sources and adjusted to 2012 prices (€) where necessary. A subgroup analysis of costs based on diabetic peripheral neuropathy (n=894), fibromyalgia (n=300), and low back pain (n=963) was performed.

Findings: About 413 physicians completed a total of 3,956 patient records forms. Total annual direct health-care costs per patient ranged from €1,939 (Italy) to €3,131 (Spain). Annual professional caregiver costs ranged from €393 (France) to €1,242 (UK), but this only represented a small proportion of total care because much care is provided by family or friends. Sick leave costs ranged from €5,492 (UK) to €7,098 (France), with 10%–32% patients prevented from working at some point by NP. Total cost (including direct and indirect costs) of NP per patient was €10,313 in France (69% of the total cost), €14,446 in Germany (78%), €9,305 in Italy (69%), €10,597 in Spain (67%), and €9,685 in the UK (57%). Indirect costs (ie, sick leave) constituted the majority of costs in all five countries: €7,098 in France, €11,232 in Germany, €6,382 in Italy, €7,066 in Spain, and €5,492 in the UK. In the subgroup analysis, total annual direct costs per patient were highest for neuropathic back pain and radiculopathy, and lowest for fibromyalgia. Mean WPAI score range was 34.4–56.1; BPI interference was 4.1–4.8; and EQ-5D was 0.57–0.74. The results suggest that a significant proportion of the patient's work time in the previous week was affected by NP, and these are relatively high compared with other diseases such as diabetes, respiratory conditions, and arthritis.

Implications: Despite differences in practice between countries, these findings suggest a high opportunity cost for society in terms of lost work and productivity due to NP. The wider costs appear significantly higher to patients, carers/families, and society as a whole than to the health system alone.

Keywords: neuropathic pain, burden of illness, chronic lower back pain, productivity

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Introduction

Chronic pain is a distinct and well-recognized condition experienced by around 25% of the European adult population.[1] While the majority of chronic pain is nociceptive

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Why does neuropathic pain exist?

› Med Hypotheses. 2012 May;78(5):641-3. doi: 10.1016/j.mehy.2012.01.044. Epub 2012 Feb 17.

Neuropathic pain: an evolutionary hypothesis

John C Ashton [1]

Affiliations + expand

PMID: 22342252 DOI: 10.1016

Abstract

Background: Whereas nociceptive pain
unexplained.
Objectives: It is argued that neuropathic
system, and that it operates on the same
evolutionary utility of motion sickness. V
activation of a system evolved to respon
acute neurotoxicity, it is proposed that n
incoherence between proprioceptive an
Results and conclusions: Evidence that s
consequences for pain theory and mana

ANNUAL REVIEWS

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Home / Annual Review of Neuroscience / Volume 32, 2009 / Costigan, pp 1-32

Neuropathic Pain: A Maladaptive Response of the Nervous System to Damage

Annual Review of Neuroscience
Vol. 32:1-32 (Volume publication date 21 July 2009)
First published online as a Review in Advance on March 17, 2009
https://doi.org/10.1146/annurev.neuro.051508.135531

Michael Costigan, Joachim Scholz, and Clifford J. Woolf
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It is proposed that Neuropathic pain arises from the activation of a system evolved to respond to incoherence between proprioceptive and sensory outputs as an indication of nerve trauma

Maladaptive pain or Malodynia

Ashton JC. Neuropathic pain: an evolutionary hypothesis. Med Hypotheses. 2012 May;78(5):641-3. doi: 10.1016/j.mehy.2012.01.044. Epub 2012 Feb 17. PMID: 22342252.

Mechanisms for Post Traumatic Neuropathic Pain

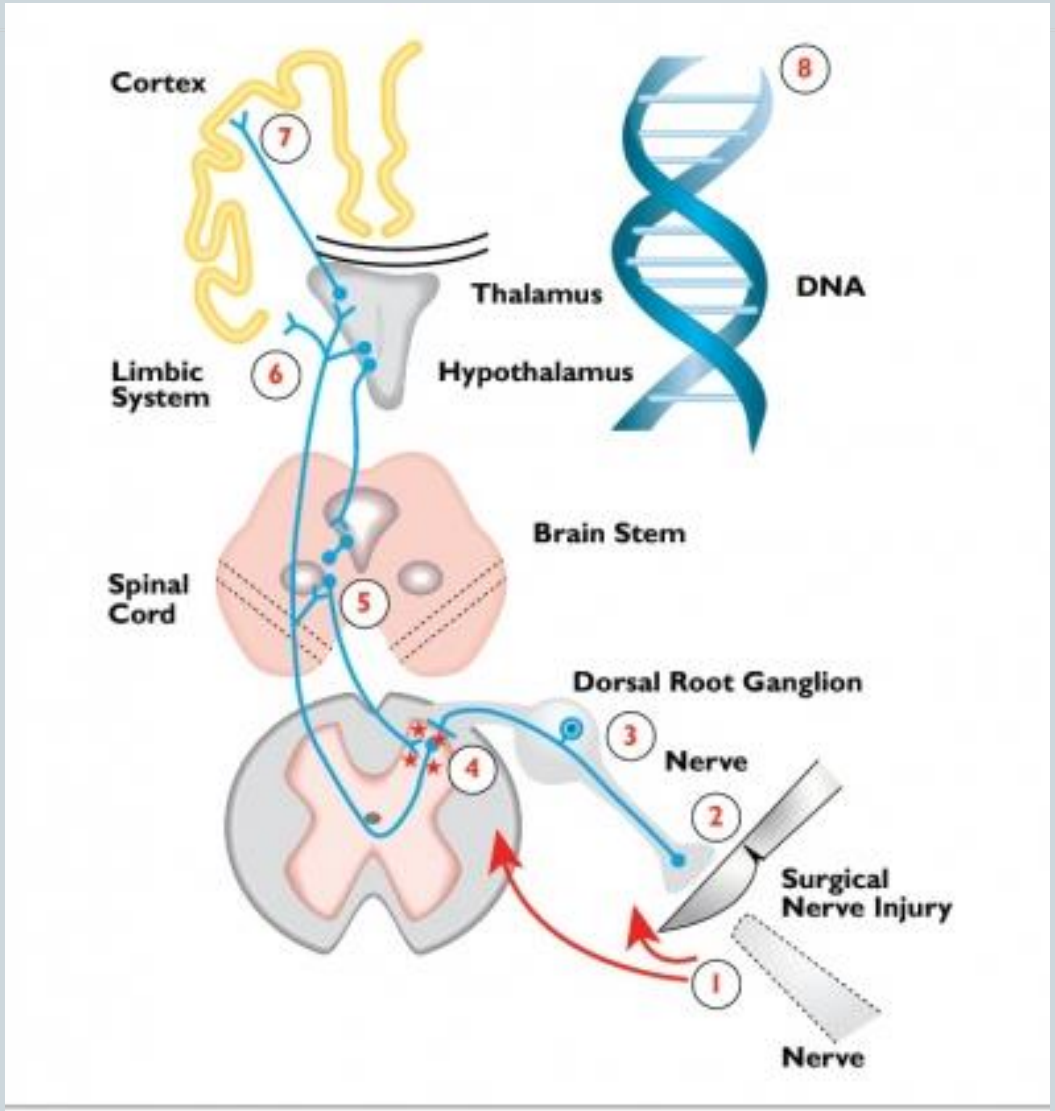

Figure 1. Sites and mechanisms of persistent postoperative pain.
Reprinted from *The Lancet*, Vol. 367, Kehlet H, et al. Persistent postsurgical pain: risk factors and prevention, pages 1618-1625, © 2006, with permission from Elsevier.

How Surgery (Wound) Can Lead to Chronic Pain

1. Denervated Schwann cells and infiltrating macrophages distal to nerve injury produce local and systemic chemicals that drive pain signaling.
2. Neuroma at site of injury is source of ectopic spontaneous excitability in sensory fibers.
3. Changes in gene expression in dorsal root ganglion after excitability, responsiveness, transmission, and survival of sensory neurons.
4. Dorsal horn is site of altered activity and gene expression, producing central sensitization, loss of inhibitory interneurons, and microglial activation, which together amplify sensory flow.
5. Brainstem descending controls modulate transmission in spinal cord.
6. Limbic system and hypothalamus contribute to altered mood, behavior, and autonomic reflexes.
7. Sensation of pain generated in cortex (past experiences, cultural inputs, and expectations converge to determine what patient feels).
8. Genomic DNA predispose (or not) patient to chronic pain and affect their reaction to treatment.

Genetic basis for Neuropathic Pain

Neuron
Review

The Genetics of Neuropathic Pain from Model Organisms to Clinical Application

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Glasgow, UK
[10]These authors contribu
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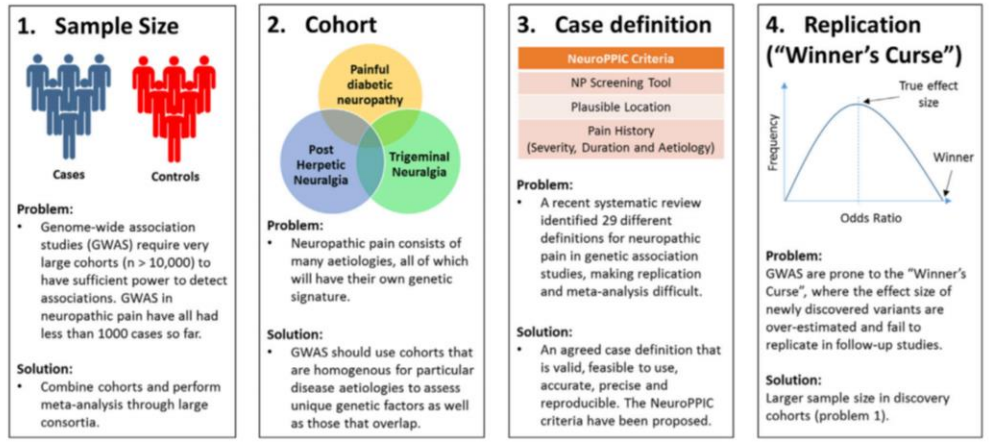
https://doi.org/10.1016/j

Neuropathic pain (N
disabling, renderin
conservation of pai



2. The Challenges of Conducting Genome-wide Association Studies in NeuP

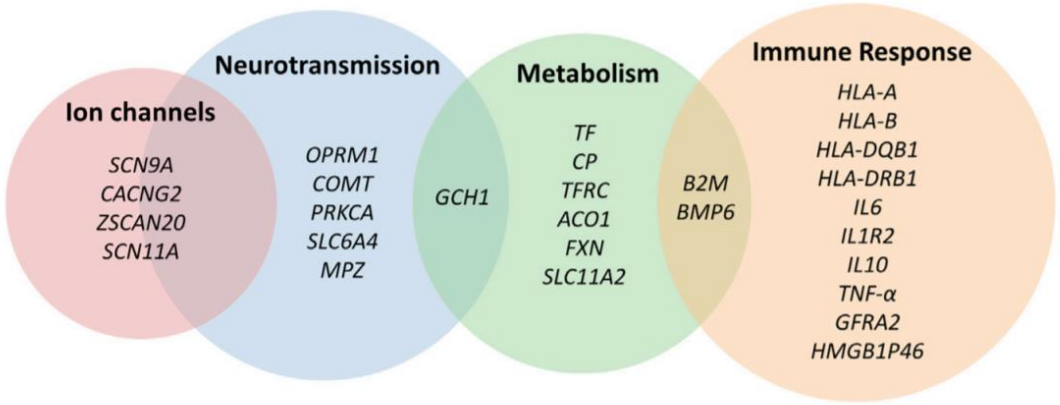


Figure 3. A Venn Diagram of Genes Reaching Study Specific or Suggestive Significance in Human Candidate Gene and Genome-wide Studies So Far in NeuP and the Overlap of Biological Pathways

These genes have been summarized in a recent systematic review of NeuP by Veluchamy et al. (2018), where the inclusion criteria were any study analyzing genetic variants in people with NeuP compared to people without NeuP. The number of genes and our understanding of their contribution within these pathways, in the context of NeuP, is likely to change as more studies are published.

Genetics and orofacial pain

J Endod. 2018 May;44(5):717-721.e1. doi: 10.1016/j.joen.2018.02.002. Epub 2018 Mar 15.

Pulp Sensitivity: Influence of Sex, Psychosocial Variables, COMT Gene, and Chronic Facial Pain

Irena Mladenovic [1], Jelena Krunic [2], Gordana Supic [3], Ruzica Kozomara [4], Dejan Bokonjic [5], Nikola Stojanovic [2], Zvonko Magic [3]

J Oral Facial Pain Headache. 2016 Fall;30(4):302-310. doi: 10.11607/ofph.1688.

Genetic Polymorphisms of Catechol-O-Methyltransferase: Association with Temporomandibular Disorders and Postoperative Pain

Irena Mladenovic, Gordana Supic, Ruzica Kozomara, Slobodan Dodic, Nedeljka Ivkovic, Bojana Milicevic, Ivana Simic, Zvonko Magic

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ENPP1 and *ESR1* genotypes influence temporomandibular disorders development and surgical-treatment response in dento-facial deformities

Romain Nicot[a], **Alexandre R. Vieira**[b], **Gwénaël Raoul**[c], **Constance Delmotte**[a], **Alain Duhamel**[d], **Joël Ferri**[c], and **James J. Sciote**[e]

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Clinical Trial > Pharmacogenet Genomics. 2010 Apr;20(4):239-48.
doi: 10.1097/FPC.0b013e328337f9ab.

Effect of catechol-O-methyltransferase polymorphism on response to propranolol therapy in chronic musculoskeletal pain: a randomized, double-blind, placebo-controlled, crossover pilot study

Inna E Tchivileva [1], Pei Feng Lim, Shad B Smith, Gary D Slade, Luda Diatchenko, Samuel A McLean, William Maixner

Sex/a COMT gene variant and TMD as a chronic painful condition may contribute to individual variation in **electric and cold pulp sensitivity**. **AA genotype of rs6269** presents less postoperative **chronic TMD pain and acute pain at a dental extraction** site. The **AA genotype of SNP rs1643821 (ESR1 gene)** as a risk factor for **dysfunctional worsening after orthognathic surgery**. In addition, we have identified **TT genotype of SNP rs858339 (ENPP1 gene) as a protective factor against TMD in a population of patients with dentofacial deformities**.

Conversely, the All these elements are particularly important to bring new screening strategies and tailor future treatment**heterozygous genotype AT was identified as a risk factor of TMD with respect to the rest of our population. COMT haplotypes may serve as genetic predictors of propranolol treatment outcome, identifying a subgroup of TMD patients who will benefit from propranolol therapy.**

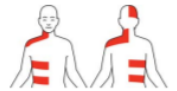
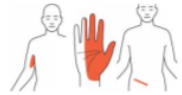
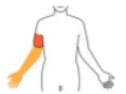
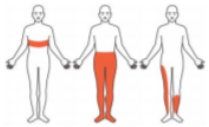
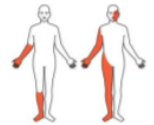
Mladenovic I, Krunic J, Supic G, Kozomara R, Bokonjic D, Stojanovic N, Magic Z. Pulp Sensitivity: Influence of Sex, Psychosocial Variables, COMT Gene, and Chronic Facial

Regional classification of neuropathic pain

- In 1994, the International Association for the Study of Pain (IASP) defined neuropathic pain as “pain initiated or caused by a primary lesion or dysfunction in the nervous system.”
- In 2008, a task force initiated by the IASP Special Interest Group on Neuropathic Pain (NeuPSIG) noted the need to distinguish neuropathic pain from nociceptive pain arising indirectly from neurological disorders and pain conditions with secondary neuroplastic changes occurring in the nociceptive system, and proposed a new definition that omitted the term “dysfunction”:
- “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system.”30
- A slightly modified version of this definition was proposed by the IASP Taxonomy Committee and accepted by the IASP: “**pain caused by a lesion or disease of the somatosensory nervous system.”**

Table 1

Common neuropathic pain conditions and neuroanatomically plausible distribution of pain symptoms and sensory signs.

Neuropathic pain condition	Neuroanatomically plausible distribution of pain and sensory signs	Illustration of typical distribution
Trigeminal neuralgia	Within the facial or intraoral trigeminal territory.	
Postherpetic neuralgia	Unilateral distributed in one or more spinal dermatomes or the trigeminal ophthalmic division.	
Peripheral nerve injury pain	In the innervation territory of the lesioned nerve, typically distal to a trauma, surgery, or compression.	
Postamputation pain	In the missing body part and/or in the residual limb.	
[illegible]	In feet, may extend to involve lower legs, thighs, and hands.	
Painful radiculopathy	Distribution consistent with the innervation territory of the nerve root.	
Neuropathic pain associated with spinal cord injury	At and/or below the level of the spinal cord lesion.	
Central poststroke pain	Contralateral to the stroke. In lateral medullary infarction, the distribution can also involve the ipsilateral side of the face.	
Central neuropathic pain associated with multiple sclerosis	Can be a combination of distributions seen in spinal cord injury and stroke.	

Trigeminal Neuralgia

Postherpetic Neuralgia

Post-traumatic Neuropathic Pain

Post limb amputation (Phantom Limb)

Poly neuropathy

Painful radiculopathy

Post spinal cord injury

Central post stroke

Multiple sclerosis

Mechanistic Classification of Neuropathic Pain:

The type of damage or related pathophysiology causing a painful neuropathic disorder can be classified as the following.

1. Mechanical nerve injury, e.g. carpal tunnel syndrome, vertebral disk herniation;
2. Metabolic disease, e.g. diabetic poly-neuropathy;
3. Neurotropic viral disease, e.g. herpes zoster, human immunodeficient virus (HIV) disease;
4. Neurotoxicity, e.g. by chemotherapy to treat cancer or tuberculosis;
5. Inflammatory and/or immunologic mechanisms, e.g. multiple sclerosis;
6. Nervous system focal ischemia. e.g. thalamic syndrome (anaesthesia dolorosa);
7. Multiple neurotransmitter system dysfunction, e.g. complex regional pain syndrome (CGRP).

Causes of neuropathy +/- pain……..

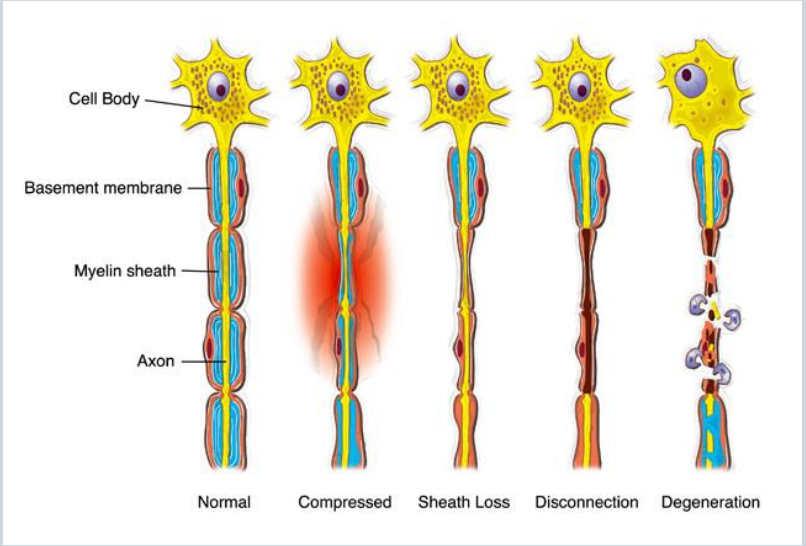
Trauma

Surgery, LA, thermal, radiation

Infections
Dental abscesses close to ID
Bacterial TB Leprosy
Viral, Herpes Zoster (PHN)
HIV, Leprosy

Toxins
Chemotherapy
Heavy metals

Metabolic
Diabetes,
Hypothyroidism
Sickle cell
Acromegaly



Nutrition
Heavy metal poisoning
Vitamin deficiency
B, E

Alcoholism

Auto immune
Demyelination (Multiple sclerosis, Guillain Barre)
Connective tissue disorders
Sarcoidosis/amyloidosis

Neoplasia

Peripheral sensory neuropathy presents with:

- Anaesthesia (numbness) +
- Altered sensation (pins and needles) +
- 50-70% Pain ongoing and or elicited (allodynia, hyperalgesia, hyperpathia)

Exclude systemic causes of Peripheral neuropathy

Table 1. Causes of Peripheral Neuropathy

Cause	*Type of neuropathy*	*Comments*	*Laboratory tests*
Diseases			
Acquired immunodeficiency syndrome	A	Mainly sensory	Human immunodeficiency virus test
Carcinoma (paraneoplastic syndrome)	A	Usually sensory	Paraneoplastic panel (anti-Hu, anti-Yo, anti-Ri, anti-Tr, anti-Ma, and anti-CV2 antibodies)
Chronic liver disease	M	Mainly demyelinating, especially in viral hepatitis	Hepatic transaminase, bilirubin, albumin, and alkaline phosphatase levels
Critical illness neuropathy	A	Usually acute or subacute	No specific laboratory test
Diabetes mellitus	M	Chronic; axonal may predominate	Fasting blood glucose level, glucose tolerance test, A1C level
End-stage renal disease	A	—	Serum creatinine and blood urea nitrogen levels
Hypothyroidism	A	Usually acute or subacute, but can be chronic	Thyroid-stimulating hormone level
Leprosy	A	Usually sensory	Phenolic glycolipid-1 antibody, skin biopsy
Lyme disease	A	—	Lyme titers
Lymphoma	M	Mainly axonal	CBC, imaging
Monoclonal gammopathy		Usually chronic	Urine and serum protein electrophoresis with immunofixation
Amyloidosis	A	Usually sensory	
Multiple myeloma	M	Axonal damage predominates after treatment	
Plasmacytoma (osteosclerotic myeloma)	D	May have some axonal damage	
Monoclonal gammopathy of undetermined significance			
IgM	D	Most common; may have some axonal damage	
IgG or IgA	M	Demyelinating features often predominate	
Porphyria	A	Acute	Porphyrin titers
Syphilis	A	—	Rapid plasma reagin, VDRL, cerebrospinal fluid analysis
Vitamin B_6 deficiency	A	Sensory more than motor	Vitamin B_6 level
Vitamin B_{12} deficiency	A	Peripheral neuropathy is intermixed with upper motor neuron signs	CBC; vitamin B_{12} and homocysteine levels; methylmalonic acid test

continued

Peripheral Neuropathy: Differential Diagnosis and Management

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…hy. Treatment should
…nptomatic treatment.
…icians.)

Table 1. Causes of Peripheral Neuropathy *(continued)*

Cause	*Type of neuropathy*	*Comments*	*Laboratory tests*
Drugs*			
Amiodarone (Cordarone)	M	Mainly axonal with sensorimotor	No specific tests
Chloroquine (Aralen)	D	May have some axonal damage	
Digoxin	A	Mainly sensory	
Heroin	A	Sensorimotor	
Hydralazine	A	Mainly sensory	
Isoniazid	A	Mainly sensory	
Lithium	A	Sensorimotor	
Metronidazole (Flagyl)	A	Mainly sensory	
Misoprostol (Cytotec)	A	Motor	
Nitrofurantoin (Furadantin)	A	Sensorimotor	
Phenytoin (Dilantin)	A	Mainly sensory	
Procainamide (Pronestyl)	D	May have some axonal damage	
Statins	A	Mainly sensory	
Vincristine (Oncovin)	A	Sensorimotor	
Vitamin B_6 excess	A	Mainly sensory	
Genetic disorders†			
Charcot-Marie-Tooth disease			Genetic testing
Type 1	D	Also called HMSN-I	
Type 2	A	Also called HMSN-II	
Metachromatic leukodystrophy	D	—	
Neuropathy with liability to pressure palsies	D	—	
Refsum disease	D	Also called HMSN-IV	
Toxins*			
Diphtheria toxin	D	Acute presentation	Histopathology
Ethanol (alcohol)	A	Sensorimotor	No specific or practical laboratory test
Heavy metals (e.g., arsenic, lead, mercury, gold)	A	Lead and mercury mainly cause motor neuropathy Arsenic causes sensorimotor neuropathy Gold may cause some demyelination	24-hour urine collection for heavy metal titers
Organophosphates	A	Sensorimotor	No specific or practical laboratory test
Tetanus	A	Motor; acute presentation	No specific or practical laboratory test
Tic paralysis	A	Motor; acute presentation	No specific or practical laboratory test
Other causes			
Idiopathic polyneuropathy	A	Diagnosis of exclusion; usually chronic	No laboratory test

A = axonal; CBC = complete blood count; D = demyelinating; HMSN = hereditary motor-sensory neuropathy; Ig = immunoglobulin; M = mixed; VDRL = Venereal Disease Research Laboratory.

ankle reflexes, and decreased distal sensations, regardless of distal muscle weakness and atrophy, makes the diagnosis of peripheral neuropathy likely.[4] The isolated presence of neuropathic symptoms or decreased ankle reflexes is less valuable for diagnosis. Some causes of peripheral neuropathy are characterized by mononeuropathy, some involve multiple nerves, and others have autonomic dysfunction or pain prominence *(Table 2)*.

DIAGNOSTIC TESTING

The evaluation of a patient with peripheral neuropathy starts with simple blood tests, including a complete blood count, comprehensive metabolic profile, and measurement of erythrocyte sedimentation rate and fasting blood glucose, vitamin B_{12}, and thyroid-stimulating hormone levels[5] *(Figure 1)*. Additional tests, if clinically indicated, may

Table 2. Causes of Peripheral Neuropathy Based on Clinical Presentation

Conditions causing mononeuropathy
Acute (trauma-related)
Chronic (nerve entrapment)

Disorders causing mononeuropathy multiplex
Acute
- Diabetes mellitus*
- Multifocal motor neuropathy
- Vasculitic syndromes

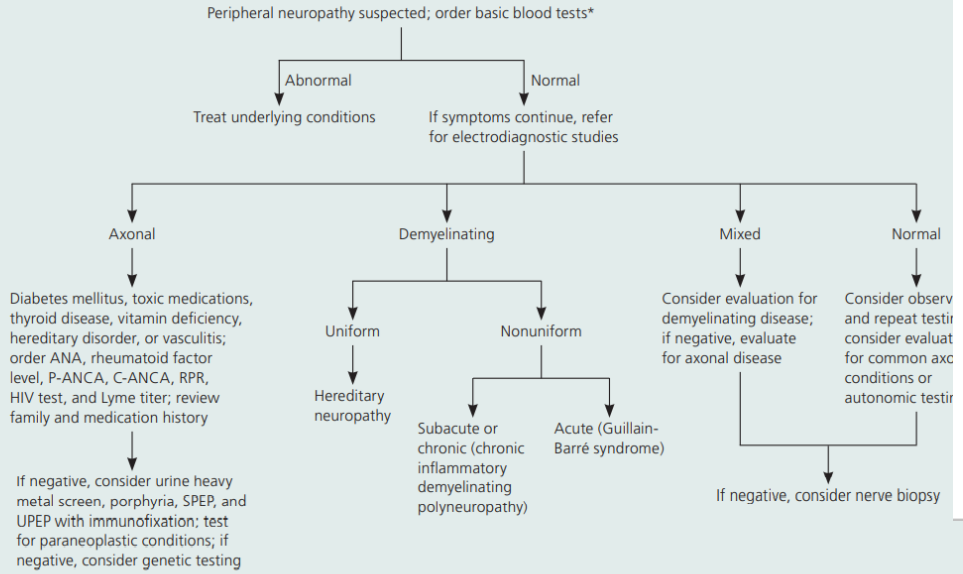
Chronic
- Acquired immunodeficiency syndrome
- Leprosy*
- Sarcoidosis

Conditions causing neuropathy with autonomic features
Alcoholism
Amyloidosis
Chemotherapy-related neuropat
Diabetes
Heavy metal toxicity
Paraneoplastic syndrome
Porphyria
Primary dysautonomia
Vitamin B_{12} deficiency

Conditions causing painful neuropathy
Alcoholism
Amyloidosis
Chemotherapy (heavy metal tox
Diabetes
Idiopathic polyneuropathy
Porphyria

*—*May cause symmetric peripheral neuropathy.*

Diagnosis of the Patient with Suspected Peripheral Neuropathy



*—Complete blood count, comprehensive metabolic panel, and measurement of erythrocyte sedimentation rate and fasting blood glucose,

Table 1 Common Types of Neuropathic Pain [Adapted from Baron [32]]

Peripheral
Acute and chronic inflammatory demyelinating polyradiculopathy
Alcoholic
Amyloid
Chemotherapy-induced
Complex regional pain syndrome
Diabetic neuropathy
Entrapment neuropathies (e.g., carpal tunnel syndrome)
HIV sensory neuropathy
Hypothyroidism
Hereditary sensory neuropathies
Ischemic neuropathy
Nerve compression, including tumor infiltration
Nutrition deficiency-related
Phantom limb/stump pain
Polyarteritis nodosa
Postherpetic neuralgia
Post-surgical (i.e., postmastectomy pain or post-thoracotomy pain)
Post-traumatic neuralgias
Postradiation plexopathy
Radiculopathy (cervical, thoracic, lumbar)
Toxin-related
Trigeminal neuralgia
Central Neuropathic Pain
Compressive myelopathy
HIV myelopathy
Multiple sclerosis-related
Parkinson's disease-related
Postischemic myelopathy
Postradiation myelopathy
Poststroke or infarction (thalamus/spinal cord) pain
Post-traumatic spinal cord injury
Syringomyelia

Table 3. Tests Indicated in Patients with Peripheral Neuropathy

Tests	*Clinical disorders*
Routine	
Complete blood count	—
Comprehensive metabolic panel	—
Erythrocyte sedimentation rate	—
Fasting blood glucose level	—
Thyroid-stimulating hormone level	—
Vitamin B_{12} level	—
If indicated by clinical suspicion	
Glucose tolerance test, A1C level	Diabetes mellitus
HIV antibodies	HIV
Hepatic panel	Liver disorders
Lyme antibodies	Lyme disease
Rapid plasma reagin, VDRL	Syphilis
Urinalysis (including 24-hour urine collection)	Heavy metal toxicity, porphyrias, multiple myeloma
Urine and serum protein electrophoresis with immunofixation	Demyelinating neuropathy
Angiotensin-converting enzyme levels	Sarcoidosis
Antinuclear antibodies, P-ANCA, C-ANCA	Vasculitis
Tests for uncommon conditions	
Paraneoplastic panel	Underlying malignancy
Antimyelin-associated glycoprotein and antiganglioside antibodies	Sensorimotor neuropathy
Antisulfatide antibodies	Autoimmune polyneuropathy
Cryoglobulins	Cryoglobulinemia
Salivary flow rate, Schirmer test, rose bengal test, labial gland biopsy	Sjögren syndrome
Cerebrospinal fluid analysis	Acute or chronic inflammatory demyelinating neuropathy
Genetic testing	Hereditary neuropathy

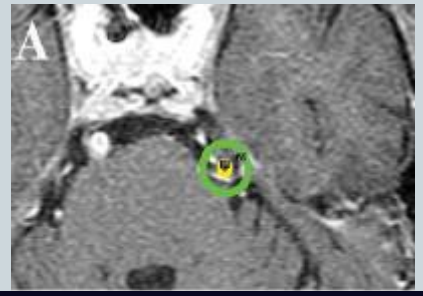
NOTE: *Tests are listed in the approximate frequency of the potential underlying disorder.*

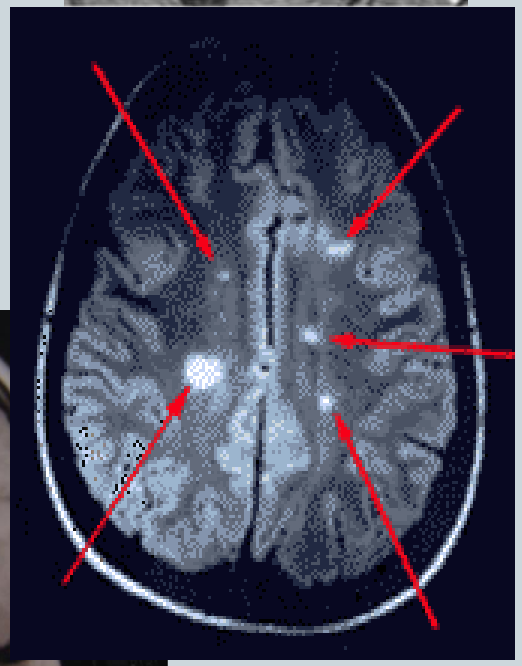
C-ANCA = cytoplasmic antineutrophil cytoplasmic antibodies; HIV = human immunodeficiency virus; P-ANCA = perinuclear antineutrophil cytoplasmic antibodies; VDRL = Venereal Disease Research Laboratory.

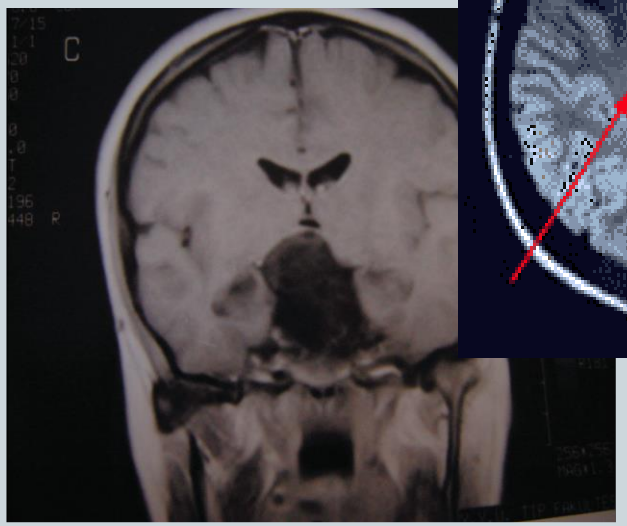
Exclude Central Causes Ne Pain

- Classical TN + NVC
  - vascular compression
- Multiple sclerosis
  - MRI plaques
- Stroke
- Vasculitis
- Central viral infection
- Tumours
  - Cervical pathology

RED FLAGS?



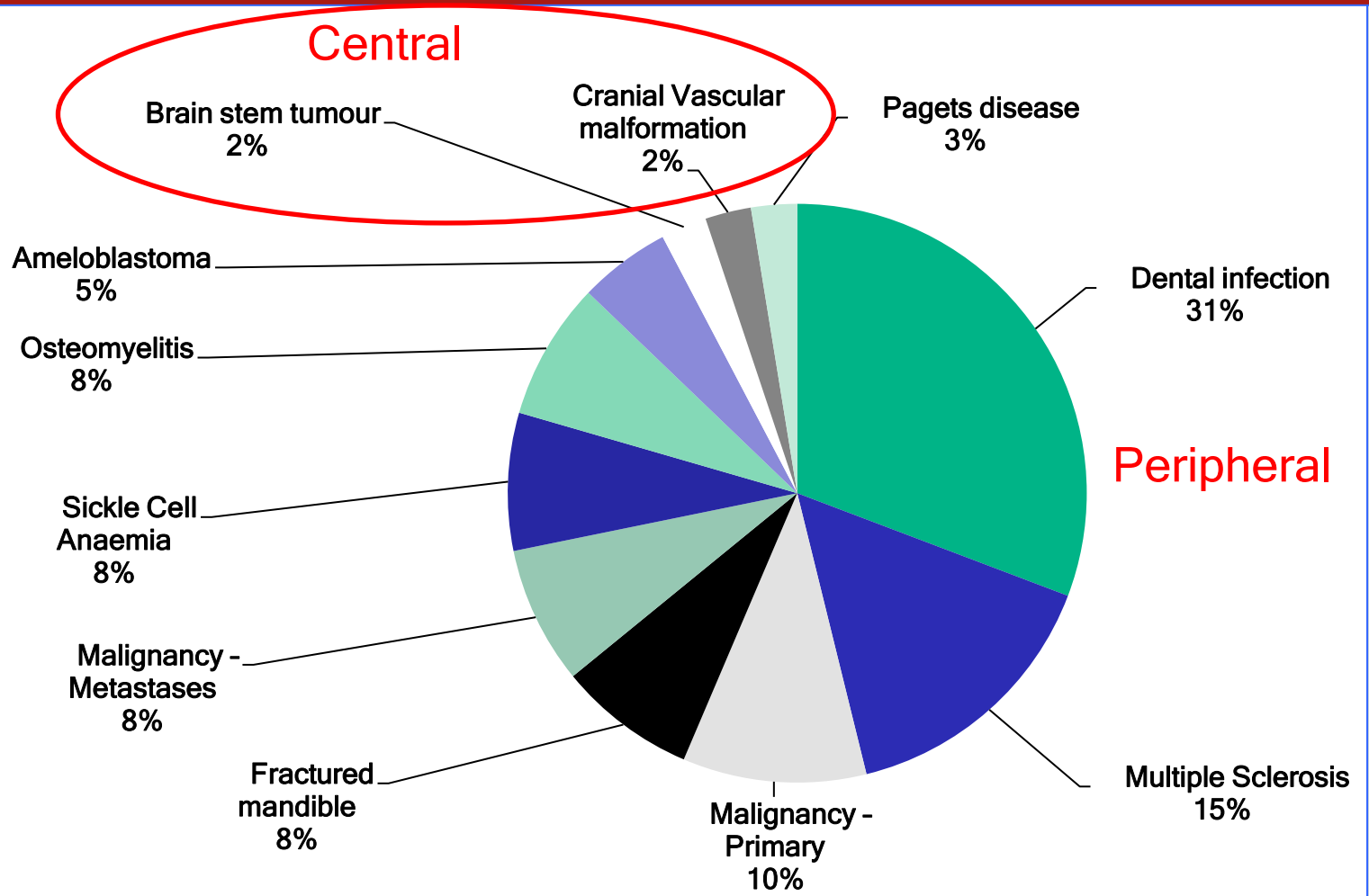


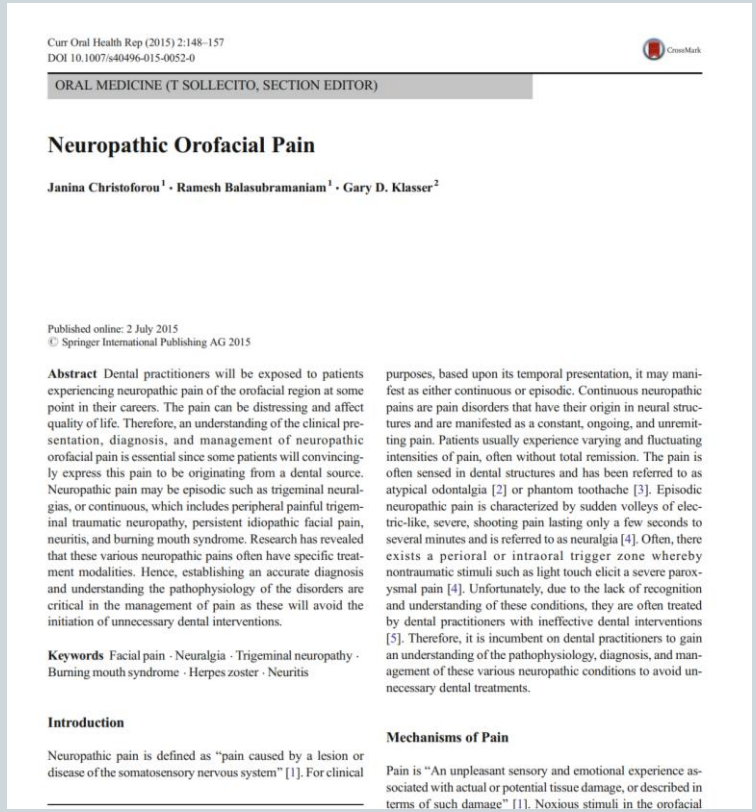


Exclude Local Secondary causes of Trigeminal Neuropathic Pain

Trigeminal neuropathy

Retrospective analysis of the case notes of 372 patients referred to the specialist nerve injury clinic between 2007 and 2014 was carried out to establish the cause of numb chin syndrome





Curr Oral Health Rep (2015) 2:148–157
DOI 10.1007/s40496-015-0052-0

ORAL MEDICINE (T SOLLECITO, SECTION EDITOR)

Neuropathic Orofacial Pain

Janina Christoforou[1] · Ramesh Balasubramaniam[1] · Gary D. Klasser[2]

Published online: 2 July 2015
© Springer International Publishing AG 2015

Abstract Dental practitioners will be exposed to patients experiencing neuropathic pain of the orofacial region at some point in their careers. The pain can be distressing and affect quality of life. Therefore, an understanding of the clinical presentation, diagnosis, and management of neuropathic orofacial pain is essential since some patients will convincingly express this pain to be originating from a dental source. Neuropathic pain may be episodic such as trigeminal neuralgias, or continuous, which includes peripheral painful trigeminal traumatic neuropathy, persistent idiopathic facial pain, neuritis, and burning mouth syndrome. Research has revealed that these various neuropathic pains often have specific treatment modalities. Hence, establishing an accurate diagnosis and understanding the pathophysiology of the disorders are critical in the management of pain as these will avoid the initiation of unnecessary dental interventions.

Keywords Facial pain · Neuralgia · Trigeminal neuropathy · Burning mouth syndrome · Herpes zoster · Neuritis

Introduction

Neuropathic pain is defined as "pain caused by a lesion or disease of the somatosensory nervous system" [1]. For clinical purposes, based upon its temporal presentation, it may manifest as either continuous or episodic. Continuous neuropathic pains are pain disorders that have their origin in neural structures and are manifested as a constant, ongoing, and unremitting pain. Patients usually experience varying and fluctuating intensities of pain, often without total remission. The pain is often sensed in dental structures and has been referred to as atypical odontalgia [2] or phantom toothache [3]. Episodic neuropathic pain is characterized by sudden volleys of electric-like, severe, shooting pain lasting only a few seconds to several minutes and is referred to as neuralgia [4]. Often, there exists a perioral or intraoral trigger zone whereby nontraumatic stimuli such as light touch elicit a severe paroxysmal pain [4]. Unfortunately, due to the lack of recognition and understanding of these conditions, they are often treated by dental practitioners with ineffective dental interventions [5]. Therefore, it is incumbent on dental practitioners to gain an understanding of the pathophysiology, diagnosis, and management of these various neuropathic conditions to avoid unnecessary dental treatments.

Mechanisms of Pain

Pain is "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [1]. Noxious stimuli in the orofacial

An update on the causes, assessment and management of third division sensory trigeminal neuropathies.Carter E, Yilmaz Z, Devine M, Renton T. Br Dent J. 2016 Jun 24;220(12):627-35. doi: 10.1038/sj.bdj.2016.444

Diagnostic Criteria Post Traumatic Painful Neuropathy (PTPN) ICHD3

Table 3. Core Diagnostic Criteria for Persistent Posttraumatic Neuropathic Pain

1. History of traumatic nerve injury or surgery associated with known risk of nerve injury.* **Traumatic event = onset**
2. Pain lasting ≥3 mo, with onset showing a temporal relation to known nerve injury (onset within days to weeks after the injury).†
3. Positive and/or negative signs of sensory disturbance in the innervation of the injured nerve as evidenced by ≥1 of the following:
   a. Mixed areas of hypo- and hypersensitivity to various sensory modalities **Neuropathic area**
   b. Hyposensitivity to nonpainful warmth (with or without changes in cold sensation) **Allodynia / Hyperalgesia = hyperaesthesia**
   c. Hypersensitivity to brush or pinprick in or around the painful area
4. No other condition (eg, inflammation, tumor) better explains the pattern of the clinical features (eg, radiculopathy) that could plausibly account for persisting pain in the affected dermatome or dermatomes. **Anaesthesia/paraesthesia = hypoaesthesia**

*This pain may occur even if there was a deliberate attempt to spare the large nerves crossing the surgical area (eg, in breast surgery).
†There is a spontaneous decline in reporting of pain >12 mo after surgery/trauma. Relevant citations in support of these diagnostic criteria are Bruehl,[34] Duffy et al,[77] Guo et al,[107] Haldar et al,[109] Pappagallo et al,[187] Teerijoki-Oksa et al,[224] and Wildgaard et al.[247]

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Focus Article

AAPT Diagnostic Criteria for Peripheral Neuropathic Pain: Focal and Segmental Disorders

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The IASP classification of chronic pain for ICD-11: chronic neuropathic pain

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Diagnostic algorithm for Neuropathic Pain

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Neuropathic pain

Luana Colloca[1], **Taylor Ludman**[1], **Didier Bouhassira**[2], **Ralf Baron**[3], **Anthony H. Dickenson**[4], **David Yarnitsky**[5], **Roy Freeman**[6], **Andrea Truini**[7], **Nadine Attal**[8], **Nanna B. Finnerup**[9], **Christopher Eccleston**[10,11], **Eija Kalso**[12], **David L. Bennett**[13], **Robert H. Dworkin**[14], and **Srinivasa N. Raja**[15]

[1]Department of Pain and Translational Symptom Science, School of Nursing and Department of

Comprehensive Review

PAIN

OPEN

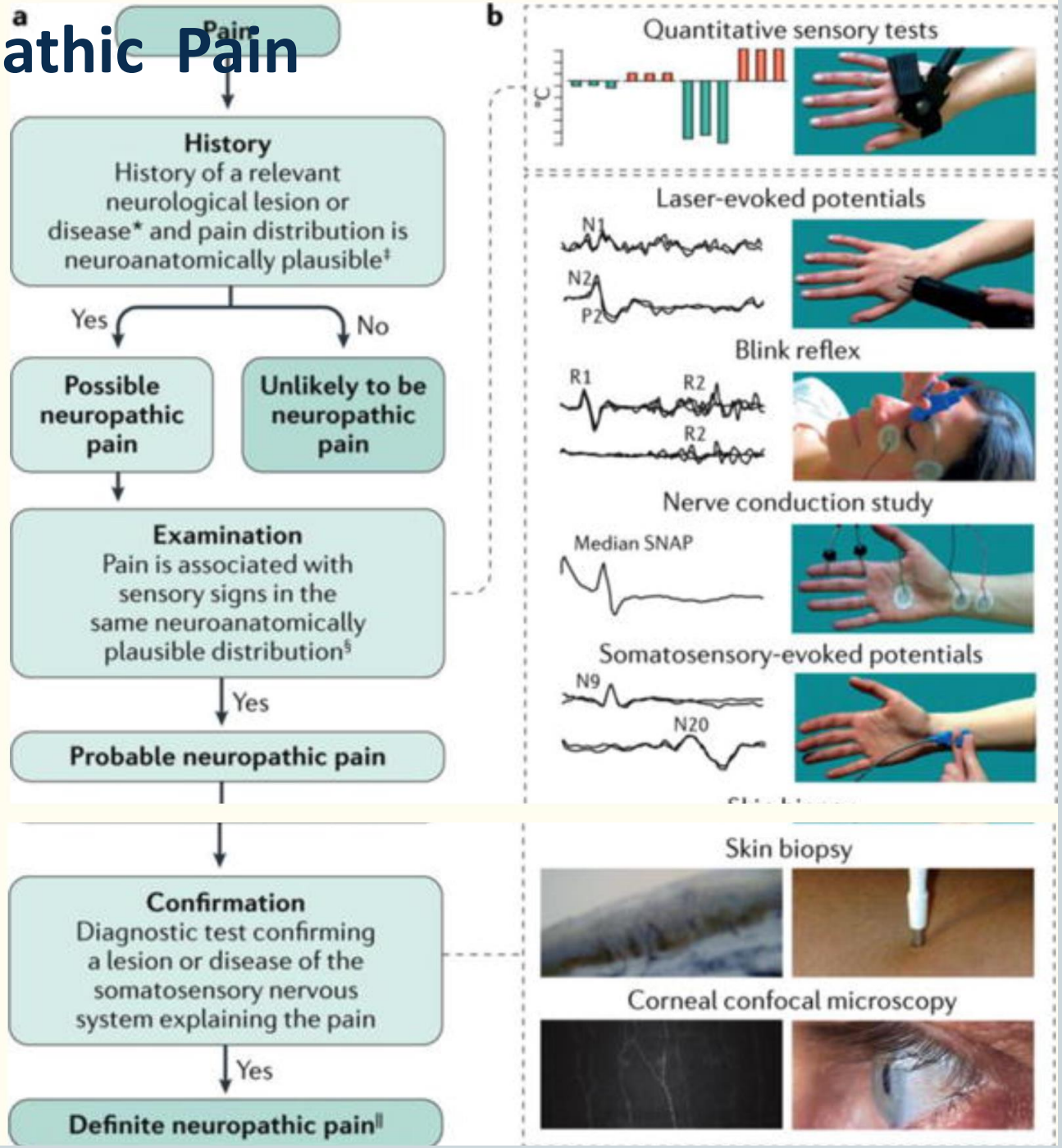
Neuropathic pain: an updated grading system for research and clinical practice

Nanna B. Finnerup[a,*], Simon Haroutounian[b], Peter Kamerman[c], Ralf Baron[d], David L.H. Bennett[e], Didier Bouhassira[f,g], Giorgio Cruccu[h], Roy Freeman[i], Per Hansson[j,k], Turo Nurmikko[l], Srinivasa N. Raja[m], Andrew S.C. Rice[n,o], Jordi Serra[p], Blair H. Smith[q], Rolf-Detlef Treede[r], Troels S. Jensen[a,s]

Abstract

The redefinition of neuropathic pain as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system," which was suggested by the International Association for the Study of Pain (IASP) Special Interest Group on Neuropathic Pain (NeuPSIG) in 2008, has been widely accepted. In contrast, the proposed grading system of possible, probable, and definite neuropathic pain from 2008 has been used to a lesser extent. Here, we report a citation analysis of the original NeuPSIG grading paper of 2008, followed by an analysis of its use by an expert panel and recommendations for an improved grading system. As of February, 2015, 608 eligible articles in Scopus cited the paper, 414 of which cited the neuropathic pain definition. Of 220 clinical studies citing the paper, 56 had used the grading system. The percentage using the grading system increased from 5% in 2009 to 30% in 2014. Obstacles to a wider use of the grading system were identified, including (1) questions about the relative significance of confirmatory tests, (2) the role of screening tools, and (3) uncertainties about what is considered a neuroanatomically plausible pain distribution. Here, we present a revised grading system with an adjusted order, better reflecting clinical practice, improvements in the specifications, and a word of caution that even the "definite" level of neuropathic pain does not always indicate causality. In addition, we add a table illustrating the area of pain and sensory abnormalities in common neuropathic pain conditions and propose areas for further research.

Keywords: Neuropathic pain, Definition, Grading, Possible, Probable, Definite



Features of Neuropathic pain

- Diagnostic features

  Neuropathic area -either hypoaesthetic or hyperaesthetic
  - **Allodynia**
  - **Hyperalgesa**
  - **Hyperpathia**
- Prior Multiple injuries or episodes of infection and pain
- Non-respondent to anti inflammatory pain killers (NSAIDs Paracetamol)
- Does not disturb sleep
- Better in mornings
- Worsens during day
- Worsens with stress, tiredness and illness
- **Pain presentation**
  - **Constant burning/dull**
  - **Elicited neuralgic/sharp/ shooting**
  - **Or a combination of both**

Table 2
Definitions of common features suggestive of neuropathic pain[29]

Paresthesia	An abnormal sensation, whether spontaneous or evoked
Dysesthesia	An unpleasant sensation, whether spontaneous or evoked
Hypoesthesia	Decreased sensitivity to stimulation (tactile or thermal; both are frequent)
Hyperesthesia	Increased sensitivity to stimulation (tactile or thermal; both are rare)
Hypoalgesia	Diminished pain response to a normally painful stimulus
Hyperalgesia	An increased response to a stimulus that is normally painful
Allodynia	Pain due to a stimulus that does not normally activate the nociceptive system

Signs and mechanisms

Neuropathic area
+
Positive or negative signs

SYMPTOMS	PHYSIOPATHOLOGICAL MECHANISMS
Paroxysmal pain	Spontaneous activity in C-fibres
Superficial pain	Spontaneous activity in Aδ- and C-fibres
Deep pain	Spontaneous activity in articular/muscular nociceptors
Paraesthesia	Spontaneous activity in Aβ-fibres

SIGNS (EVOKED PAIN)	PHYSIOPATHOLOGICAL MECHANISMS
Cold hyperalgesia	Central sensitization/loss of central inhibition
Heat hyperalgesia	Peripheral sensitization
Punctate hyperalgesia	Central sensitization mediated by Aδ-fibres
Mechanical allodynia	Heterosynaptic central sensitization
Temporal summation of pain	Homosynaptic central sensitization
After-sensations	Homosynaptic central sensitization

Hyperaesthetic

NEUROPATHIC PAIN SYNDROMES

Coexistence of negative symptoms/signs (loss-of-function of the somatosensory system) and positive symptoms/signs (gain-of-function of the somatosensory system)

Hypoaesthetic

SYMPTOMS	PHYSIOPATHOLOGICAL MECHANISMS
Hypalgesia	Aδ-fibres lesion

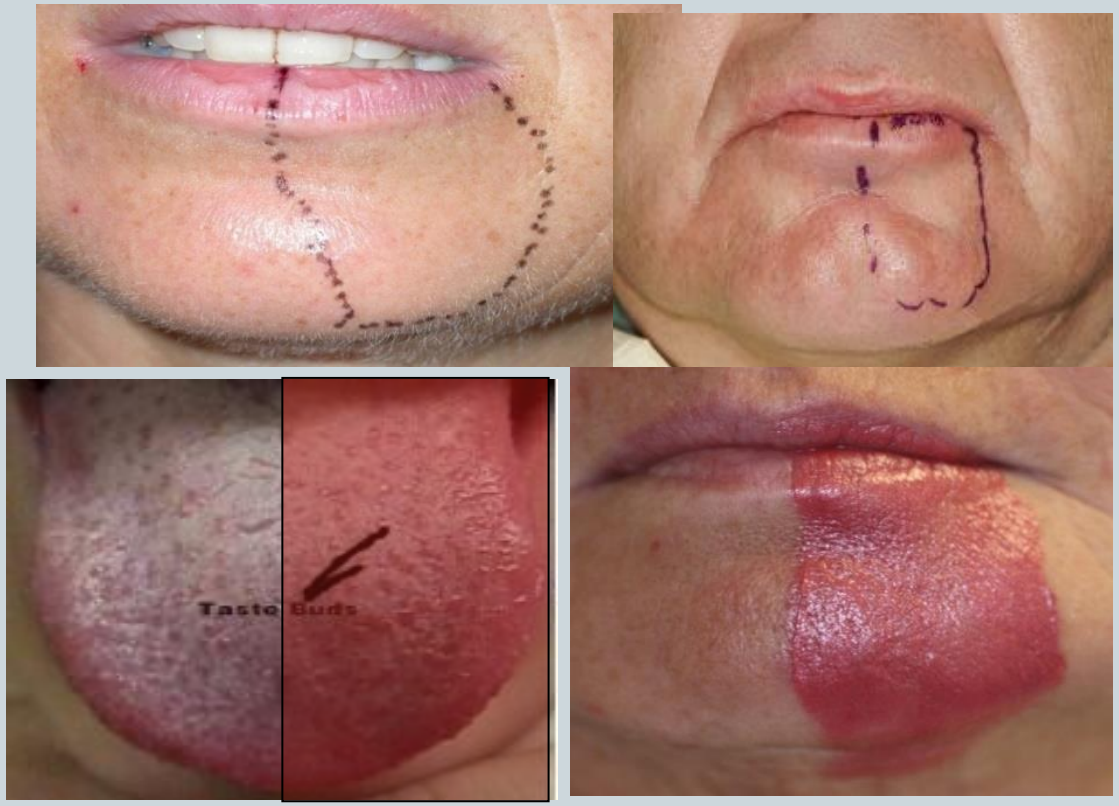
SIGNS	PHYSIOPATHOLOGICAL MECHANISMS
Tactile hypesthesia	Aβ-fibres lesion
Hypopallesthesia	Aβ-fibres lesion
Thermal hypesthesia	Aδ- and C-fibres lesion
Punctate hypesthesia	Aδ-fibres lesion

Diagnosis nerve injury/neuropathic area

Confirm Neuropathic area +/- pain

Temporary or permanent?

- **Mechanism**
- **Duration**
- Identify the extent of injury
  - Size neuropathic area
  - Subjective function
  - Mechanosensory function
  - Disability
  - Pain / discomfort
    - Allodynia
    - Hyperalgesia
    - Spontaneous or elicited?



Patient's story and expectations?

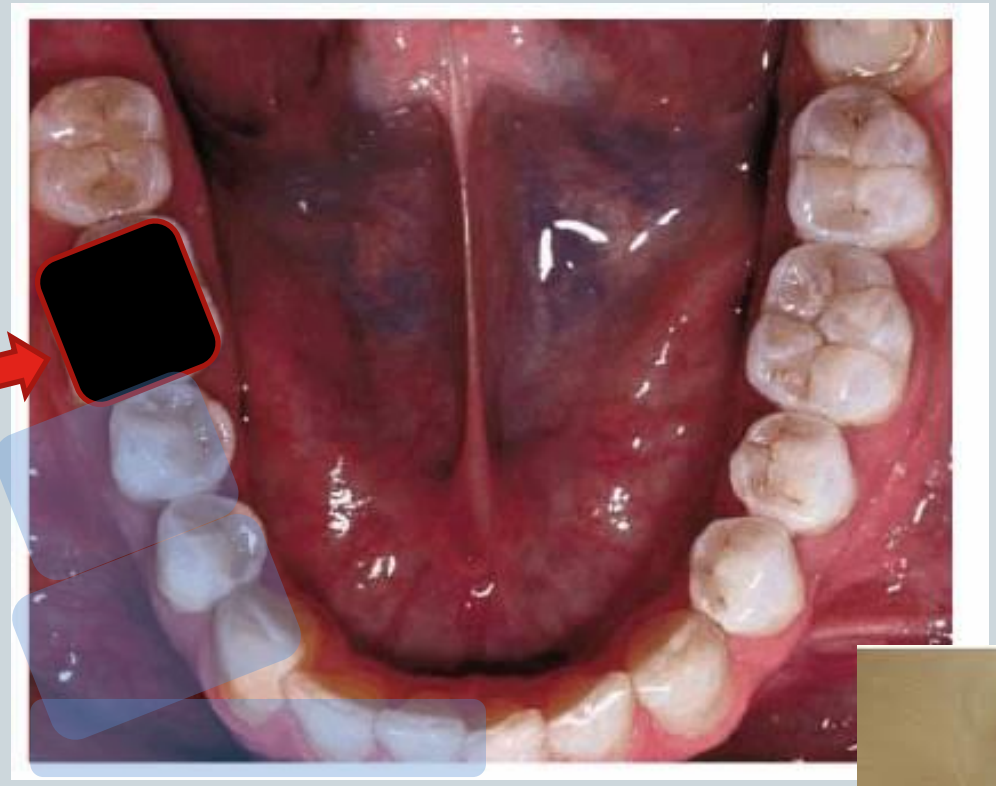
Renton T, Thexton A, SJ Crean, Hankins M. Simplifying assessment of recovery of the lingual nerve from injury. BDJ 2006 10:569-573 **Renton T**, Thexton A, Mcgurk M. New method for the objective evaluation of injury to the lingual nerve after operation on third molars.Br J Oral Maxillofac Surg. 2005 Jun;43(3):238-45. **Renton T**, Thexton A, Mcgurk M. Objective evaluation of iatrogenic lingual nerve injuries using the jaw-opening reflex. Br J Oral Maxillofac Surg. 2005 Jun;43(3):233-8

Diagnosis nerve injury/neuropathic area

Implant extraction or endodontic procedure undertaken with resultant numbness of mouth& lip with pain

Neuropathic area should affect 'DISTAL' domain of dermatome

In some cases only socket area can be affected with localised hypersensitivity



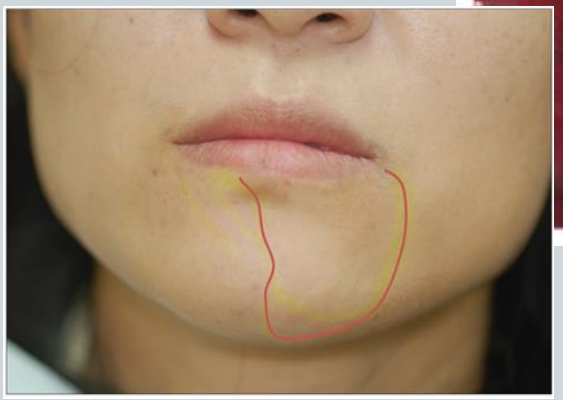
Neuropathic area you can use dental vitality tests but not very reliable

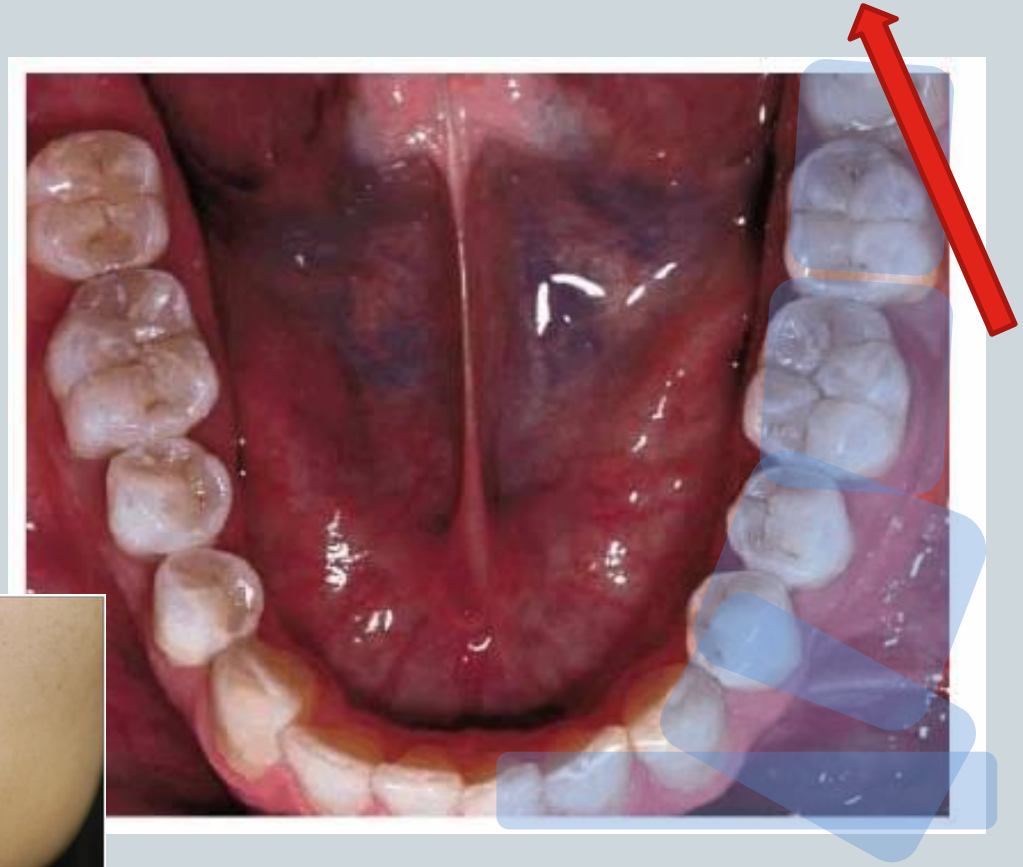
Extraoral area may be complete **or partial Below illustrates 40% affected area**

Diagnosis nerve injury/neuropathic area

Neuropathic area you can use dental vitality tests but not very reliable

Extraoral neuropathy affecting 90% of area





Inferior dental block undertaken with resultant numbness of mouth&lip with pain

Neuropathic area should affect ‘DISTAL’ domain of dermatome

Sensory testing
Do we need Quantitative testing?

Possible Neuropathic pain-pain since event

Probable neuropathic pain (check patient not in remission)

- **Identify neuropathic area and +ve or –ve signs**
  - Mechanical and or thermal allodynia
  - Hyperalgesia
  - Hyperpathia
  - (Refractory period =TN)
- Qualitative sensory testing

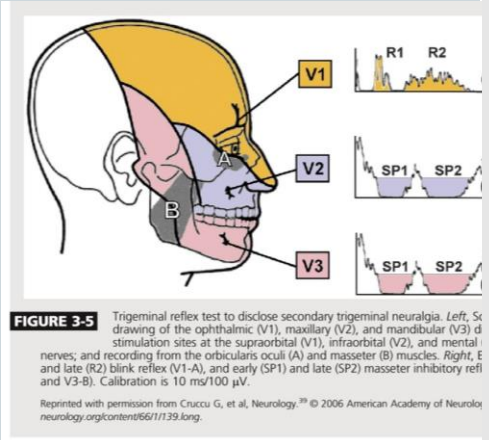


FIGURE 3-5 Trigeminal reflex test to disclose secondary trigeminal neuralgia. *Left*, Sc drawing of the ophthalmic (V1), maxillary (V2), and mandibular (V3) d stimulation sites at the supraorbital (V1), infraorbital (V2), and mental nerves; and recording from the orbicularis oculi (A) and masseter (B) muscles. *Right*, E and late (R2) blink reflex (V1-A), and early (SP1) and late (SP2) masseter inhibitory refl and V3-B). Calibration is 10 ms/100 μV.

Reprinted with permission from Cruccu G, et al, Neurology.[39] © 2006 American Academy of Neurolo *neurology.org/content/66/1/139.long.*

Definite neuropathic pain

- Quantitative sensory testing
  - Trigeminal reflex testing is an established neurophysiologic assessment of nerve function, requires only standard nerve conduction study equipment. Blink, jaw closing, jaw opening)
  - Method of Limens thermo-sensory testing
  - Evoked potentials after electric or thermal stimuli have been studied in trigeminal neuralgia. In contrast to trigeminal reflex testing, which is normal in idiopathic or classic trigeminal neuralgia, evoked potentials may be altered, but their mean specificity of 64% is low

CONTINUUM **Review Article**

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Relationship Disclosure:

Trigeminal Neuralgia

Giorgio Cruccu, MD

Journal of Medicine and Life Vol. 6, Issue 4, October-December 2013, **pp.383-388**

Pain in trigeminal neuralgia: neurophysiology and measurement: a comprehensive review

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Randomized Controlled Trial › J Oral Rehabil. 2017 Jan;44(1):30-42. doi: 10.1111/joor.12455. Epub 2016 Nov 16.

Agreement between quantitative and qualitative sensory testing of changes in oro-facial somatosensory sensitivity

J Agbaje [1], A De Laat [2], P Constantinus [1 3], P Svensson [4 5 6], L Baad-Hansen [4 5]

Affiliations + expand

PMID: 27770480 DOI: 10.1111/joor.12455

Abstract

Qualitative somatosensory testing (QualST) is a simple chairside test. It can be used to roughly assess the presence or absence of altered somatosensory function. To use QualST clinically, it is important to assess its agreement with quantitative sensory testing (QST). The aims of this study were to assess the agreement between QST and QualST when testing the modulation of facial sensitivity by capsaicin in healthy participants and to explore the agreement between QST and QualST in assessing the intraoral sensory function in clinical atypical odontalgia (AO) patients. Eighteen healthy pain-free adults and data from 27 AO patients were included in the study. Thirteen QST and three QualST parameters were evaluated at each site. Z-scores were computed for healthy participants, and Loss-Gain scores were

Sensory testing
Do we need Quantitative testing?

Possible Neuropathic pain-pain since event

Probable neuropathic pain (check patient not in remission)

- **Identify neuropathic area and +ve or –ve signs**
  - Mechanical and or thermal allodynia
  - Hyperalgesia
  - Hyperpathia
  - (Refractory period =TN)
- Qualitative sensory testing

Definite neuropathic pain

- Quantitative sensory testing
  - Trigeminal reflex testing is an established neurophysiologic assessment of nerve function, requires only standard nerve conduction study equipment. Blink, jaw closing, jaw opening)
  - Method of Limens thermo-sensory testing
  - Evoked potentials after electric or thermal stimuli have been studied in trigeminal neuralgia. In contrast to trigeminal reflex testing, which is normal in idiopathic or classic trigeminal neuralgia, evoked potentials may be altered, but their mean specificity of 64% is low

We don't need complex quantitative testing?

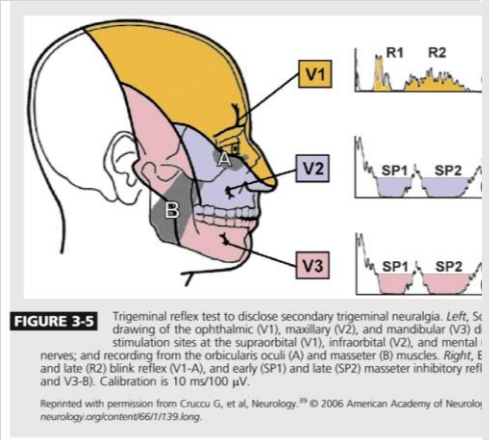

FIGURE 3-5 Trigeminal reflex test to disclose secondary trigeminal neuralgia. *Left*, Sc drawing of the ophthalmic (V1), maxillary (V2), and mandibular (V3) d stimulation sites at the supraorbital (V1), infraorbital (V2), and mental nerves; and recording from the orbicularis oculi (A) and masseter (B) muscles. *Right*, E and late (R2) blink reflex (V1-A), and early (SP1) and late (SP2) masseter inhibitory refl and V3-B). Calibration is 10 ms/100 μV.

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CONTINUUM **Review Article**

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Relationship Disclosure:

Trigeminal Neuralgia

Giorgio Cruccu, MD

Pain in trigeminal neuralgia: neurophysiology and measurement: a comprehensive review

Kumar S*, Rastogi S**, Kumar S**, Mahendra P**, Bansal M***, Chandra L**
Private Practice*
**Department of Oral and Maxillofacial Surgery and Oral Implantology, Institute of Technology and Sciences- Centre for Dental Studies and Research, Murad Nagar, Ghaziabad, India-201206
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Randomized Controlled Trial › J Oral Rehabil. 2017 Jan;44(1):30-42. doi: 10.1111/joor.12455. Epub 2016 Nov 16.

Agreement between quantitative and qualitative sensory testing of changes in oro-facial somatosensory sensitivity

J Agbaje [1], A De Laat [2], P Constantinus [1 3], P Svensson [4 5 6], L Baad-Hansen [4 5]

Affiliations + expand

PMID: 27770480 DOI: 10.1111/joor.12455

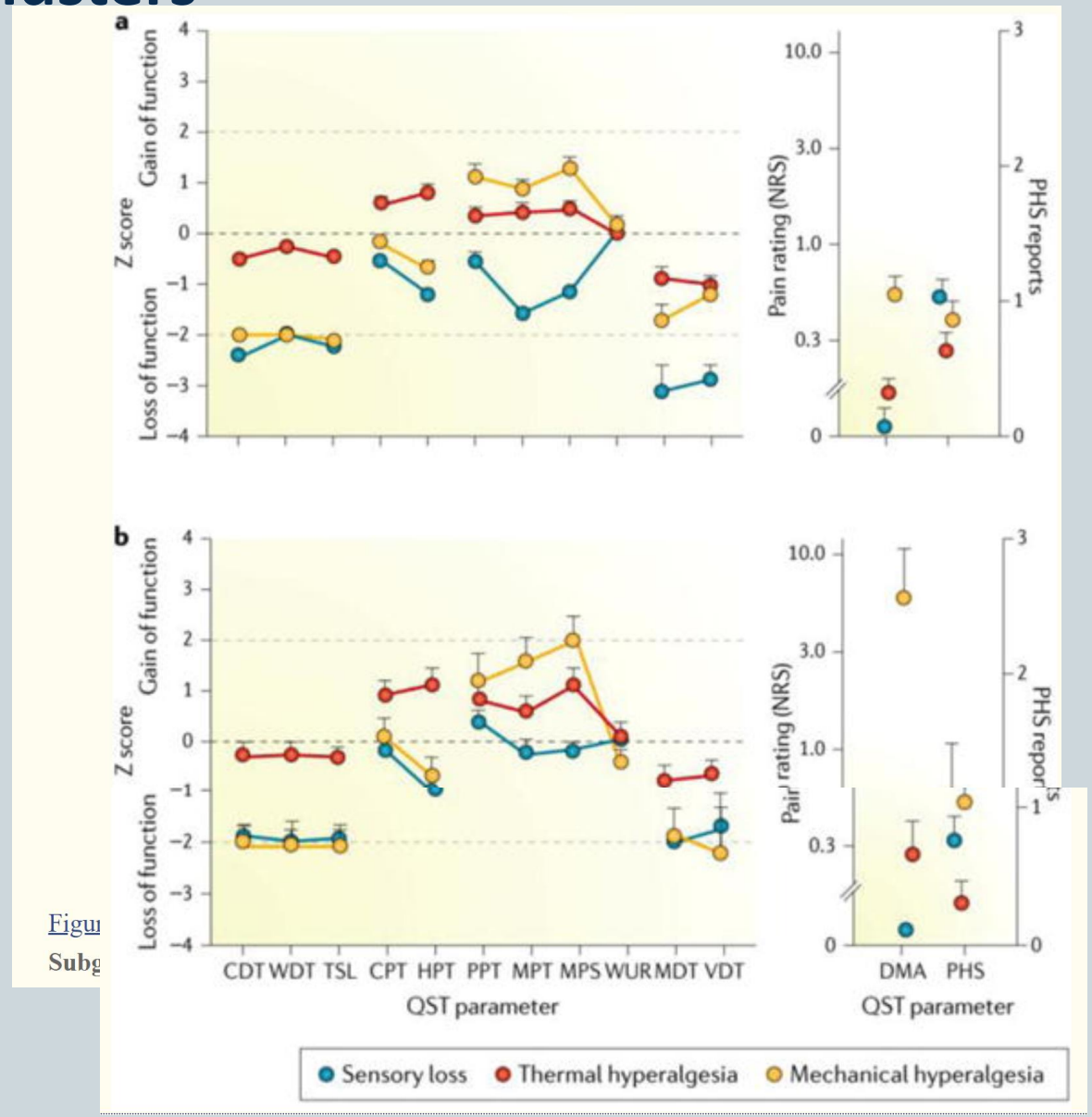
Abstract

Qualitative somatosensory testing (QualST) is a simple chairside test. It can be used to roughly assess the presence or absence of altered somatosensory function. To use QualST clinically, it is important to assess its agreement with quantitative sensory testing (QST). The aims of this study were to assess the agreement between QST and QualST when testing the modulation of facial sensitivity by capsaicin in healthy participants and to explore the agreement between QST and QualST in assessing the intraoral sensory function in clinical atypical odontalgia (AO) patients. Eighteen healthy pain-free adults and data from 27 AO patients were included in the study. Thirteen QST and three QualST parameters were evaluated at each site. Z-scores were computed for healthy participants, and Loss-Gain scores were

Sub types of neuropathic pain
Phenotyping patients with NePain- 3 clusters

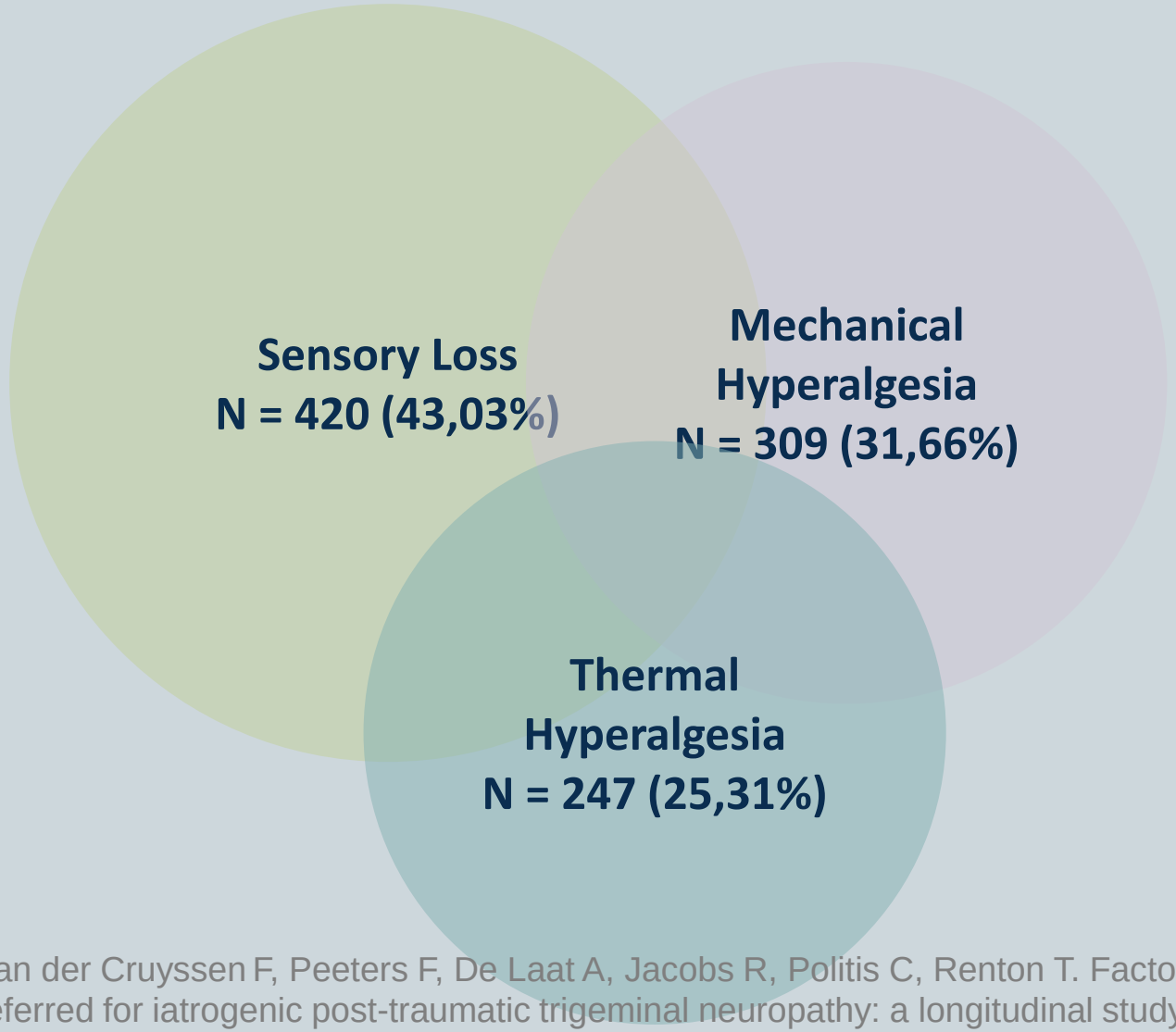
Furthermore, the first clinical trial to show phenotype stratification based on these sensory profiles has predictive power for treatment response.

Error bars are the graphical representation of the variability of the data present in the database. CDT, cold detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; PPT, pressure pain threshold; QST, quantitative sensory test; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio.



Baron, R. *et al.*, Peripheral neuropathic pain: a mechanism-related organizing principle based on sensory profiles, *Pain*, **158**, 2, 261–272,

Similar Clustering of Sensory Profiles Trigeminal PTNP (N = 976)



Received: 9 December 2019 | Revised: 7 May 2020 | Accepted: 10 July 2020
DOI: 10.1111/joor.13058

ORIGINAL ARTICLE

JOURNAL OF ORAL REHABILITATION WILEY

Signs and symptoms, quality of life and psychosocial data in 1331 post-traumatic trigeminal neuropathy patients seen in two tertiary referral centres in two countries

Fréderic Van der Cruyssen[1,2] | Frederik Peeters[1,2] | Thomas Gill[3] | Antoon De Laat[4,5] | Reinhilde Jacobs[2,6] | Constantinus Politis[1,2] | Tara Renton[3]

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Abstract

Background: Post-traumatic trigeminal neuropathy (PTN) is a disturbance of function or pathological change of the trigeminal nerve branches following trauma and has an important impact on patient's quality of life (QoL).

Objectives: To provide diagnostic data on PTN and illustrate differences in aetiology, injured nerve, pain distribution, sensory profile and QoL between PTN subgroups.

Methods: 1331 patients with painful or non-painful PTN were retrospectively re-viewed in two centres, extracting demographic data, time and cause of trauma, clinical findings including signs and symptoms, basic neurosensory testing, imaging modalities, treatments, and QoL or psychosocial assessment.

Results: More females were represented (70%) than males. The inferior alveolar nerve was most frequently damaged (60%) followed by the lingual nerve (28%). Wisdom teeth removal was considered the main cause (48%). Pain was reported in 63% of patients and pain frequency increased with age without clinically significant gender differences. Numbness was reported in 50% of PTN patients. Neurosensory testing showed larger affected dermatome involvement in persistent injuries, with no differences between the non-painful and painful PTN groups. Patient clustering indicated different sensory profile distributions when stratified according to aetiol-ogy or affected nerve branch. High interference with lifestyle was reported (78%), and patients suffering from painful PTN had worse QoL and psychosocial outcomes.

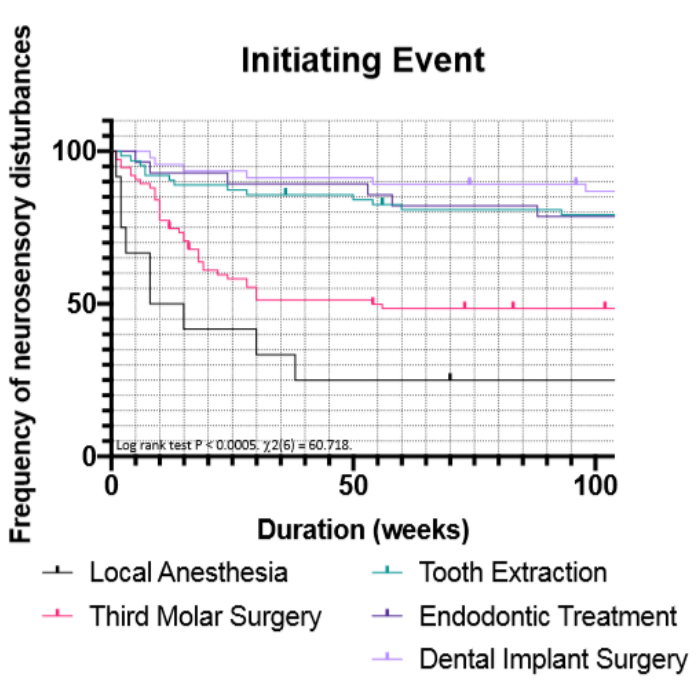
Conclusion: Patients with painful PTN had different clinical profiles and lower QoL scores than those with non-painful PTN. Sensory profiles may provide important prognostic and therapeutic information; however, more research is needed to assess the clustering procedure and link these clusters to therapeutic guidelines.

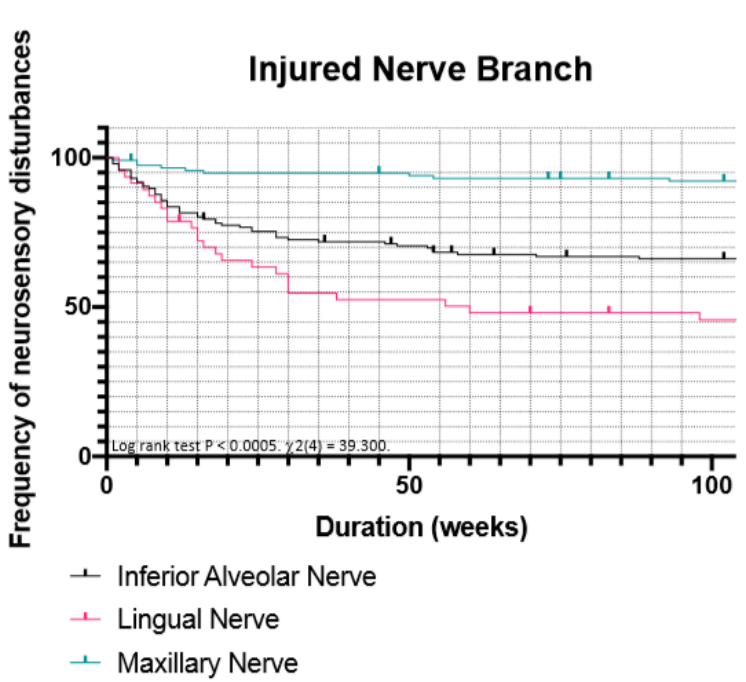
KEYWORDS
diagnosis, neuropathic pain, quality of life, trigeminal nerve, trigeminal nerve disorder

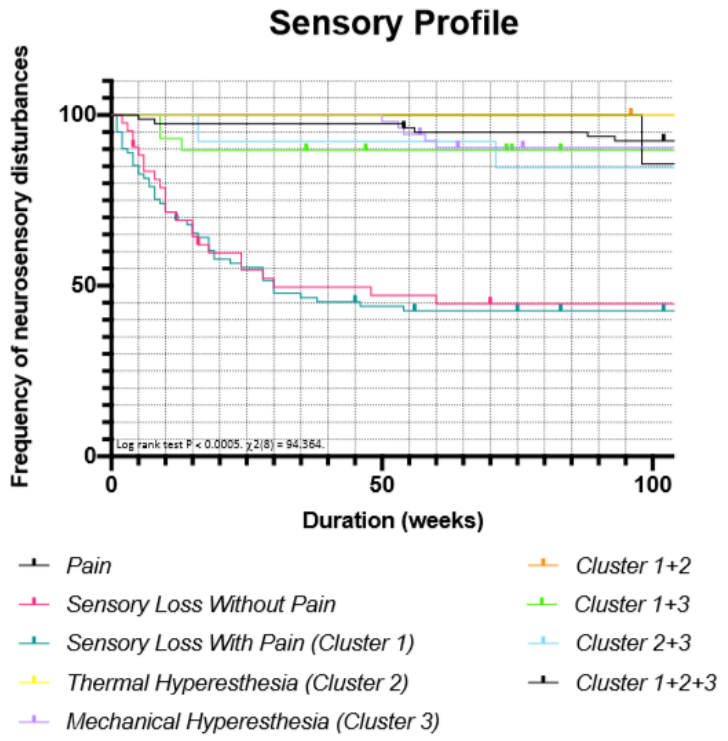
Van der Cruyssen F, Peeters F, De Laat A, Jacobs R, Politis C, Renton T. Factors affecting evolution of symptoms and quality of life in patients referred for iatrogenic post-traumatic trigeminal neuropathy: a longitudinal study in two tertiary referral centers in UK and Belgium. Pain 2020
Van der Cruyssen F, Peeters F, Gill T, De Laat A, Jacobs R, Politis C, Renton T. Signs and symptoms, quality of life and psychosocial data in 1331 post-traumatic trigeminal neuropathy patients seen in two tertiary referral centres in two countries. J Oral Rehabil. 2020 Oct;47(10):1212-1221. doi: 10.1111/joor.13058. Epub 2020 Aug 2. PMID: 32687637; PMCID: PMC7540026.

Prognosis of Post Traumatic Neuropathy N=1331

Kaplan–Meier analysis of neurosensory disturbances over time comparing the injured nerve branch (A), initiating event (B), and sensory profile (C).

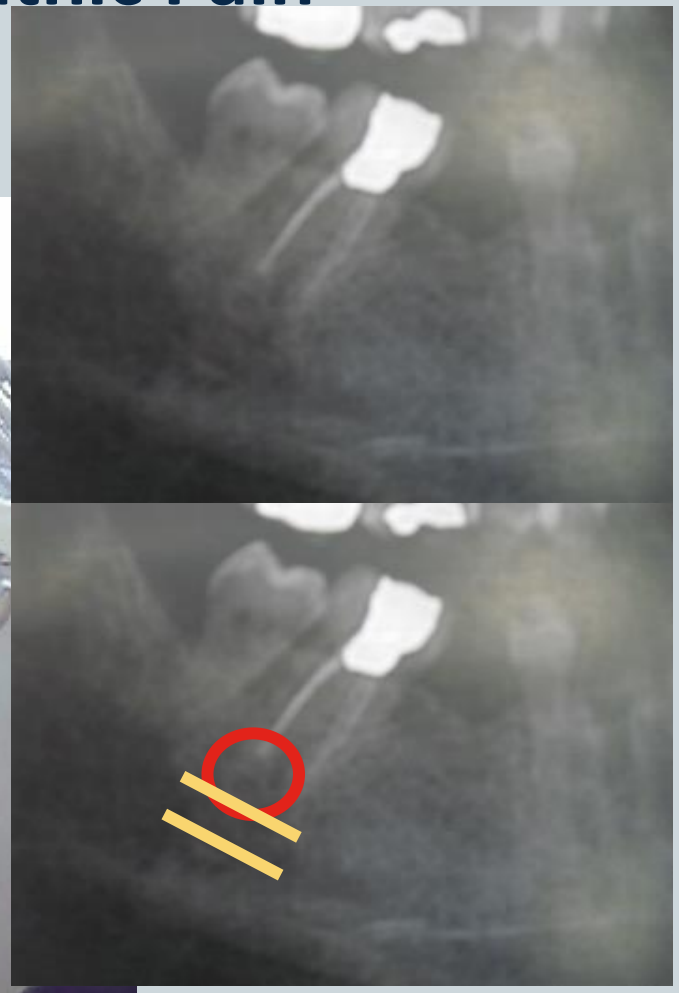






Van der Cruyssen F, Peeters F, De Laat A, Jacobs R, Politis C, Renton T. Factors affecting evolution of symptoms and quality of life in patients referred for iatrogenic post-traumatic trigeminal neuropathy: a longitudinal study in two tertiary referral centers in UK and Belgium. Pain 2020 in press

Example of Endo Related Post Traumatic Neuropathic Pain



Inferior dental canal

Periapical area

Primary headaches V2/3 Migraine / Trigeminal autonomic cephalalgias (TACs) or Toothache?

What's in a name?

- Facial Migraine
- Below orbito-meatal migraine
- Neurovascular orofacial pain
- Headache attributed to facial pain (ICHD3)

Key features

- Older pain cohort
- More autonomic signs
- Trauma onset (dental or ENT surgery)

3 types

- Patients who get migraine affecting V1 + V2 +/- V3
- Patients with previous classic migraine V1 for many years then absent then represents as Facial V2 +/- V3 migraine
- Patients presenting with de novo V2 +/- V3 migraine

Recommendation?

- Educate dentists in recognition of concomitant migrainoid and autonomic signs

Migraine presenting as isolated facial pain: A prospective clinical analysis of 58 cases

Giorgio Lambru, Leigh-Ann Elias, Pankaew Yakkaphan, more... Show all authors

First Published June 17, 2020 | Research Article | Find in PubMed | Check for updates

https://doi.org/10.1177/0333102420933277

Article information

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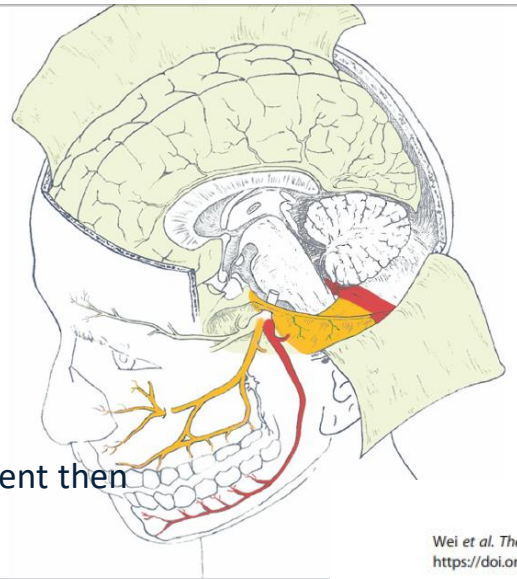


e of migraine presenting as isolated facial pain.

udit, part of our multidisciplinary facial pain service

ine presenting as isolated facial pain who attended our

Wei et al. The Journal of Headache and Pain (2019) 20:69

https://doi.org/10.1186/s10194-019-1019-7

The Journal of Headache and Pain

RESEARCH ARTICLE Open Access

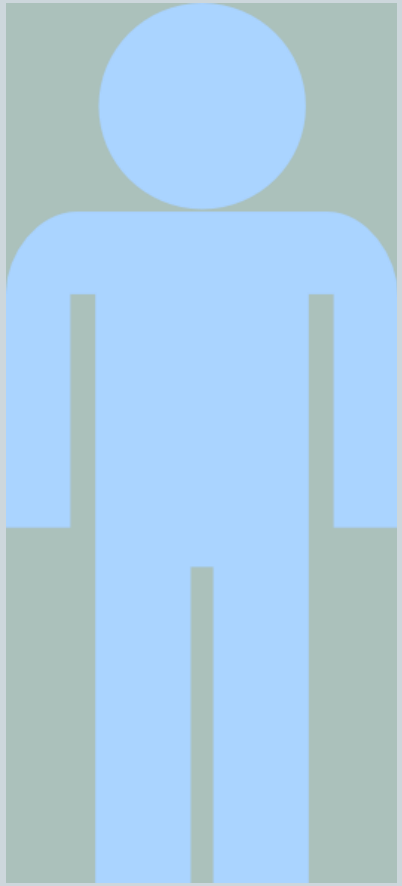
Trigeminal autonomic cephalalgias presenting in a multidisciplinary tertiary orofacial pain clinic

D. Y. Wei, D. Moreno-Ajona, T. Renton and P. J. Goadsby

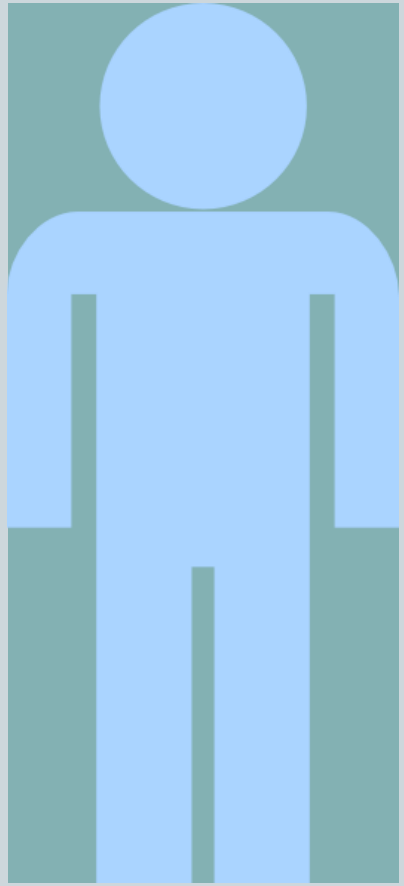
Migraine presenting as isolated facial pain: A prospective clinical analysis of 58 cases.**Lambru G**, Elias LA, Yakkaphan P, **Renton T.**Cephalalgia. 2020 Oct;40(11):1250-1254. doi: 10.1177/0333102420933277. Epub 2020 Jun 17.PMID: 32551980

Overview

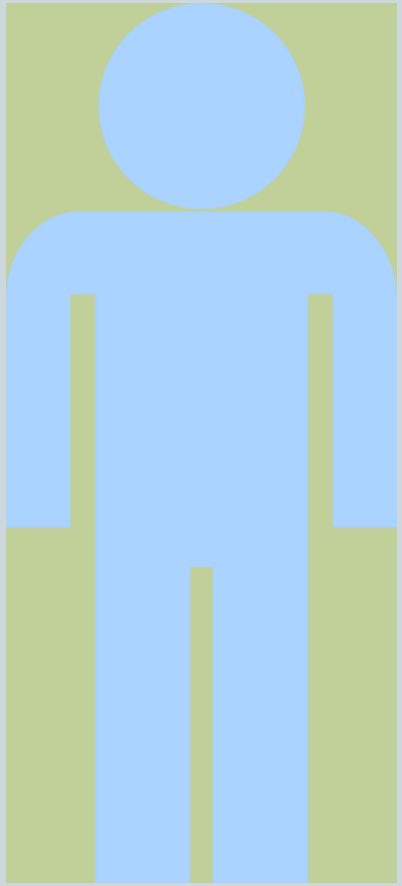
Neuropathic pain
Definitions &
Diagnosis



Neuropathic pain
Classification &
Trigeminal
presentation



Neuropathic pain
prevention of
nerve injuries



Prognosis and
outcome &
management

International Classification of OFP (ICOP) 2020

Cephalalgia
An International Journal of Headache
International Headache Society

Cephalalgia
2020, Vol. 40(2) 129–221

DOI: 10.1177/0333102419893823
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International Classification of Orofacial Pain, 1st edition (ICOP)

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The Orofacial Pain Classification Committee

The committee is a collaborative group consisting of members of the Orofacial and Head Pain Special Interest Group (OFHP SIG) of the International Association for the Study of Pain (IASP), the International Network for Orofacial Pain and Related Disorders Methodology (INfORM), the American Academy of Orofacial Pain (AAOP) and the International Headache Society (IHS).

International Classification of Pain

Neuropathic pain

ICOP-I

Cephalalgia
An International Journal of Headache
International Headache Society

Cephalalgia
2020, Vol. 40(2) 129–221

DOI: 10.1177/0333102419893823
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International Classification of Orofacial Pain, 1st edition (ICOP)

Transl

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Classification overview

1. ***Orofacial pain attributed to disorders of dentoalveolar and anatomically related structures***
   - **1.1 Dental pain**
     - 1.1.1 Pulpal pain
     - 1.1.2 Periodontal pain
     - 1.1.3 Gingival pain
   - **1.2 Oral mucosal, salivary gland and jaw bone pains**
     - 1.2.1 Oral mucosal pain
     - 1.2.2 Salivary gland pain
     - 1.2.3 Jaw bone pain
   - **References**

2. ***Myofascial orofacial pain***
   - **2.1 Primary myofascial orofacial pain**
     - 2.1.1 Acute primary myofascial orofacial pain
     - 2.1.2 Chronic primary myofascial orofacial pain
   - **2.2 Secondary myofascial orofacial pain**
     - 2.2.1 Myofascial orofacial pain attributed to tendonitis
     - 2.2.2 Myofascial orofacial pain attributed to myositis
     - 2.2.3 Myofascial orofacial pain attributed to muscle spasm
   - **References**

3. ***Temporomandibular joint (TMJ) pain***
   - **3.1 Primary temporomandibular joint pain**
     - 3.1.1 Acute primary temporomandibular joint pain
     - 3.1.2 Chronic primary temporomandibular joint pain
   - **3.2 Secondary temporomandibular joint pain**
     - 3.2.1 Temporomandibular joint pain attributed to arthritis
     - 3.2.2 Temporomandibular joint pain attributed to disc displacement
     - 3.2.3 Temporomandibular joint pain attributed to degenerative joint disease
     - 3.2.4 Temporomandibular joint pain attributed to subluxation
   - **References**

4. ***Orofacial pain attributed to lesion or disease of the cranial nerves***
   - **4.1 Pain attributed to lesion or disease of the trigeminal nerve**
     - 4.1.1 Trigeminal neuralgia
     - 4.1.2 Other trigeminal neuropathic pain
   - **4.2 Pain attributed to lesion or disease of the glossopharyngeal nerve**
     - 4.2.1 Glossopharyngeal neuralgia
     - 4.2.2 Glossopharyngeal neuropathic pain
   - **References**

5. ***Orofacial pains resembling presentations of primary headaches***
   - **Introduction**
   - **5.1 Orofacial migraine**
     - 5.1.1 Episodic orofacial migraine
     - 5.1.2 Chronic orofacial migraine
   - **5.2 Tension-type orofacial pain**
   - **5.3 Trigeminal autonomic orofacial pain**
     - 5.3.1 Orofacial cluster attacks
     - 5.3.2 Paroxysmal hemifacial pain
     - 5.3.3 Short-lasting unilateral neuralgiform facial pain attacks with cranial autonomic symptoms (SUNFA)
     - 5.3.4 Hemifacial continuous pain with autonomic symptoms
   - **5.4 Neurovascular orofacial pain**
     - 5.4.1 Short-lasting neurovascular orofacial pain
     - 5.4.2 Long-lasting neurovascular orofacial pain
   - **References**

6. ***Idiopathic orofacial pain***
   - **6.1 Burning mouth syndrome (BMS)**
     - 6.1.1 Burning mouth syndrome without somatosensory changes
     - 6.1.2 Burning mouth syndrome with somatosensory changes
     - 6.1.3 Probable burning mouth syndrome
   - **6.2 Persistent idiopathic facial pain (PIFP)**
     - 6.2.1 Persistent idiopathic facial pain without somatosensory changes
     - 6.2.2 Persistent idiopathic facial pain with somatosensory changes
     - 6.2.3 Probable persistent idiopathic facial pain
   - **6.3 Persistent idiopathic dentoalveolar pain**
     - 6.3.1 Persistent idiopathic dentoalveolar pain without somatosensory changes
     - 6.3.2 Persistent idiopathic dentoalveolar pain with somatosensory changes
     - 6.3.3 Probable persistent idiopathic dentoalveolar pain
   - **6.4 Constant unilateral facial pain with additional attacks (CUFPA)**
   - **References**

7. ***Psychosocial assessment of patients with orofacial pain***
   - **Introduction**
   - **Levels of psychosocial assessment**
   - **Pain- and function-related constructs and instruments for OFPs**
     - Extent of pain
     - Pain intensity and pain-related disability
     - Functional limitation
     - Over-use behaviours
   - **Psychosocial constructs and instruments for OFPs**
     - Depression and anxiety
     - Somatoform disorders

PTNP
TN
PHN

BMS
PDAP

ICOP Definitions and Diagnostic Criteria
Trigeminal Neuralgia (TN)

IASP defines trigeminal neuralgia as " a sudden, usually unilateral, severe, brief, stabbing, recurrent pain in the distribution of one or more branches of the fifth cranial nerve".

4.1.1.1 Classical trigeminal neuralgia
Previously used term: Primary trigeminal neuralgia.
192 Cephalalgia 40(2) International Headache Society 2020

Description: Trigeminal neuralgia developing without apparent cause other than neurovascular compression.
Diagnostic criteria:

A. Recurrent paroxysms of unilateral pain fulfilling criteria for 4.1.1 Trigeminal neuralgia
B. B. Demonstration on magnetic resonance imaging (MRI) or during surgery of neurovascular compression (not simply contact), with morphological changes1 in the trigeminal nerve root.

- Classical TN
  - Paroxysmal pain ONLY pain in V" and V2, unilateral in patients over 60 years with Neurovascular conflict
  - With background pain and NVC conflict

- Secondary TN
  MS, SOL or other cause
  bilateral, neuropathy, younger age

- Idiopathic TN
  - Not secondary
  - No NVC

Diagnostic algorithm for TN

CONTINUUM **Review Article**

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Relationship Disclosure:
Dr Cruccu has received personal compensation for serving on the advisory board of and as a consultant for Angelini and Biogen, Inc and has received personal compensation for serving on the advisory board of and as a speaker for Sigma Tau Pharmaceuticals, Inc. Dr Cruccu has received research/grant support from Sapienza University of Rome and Sigma Tau Pharmaceuticals, Inc.

Unlabeled Use of Products/Investigational Use Disclosure:
Dr Cruccu discusses the unlabeled/investigational use of BIIB074 for the treatment of elderly pa
trigeminal ne

Trigeminal Neuralgia

Giorgio Cruccu, MD

ABSTRACT

Purpose of Review: Although trigeminal neuralgia is well known to neurologists, recent developments in classification and clinical diagnosis, new MRI methods, and a debate about surgical options necessitate an update on the topic.

Recent Findings: Currently, a worldwide controversy exists regarding the classification, diagnostic process, and surgical treatment of trigeminal neuralgia. This controversy has been caused on one side by the recognition that some 50% of patients with trigeminal neuralgia, apart from characteristic paroxysmal attacks, also have continuous pain in the same territory, which results in greater diagnostic difficulties and is associated with a lower response to medical and surgical treatments. In contrast, recent developments in MRI methods allow differentiation between a mere neurovascular contact and an effective compression of the trigeminal root by an anomalous vessel, which implies more difficulties in the choice of surgical treatment, with the indication for microvascular decompression becoming more restricted.

Summary: This article proposes that the diagnosis of trigeminal neuralgia, with or

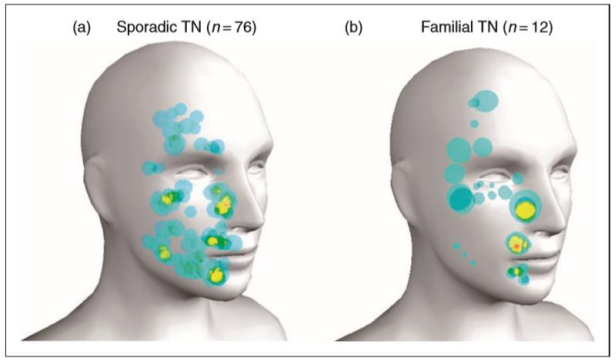
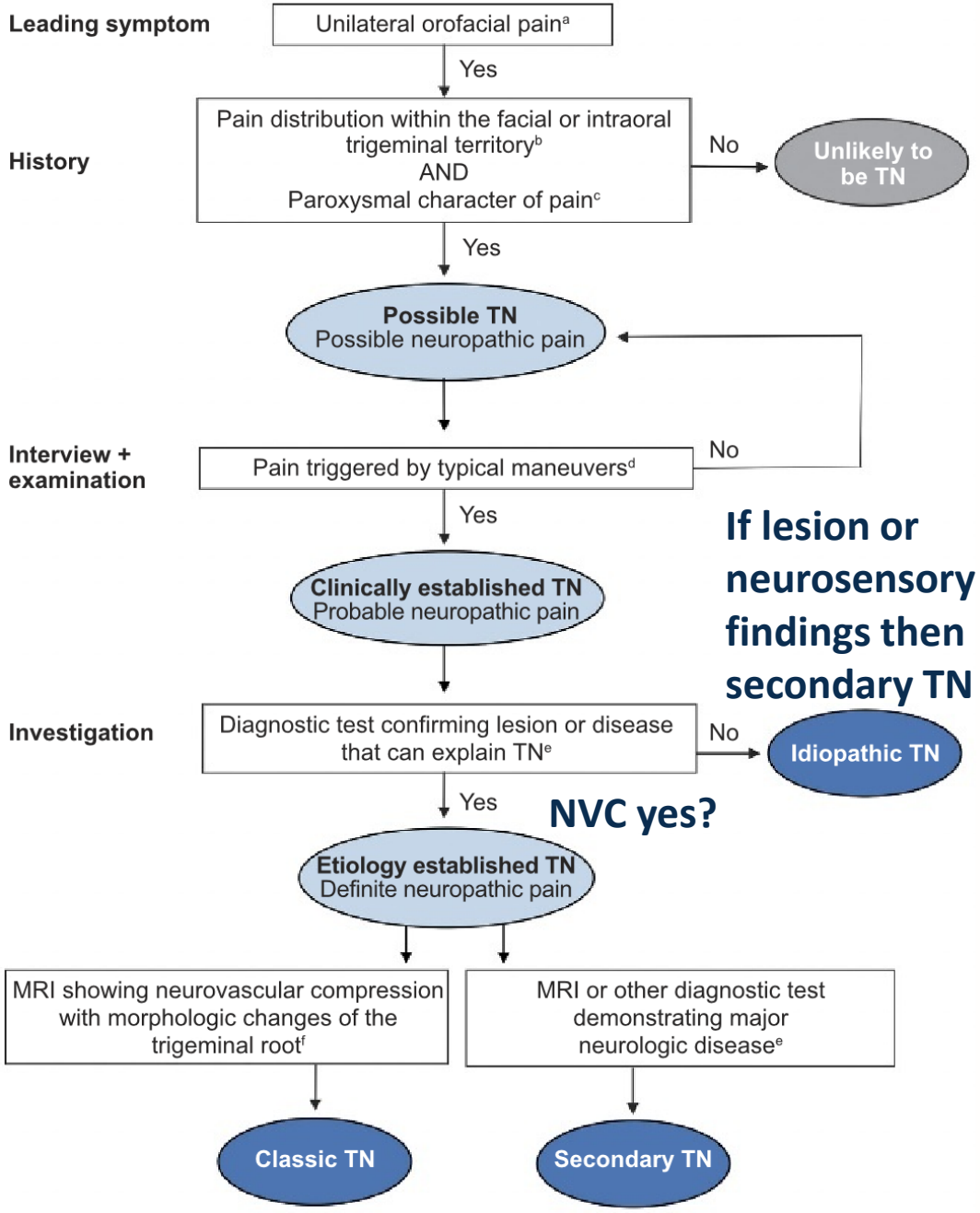


Figure 1. Trigger zones overlap profiling in patients with sporadic (a) and familial (b) TN. The number of superimpositions ranged from 2 (dark cyan) to 15 (dark orange), in sporadic forms, and between 2 (dark cyan) and 7 (dark orange) in familial forms.



ICOP Definitions and Diagnostic Criteria
Post Traumatic Neuropathic pain (PTNP)

4. *Orofacial pain attributed to lesion or disease of the cranial nerves*
4.1 Pain attributed to lesion or disease of the trigeminal nerve
4.1.1 Trigeminal neuralgia
4.1.2 Other trigeminal neuropathic pain
4.2 Pain attributed to lesion or disease of the glossopharyngeal nerve
4.2.1 Glossopharyngeal neuralgia
4.2.2 Glossopharyngeal neuropathic pain

4.1.2.3 Post-traumatic trigeminal neuropathic pain

- Previously used terms: Anaesthesia dolorosa; painful post-traumatic trigeminal neuropathy.
- Description: Unilateral or bilateral facial or oral pain following and caused by trauma to the trigeminal nerve(s), with other symptoms and/or clinical signs of trigeminal nerve dysfunction, and persisting or recurring for more than 3 months.
- *4.1.2.3.1 Probable post-traumatic trigeminal neuropathic pain*
- *Diagnostic criterion: A. Pain fulfilling all but criterion B2 for 4.1.2.3 Posttraumatic trigeminal neuropathic pain*.

4.1.2.4 Trigeminal neuropathic pain attributed to other disorder

4.1.2.5 Idiopathic trigeminal neuropathic pain

Description: Unilateral or bilateral facial pain in the distribution(s) of one or more branches of the trigeminal nerve

Diagnostic criteria:

A. Pain, in a neuroanatomically plausible area within the distribution(s) of one or both trigeminal nerve(s), persisting or recurring for >3 months and fulfilling criteria C and D

B. Both of the following:

1. history of a mechanical, thermal, radiation or chemical injury to the peripheral trigeminal nerve(s)
2. diagnostic test confirmation1 of a lesion of the peripheral trigeminal nerve(s) explaining the pain2

C. Onset within 6 months after the injury

D. Associated with somatosensory symptoms and/or signs4 in the same neuroanatomically plausible distribution

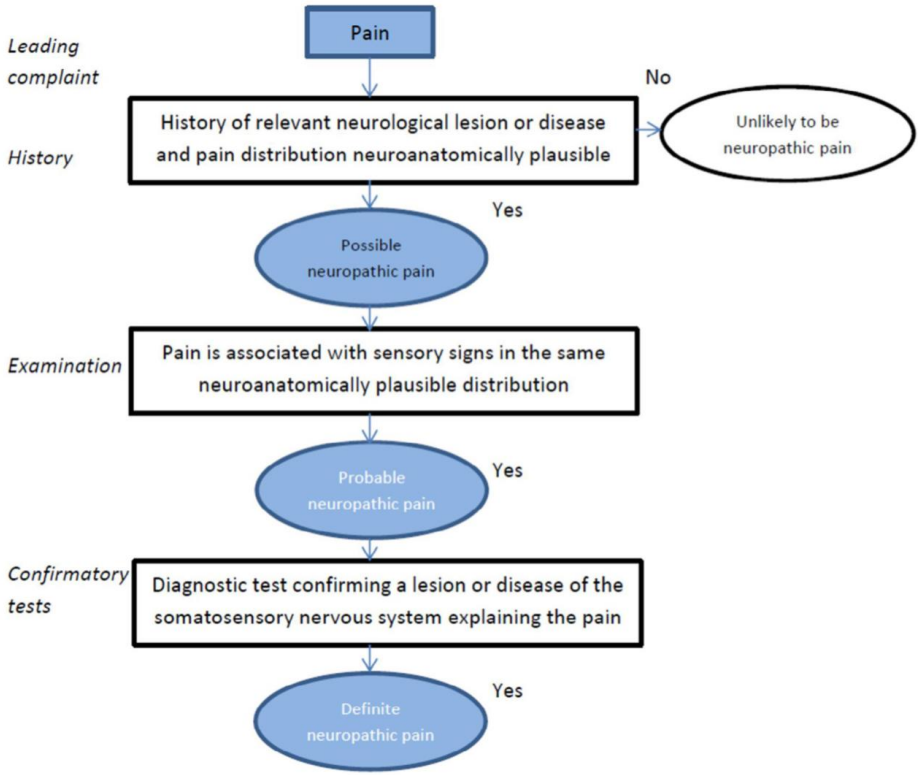
E. Not better accounted for by another ICOP or ICHD-3 diagnosis.

Diagnostic algorithm for Trigeminal PTNP

Vol. 125 No. 6 June 2018

Identifying criteria for diagnosis of post-traumatic pain and altered sensation of the maxillary and mandibular branches of the trigeminal nerve: a systematic review

Maria Devine, BDS, MFDS (RCS Ed), M Oral Surg, RCS, FHEA,[a] Murtaza Hirani, BDS, MFDS (RCS Ed),[a] Justin Durham, BDS, MFDS (RCS Ed), PhD, FCS (OS) RCS,[b] Donald R. Nixdorf, DDS, MS,[c] and Tara Renton, PhD, MDSc, BDS, FDS, RCS, FRACDS (OMS), FHEA[a]



Proposed grading system for neuropathic pain (Finnerup et al 2016).

Table VI. Proposed diagnostic criteria for PPTTN

Diagnostic criteria	*Notes*
A Spontaneous or touch-evoked (stimulus dependent) pain predominantly affecting the receptive field of one or more divisions of the trigeminal nerve.	Pain tends to spread with time and is mostly unilateral without crossing the midline. Paroxysmal pain patients may also have constant background pain. Time pattern may change over the course of the disease.
Duration ranges widely from episodic (minutes to days) and may also be constant	
B Develops within 3 months of an identifiable traumatic event to the painful area or relevant innervation.	Trauma, surgery, invasive dental treatment.
Continues for >3 months.	*Usually localized pain †Likely to cause dermatomal pain, may spread due to central mechanisms
C At least one clinically evident neurologic dysfunction:	Must be a constant feature and reproducible. Nonvital tooth is evidence of nerve damage.
Positive sign	Clinical examination may be suitable.
- Hyperalgesia	If area is amenable, quantitative sensory testing may reveal changes.
- Allodynia	Advanced neurophysiologic testing is not always available but certainly valuable (e.g., nerve conduction studies, electromyography, laser-evoked potentials, blink reflex, masseter inhibitory reflex). Convincing data from C may be considered sufficient.
- Swelling or flushing	
And/or negative sign	
- Anesthesia	
- Hypoesthesia	
D Imaging or neurophysiology demonstrating a neurologic lesion and its location	Imaging may often be historical, e.g., zygomatic fractures affecting the infraorbital nerve that have been decompressed, dental implants that impinged on nerve bundles but may have been removed. Root canal therapy is considered evidence of nerve damage. Neurophysiology (see above)
E Not attributed to another disorder	Other causes are ruled out by history, physical examination, and special investigations, if necessary
Diagnostic level	Possible NP
Fulfils criteria A, B, and E	Probable NP
Fulfils criteria A, B, C or D, and E	Definite NP
Fulfils criteria A, B, C, D and E	

ICOP Definitions and Diagnostic Criteria
Burning Mouth Syndrome (BMS)

Diagnostic criteria:

- A. Oral pain fulfilling criteria B and C
- B. Recurring daily for >2 hours per day for >3 months1
- 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 local or systemic causes have been excluded

E. Not better accounted for by another ICOP or ICHD-3 diagnosis.

6.1 Burning mouth syndrome (BMS)

Previously used terms:
Stomatodynia; glossodynia (when confined to the tongue); primary burning mouth syndrome.

Description:
An intraoral burning or dysaesthetic sensation, recurring daily for more than 2 hours per day for more than 3 months, without evident causative lesions on clinical examination and investigation.

6.1.3 Probable burning mouth syndrome

Description:
An intraoral burning or dysaesthetic sensation, recurring daily for more than 2 hours per day but for less than 3 months, without evident causative lesions on clinical examination and investigation.

Diagnostic criterion:

A. Oral pain fulfilling criteria for 6.1 *Burning mouth syndrome* except that it has been present for <3 months.[1]

Note:

1. Once 3 months have elapsed, the diagnosis becomes 6.1 *Burning mouth syndrome* (or one of its subtypes).

Comment:
Subforms are not formally classified but may be coded 6.1.3.1 *Probable burning mouth syndrome without somatosensory changes* or 6.1.3.2 *Probable burning mouth syndrome with somatosensory changes* according to the criteria above.

subforms of 1.1.3 *Gingival pain* or 1.2.1 *Oral mucosal pain*. They have previously been known as 'secondary burning mouth syndrome', but should be coded to these disorders. 6.1 *Burning mouth syndrome* is diagnosed only when all local and systemic causes have been excluded (hence, previously, 'primary burning mouth syndrome').

6.1.1 Burning mouth syndrome without somatosensory changes

Description:
An intraoral burning or dysaesthetic sensation, recurring daily for more than 2 hours per day for more than 3 months, unaccompanied by somatosensory changes and without evident causative lesions on clinical examination and investigation.

Diagnostic criteria:

A. Oral pain fulfilling criteria for 6.1 *Burning mouth syndrome*
B. Somatosensory changes are not present on qualitative or quantitative somatosensory testing.

6.1.2 Burning mouth syndrome with somatosensory changes

Description:
An intraoral burning or dysaesthetic sensation, recurring daily for more than 2 hours per day for more than 3 months and accompanied by negative and/or positive somatosensory changes, without evident causative lesion(s) on clinical examination and investigation.

Diagnostic criteria:

A. Oral pain fulfilling criteria for 6.1 *Burning mouth syndrome*
B. Somatosensory changes are present on qualitative and/or quantitative somatosensory testing.[1]

ICOP Definitions and Diagnostic Criteria
Persistent Dentoalveolar pain (PDAP)

- **Other previous terminology**
  - **atypical odontalgia**
  - **phantom pain**
  - **persistent idiopathic facial pain**
  - **deafferentation pain**

6.3 Persistent idiopathic dentoalveolar pain

Previously used terms:
Atypical odontalgia; primary persistent dentoalveolar pain disorder (PDAP); phantom tooth pain.

Diagnostic criteria:

A. Intraoral dentoalveolar pain fulfilling criteria B and C

B. Recurring daily for >2 hours/day for >3 months1

C. Pain has both of the following characteristics:

1. localized to a dentoalveolar site (tooth or alveolar bone)
2. deep, dull, pressure-like quality

D. Clinical and radiographic examinations are normal and local causes have been excluded

E. Not better accounted for by another ICOP or ICHD-3 diagnosis.

6.3.1 Persistent idiopathic dentoalveolar pain without somatosensory changes

Description:
Persistent unilateral intraoral dentoalveolar pain, rarely occurring in multiple sites, with variable features, recurring daily for more than 2 hours per day for more than 3 months, unaccompanied by somatosensory changes and in the absence of any preceding causative event.

Diagnostic criteria:

A. Intraoral pain fulfilling criteria for 6.3 *Persistent idiopathic dentoalveolar pain*
B. Somatosensory changes are not present on qualitative or quantitative somatosensory testing.

6.3.2 Persistent idiopathic dentoalveolar pain with somatosensory changes

Description:
Persistent unilateral intraoral dentoalveolar pain, rarely occurring in multiple sites, with variable features, recurring daily for more than 2 hours per day for more than 3 months and accompanied by negative and/or positive somatosensory changes, in the absence of any preceding causative event.

Diagnostic criteria:

A. Intraoral pain fulfilling criteria for 6.3 *Persistent idiopathic dentoalveolar pain*
B. Somatosensory changes are present on qualitative and/or quantitative somatosensory testing.[1]

6.3.3 Probable persistent idiopathic dentoalveolar pain

Description:
Unilateral intraoral dentoalveolar pain, rarely occurring in multiple sites, with variable features, recurring daily for more than 2 hours per day but for less than 3 months, in the absence of any preceding causative event.

Diagnostic criterion:
A. Oral pain fulfilling criteria for 6.3 *Persistent idiopathic dentoalveolar pain* except that it has been present for <3 months.[1]

Note:

1. Once 3 months have elapsed, the diagnosis becomes 6.3 *Persistent idiopathic dentoalveolar pain* (or one of its subtypes).

Comment:
Subforms are not formally classified, but may be coded 6.3.3.1 *Probable persistent idiopathic dentoalveolar pain without somatosensory changes* or 6.3.3.2 *Probable persistent idiopathic dentoalveolar pain with somatosensory changes* according to the criteria above.

6.4 Constant unilateral facial pain with additional attacks (CUFPA)

Description:
Constant (unremitting) dull unilateral facial pain of mild to moderate intensity, accompanied by distinct attacks of moderate to severe pain in the same location lasting 10–30 minutes. There are no typical autonomic and/or migrainoid features accompanying either the constant pain or the additional pain attacks.

Diagnostic criteria:

A. Constant strictly unilateral facial pain fulfilling criterion B, with exacerbations fulfilling criterion C

Is PDAP or Chronic post surgical pain (CPSP)?
Persistent pain and no identifiable neuropathic area in 69% of cases

Persistent postsurgical pain (PPSP) is a frequent and often disabling complication of many surgical procedures.

Nerve injury-induced neuropathic pain (NeuP) has repeatedly been proposed as a major cause of PPSP. However, there is a lack of uniformity in NeuP assessment across studies, and the prevalence of NeuP may differ after various surgeries.

We performed a systematic search of the PubMed, CENTRAL, and Embase databases and assessed 281 studies that investigated PPSP after 11 types of surgery.

The prevalence of PPSP in each surgical group was examined. The prevalence of NeuP was determined by applying the recently published NeuP probability grading system. The prevalence of probable or definite NeuP was high in patients with persistent pain after thoracic and breast surgeries-66% and 68%, respectively. In patients with PPSP after groin hernia repair, the *prevalence of NeuP was 31%,* and after total hip or knee arthroplasty it was 6%.

The results suggest that the prevalence of NeuP among PPSP cases differs in various types of surgery, probably depending on the likelihood of surgical iatrogenic nerve injury. Because of large methodological variability across studies, a more uniform approach is desirable in future studies for evaluating persistent postsurgical NeuP.

Haroutiunian S, Nikolajsen L, Finnerup NB, Jensen TS. The neuropathic component in persistent postsurgical pain: a systematic literature review. Pain. 2013 Jan;154(1):95-102. doi: 10.1016/j.pain.2012.09.010.

	Estimated incidence of chronic pain	Estimated chronic severe (disabling) pain (>5 out of score of 10)	US surgical volumes (1000s)†
Amputation[2]	30–50%	5–10%	159 (lower limb only)
Breast surgery (lumpectomy and mastectomy)[3]	20–30%	5–10%	479
Thoracotomy[4-7]	30–40%	10%	Unknown
Inguinal hernia repair[8-10]	10%	2–4%	609
Coronary artery bypass surgery[11-13]	30–50%	5–10%	598
Caesarean section[14]	10%	4%	220

*Gall bladder surgery not included, since preoperative diagnosis of pain specifically from gall bladder is difficult and persistent postoperative pain could therefore be related to other intra-abdominal disorders. †National Center For Health Statistics, Ambulatory and Inpatients Procedures, USA, 1996.

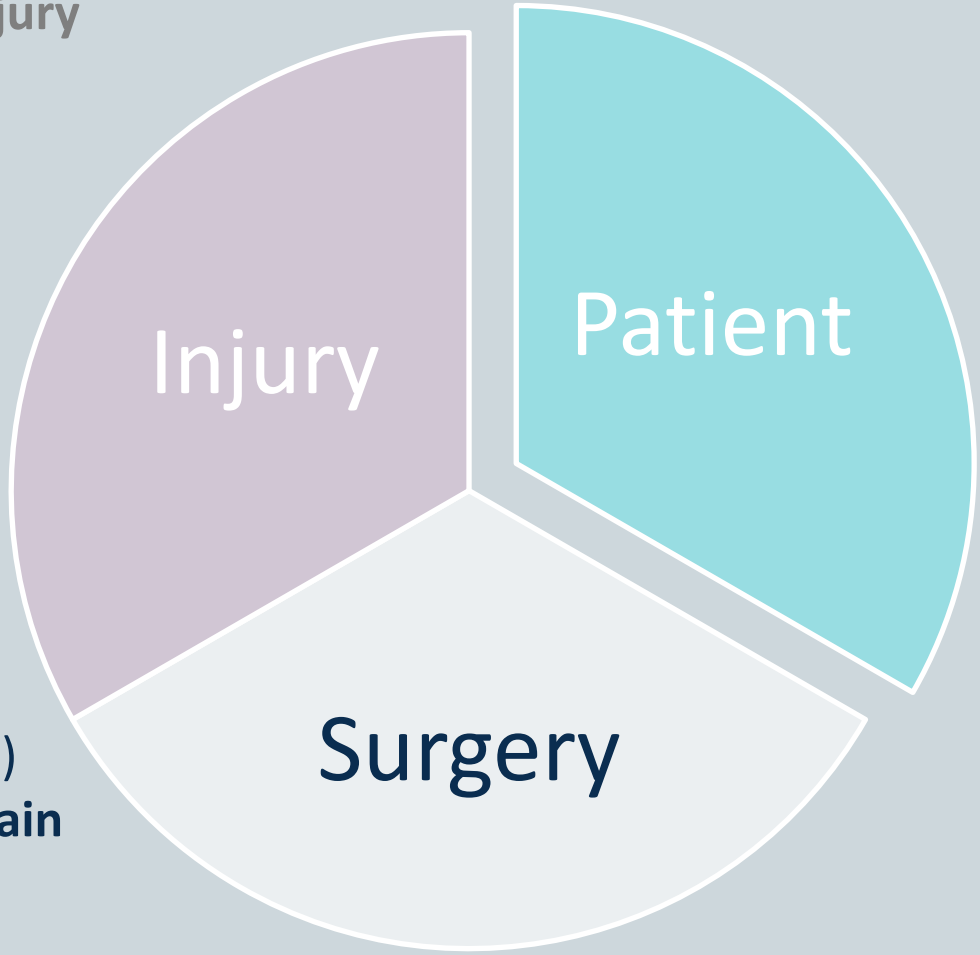
Table 1: **Estimated incidence of chronic postoperative pain and disability after selected surgical procedures***

30% get persistent pain 10% are <u>severely</u> affected
Very few related to dentistry likely due to LA
1.6-5% after endodontics
After all of dental procedures???????

Kehlet H *et al*, 2006 Lancet

Patient and Surgical factors predictive for chronic post surgical pain (CPSP)

Resultant sensory nerve injury
Large neuropathic area
Thermal allodynia
Mechanical allodynia
Hyperalgesia



Age > 50 yrs
Female
Multiple pain conditions Social Factors

Axis II Psychological factors
Mood anxiety / depression
Introversion, neuroticism, hypervigilance, catastrophising
Fear of surgery
Fear of pain

Poor pain modulation DNIC positive tests
Genetics
COMPT CA channels
Epigenetics
Prior abuse and neglect
OMICS ????

<u>Surgical factors</u>
Type of surgery
Site
Minimise nerve injury
(Tissue tension & Duration)
High level perioperative pain
(Lack of local anaesthesia)

Joel Katz & Ze'ev Seltzer Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert Review of Neurotherapeutics Volume 9, 2009 - Issue 5

Predictive factors for chronic post-surgical pain/Nepain

Performing preoperative screening for patient-specific factors such as the following prior to surgery may also help predict the risk of post-surgical neuropathy:

- *Genetics:* **Haplotype for catechol-O-methyltransferase**
- *Preceding pain:* Intensity and chronicity
- *Psychosocial factors:* Anxiety, depression, fear avoidance, self-efficacy, work, physical levels of activity, somatization, anxiety, catastrophizing
- *Younger age:* Increased risk of neuropathic pain following breast surgery and herniorrhaphy
- *Older age:* Increased risk of neuropathic pain following other surgery
- *Female sex:* Increased risk of neuropathic pain

Preoperative medication may play a role in minimising the development of post traumatic neuropathic pain, but the evidence is limited. In a systematic review of prevention and management of chronic postsurgical (neuropathic) pain, the authors found that while some studies have shown benefit of perioperative pregabalin in reduction of chronic pain development at 6 and 12 months others have demonstrated no difference (REF). Martinez et al's more recent systematic review (REF) identified no difference in the development of chronic postsurgical pain when comparing treatment with pregabalin or a placebo. Gabapentinoids, may however have an impact on reducing the development of chronic postsurgical (neuropathic) pain however, more comprehensive studies are required.

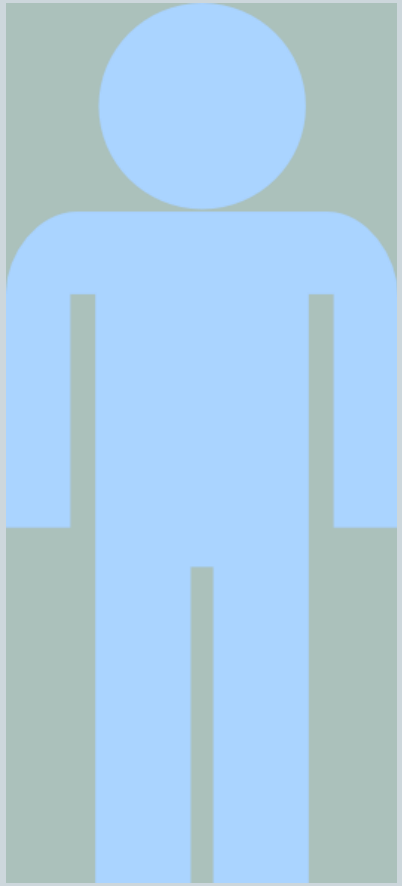
Surgical risk factors may be potentially modifiable. They include the duration and extent of surgical procedure and technique (eg, tension due to retraction of tissues) and level of reported perioperative pain intensity. Modifications to account for these risk factors may include:

- Multimodal management of severe acute postsurgical pain
- Minimal access surgery
- Intraoperative use of local anesthesia when patient is undergoing general anesthetic

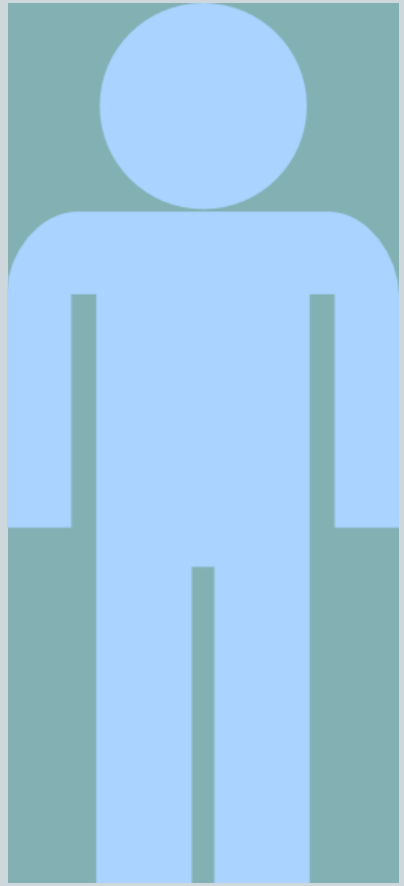
Thapa P, Euasobhon P. Chronic postsurgical pain: current evidence for prevention and management. Korean J Pain. 2018;31(3):155–73.
Mishriky BM, Waldron NH, Habib AS. Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis. Br J Anaesth. 2015;114(1):10–31. 32.Martinez V, Pichard X, Fletcher D. Perioperative pregabalin administration does not prevent chronic postoperative pain: systematic review with a metaanalysis of randomized trials. Pain. 2017;158(5): 775–83

Overview

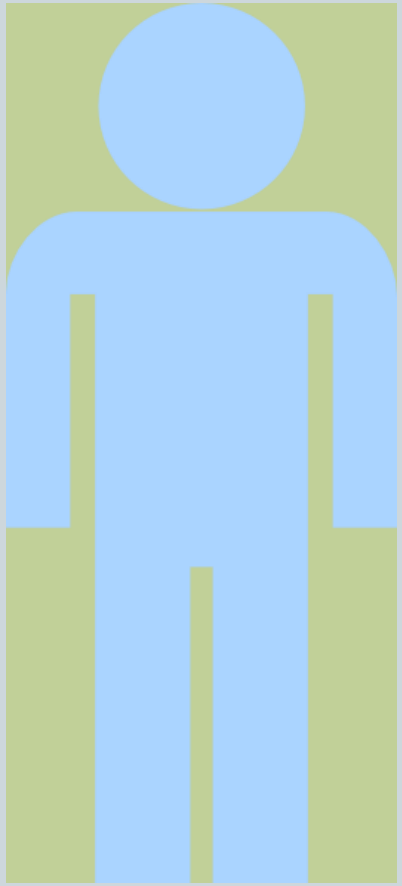
Neuropathic pain
Definitions &
Diagnosis



Neuropathic pain
Classification &
Trigeminal presentation

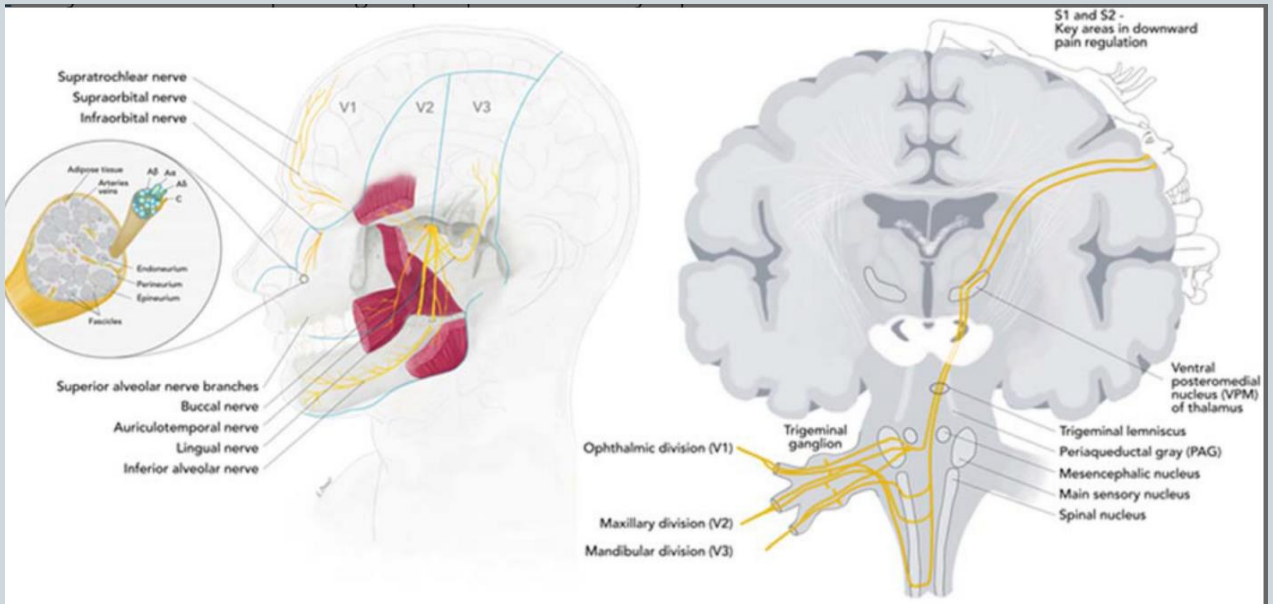


Neuropathic pain prevention of nerve injuries



Prognosis and
outcome &
management

Post traumatic trigeminal neuropathic pain



Peripheral

1. Wallerian degeneration may favour the development of abnormal activity, including neurochemical abnormalities in the contiguous intact root ganglion, with overexpression of transient receptor potential vanilloid receptor 1 (TRPV1), neurotrophic factors such as brain-derived neurotrophic factor (BDNF), and mRNA for nociceptive neurotransmitters such as CGRP, in fibers spared by the lesion.
2. Ectopic discharges in lesioned fibers and their corresponding ganglia. Within sites of axonal demyelination owing to altered distribution of voltage-dependent sodium channels in the demyelinated segments of the membrane.
3. High frequency stimulation of small myelinated fibers (Aδ) generates pain, and a great deal of data favour the implication of large Aβ fibers in touch allodynia and secondary hyperalgesia. In addition, the temporal dynamics of tactile allodynia after nerve section closely follow those of ectopic discharges in myelinated A fibers, while such discharges are not observed in non myelinated C axons
4. Abnormal activity in axons undamaged by the lesion due to newly inserted sodium channels include; Nav 1.7, 1.3, 1.8 and 1.9
5. Alterations in the expression and regulation of intracellular calcium ions and modulatory receptors on primary afferent terminals.
6. Neuroimmune interactions resulting in enhanced and/or altered production of inflammatory signalling molecules.
7. Sensory-sympathetic coupling and other alterations in receptor signalling.

Central

Ectopic neural activity After a peripheral nerve lesion, spontaneous activity is evident in both injured and neighbouring uninjured nociceptive afferents. Increasing levels of mRNA for voltage-gated sodium channels seem to correlate with ectopic activity, and increased expression of sodium channels in lesioned and intact fibers might lower action potential threshold until ectopic activity takes place. Similar changes within second-order nociceptive neurons are thought to occur after central lesions, leading to central neuropathic pain.

Central sensitisation Secondary allodynia and hyperalgesia (ie, evoked pain, in particular dynamic mechanical allodynia) in the area adjacent to the innervation territory of the lesioned nerves requires involvement of the CNS. Central sensitisation might develop as a consequence of ectopic activity in primary nociceptive afferent fibers and structural damage within the CNS itself might not be necessarily involved. Ongoing discharges of peripheral afferent fibers that release excitatory aminoacids and neuropeptides within the dorsal horn of the spinal cord lead to postsynaptic changes of second-order nociceptive neurons, such as phosphorylation of NMDA and AMPA receptors or expression of voltage-gated sodium channels. These changes induce neuronal hyperexcitability that enables low-threshold mechanosensitive Aβ and Aδ afferent fibers to activate second-order nociceptive neurons. This means that normally innocuous tactile stimuli such as light brushing or pricking the skin become painful. Similar mechanisms might take place not only within the spinal cord, but also at supraspinal levels, as has been reported in patients with central pain.

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INVITED REVIEW

Diagnosis, pathophysiology, management and future issues of trigeminal surgical nerve injuries

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Key words:
chronic postsurgical pain, neuropathic pain, painful post-traumatic trigeminal neuropathy, post-traumatic trigeminal neuropathic pain, trigeminal nerve injury

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Abstract

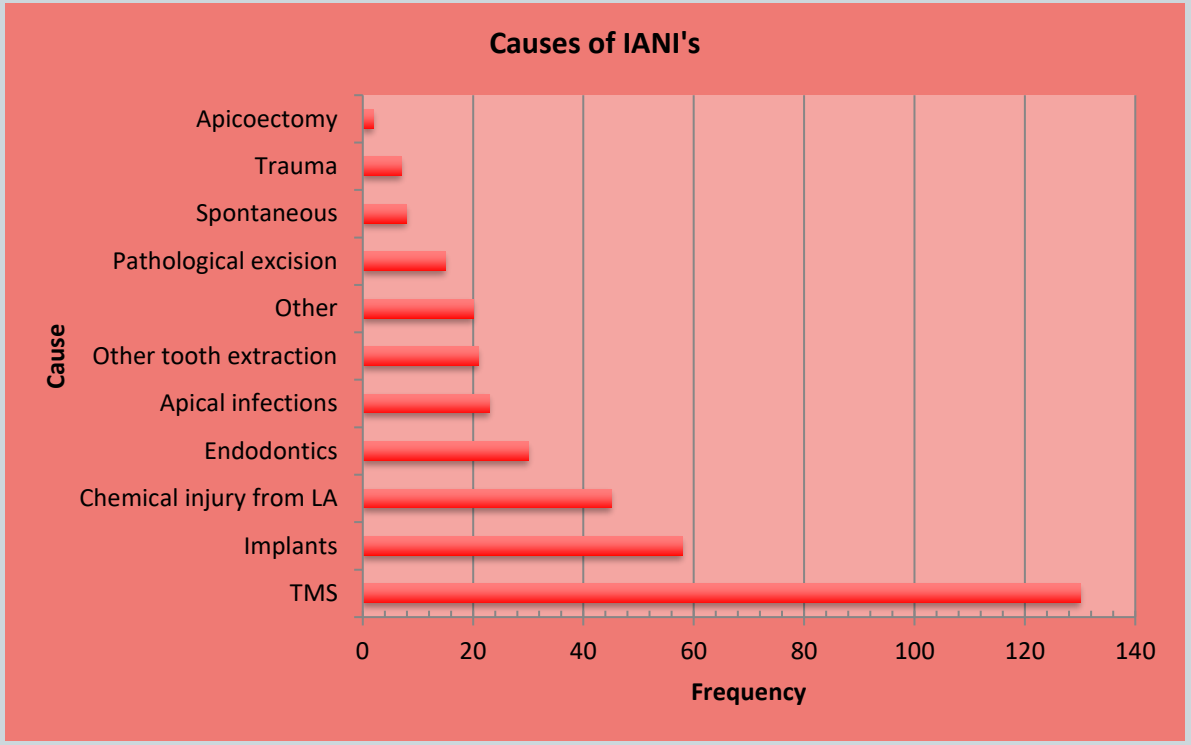
The trigeminal nerve constitutes the largest sensory cortex representation in the brain compared with other sensory nerves. This is likely due to the fact that the trigeminal nerve underpins our very existence, as it sensorially protects, our five senses including the organs that provide sight, smell, taste, hearing, speech and meninges protecting our brain. Thus, when trigeminal nerve injuries occur, which in the main are preventable and painful, the majority of patients experience mixed symptoms including altered sensation, numbness and ongoing or elicited neuropathic pain. These neuropathic features cause significant impact on the patients' ability to function, for example cold allodynia prevents the patient enjoying cold foods and drinks and undertaking out-door activities or mechanical allodynia frequently interferes with eating, speaking, kissing and sleep. The resultant chronic symptoms and functional impedance result in significant psychological morbidity. Prevention of nerve injuries related to local anaesthesia (LA), endodontics, implants and third molar surgery is imperative as there is no magic bullet to repair these sensory nerve injuries with their related neuropathic pain. Some causes have higher levels of resolution (third molar surgery and LA) some lower levels of resolution (implant surgery and endodontics) and many patient factors will dictate the prevalence of chronic neuropathic pain. The patient must have appropriate consent and their expectations managed with understanding the potential benefits and risks for their chosen interventions. The authors have aimed to provide an up to date evidence base for diagnosis and management of trigeminal nerve injuries.

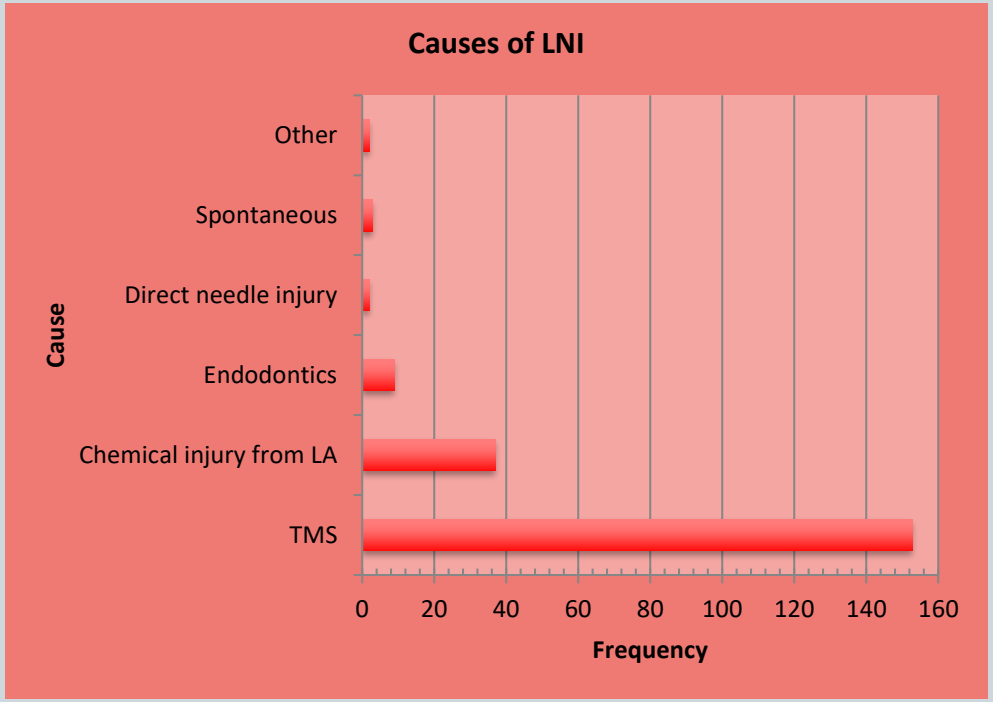
Background

Trigeminal nerve injury (TNI) and subsequent post-traumatic trigeminal neuropathic pain (PTNP), is a problematic consequence of dental or oromaxillofacial surgical procedures with major medico-legal implications.[1] The incidence of lingual nerve injury has remained static in the UK over the last 30 years, but is increasing in the US, as is the incidence of inferior alveolar nerve (IAN) injury in the UK; the latter being due to implant surgery and endodontic therapy.[2] Trigeminal nerve injuries are generally classified as temporary but can persist and become permanent (by definition after 3 months). Based upon the limited evidence base, nerve injuries caused by implant and endodontic treatments are mainly painful and permanent.[3] Temporary nerve injuries are more likely related to local anaesthesia (LA) or third molar surgery, with mandibular related surgery patients are advised that the rate of permanent inferior alveolar or lingual nerve injuries occur between 0.1–2% of cases.[4,5] LA nerve injuries have a 75% likelihood of recovery.[6,7]

The fifth cranial nerve divisions two and three are the most commonly damaged, caused by implants,

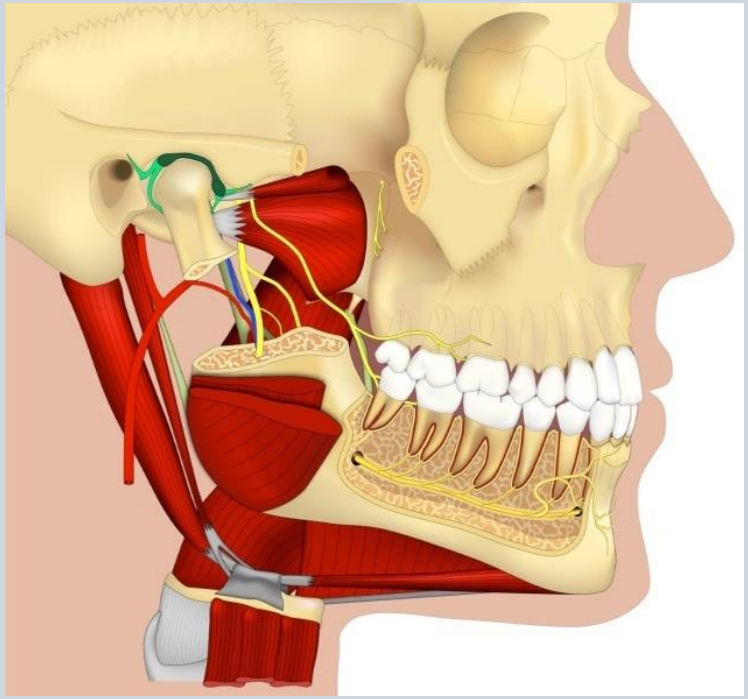
Dental procedural related post traumatic neuropathy

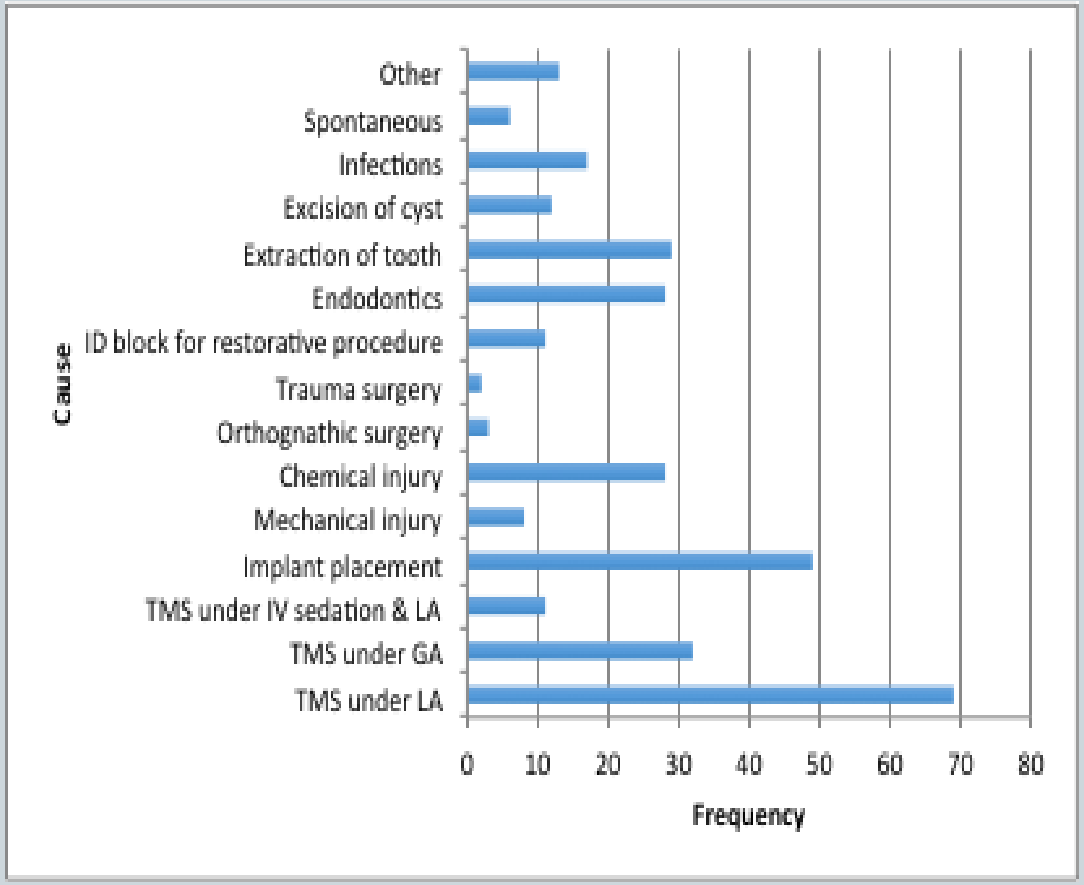




- **Summary of nerve injury patients** March 2008 –2016
- 400 IANI patients (73% F: 26.8% M; mean age = 46.5 years [range 18 – 85])
- 214 LNI patients (64.5% F: 34.6% M; mean age = 38.6 years [range 20 -73])

Specific dental surgical risk factors and PTTNP





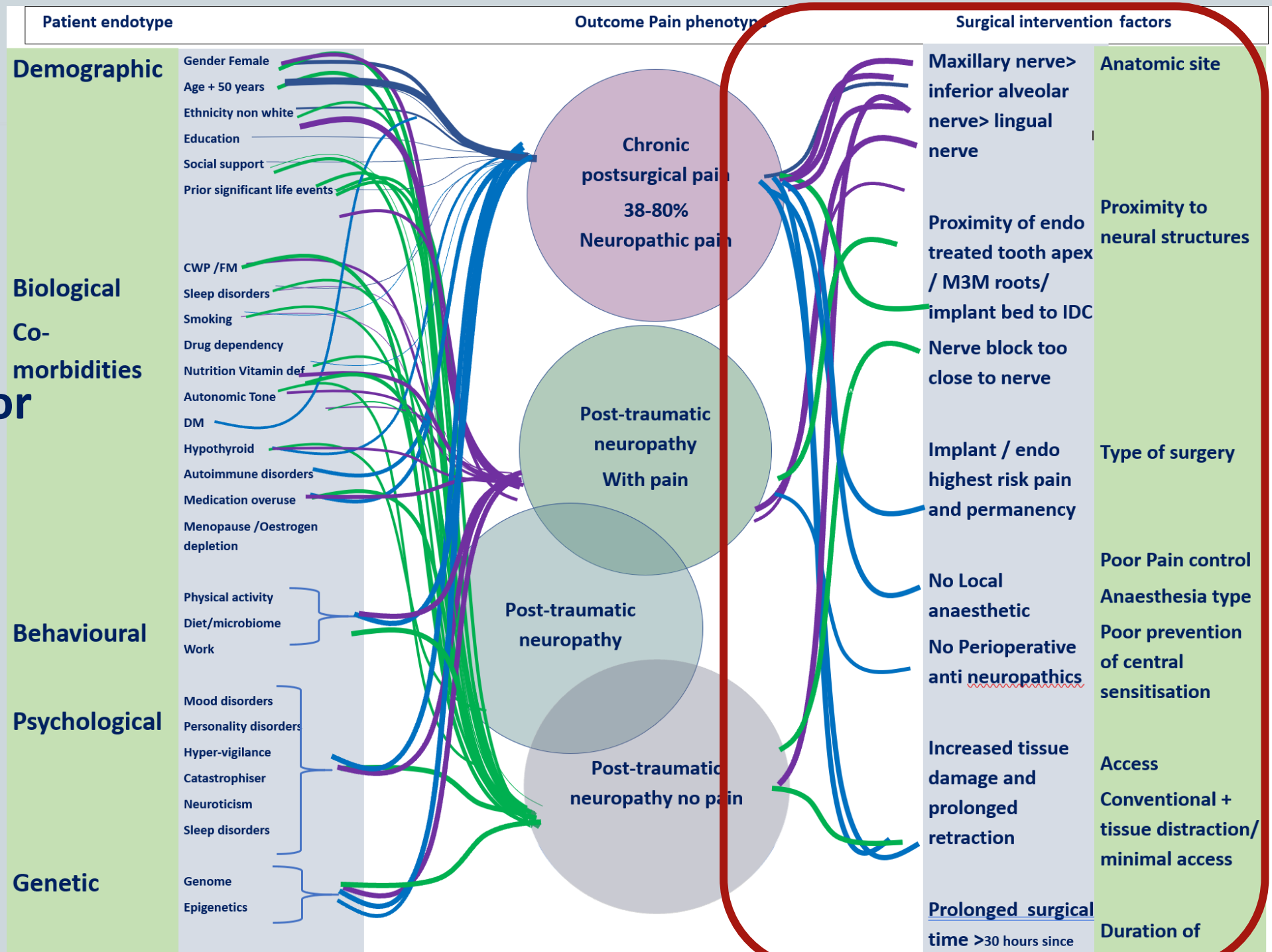
Local anaesthesia
Dental Implants
Endodontics
Third molar surgery

Surgical Predictors for Trigeminal PTNP

Site

Proximity to neural structures

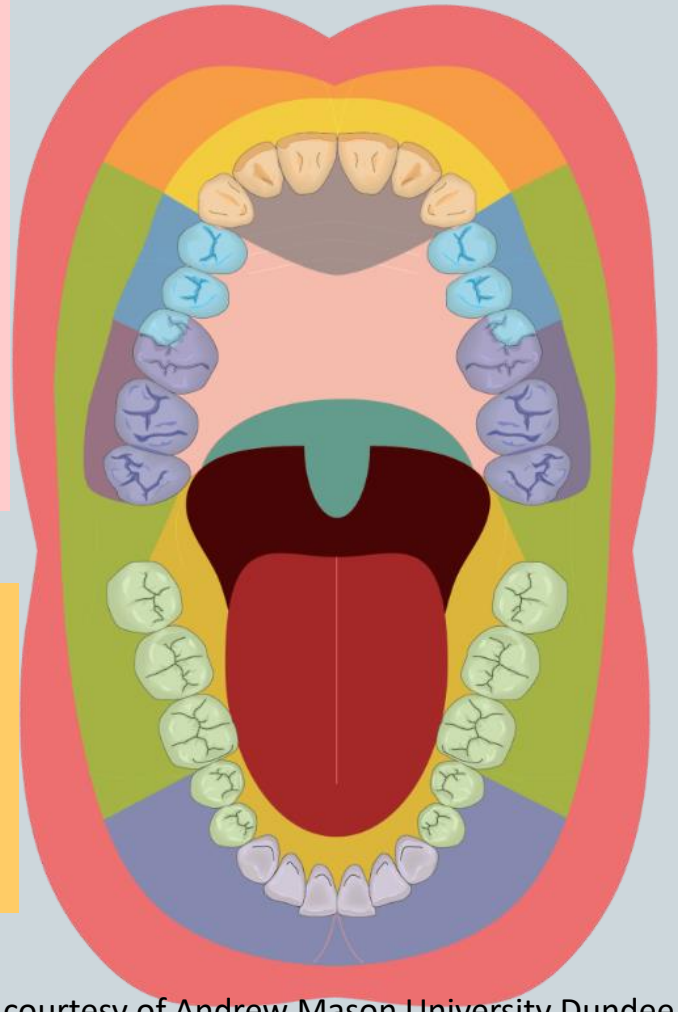
Type of surgery



LA related nerve injuries –can be mitigated by avoiding blocks
Infiltration dentistry is dependant upon the site and procedure

Maxillary dentistry can be performed entirely using Lidocaine 2% with adrenaline for all procedures
Buccal infiltration with intra-septal injections
No additional benefit using 4% Articaine
No palatal or incisal blocks are indicated

IDBS needed for
Posterior mandibular molar
Endodontic procedures may require IDBs or higher techniques (Gow Gates or Akinosi)



Mandibular 7s and 8s for **perio, restorations or implants**
Articaine 4% buccal infiltration and Lidocaine 2% lingual infiltrations OR for **extractions** intraligamental
If fails may need lidocaine IDB

Mandibular 1st molars for **perio, restorations or implants**
Articaine 4% buccal +/- Lidocaine 2% crestal or lingual infiltration s OR for **extractions** add lidocaine lingual **of** intra-ligamental

Mandibular premolars, canines incisors for **perio, restorations or implants**
Articaine buccal infiltration (incisal nerve block using 30% cartridge) adjacent not in the mental foramen and massage over region. If fails repeat or add crestal or lingual infiltration OR for **extractions,** intra-ligamental

Illustration modified from figure courtesy of Andrew Mason University Dundee

LA nerve injury risk factors

Risk factors for persistent neuropathy related to IDBs
In order to minimise complications related to dental LA you need to consider modifying the following risks;

- Block anaesthesia Nerve block injections should be undertaken without intent on direct 'hit' of ...s who experience the 'funny bone' neuralgia due to the IDB needle being placed too close to the lingual ...es experience persistent neuropathy (20)
- Lingual nerve > IAN Is this technique related or anatomically related (less fascicles in LN lower ... the direct IDB approach may place the lingual nerve at increased risk compared with eth indirect ...ique
- Concentration of LA Any increased concentration of any agent leads to increased neu...
- Volume of LA There is no evidence to support this suggestion but all ch... ...ndent upon the proximity, LA concentration, neural damage additional volume would add to potenti...
- Multiple injections Second or subsequent injections that impede directly on or in neura... ...le in... usual 'funny bone' neuralgic pain. Thus the patient does not self-protect as effectively possibly rend... of direct damage.
- Severe pain on injection 60% increased occurrence of persistent neuropathy after IDBs (21)
- Type of LA Agent Bupivicaine most neurotoxic of all LA agents
- Type of vasoconstrictor? The role of vasoconstrictor in nerve damage is unknown
- Sedated or anaesthetized patients? There is no evidence to support unresponsive patients... ...ect themselves when neuralgia (funny bone reaction) occurs as the IDB needle encroaches too close to the...
- Lack of LA aspiration? Again there is no evidence to support that aspiration during IDB ... ...athies but a pragmatic view may infer less chemical injected intra neurally will cause less chemical nerve ...

Block injections

Multiple injections

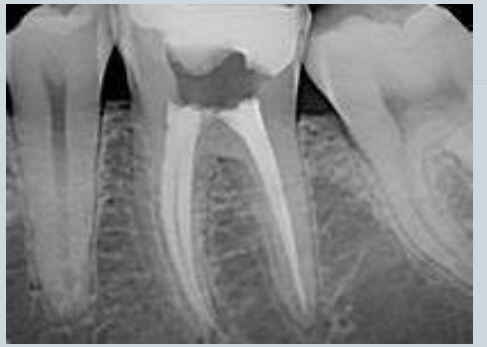
Type and concentration of LA agents

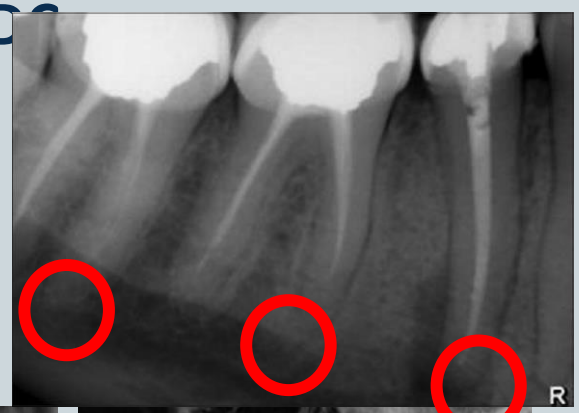
Extreme pain during injections

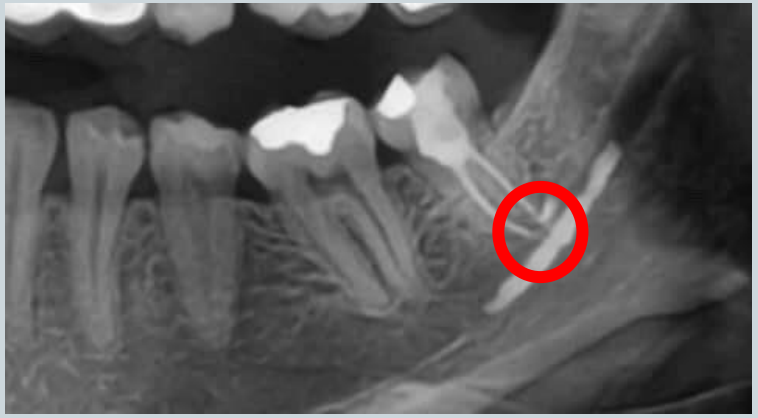
Endodontic related nerve injury risk factors

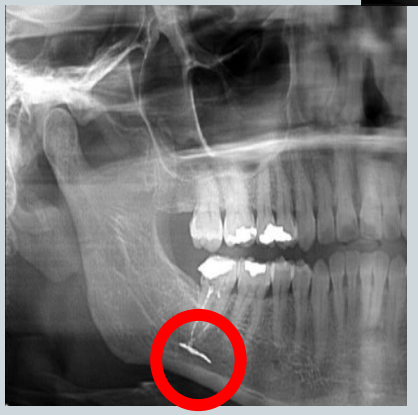
- Proximity of tooth apex to inferior dental canal (IDC)
- Loss of apical seal and CHEMICAL leakage into bone and IDC
- Chemicals used in endodontics pH ranges 12-14
  - Calcium hydroxide (CaOH)
  - Sodium hydroxide (NaOH)

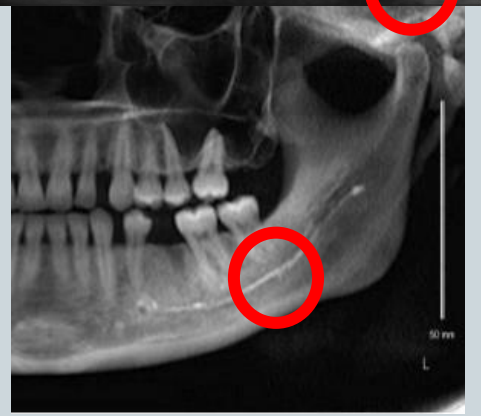
Where is the IDC?











Fanibunda K, Whitworth J, Steele J (1998) The management of thermomechanically compacted gutta percha extrusion in the inferior dental canal. Br Dent J. 1998 Apr 11;184(7):330-2

Endo nerve injury risk factors

Tooth apex position
Proximity to IDC
Related root morphology

Poor technique
Lack apical seal
Over instrumentation
Over filling

Postoperative
Late recognition and late tooth or overfill removal

Prevention of Endodontic related neuropathy: Risk factors

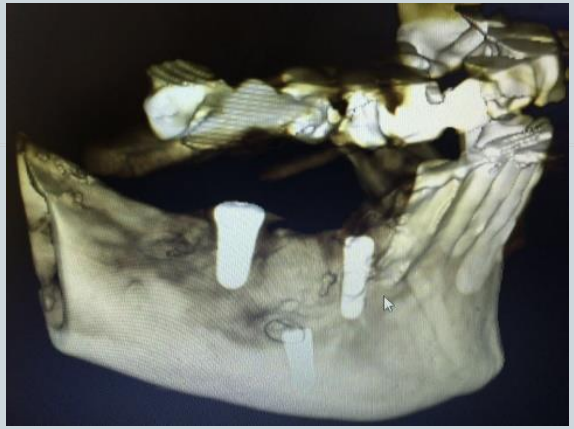
A. Inadequate preoperative assessment and planning due to
- Lack of knowledge
  - GDP (80% of referrals) GDP endodontic success rates are significantly lower
  - The American Association of Endodontists have made several recommendatic ...its
- Inability to read the radiographs or CBCT
- Inadequate informed consent-all options provided and related risk b
- Lack of identification of existing pre-surgical neuropathy (periapical lesions).

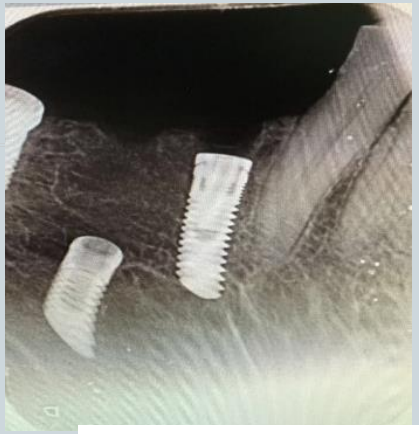
B. Premolar teeth & Proximity of tooth apex to IDC – 90% of the mandibular teeth in this series, were close to the IAN canal or premolars adjacent to the mental foramen. Proximity to the apex to the IAN/ breach apical seal and over chemical or ...rumentation
- Tantanapornkul et al (33) reported the specificity and sensitivity of CBCT versus panorals in ide... of the IAN to the tooth roots in 161 mandibular third molars 161; for it was CBCT 93% and 77% ... not significantly different.
- Patel et al (34) have reported on the use of CBCT in managing complic... periapicals.

C. Poor technique
- Breach of apex causing pain during surgery on irrigation or during instrumentation and da... periapical tissues
- Over instrumentation
- Overfill Detectable overfill occurred in 60% of cases and over instrumentation during preparation

D. Early recognition and intervention for Endodontic related nerve injuries
- ALWAYS undertake HOMECHECK , review patient and confirm neuropathy
- Neuropathy related to endodontics can be delayed and the patient must be encoura... treatment (Renton et al unpublished).
- If nerve injury is suspected, you will already be aware of the proximity of the too... apex, over instrumentation or deposition of endodontic material into the IAN canal.
- If there is suspected the material, the apex and or tooth must be removed within 48 hours o... in order to max... very from nerve injury (9). If the patient is insistent on keeping the tooth urgent referral of the patient may be indicated for mandibular decompression

Implant related nerve injury Risk factors

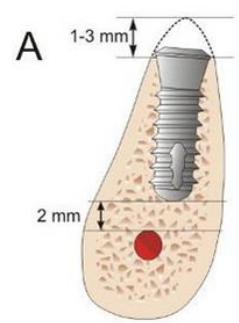


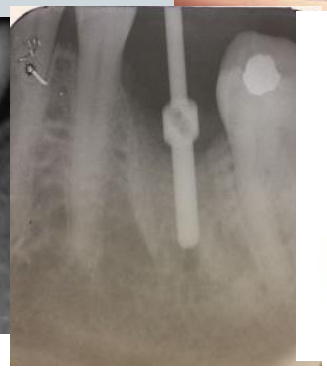


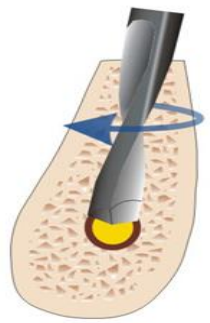
Most nerve injuries occur:

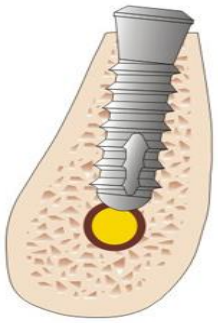
- **In the parasymphyseal region**
- **During preparation of implant bed**
- **Using Implants >10mm**
- **When the patient experiences severe pain**
  - during prep or implant placement
  - severe pain post surgery
  - Intraoperative bleed during prepping

Safety zone of 2mm is insufficient with implant drills 1.5mm longer than the implants = resultant safety zone of 0.5mm!!!! 4mm!









Yilmaz Z, Ucer C, Scher E, Suzuki J, **Renton T**. A Survey of the Opinion and Experience of UK Dentists: Part 1: The Incidence and Cause of Iatrogenic Trigeminal Nerve Injuries Related to Dental Implant Surgery. Implant Dent. 2016 Oct;25(5):638-45.

Short Implants (5 to 8 mm) Versus Longer Implants (>8 mm) with Sinus Lifting in Atrophic Posterior Maxilla: A Meta-Analysis of RCTs

Implant nerve injury risk factors

Lack of knowledge/inexperience

Inadequate informed consent and management of patient expectations

Lack of identification of existing pre-surgical neuropathy.

Additional risk assessment of mandibular premolars and molars

Poor planning

Know where the nerve is. Nerve localisation, risk factors when assessing
(Mental loop, characteristics of IAN position in various sites of mandible).

Parasymphyseal zone high risk.

The accuracy of estimating the position of th
or CT scans is highlighted in the radiographic as

Insufficient Safety zone- Risk perforat
the nerve.

Poor surgical technique

Poor recognition of intraoperative problems

Poor implant placement

Selection of implants 10mm plus

(evidence supports shorter implants -short implant
procedure and minimise morbidity**)**

Poor Planning

Insufficient Safety zone
Inappropriate radiographs
Inability to read CBCT
Using implants > 8mm

Operative

Poor technique reducing Safety zone/ lack use drill stops, guides/ intraoperative LCPAs
Lack of recognition risks bleeding/ drill sink

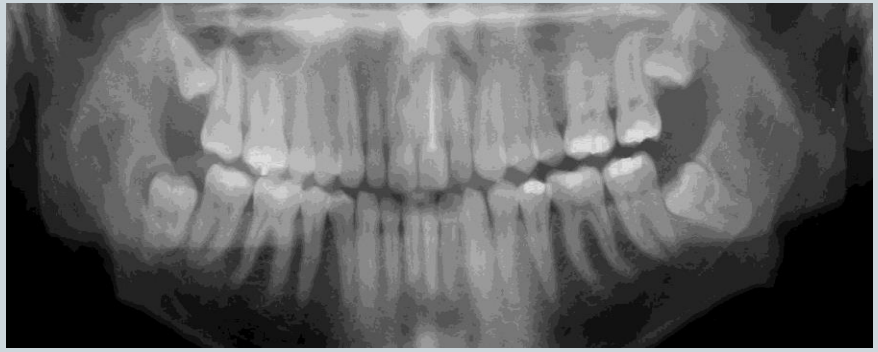
Post operative

Late recognition of nerve injury
Lack removal implant within 30 hours

M3M surgery related nerve injury risk factors

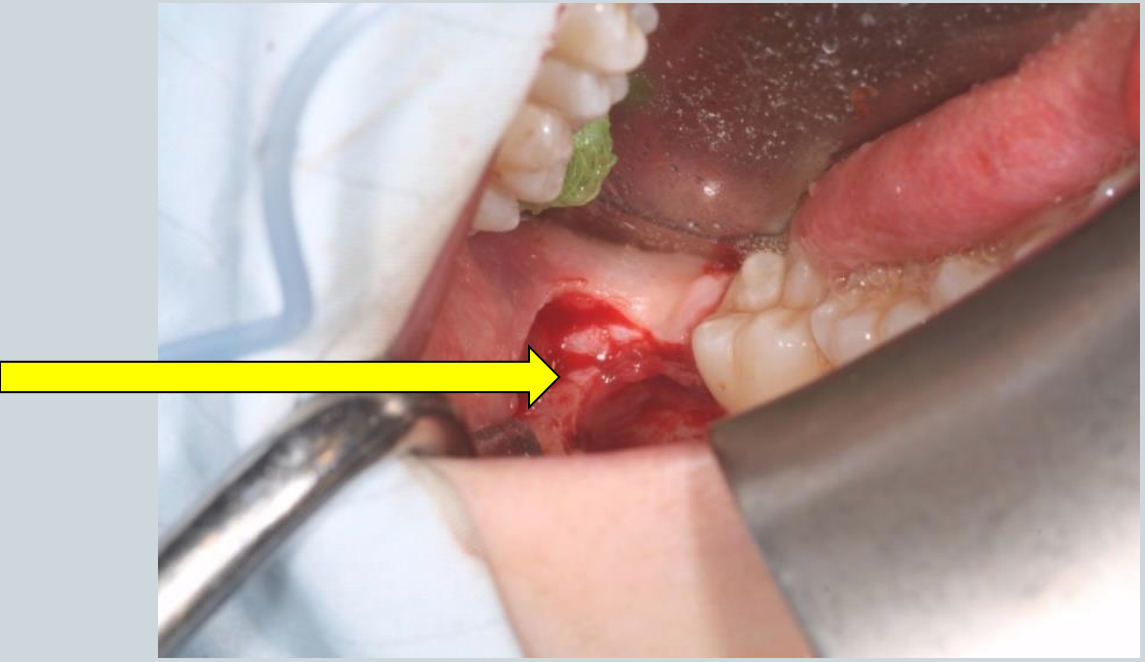
Inferior alveolar nerve
Age of the patient
- Intra-operatory exposure of the nerve
- Un-erupted tooth

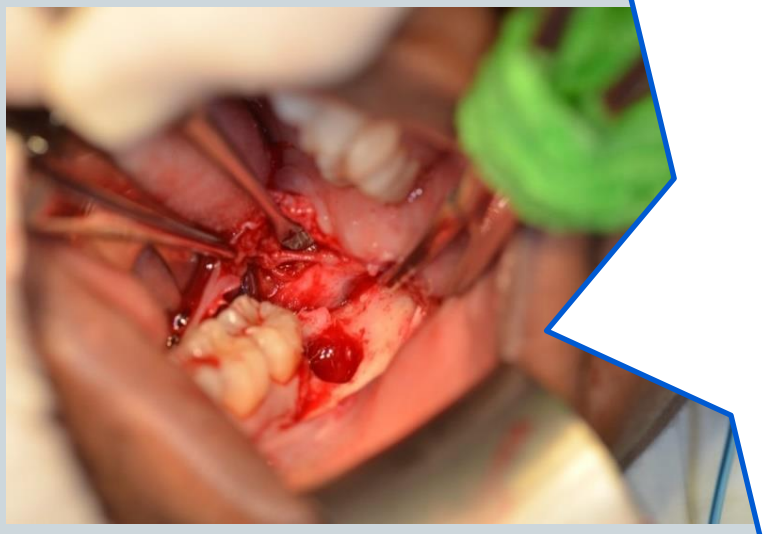
Poor Radiographic risk assessment
  - Perforation of tooth roots by IDC
  - Proximity of tooth roots to inferior dental canal (IDC)
  - Plain film
    - IDC loss LD
    - Darkening of roots
    - Deviation of IDC
  - CBCT lack cortication, distortion of canal.
  - Lingual IDC



Lingual nerve
Age of the patient
Poor surgical technique
  - Junior surgeons
  - Duration of surgery
  - Lingual access surgery
  - Distal bone removal and lingual nerve injury
    - Use Buccal approach
    - Minimal access
  - ‘aberrant’ Lingual nerve anatomy
    - 11-18% of lingual nerve above alveolar crest distal to M3Ms

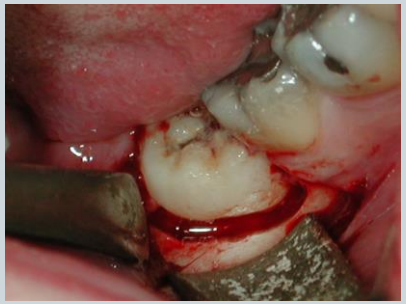
Lingual nerve injury risk in M3M surgery

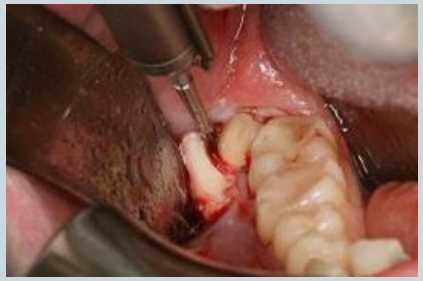


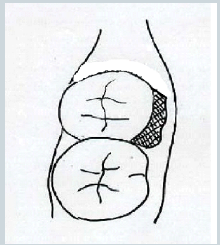


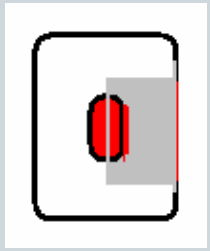
Avoid going anywhere near the lingual nerve or lingual plate! B using buccal approach

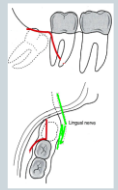
Mitigated by surgical approach



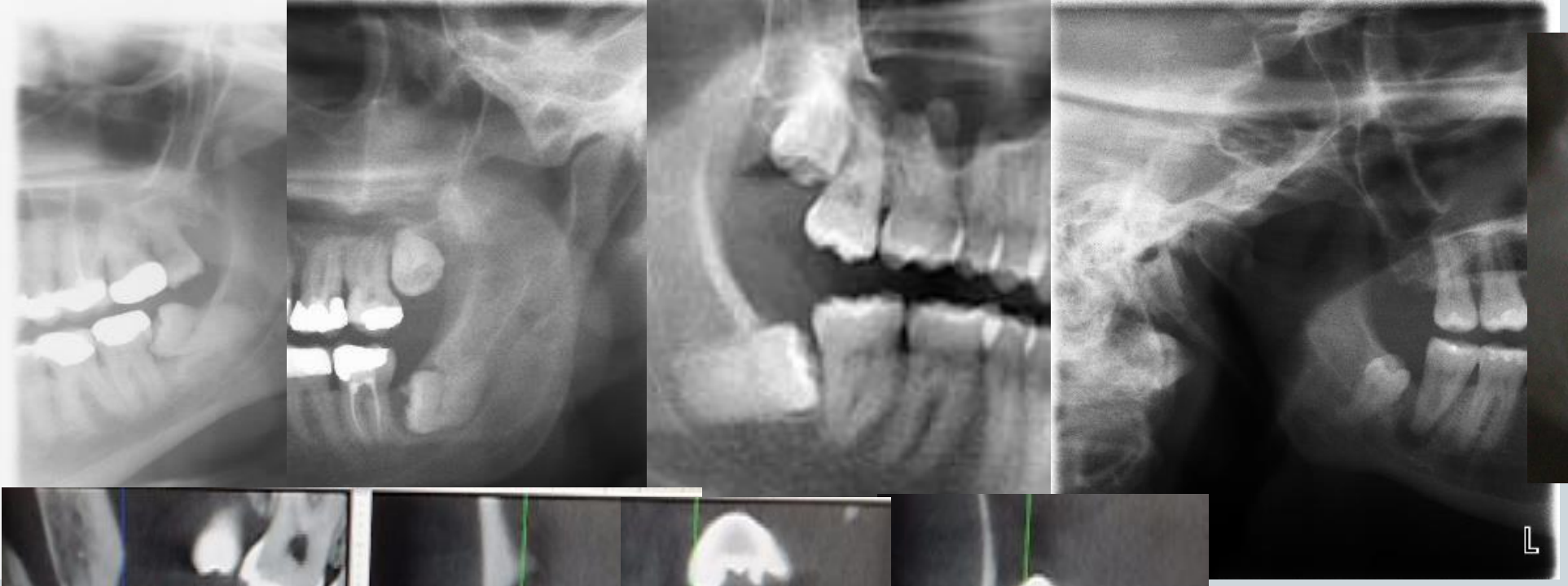


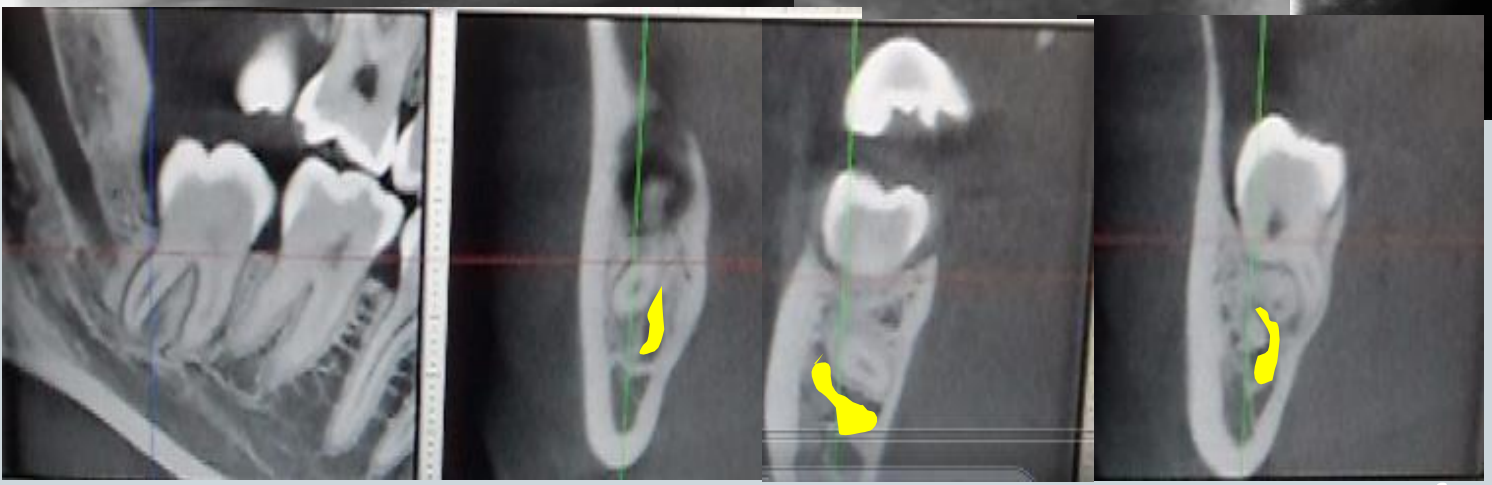






Evaluation of trigeminal nerve injuries in relation to third molar surgery in a prospective patient cohort. Recommendations for prevention. **Renton T**, Yilmaz Z, Gaballah K. Int J Oral Maxillofac Surg. 2012 Dec;41(12):1509-18.





10 x

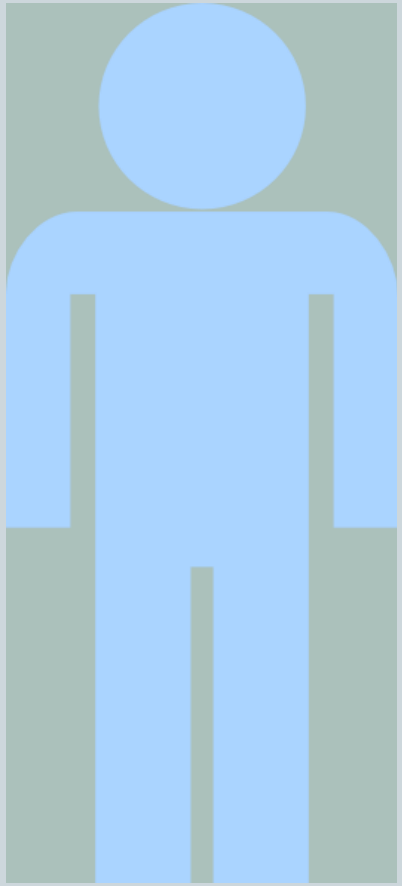
- Céspedes-Sánchez JM, Ayuso-Montero R, Marí-Roig A, Arranz-Obispo C, López-López J The importance of a good evaluation in order to prevent oral nerve injuries: A review. Acta Odontol Scand.2013 Jul 4.
- Factors that are associated with injury to the IAN in high-risk patients after removal of third Molars. Selvi, Dodson, Nattestad, Robertson, Tolstunov. BJOMS 51 (2013) 868–873. with permission.

Inferior alveolar nerve injury risk in M3M surgery

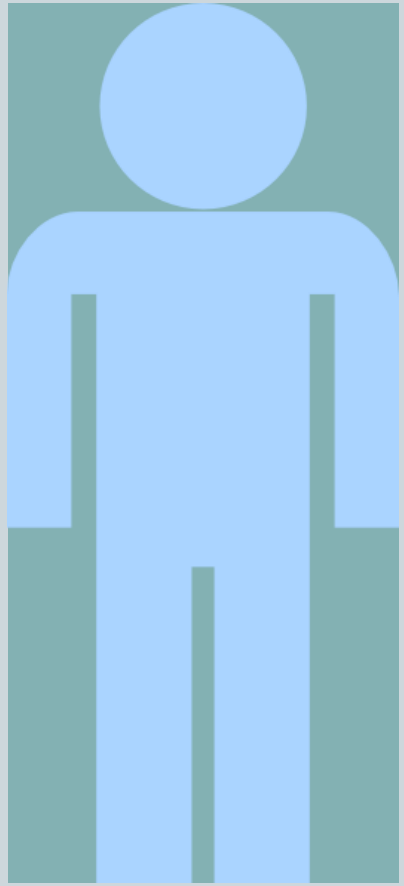
Proximity of M3M root to IDC

Overview

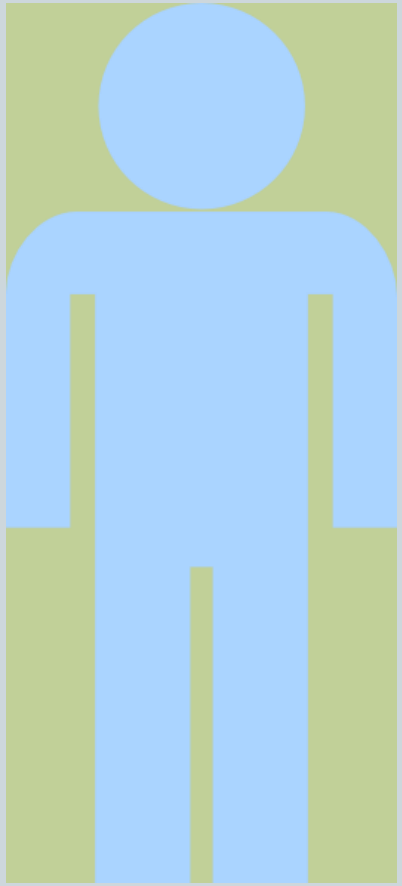
Neuropathic pain
Definitions &
Diagnosis



Neuropathic pain
Classification &
Trigeminal presentation



Neuropathic pain
prevention of
nerve injuries



Prognosis and outcome & management

Predicting outcome of Trigeminal PTNP

Received: 9 December 2019 | Revised: 7 May 2020 | Accepted: 10 July 2020
DOI: 10.1111/joor.13058

ORIGINAL ARTICLE

JOURNAL OF ORAL REHABILITATION WILEY

Signs and symptoms, quality of life and psychosocial data in 1331 post-traumatic trigeminal neuropathy patients seen in two tertiary referral centres in two countries

Fréderic Van der Cruyssen[1,2] | Frederik Peeters[1,2] | Thomas Gill[3] | Antoon De Laat[4,5] | Reinhilde Jacobs[2,6] | Constantinus Politis[1,2] | Tara Renton[3]

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Email:frederic.vandercruyssen@uzleuven.be

Abstract

Background: Post-traumatic trigeminal neuropathy (PTN) is a disturbance of function
or pathol
importan
Objectiv
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Methods
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clinical fi
modalitie
Results:
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diagnosis,

J Oral Maxillofac Surg. 2021 Jan 5;S0278-2391(20)31547-0. doi: 10.1016/j.joms.2020.12.049. Online ahead of print.

Degree of Compression of the Inferior Alveolar Canal on Cone-Beam Computed Tomography and Outcomes of Postoperative Nerve Injury in Mandibular Third Molar Surgery

Anton Sklavos [1], Seth Delpachitra [2], Tom Jaunay [3], Ricky Kumar [4], Arun Chandu [5]

Affiliations + expand

PMID: 33529607 DOI: 10.1016/j.joms.2020.12.049

Abstract

Purpose: Cone-beam computed tomography (CBCT) offers the advantage of a 3-dimensional representation of the anatomic relationship of the mandibular third molar tooth and the inferior alveolar canal (IAC), as compared to a panoramic radiograph. We hypothesized that a novel method of categorizing the degrees of compression of the IAC were reliable predictors for postoperative nerve injuries.

Methods: We conducted a retrospective analysis of the outcomes in third molar surgery for patients who obtained a CBCT scan in additional to a plain film radiograph over a 12 months period and underwent surgical removal of their mandibular third molars; 257 consecutive patients were identified, and 416 mandibular third molars were surgically removed.

Results: Patients who had severe compression of the inferior alveolar canal (IAC) on CBCT imaging

Journal of Oral & Facial Pain and HEADACHE
Rafael Benoliel Editor-in-Chief

Volume 35 , Issue 1
Winter 2021
Pages 35–40

The Diagnostic Value of Magnetic Resonance Imaging in Posttraumatic Trigeminal Neuropathic Pain

Frederik Peeters, MD/Fréderic Van der Cruyssen, MD, DDS/Jan W. Casselman, MD, PhD/Robert Hermans, MD, PhD/Tara Renton, BDS, MDSc, PhD/Reinhilde Jacobs, DDS, MS, PhD/Constantinus Politis, MD, DDS, MHA, MM, PhD

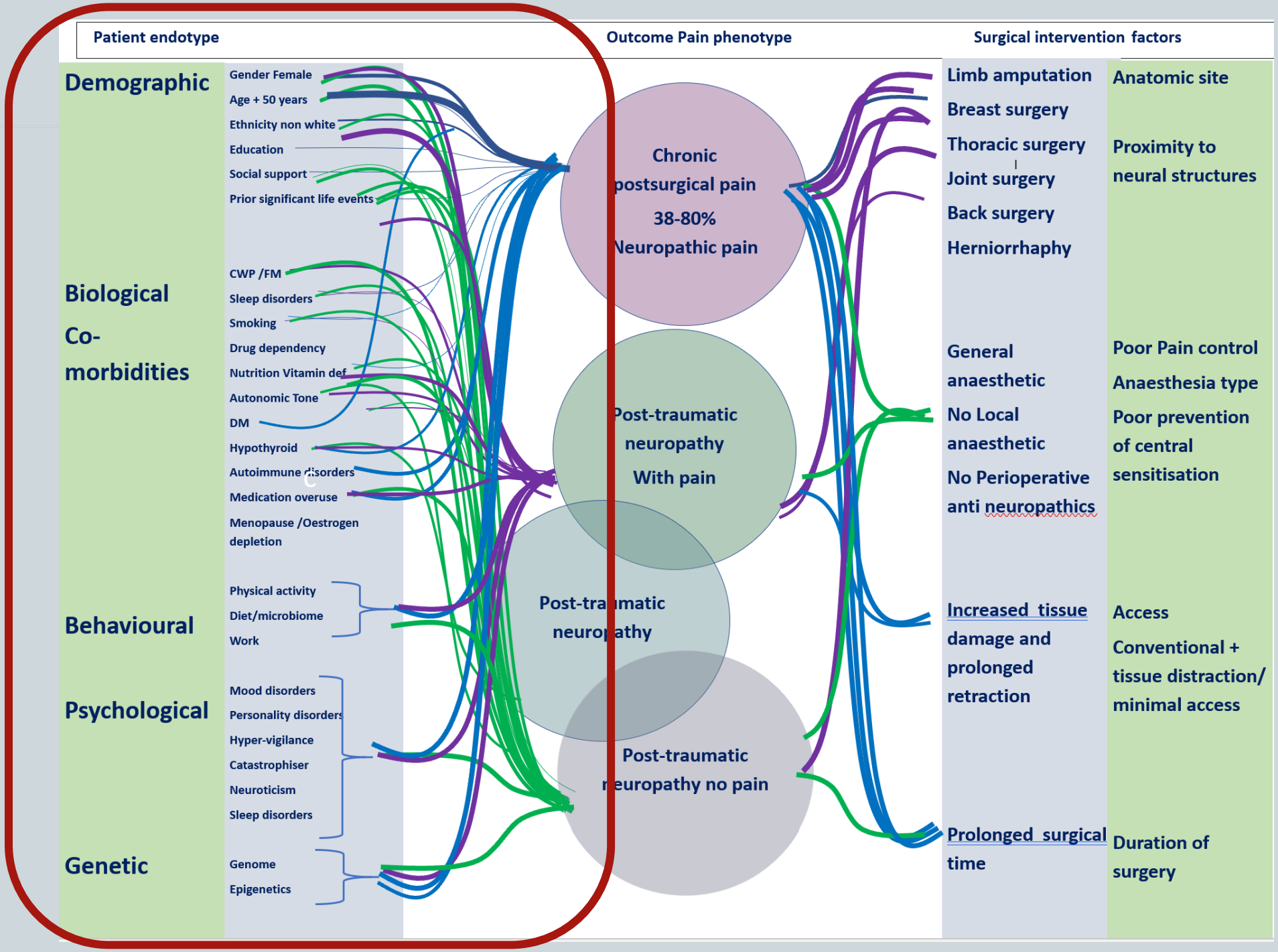
DOI: 10.11607/ofph.2732

Aims: To evaluate the diagnostic value of non–nerve-selective MRI sequences in posttraumatic trigeminal neuropathic pain (PTNP). Methods: This study retrospectively analyzed all MRI protocols performed between February 2, 2012 and June 20, 2018 commissioned by the Department of Oral and Maxillofacial Surgery, University Hospitals Leuven. Demographic, clinical, and radiologic data were extracted from the records of patients with an MRI in the context of PTNP. A contingency table was constructed based on the opinions of the treating physician and the

General sensory nerve injury recovery predictors

- Degree and site of nerve damage
- Delay in presentation
- Age of patient
- Medical factors?
- Social factors?
- Psychological factors?

Predictors for chronic post surgical pain (CPSP) Post Traumatic neuropathic pain (PTNP) Patient



Biennial Review of Pain
PAIN

Neuropathic pain in the community: prevalence, impact, and risk factors

Blair H. Smith*, Harry L. Hébert, Abirami Veluchamy

1. Introduction

Neuropathic pain arises as a direct consequence of a lesion or disease affecting the somatosensory system.[87] It can be peripheral in origin, as a result of nerve injury or disease (eg, lumbar radiculopathy, postherpetic neuralgia, diabetic or HIV-related neuropathy, or postsurgical pain), or central (eg, poststroke or spinal cord injury). It is characterized by unpleasant symptoms, such as shooting or burning pain, numbness, allodynia, and other sensations that are very difficult to describe. Clinically, particularly in primary care (where time for assessment is limited), it is important to identify (possible) neuropathic pain, distinguishing it from other pain types (including nociceptive pain), as it generally fails to respond to standard analgesics (eg, nonsteroidal anti-inflammatories) but requires a different analgesic approach.[25] As all analgesics potentially cause harm as well as benefit, the distinction will promote safe and effective prescribing.

However, "definite" neuropathic pain can relatively rarely be confirmed, particularly in nonspecialist settings. According to the widely accepted grading system proposed by the International Association for the Study of Pain (IASP)'s Special Interest Group on Neuropathic Pain (NeuPSIG), this diagnosis requires (1) a history of a relevant neurological lesion or disease, and pain in a neuroanatomically plausible distribution; (2) sensory signs in the same distribution; and (3) a diagnostic test confirming the lesion or disease in the somatosensory system.[26] Diagnostic tests might include imaging (eg, magnetic resonance imaging to demonstrate nerve lesion), intraepidermal nerve fibre density measurement on skin biopsy, neurophysiological testing (eg, nerve conduction studies), or genetic testing to demonstrate a relevant hereditary disorder (eg, erythromelalgia). Note that the term "definite" in this grading system is itself relative, and the above tests do not always confirm causality.

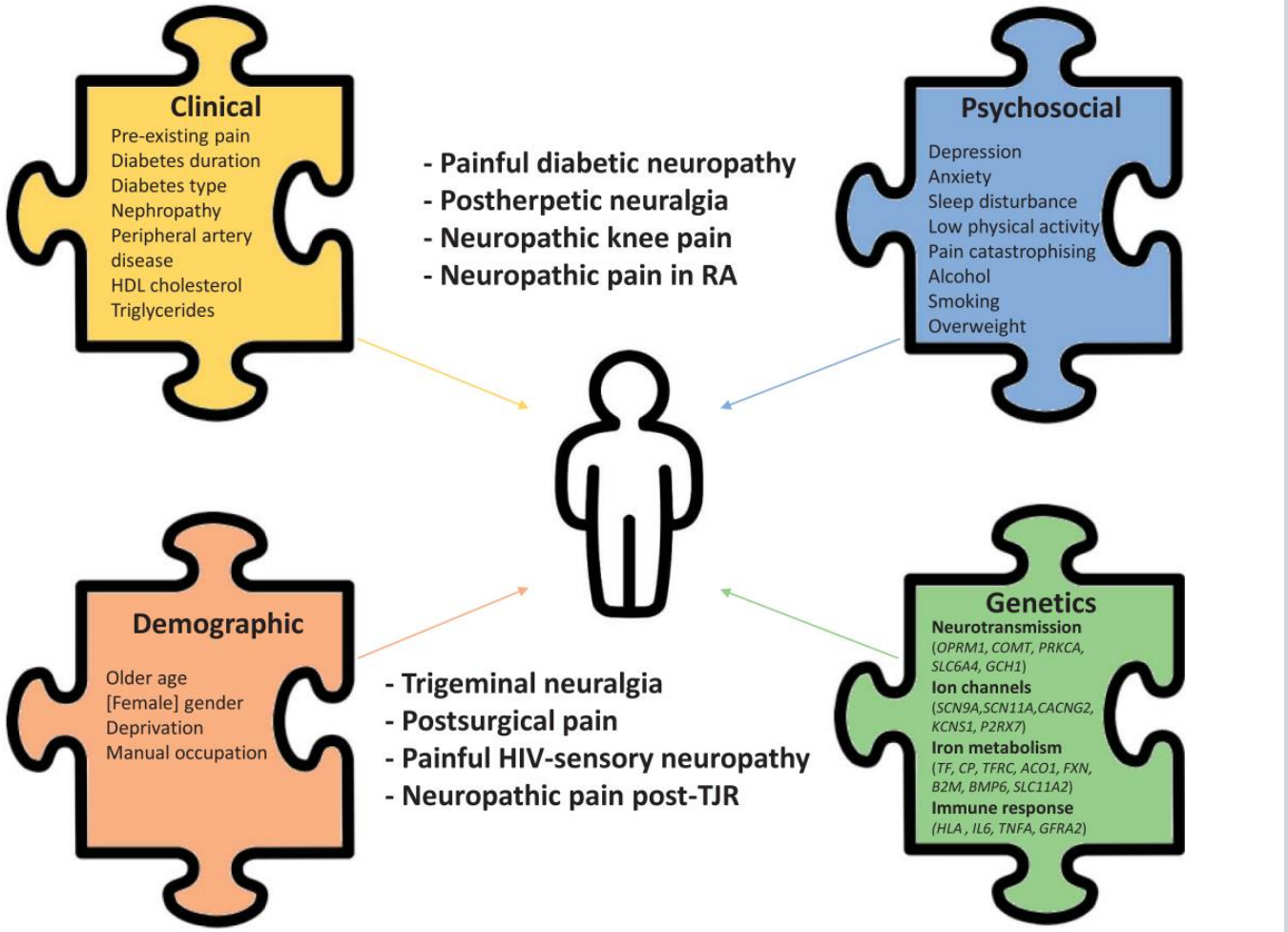


Figure 1. Summary of genetic and nongenetic factors shown to be associated with the presence and/or severity of neuropathic pain.

Predictive factors for chronic post-surgical pain/Nepain

Performing preoperative screening for patient-specific factors such as the following prior to surgery may also help predict the risk of post-surgical neuropathy:

- ***Genetics:*** **Haplotype for catechol-O-methyltransferase**
- ***Preceding pain:*** **Intensity and chronicity**
- ***Psychosocial factors:*** **Anxiety, depression, fear avoidance, self-efficacy, work, physical levels of activity, somatization, anxiety, catastrophizing**
- ***Younger age:*** **Increased risk of neuropathic pain following breast surgery in herniorrhaphy/ breast surgery**
- ***Older age:*** **Increased risk of neuropathic pain following other surgery**
- ***Female sex:*** **Increased risk of neuropathic pain**

Preoperative medication may play a role in minimising the development of post traumatic neuropathic pain, but the evidence is limited. In a systematic review of prevention and management of chronic postsurgical (neuropathic) pain, the authors found that while some studies have shown benefit of perioperative pregabalin in reduction of chronic pain development at 6 and 12 months others have demonstrated no difference. Martinez et al's more recent systematic review, identified no difference in the development of chronic postsurgical pain when comparing treatment with pregabalin or a placebo. Gabapentinoids, may however have an impact on reducing the development of chronic postsurgical (neuropathic) pain however, more comprehensive studies are required.

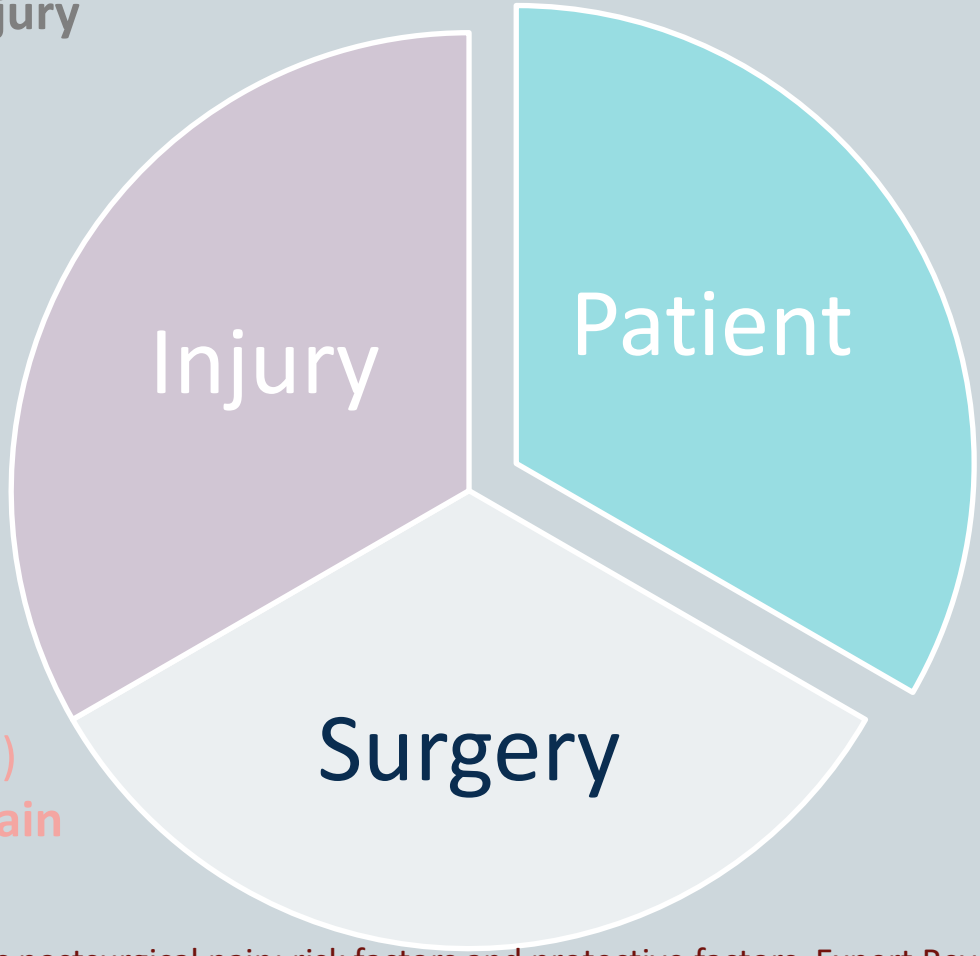
Surgical risk factors may be potentially modifiable. They include the duration and extent of surgical procedure and technique (eg, tension due to retraction of tissues) and level of reported perioperative pain intensity. Modifications to account for these risk factors may include:

- Multimodal management of severe acute postsurgical pain
- Minimal access surgery
- Intraoperative use of local anaesthesia when patient is undergoing general anesthetic

Thapa P, Euasobhon P. Chronic postsurgical pain: current evidence for prevention and management. Korean J Pain. 2018;31(3):155–73.
Mishriky BM, Waldron NH, Habib AS. Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis. Br J Anaesth. 2015;114(1):10–31. 32.Martinez V, Pichard X, Fletcher D. Perioperative pregabalin administration does not prevent chronic postoperative pain: systematic review with a metaanalysis of randomized trials. Pain. 2017;158(5): 775–83

Patient factors predictive for chronic post surgical pain (CPSP)

Resultant sensory nerve injury
Large neuropathic area
Thermal allodynia
Mechanical allodynia
Hyperalgesia



Surgical factors
Type of surgery
Site
Minimise nerve injury
(Tissue tension & Duration)
High level perioperative pain
(Lack of local anaesthesia)

Patient factors
Age > 50 yrs most surgery
<40 yrs breast surgery and herniorraphy
Female
Multiple pain conditions Social Factors

Axis II Psychological factors
Mood anxiety / depression
Introversion, neuroticism, hypervigilance, catastrophising
Fear of surgery
Fear of pain

Poor pain modulation DNIC positive tests
Genetics
COMPT CA channels
Epigenetics
Prior abuse and neglect

Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert Rev Neurother. 2009 May;9(5):723-44. doi: 10.1586/ern.09.20. Review.
Joel Katz & Ze'ev Seltzer Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert Review of Neurotherapeutics Volume 9, 2009 - Issue 5

Risk factors for pain chronicity

Determinants for onset and maintenance of chronic pain

Biopsychosocial

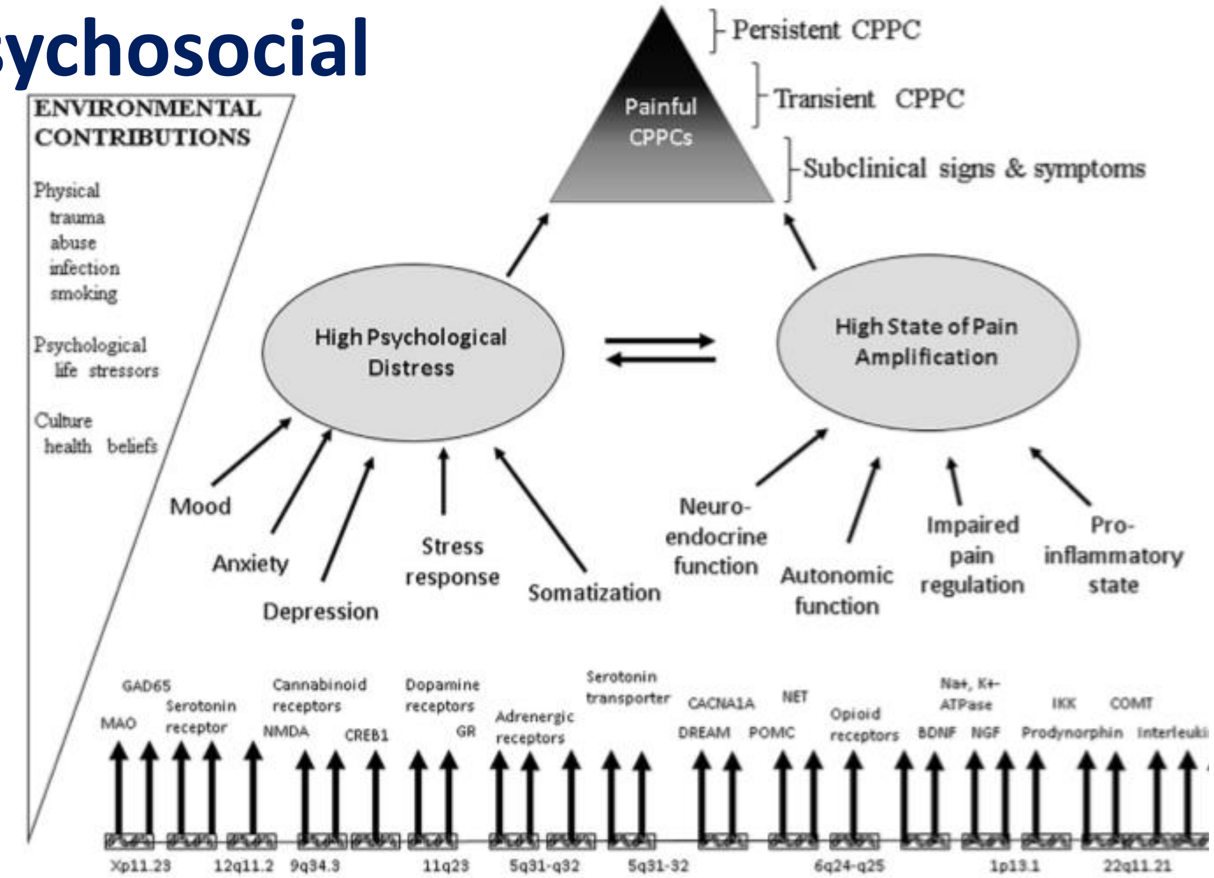


Figure 4. This model depicts likely determinants that contribute to the risk of onset and maintenance of common chronic overlapping pain conditions (COPCs). These factors are determined by genetic variability and environmental events that determine an individual's psychological profile and pain amplification status. These 2 primary domains are interactive and influence the risk of pain onset and persistence. Likely modifiers of the interaction between genetic and environmental factors include sex and ethnicity. Abbreviations: MAO, monoamine oxidase; GAD65, glutamate decarboxylase; NMDA, *N*-Methyl-D-aspartic acid; CREB1, CAMP responsive element binding protein 1; GR, glucocorticoid receptor; CACNA1, calcium channel, voltage-dependent, T type, alpha 1I subunit; POMC, proopiomelanocortin; NET, norepinephrine transporter; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor; IKK, IκB kinase; COMT, catechol-O-methyl transferase.

COMMENTARY

Check for updates

Pain chronification: what should a non-pain medicine specialist know?

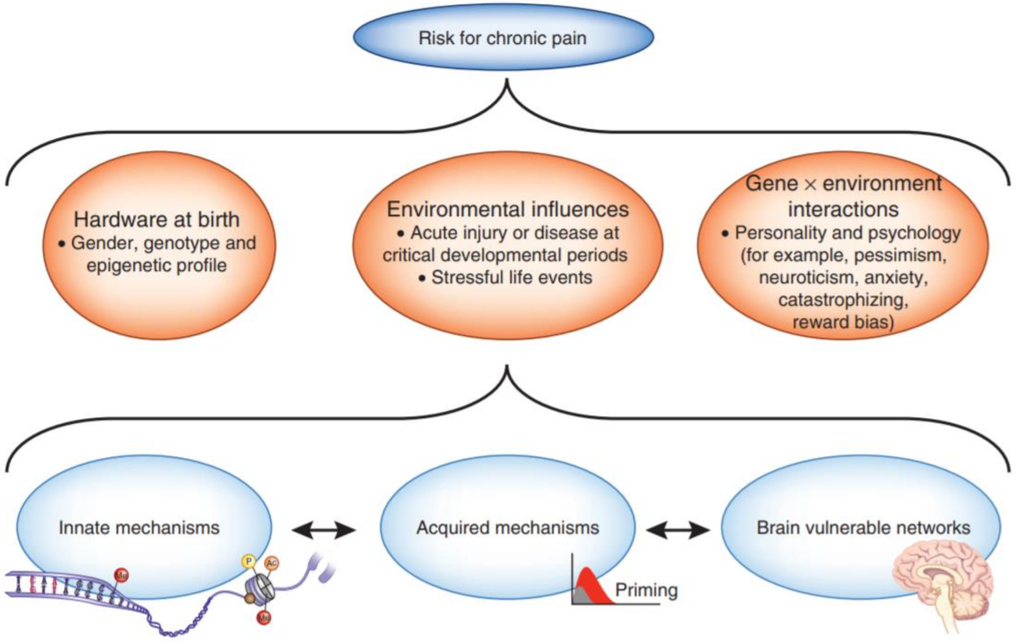
... ena Kocot-Kepska[d], Joseph Pergolizzi[e],

[a]Leuven Centre for Algology & Pain Management, University Hospitals Leuven, KU Leuven, Belgium; [b]Department of Medical and Surgical Sciences and Biotechnologies Unit of Anaesthesia, Intensive Care and Pain Medicine, Sapienza University of Rome, Rome, Italy; [c]Royal Hampshire County Hospital, Winchester, UK; [d]Department of Pain Research and Treatment, Jagiellonian University Medical College, Kraków, Poland; [e]Global Pain Initiative, Golden, CO, USA and Naples Anesthesia and Pain Associates, Naples, FL, USA; [f]Hospital de Santo André, Leiria, Portugal; [g]Capio St Görans Hospital, Stockholm, Sweden; [h]Pain Clinic, Departments of Anaesthesiology, Intensive Care, and Pain Medicine, Helsinki University Central Hospital, Helsinki, Finland

ABSTRACT

Objective: Pain is one of the most common reasons for an individual to consult their primary care physician, with most chronic pain being treated in the primary care setting. However, many primary

ARTICLE HISTORY
Received 18 December 2017
Revised 5 March 2018

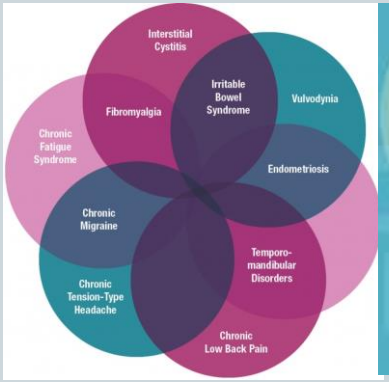


Denk F, McMahon SB **Neurobiological basis for pain vulnerability: why me?** Pain. 2017 Apr;158 Suppl 1:S108-S114.

Patient predictive factors for chronic pain

Demographic

Age
Gender
Ethnicity



Medical Co-morbidities

CWP /FM
Sleep disorders
Smoking
Drug dependency
Vitamin C and D def
Malnutrition
DM, Hypothyroid, Autoimmune disorders
Medication overuse

Psychological factors

Anxiety
Depression
Neuroticism
Catastrophising
Introversion
Hypervigilance
Narcissism

Social factors

Support
Culture
Education level
Income
Prior significant life events
Culture
Ethnicity
Religion
Beliefs

Physiological Factors

Microbiome?
Endogenous pain modulation?
Autonomic tone
Neural plasticity
Gray / white matter degeneration
Connectivity
Neuropathy

Genetic Profile

Genome
Ehlers Danlos
Epigenetics

Psychosocial factors CPSP

Studies examining the influence of psychological factors on chronic post-surgical pain are few, with contradictory results.
Kock has suggested that chronic post-surgical pain can be caused by;

- **Hypervigilant state**
- **Fear of surgery**
- **Anxiety**
- **Psychological vulnerability, specifically pain-related fear and coping skills-**
- **Personality disorders These might reflect psychosocial vulnerabilities in coping skills that are antecedents to chronic pain.**
- **Depression and neuroticism might lead to higher incidences of chronic pain after surgery.**

The psychological factors that seem to be the risk factors for acute pain do not show the same association with chronic post-surgical pain. Cognitive factors such as fear of pain seem to play a greater role than factors such as pain intensity. Given this observation, it appears that psychosocial factors are important in chronic post-surgical pain. **As it is known that limbic regions of the brain can influence the RVM, a region that has descending projections to modulate activity of the dorsal horn involved in the maintenance of nerve injury-induced pain predominantly via a 5-HT3 mechanism**

HHS Public Access
Author manuscript
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Psychosocial predictors in the transition from acute to chronic pain: a systematic review

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Abstract

Chronic non-cancer pain (CNCP) is a major health problem which psychosocial factors have significant implications in. There is a gap in regards to evidence for the prevention of chronicity specifically addressing psychological and social domains. Four databases were searched with terms related to "psychosocial", "acute pain", and "chronic pain". A total of 1,389 studies were identified in which titles, abstracts, and full texts were assessed for inclusion criteria. A data template was used to capture pertinent details, and overall themes and patterns were organized according to type of pain examined and psychosocial variables measured. Of the 18 articles that met inclusion criteria, fifteen (83%) of the articles reported an association between psychosocial factors and chronicity. A total of 5 of the studies (29%) demonstrated that depression was a possible predictor and 6 (35%) of the studies found fear-avoidance to be associated with chronicity. This review provides evidence that psychosocial factors are associated with chronicity within CNCP. These results suggest a need for targeting psychosocial predictors in prevention and early intervention through clinical guidelines and a national strategy to support a cultural change in pain care.

Keywords

systematic review; chronic pain; chronicity; psychosocial; mental health

Introduction

Chronic pain has significant medical, social, and economic implications. In the US, chronic pain affects 100 million adults and annual costs are estimated to be between $560 and 635 billion a year (Gaskin & Richard, 2012). The impact on individuals' quality of life, health care utilization, and social resource expenditures provides a compelling motive to better understand the mechanisms involved in the transition of acute to chronic pain (Häuser et al., 2014). While there is growing evidence that psychosocial factors play a significant role in the transition from acute to chronic pain (Katz & Seltzer, 2009; Liu et al., 2012; VanDenKerkhof, Peters, & Bruce, 2013) there is still a need to enhance the evidence

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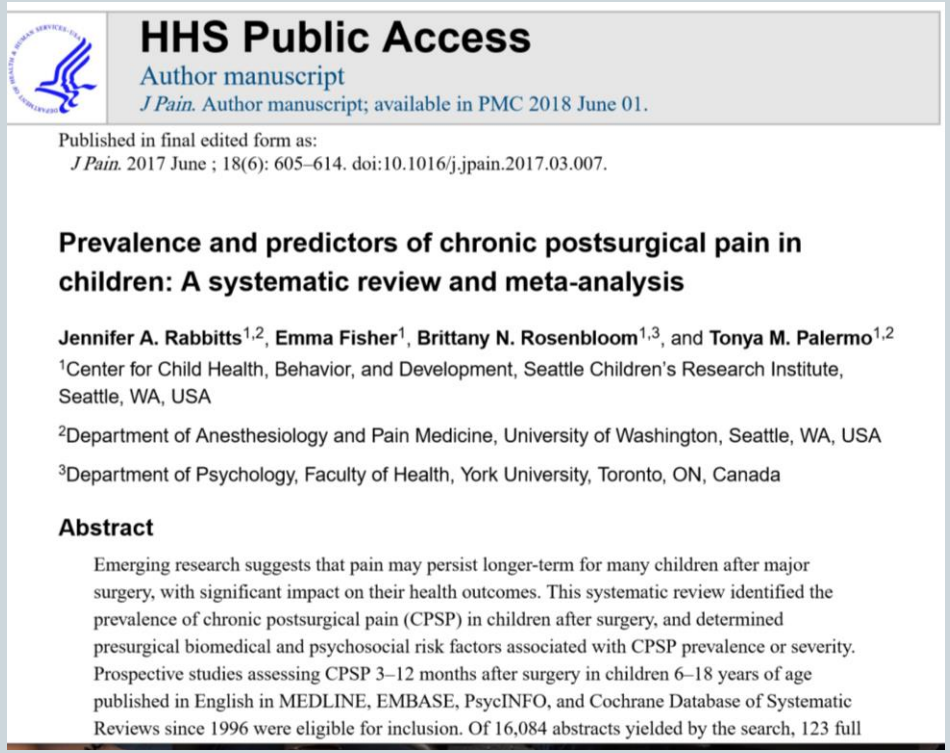
Disclosure statement
The authors declare that they have no conflict of interest.

Predictive persistent pain child patient factors

- **Presurgical pain intensity**
- **child anxiety**
- **child pain coping efficacy,**
- **and parental pain catastrophizing** were the only presurgical factors identified as predictive of CPSP.
- Biological and medical factors assessed were not associated with CPSP in any study. Well-designed studies examining prevalence and predictors of CPSP are critically needed in children.
- The biopsychosocial model of pain is central to our understanding of factors involved in the development and maintenance of CPSP.
- **Several presurgical risk factors for CPSP have been consistently identified in adults undergoing surgery, including biological factors (older age, female sex), medical factors (greater presurgical pain), and psychosocial factors (higher levels of presurgical anxiety and pain catastrophizing)7–10.**



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Prevalence and predictors of chronic postsurgical pain in children: A systematic review and meta-analysis

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Abstract

Emerging research suggests that pain may persist longer-term for many children after major surgery, with significant impact on their health outcomes. This systematic review identified the prevalence of chronic postsurgical pain (CPSP) in children after surgery, and determined presurgical biomedical and psychosocial risk factors associated with CPSP prevalence or severity. Prospective studies assessing CPSP 3–12 months after surgery in children 6–18 years of age published in English in MEDLINE, EMBASE, PsycINFO, and Cochrane Database of Systematic Reviews since 1996 were eligible for inclusion. Of 16,084 abstracts yielded by the search, 123 full

Hinrichs-Rocker A, Schulz K, Jarvinen I, Lefering R, Simanski C, Neugebauer EA. Psychosocial predictors and correlates for chronic post-surgical pain (CPSP) - a systematic review. Eur J Pain. 2009; 13:719–30. [PubMed: 18952472] 8. Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert Rev Neurother. 2009; 9:723–44. [PubMed: 19402781] 9. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006; 367:1618–25. [PubMed: 16698416] 10. Kehlet, H., Edwards, RR., Brennan, T. Persistent Postsurgical Pain: Pathogenic Mechanisms and Preventive Strategies, Pain 2014. In: Srinivasa, RN., Sommer, CL., editors. Refresher Courses, 15th World Congress of Pain. Washington, D.C: IASP Press; 2014.

Risk factors for neuropathic pain- Genetics

Neuron
Review

CellPress

The Genetics of Neuropathic Pain from Model Organisms to Clinical Application

Margarita Calvo,[1,10] Alexander J. Davies,[2,10] Harry L. Hébert,[3,10] Greg A. Weir,[2,9,10] Elissa J. Chesler,[4] Nanna B. Fi
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[8]Departments of Anesthesia and Neurobiology, Children's Hospital Boston and Harvard Medical School, Boston, MA, USA
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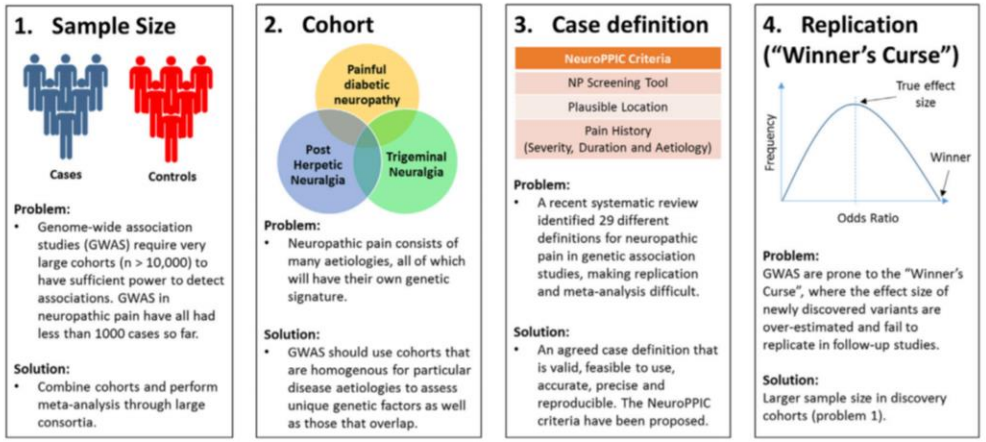
Glasgow, UK
[10]These authors contribu
*Correspondence: micha
https://doi.org/10.1016/j

Neuropathic pain (N
disabling, renderin
conservation of pai



2. The Challenges of Conducting Genome-wide Association Studies in NeuP

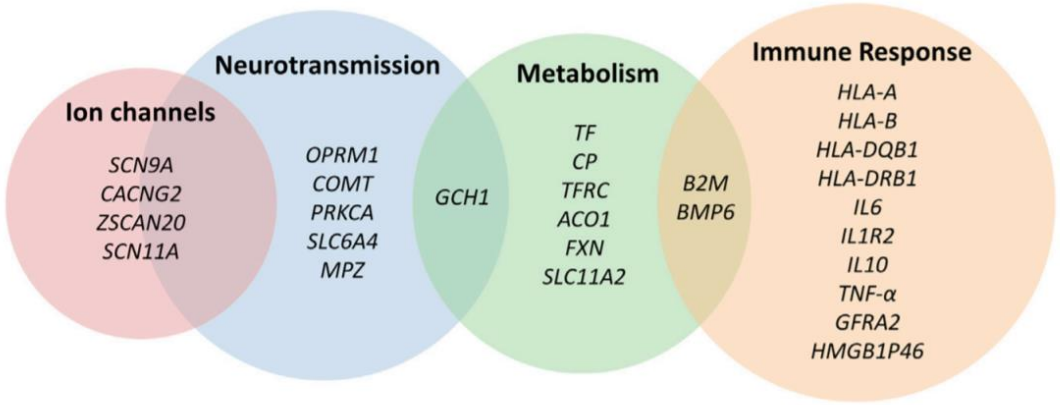
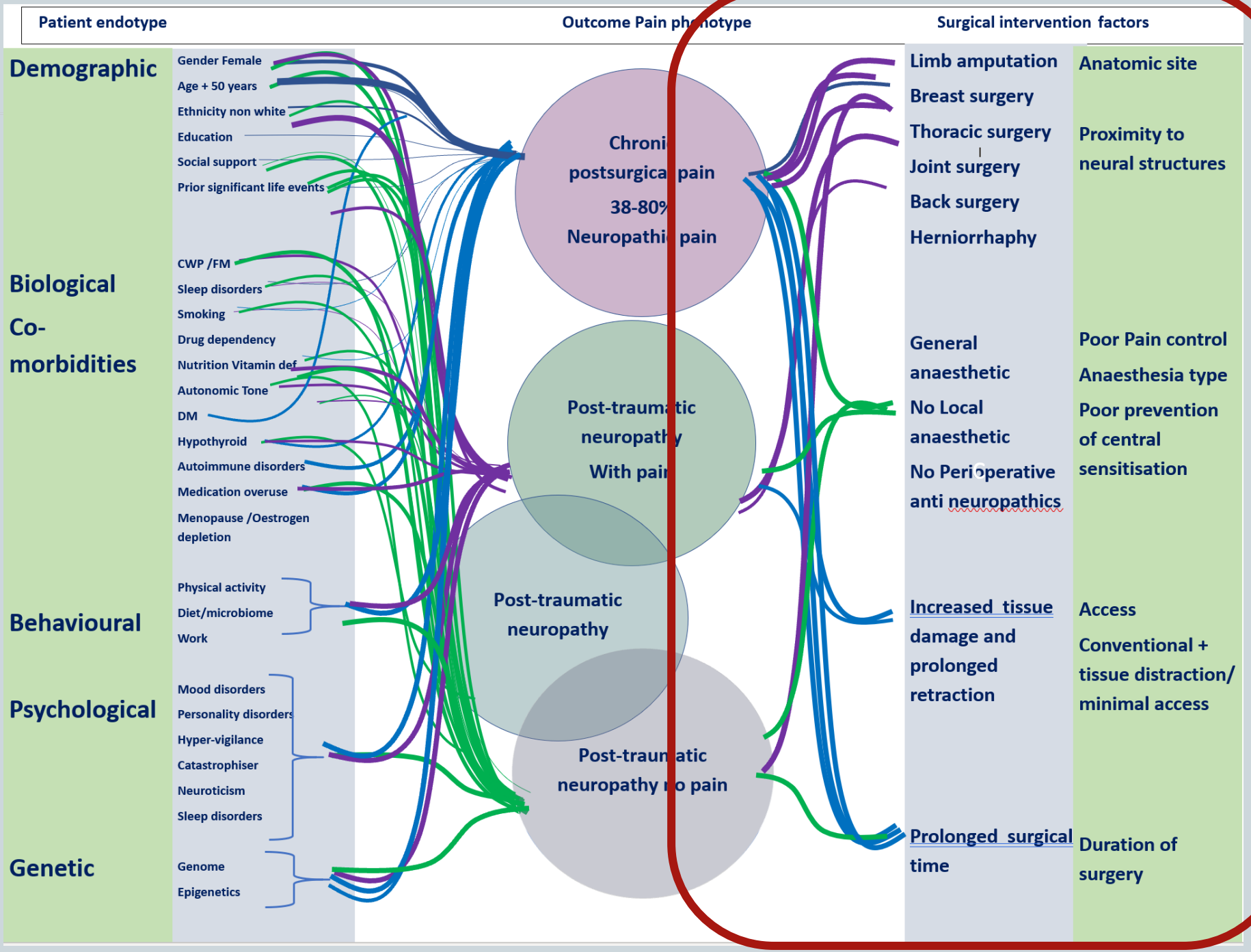


Figure 3. A Venn Diagram of Genes Reaching Study Specific or Suggestive Significance in Human Candidate Gene and Genome-wide Studies So Far in NeuP and the Overlap of Biological Pathways

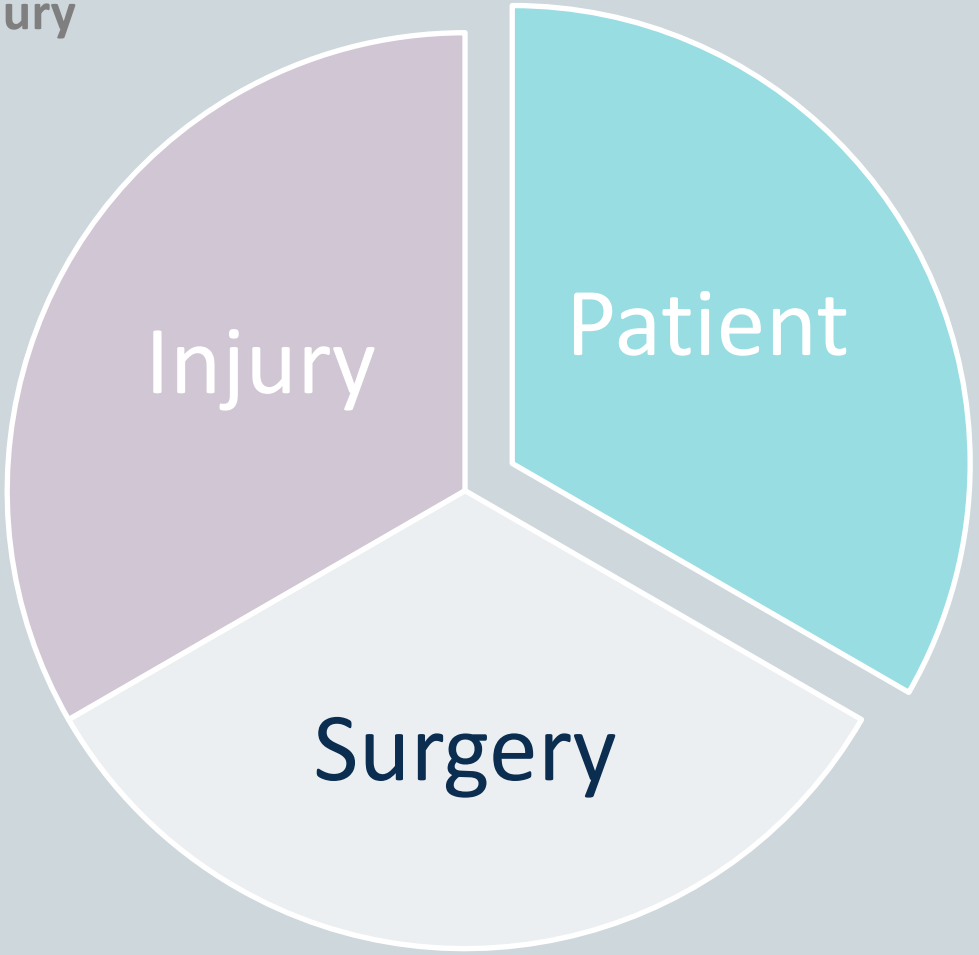
These genes have been summarized in a recent systematic review of NeuP by Veluchamy et al. (2018), where the inclusion criteria were any study analyzing genetic variants in people with NeuP compared to people without NeuP. The number of genes and our understanding of their contribution within these pathways, in the context of NeuP, is likely to change as more studies are published.

Predictors for chronic post surgical pain (CPSP) Post Traumatic neuropathic pain (PTNP) surgical



Patient and Surgical factors predictive for chronic post surgical pain (CPSP)

Resultant sensory nerve injury
Large neuropathic area
Thermal allodynia
Mechanical allodynia
Hyperalgesia



Age > 50 yrs
Female
Multiple pain conditions Social Factors

Axis II Psychological factors
Mood anxiety / depression
Introversion, neuroticism, hypervigilance, catastrophising
Fear of surgery
Fear of pain

Poor pain modulation DNIC positive tests
Genetics
COMPT CA channels
Epigenetics
Prior abuse and neglect
OMICS ????

<u>Surgical factors</u>
Site
Type of surgery
Minimise nerve injury
(Tissue tension & Duration)
High level perioperative pain
(Lack of local anaesthesia)

Joel Katz & Ze'ev Seltzer Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert Review of Neurotherapeutics Volume 9, 2009 - Issue 5

CPSP Anatomical risk
(No identifiable neuropathic area in 69% of cases)

Persistent postsurgical pain (PPSP) is a frequent and often disabling complication of many surgical procedures.

Nerve injury-induced neuropathic pain (NeuP) has repeatedly been proposed as a major cause of PPSP. However, there is a lack of uniformity in NeuP assessment across studies, and the prevalence of NeuP may differ after various surgeries.

We performed a systematic search of the PubMed, CENTRAL, and Embase databases and assessed 281 studies that investigated PPSP after 11 types of surgery.

The prevalence of PPSP in each surgical group was examined. The prevalence of NeuP was determined by applying the recently published NeuP probability grading system. The prevalence of probable or definite NeuP was high in patients with persistent pain after thoracic and breast surgeries-66% and 68%, respectively. In patients with PPSP after groin hernia repair, the *prevalence of NeuP was 31%,* and after total hip or knee arthroplasty it was 6%.

The results suggest that the prevalence of NeuP among PPSP cases differs in various types of surgery, probably depending on the likelihood of surgical iatrogenic nerve injury. Because of large methodological variability across studies, a more uniform approach is desirable in future studies for evaluating persistent postsurgical NeuP.

	Estimated incidence of chronic pain	Estimated chronic severe (disabling) pain (>5 out of score of 10)	US surgical volumes (1000s)†
Amputation[2]	30–50%	5–10%	159 (lower limb only)
Breast surgery (lumpectomy and mastectomy)[3]	20–30%	5–10%	479
Thoracotomy[4-7]	30–40%	10%	Unknown
Inguinal hernia repair[8-10]	10%	2–4%	609
Coronary artery bypass surgery[11-13]	30–50%	5–10%	598
Caesarean section[14]	10%	4%	220

*Gall bladder surgery not included, since preoperative diagnosis of pain specifically from gall bladder is difficult and persistent postoperative pain could therefore be related to other intra-abdominal disorders. †National Center For Health Statistics, Ambulatory and Inpatients Procedures, USA, 1996.

Table 1: **Estimated incidence of chronic postoperative pain and disability after selected surgical procedures***

30% get persistent pain 10% are <u>severely</u> affected

Haroutiunian S, Nikolajsen L, Finnerup NB, Jensen TS. The neuropathic component in persistent postsurgical pain: a systematic literature review. Pain. 2013 Jan;154(1):95-102. doi: 10.1016/j.pain.2012.09.010.

Kehlet H *et al*, 2006 Lancet

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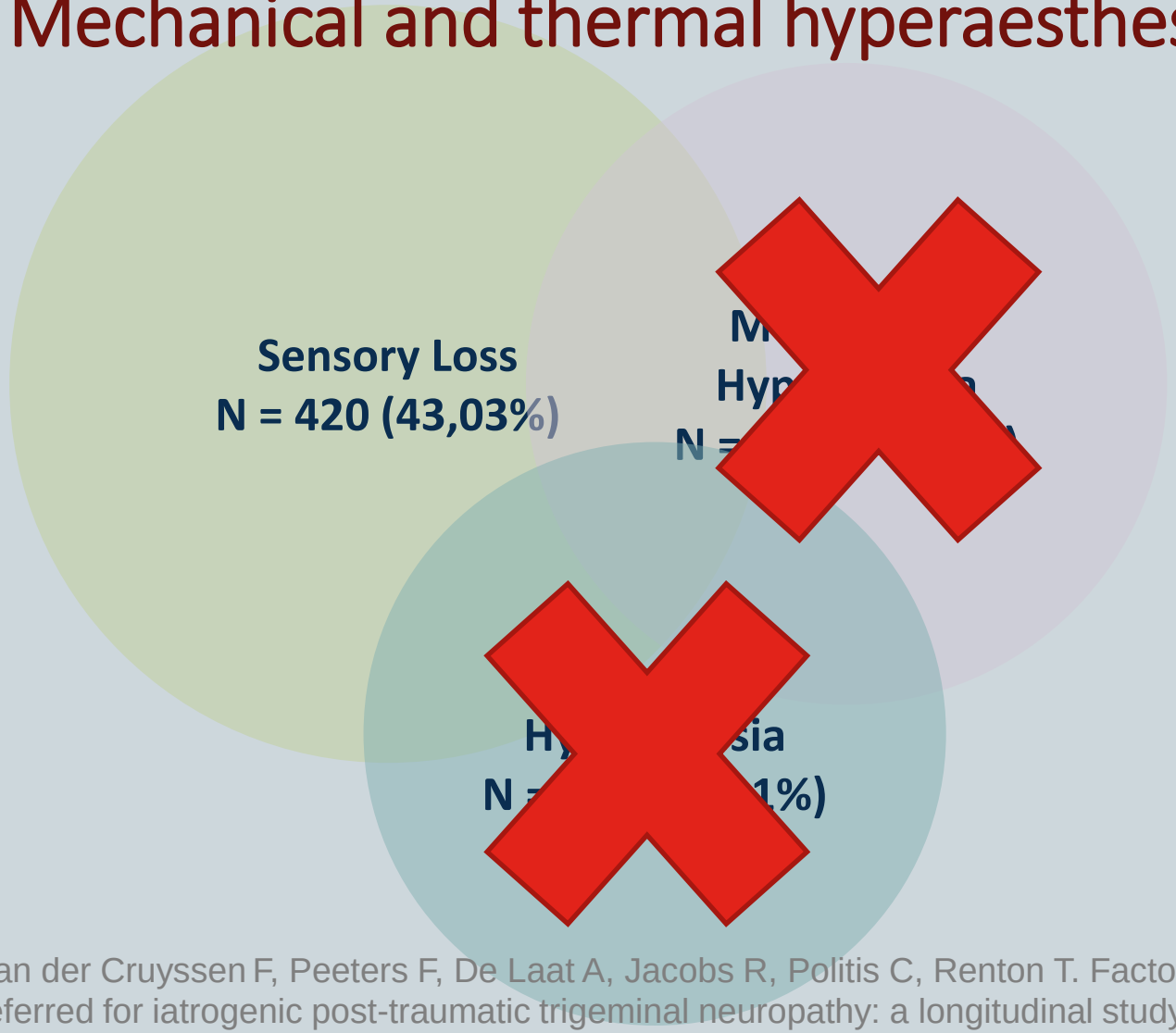
Very low CPSP/ PTNP related to dentistry likely due to the use of Local Anesthesia (1.6-5% after endodontics)

Haroutiunian S, Nikolajsen L, Finnerup NB, Jensen TS. The neuropathic component in persistent postsurgical pain: a systematic literature review. Pain. 2013 Jan;154(1):95-102. doi: 10.1016/j.pain.2012.09.010.

Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006 May 13;367(9522):1618-25. doi: 10.1016/S0140-6736(06)68700-X. PMID: 16698416.

Clustering of Sensory Profiles Trigeminal PTNP (N = 976)
Mechanical and thermal hyperaesthesia less likely to recover?



DOI: 10.1111/joor.13058

ORIGINAL ARTICLE

JOURNAL OF ORAL REHABILITATION WILEY

Signs and symptoms, quality of life and psychosocial data in 1331 post-traumatic trigeminal neuropathy patients seen in two tertiary referral centres in two countries

Fréderic Van der Cruyssen[1,2] | Frederik Peeters[1,2] | Thomas Gill[3] | Antoon De Laat[4,5] | Reinhilde Jacobs[2,6] | Constantinus Politis[1,2] | Tara Renton[3]

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Abstract

Background: Post-traumatic trigeminal neuropathy (PTN) is a disturbance of function or pathological change of the trigeminal nerve branches following trauma and has an important impact on patient's quality of life (QoL).

Objectives: To provide diagnostic data on PTN and illustrate differences in aetiology, injured nerve, pain distribution, sensory profile and QoL between PTN subgroups.

Methods: 1331 patients with painful or non-painful PTN were retrospectively re-viewed in two centres, extracting demographic data, time and cause of trauma, clinical findings including signs and symptoms, basic neurosensory testing, imaging modalities, treatments, and QoL or psychosocial assessment.

Results: More females were represented (70%) than males. The inferior alveolar nerve was most frequently damaged (60%) followed by the lingual nerve (28%). Wisdom teeth removal was considered the main cause (48%). Pain was reported in 63% of patients and pain frequency increased with age without clinically significant gender differences. Numbness was reported in 50% of PTN patients. Neurosensory testing showed larger affected dermatome involvement in persistent injuries, with no differences between the non-painful and painful PTN groups. Patient clustering indicated different sensory profile distributions when stratified according to aetiol-ogy or affected nerve branch. High interference with lifestyle was reported (78%), and patients suffering from painful PTN had worse QoL and psychosocial outcomes.

Conclusion: Patients with painful PTN had different clinical profiles and lower QoL scores than those with non-painful PTN. Sensory profiles may provide important prognostic and therapeutic information; however, more research is needed to assess the clustering procedure and link these clusters to therapeutic guidelines.

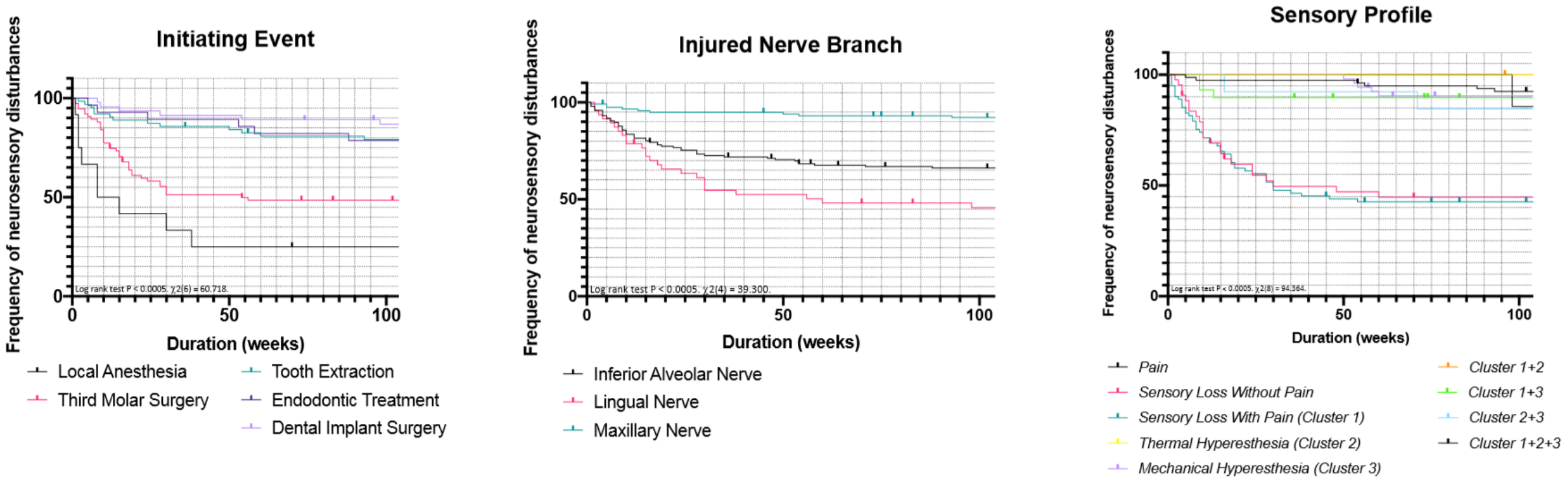
KEYWORDS
diagnosis, neuropathic pain, quality of life, trigeminal nerve, trigeminal nerve disorder

Van der Cruyssen F, Peeters F, De Laat A, Jacobs R, Politis C, Renton T. Factors affecting evolution of symptoms and quality of life in patients referred for iatrogenic post-traumatic trigeminal neuropathy: a longitudinal study in two tertiary referral centers in UK and Belgium. Pain 2020
Van der Cruyssen F, Peeters F, Gill T, De Laat A, Jacobs R, Politis C, Renton T. Signs and symptoms, quality of life and psychosocial data in 1331 post-traumatic trigeminal neuropathy patients seen in two tertiary referral centres in two countries. J Oral Rehabil. 2020 Oct;47(10):1212-1221. doi: 10.1111/joor.13058. Epub 2020 Aug 2. PMID: 32687637; PMCID: PMC7540026.

Predicting resolution of Trigeminal Post Traumatic Neuropathy

LA> M3M> Endo Implant & non M3M extraction
Lingual nerve > Inferior alveolar and maxillary nerve
Hypoaesthesia> hyperaesthesia

Kaplan–Meier analysis of neurosensory disturbances over time comparing the injured nerve branch (A), initiating event (B), and sensory profile (C).



Van der Cruyssen F, Peeters F, De Laat A, Jacobs R, Politis C, Renton T. Factors affecting evolution of symptoms and quality of life in patients referred for iatrogenic post-traumatic trigeminal neuropathy: a longitudinal study in two tertiary referral centers in UK and Belgium. Pain 2020 in press

Opportunities for further evaluation; Psychological vulnerability/ Poor endogenous pain modulation/ Autonomic tone/ Compromised healing?

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When pain gets stuck: the evolution of pain chronification and treatment resistance

David Borsook[1,2], **Andrew M Youssef**[1], **Laura Simons**[3], **Igor Elman**[4], and **Christopher Eccleston**[5,6]

REVIEW FOCUS ON PAIN

nature neuroscience

Pain vulnerability: a neurobiological perspective

Franziska Denk[1], Stephen B McMahon[1] & Irene Tracey[2]

There are many known risk factors for chronic pain conditions, yet the biological underpinnings that link these factors to abnormal processing of painful signals are only just beginning to be explored. This Review will discuss the potential mechanisms that have been proposed to underlie vulnerability and resilience toward developing chronic pain. Particular focus will be given to genetic and epigenetic processes, priming effects on a cellular level, and alterations in brain networks concerned with reward, motivation/learning and descending modulatory control. Although research in this area is still in its infancy, a better understanding of how pain vulnerability emerges has the potential to help identify individuals at risk and may open up new therapeutic avenues.

Considerable advances have been made in understanding the neurobiology of chronic pain over the last two decades. The molecular mechanisms leading to amplification of pain-related signals in chronic pain states have been dissected. An unexpected contribution of non-neuronal cells in the CNS has been discovered, and functional, as well

likely to develop certain chronic pain conditions, as are older people, although age may function as a protective factor in some instances. The influence of genetics is supported by twin and population-based studies, which clearly indicate that painful conditions and acute pain sensitivity *per se* are heritable (see ref. 5 for a recent review). Other

Figure

COMMENTARY

Check for updates

Pain chronification: what should a non-pain medicine specialist know?

Bart Morlion[a], Flaminia Coluzzi[b], Dominic Aldington[c], Magdalena Kocot-Kepska[d], Joseph Pergolizzi[e], Ana Cristina Mangas[f], Karsten Ahlbeck[g] and Eija Kalso[h]

[a]Leuven Centre for Algology & Pain Management, University Hospitals Leuven, KU Leuven, Belgium; [b]Department of Medical and Surgical Sciences and Biotechnologies Unit of Anaesthesia, Intensive Care and Pain Medicine, Sapienza University of Rome, Rome, Italy; [c]Royal Hampshire County Hospital, Winchester, UK; [d]Department of Pain Research and Treatment, Jagiellonian University Medical College, Kraków, Poland; [e]Global Pain Initiative, Golden, CO, USA and Naples Anesthesia and Pain Associates, Naples, FL, USA; [f]Hospital de Santo André, Leiria, Portugal; [g]Capio St Görans Hospital, Stockholm, Sweden; [h]Pain Clinic, Departments of Anaesthesiology, Intensive Care, and Pain Medicine, Helsinki University Central Hospital, Helsinki, Finland

ABSTRACT

Objective: Pain is one of the most common reasons for an individual to consult their primary care physician, with most chronic pain being treated in the primary care setting. However, many primary care physicians/non-pain medicine specialists lack enough awareness, education and skills to manage

ARTICLE HISTORY

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nification;

Neuropathic

Research Paper

OPEN

PAIN REPORTS

Prolonged time of after-sensation after experimental pain stimuli despite efficient conditioned pain modulation in patients with chronic neuropathic pain after traumatic nerve injuries in upper extremity

Adriana Miclescu[a*], Marie Essemark[a], Mathias Astermark[a], Panagiota Gkatziani[a], Antje Straatmann[a], Stephen Butler[a,b], Rolf Karlsten[a], Torsten Gordh[a]

Abstract

Background: As yet, there is limited research that can identify factors that differentiate between painful and nonpainful neuropathies after traumatic nerve injury. The aim of this study was to compare subjects with pain and without pain, all after operative nerve repair in the upper extremities.

Methods: Subjects in both groups (pain, n = 69; painless, n = 62) underwent clinical assessment of sensory nerve function and psychophysical tests: quantitative sensory testing and conditioned pain modulation (CPM). Conditioned pain modulation was assessed by pain ratings to 120 seconds pressure stimuli administered before and after a 60 seconds noxious 4°C cold conditioning stimulus (CS). Time of recovery (time off) of pain intensity from peak VAS_{max} after CS was recorded. Questionnaires about the quality of life (RAND-36) and disability of the extremity (QuickDash) were completed.

Results: There were no significant differences between groups for CPM ($P = 0.19$). Time off was 42 seconds in subjects with pain in comparison with 28 seconds in those without pain ($P < 0.0001$). Compared with individuals reporting no pain, participants with neuropathic pain after nerve injuries had 1.8 times the odds of recovering later after CS, gain of function findings at sensory examination ($P < 0.0001$), lower scores of the physical component of RAND-36 ($P < 0.0001$), and increase arm disability ($P < 0.0001$). Hyperesthesia to cold pain stimulation ($P = 0.03$) and lowered pain pressure threshold ($P = 0.01$) were found in the pain group.

is

Correct treatment planning involves……..

Endotyping the patient

Demographics
Age, gender, ethnicity, social, education

Culture, Religion, Beliefs, Previous significant life events

Psychological
Mood disorders, personality disorders

Lifestyle
Diet, exercise, smoking, alcohol, caffiene

Comorbid pain conditions

Sleep disorders

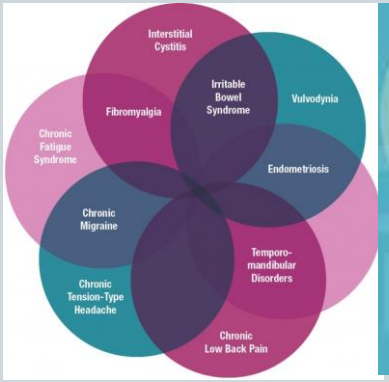
Microbiome

Endogenous pain (CPM offset)
HRV

Medicine sensitivity

Factors that may predict and potentiate and influence the outcome for treatment for Chronic neuropathic pain

Clinical phenotype
Age
Gender
Ethnicity

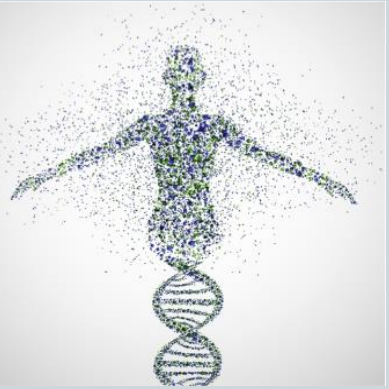


Medical Co-morbidities
CWP /FM
Sleep disorders
Smoking
Drug dependency
Vitamin C and D def
Malnutrition
DM, Hypothyroid, Autoimmune disorders
Medication overuse

Psychological factors
Anxiety
Depression
Neuroticism
Catastrophising
Introversion
Hypervigilance
Narcissism

Social factors
Support
Culture
Education level
Income
Prior significant life events
Culture
Ethnicity
Religion
Beliefs

Physiological
Factors
Microbiome
Endogenous pain modulation
Neural plasticity
Gray / white matter degeneration
Connectivity
Neuropathy



Genetic Profile
Genome
Epigenetics

Managing the neuropathic pain patient is more than just drugs……

Drug[1]	Starting Dose	Typical Dose
Antidepressants[2]		
Nortriptyline	10 mg orally at bedtime	10–50 mg orally at bedtime
Desipramine	10 mg orally at bedtime	10–50 mg orally at bedtime
Calcium-channel alpha2-delta ligands		
Gabapentin[3]	100–300 mg orally once to three times daily	300–1200 mg orally three times daily
Pregabalin[4]	50 mg orally three times daily	100 mg orally three times daily
Selective serotonin norepinephrine reuptake inhibitors		
Duloxetine	60 mg orally daily or 20 mg orally twice daily in elders	60–120 mg orally daily
Venlafaxine[5]	75 mg orally daily divided into two or three doses	150–225 mg orally daily divided into two or three doses
Opioids	**(see Table 5–3)**	**(see Table 5–3)**
Other medications		
Lidocaine transdermal	5% patch applied daily, for a maximum of 12 hours	1–3 patches applied daily for a maximum of 12 hours
Tramadol hydrochloride	50 mg orally four times daily	100 mg orally two to four times daily

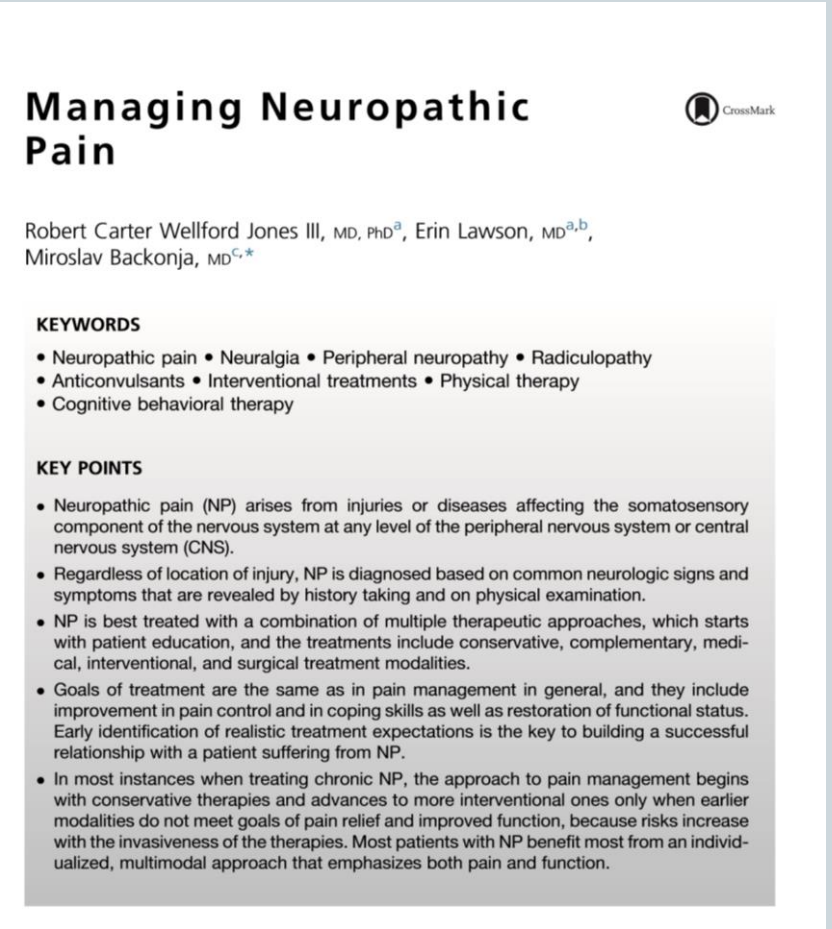
Multidisciplinary management

Regardless of location of injury, NP is diagnosed based on common neurologic signs and symptoms that are revealed by history taking and on physical examination.

NP is best treated with a combination of multiple therapeutic approaches, which starts with patient education, and the treatments include conservative, complementary, medical, interventional, and surgical treatment modalities.

Goals of treatment include improvement in **pain control and in coping skills as well as restoration of functional status.** Early identification of realistic treatment expectations is the key to building a successful relationship with a patient suffering from NP.

In most instances when treating chronic NP, the approach to pain management begins with conservative therapies and advances to more interventional ones only when earlier modalities do not meet goals of pain relief and improved function, because risks increase with the invasiveness of the therapies. Most patients with NP benefit most from an individualized, multimodal approach that emphasizes both pain and function.



Managing Neuropathic Pain

Robert Carter Wellford Jones III, MD, PhD[a], Erin Lawson, MD[a,b], Miroslav Backonja, MD[c,*]

KEYWORDS

• Neuropathic pain • Neuralgia • Peripheral neuropathy • Radiculopathy
• Anticonvulsants • Interventional treatments • Physical therapy
• Cognitive behavioral therapy

KEY POINTS

- Neuropathic pain (NP) arises from injuries or diseases affecting the somatosensory component of the nervous system at any level of the peripheral nervous system or central nervous system (CNS).
- Regardless of location of injury, NP is diagnosed based on common neurologic signs and symptoms that are revealed by history taking and on physical examination.
- NP is best treated with a combination of multiple therapeutic approaches, which starts with patient education, and the treatments include conservative, complementary, medical, interventional, and surgical treatment modalities.
- Goals of treatment are the same as in pain management in general, and they include improvement in pain control and in coping skills as well as restoration of functional status. Early identification of realistic treatment expectations is the key to building a successful relationship with a patient suffering from NP.
- In most instances when treating chronic NP, the approach to pain management begins with conservative therapies and advances to more interventional ones only when earlier modalities do not meet goals of pain relief and improved function, because risks increase with the invasiveness of the therapies. Most patients with NP benefit most from an individualized, multimodal approach that emphasizes both pain and function.

Summary Background—Neuropathic pain is difficult to treat. New treatments, clinical trials and standards of quality for assessing evidence justify an update of evidence-based recommendations for its pharmacological treatment.

- **a strong GRADE recommendation for use and proposal as first line for TCAs, SNRIs, pregabalin, gabapentin and gabapentin ER/enacarbil in neuropathic pain** :
- NNTs were 3·6 (95 % CI 3·0–4·4) for **tricyclic antidepressants** (TCAs), 6·4 (95 % CI 5·2–8·4)
- for **serotonin- noradrenaline reuptake inbibitor (SNRI)** antidepressants duloxetine and venlafaxine, 7·7 (95 % CI 6·5–9·4)
- for **pregabalin** and 6·3 (95 % CI 5·0–8·3)
- for gabapentin. NNTs were higher for **gabapentin** ER/enacarbi
- For **capsaicin high concentration patches**,
- **a weak recommendation for use and proposal as second line for lidocaine patches, capsaicin patches and tramadol,**
- opioids
- Final quality of evidence was lower for lidocaine patches and BTX-A. Tolerability/safety and values/preferences were high for lidocaine patches and lower for opioids and TCAs.

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Author manuscript
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Pharmacotherapy for neuropathic pain in adults: systematic review, meta-analysis and updated NeuPSIG recommendations

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[*]N Attal and NB Finnerup contributed equally to this work.

Conflicts of interest

NA has served on the advisory boards or speakers panels of Astellas Pharma, Adir Servier, Eli Lilly, Grunenthal, Johnson and Johnson, Sanofi Pasteur Merieux and Pfizer and has been investigator of studies sponsored by Astellas, Grunenthal and Astra Zeneca. RB has received grant/research support from Pfizer, Genzyme, Grünenthal, German Federal Ministry of Education and Research (BMBF): German Research Network on Neuropathic Pain, NoPain system biology and German Research Foundation (DFG). He has received speaker honorarium from Pfizer, Genzyme, Grünenthal, Mundipharma, Sanofi Pasteur, Medtronic, Eisai, Lilly, Boehringer Ingelheim, Astellas, Desitin, Teva Pharma, Bayer-Schering, MSD and served as consultant for Pfizer, Genzyme, Grünenthal, Mundipharma, Allergan, Sanofi Pasteur, Medtronic, Eisai, Lilly, Boehringer Ingelheim, Astellas, Novartis, Bristol-Myers Squibb, Biogenidec, AstraZeneca, Merck, Abbvie. RHD has received research grants from US Food and Drug Administration and US National Institutes of Health, and compensation for activities involving clinical trial research methods from Acorda, Adynxx, Allergan, Analgesic Solutions, Anika, Astellas, AstraZeneca, Avanir, Axsome, Bayer, Biogen, Bioness, Bristol-Myers Squibb, Cardiome, Centrexion, Charleston, Chromocell, Collegium, Concert, Daiichi Sankyo, Depomed, Depuy, Eli Lilly, Epicept, Flexion, Genzyme, Glenmark, Inhibitex, Johnson & Johnson, Lpath, Medicinova, Merck, Metys, MMS Holdings, Nektar, Neura, NeurogesX, Olatec, Ono, Periphagen, Pfizer, Phillips, Phosphagenics, Prolong, Q-Med, QRx Pharma, Regenesis, Relmada, Sanofi-Aventis, Salix, Smith & Nephew, Sorrento, Spinifex, Takeda, Taris, Teva, Theravance, and Xenon. NBF has received speaker's honorarium from Pfizer, Grunenthal, and Norpharma, research grant from Grünenthal, and consultancy fee from Astellas. MH has received honoraria from Eli Lilly, Janssen-Cilag, MSD, Mundipharma, Orion, Sanofi-Aventis for lecture, honoraria from Pfizer, Allergan, Astellas for lecture and consulting and honoraria from Abbvie for consulting TSJ have received honoraria from Pfizer, Grünenthal, Astellas, Orion and Sanofi Pasteur as speaker, advisory Board participant or grant. PK has served on advisory board for Reckitt Benckizer, and received speakers' honoraria from Pfizer. KL has received travel grants from Pfizer and Astellas. EM reports grants from Richard Saltonstall Charitable Foundation, USA, during the conduct of the study. AM has received speaker's honorarium from Pfizer, speaker's honorarium and consultancy fees from Eli Lilly and Grünental and research grant from Grünenthal. SNR has served on the advisory boards of Purdue Pharma, QRx pharma, Salix Pharmaceuticals, and Shionogi. ASCR has share options in Spinifex Pharmaceuticals. He undertakes consulting for Imperial College Consultants, and has received fees from Spinifex Pharmaceuticals, Astellas, Servier, Allergan, Asahi Kasei, and Medivir. Through EuroPain, ASCR's laboratory has received funding for research studentships from Pfizer and Astellas. Other recent or current grant/studentship funding for ASCR's laboratory are: Wellcome Trust (London Pain Consortium), Dunhill Medical Trust, NC3Rs, Westminster Medical School Research Trust, International Association for the Study of Pain, National Institute of Academic Anaesthesia, Derek Butler Trust, Medical Research Council Industrial, Biotechnology and Biological Sciences Research Council and Pfizer/Christian-Albrechts University of Kiel (Neuropain). ASCR is a member of the England and Wales Joint Committee on Vaccination and Immunisation (varicella subgroup). MR reports personal fees and other from Afferent Pharmaceuticals, Centrexion, Nektar Therapeutics, Xenoport, ViroBay, Chromocell, Adynxx, Lilly, Zalicus, Biogen IDEC outside the submitted work. PS has a patent System and method for detecting pain and its components using magnetic resonance spectroscopy, US Patent 08755862 issued. BHS has consulted for Pfizer and Napp, and received unconditional educational grants from Pfizer to support epidemiological research. MW reports personal fees from Boston Scientific, Jazz Pharmaceutical, Spinal Modulations, Depomed and Inergetics. RB, NBF, KL, TSJ and ASCR are also members of the IMI "Europain" collaboration and industry members of this are: Astra Zeneca, Pfizer, Esteve, UCB-Pharma, Sanofi Aventis, Grünenthal, Eli Lilly, Boehringer Ingelheim, Astellas, Abbott and Lundbeck. The other authors have no conflicts of interest to disclose.

Contributors

NA, NF, SH, KL, and EM did the search and extracted data. NF performed the meta-analysis. ES did the analysis of publication bias. NA and NF drafted the manuscript and the tables. PH, MR, PS and MW were external reviewers for the manuscript. All panel members contributed to the guidelines in formulating the recommendations, revising and editing the final text. All panel members and external reviewers contributed to the final text version.

Finnerup et al. Lancet Neurol. Author manuscript; available in PMC 2016 February 01.

Go to drugs

Nortriptyline (TCA) (10-40mgs nocte)

Lyrica Pregabalin (25mgs nocte / BD)

Indication	Dosing regimen	Maximum dose
DPN pain	3 divided doses per day	300 mg/day within 1 week
PHN	2 or 3 divided doses per day	300 mg/day within 1 week. Maximum dose of 600 mg/day
Adjunctive therapy for adult patients with partial onset seizures	2 or 3 divided doses per day	Maximum dose of 600 mg/day
Fibromyalgia	2 divided doses per day	300 mg/day within 1 week Maximum dose of 450 mg/day
Neuropathic pain associated with spinal cord injury	2 divided doses per day	300 mg/day within 1 week. Maximum dose of 600 mg/day

	Gabapentin	Pregabalin
Chemistry	Analog of GABA	Substituted analog of gabapentin
Absorption	Saturable	Non-saturable
Oral bioavailability	60% – 300 mg 33% – 3600 mg 27% – 4800 mg	90%
Onset of action	≥ 9 days	1–3 days
Renal elimination (half-life)	70–80% (5–7 hours)	90–99% (5–7 hours)
Dose (normal renal function)	300 mg po TID; ↑ q week as tolerated to maximum 3600 mg/day	75 mg po BID; ↑ every 3–7 days as tolerated to maximum 600 mg/day
T_{max}	0.7–1.5 hours	
Half-life	4.6–6.8 hours	5–7 hours
Percent excreted uncharged in urine	98%	

Actions for Commissioning Teams

21

Pregabalin or gabapentin?

- Pregabalin and gabapentin are structurally related and have a similar pharmacological action and adverse events.
- Limited data - no published head-to-head RCTs comparing gabapentin and pregabalin in post-herpetic neuralgia or diabetic neuropathy. One small trial in neuropathic cancer pain.
- Pregabalin is much more expensive than gabapentin (see next slide)
  - In 2012, the NHS in West Midlands spent nearly £19 million on pregabalin . Although it has other indications, the majority of pregabalin prescriptions are for neuropathic pain. If half of the pregabalin prescriptions had been prescribed as gabapentin, this could have saved more than £8 million.
- Current NICE guidance for neuropathic pain recommends pregabalin as a first line option but does not recommend gabapentin.[23]
  - NICE concluded that pregabalin is more effective than gabapentin based on indirect comparisons of the two treatments. Pregabalin *vs.* gabapentin, has lower number needed to treat (NNT) values for at least 30% pain reduction and 50% pain reduction.
- Decision by NICE to recommend pregabalin over gabapentin has been heavily criticised because of the associated costs to the NHS; NICE have agreed to review their decision.

Side effects and compliance

only 11% of PTNP patients continue with medication

TABLE 4

MOST COMMON ADVERSE SNRI DRUG REACTIONS[1-4]

Venlafaxine[1]	*Duloxetine*[2]	*Milnacipran*[3]	*Desvenlafaxine*[4]
Nausea	Nausea	Anxiety	Nausea
Sweating	Increased sweating	Excessive sweating	Hyperhidrosis
Somnolence	Somnolence	Vertigo	Somnolence
Anorexia	Decreased appetite	Hot flush	Decreased appetite
Tremor	Constipation	Dysuria	Constipation
Nervousness	Fatigue		Anxiety
Dry mouth	Dry mouth		
Dizziness			
Abnormal dreams			
Abnormal ejaculation			

Adverse reactions as defined as oc
twice the rate for placebo for venlafa
European Medicines Agency for miln

SNRI=serotonin norepinephrine reup

Shelton RC. *Primary Psychiatry.* Vol

Common side effects associated with tricyclic antidepressants

	Sedation	Anti-cholinergic effects	Hypo-tension	Cardiac effects	Seizures	Weight gain
Amitriptyline	+++	+++	+++	+++	++	++
Clomipramine	++	+++	++	+++	+++	+
Desipramine	0/+	+	+	++	+	+
Nortriptyline	+	+	+	++	+	+

0/+=minimal; +=mild; ++=moderate; +++=moderately severe.
From Goodman and Gilman's, *The Pharmacological Basis of Therapeutics*, 9th edition.

Table 2. Common Adverse Effects from Treatment for Diabetic Peripheral Neuropathic Pain

Drug	*Adverse effect*	*Patients who experienced effect (%)*
Amitriptyline*[8,30]	Constipation	14
	Dizziness	28
	Dry mouth	90
	Somnolence	66
Capsaicin cream (Zostrix)[19]	Cough	8
	Skin irritation	54
Duloxetine (Cymbalta)[5,19]	Constipation	9
	Diarrhea	6
	Fatigue	9
	Headache	10
	Nasopharyngitis	6
	Nausea	22
	Somnolence	8
	Sweating	6
abapentin (Neurontin)[11]	Confusion	7
	Diarrhea	10
	Dizziness	24
	Headache	10
	Nausea	8
	Somnolence	20
docaine 5% patch (Lidoderm)[20]	No adverse effects significantly different from placebo	—

Drug	*Adverse effect*	*Patients who experienced effect (%)*
Opiates[14]	Constipation	33
	Dizziness	21
	Nausea	33
	Somnolence	29
	Vomiting	15
Pregabalin (Lyrica)†[9,10]	Dizziness	7 to 28
	Edema	6 to 16
	Somnolence	5 to 13
	Weight gain	4 to 9
Tramadol (Ultram)[18]	Constipation	22
	Headache	17
	Nausea	23
	Somnolence	12
Venlafaxine (Effexor)[8]	Anorexia	5
	Dyspepsia	10
	Flatulence	6
	Impotence	5
	Insomnia	10
	Myalgia	5
	Nausea	10
	Sinusitis	7
	Somnolence	15
	Sweating	10
	Vomiting	5

—Amitriptyline chosen to represent tricyclic antidepressants.
—Range of percentages is based on range of doses in study; adverse effects were dose-related.
formation from references 5, 8 through 11, 14, 18 through 20, and 30.

Botoxin A

Grade B for TN but low evidence for PTNP

Burmeister *et al. Trials* (2015) 16:550
DOI 10.1186/s13063-015-1052-z

TRIALS

STUDY PROTOCOL Open Access

Botulinum neurotoxin type A in the treatment of classical Trigeminal Neuralgia (BoTN): study protocol for a randomized controlled trial

Jan Burmeister[1*], Dagny Holle[1], Eva Bock[2], Claudia Ose[2], Hans-Christoph Diener[1] and Mark Obermann[1]

Abstract

Background: Trigeminal neuralgia is characterized by paroxysmal facial pain attacks. Adequate prophylactic drug therapy is often limited by the lack of efficacy and intolerance due to central nervous system side effects. Subcutaneous injections of botulinum toxin type A are a promising treatment option for patients with unsatisfactory response to drug therapy or neurosurgical intervention. Its effects are expected to last for at least 3 months, so it could be a potential long-term treatment.
This is the study protocol of a prospective, placebo-controlled, double blind clinical trial investigating the add-on therapy of subcutaneous administration of botulinum toxin type A injections to standard treatment in therapy-refractory classical trigeminal neuralgia.

Methods and design: BoTN is a prospective, double blind, placebo-controlled trial with a randomized withdrawal design in which a single blind phase is followed by a double blind phase (see also Methods and design). Eligible patients with classical trigeminal neuralgia who are otherwise refractory to medical and neurosurgical treatment will receive subcutaneous injections of botulinum toxin type A into injection sites of the affected trigeminal branch. In the first phase all patients will receive botulinum toxin type A in a single blinded intervention. Twelve weeks later therapy responders will be allocated to the *verum* or placebo (saline) arm in a double blind, randomized manner. These injections will be performed at the same sites as the first injections.
This trial will be conducted in a tertiary outpatient clinic specialized in the treatment of headache and facial pain. There will be three investigators performing the injections who are experienced in the treatment of headache and facial pain and trained in botulinum toxin type A injections.

Discussion: BoTN is designed to assess the efficacy and safety of subcutaneous botulinum toxin type A injections in addition to standard prophylactic treatment in therapy-refractory trigeminal neuralgia.

Trial registration number: EU Clinical Trials Register: EudraCT-No: 2014-001959-24 https://www.clinicaltrials register.eu/ctr-search/rest/download/trial/2014-001959-24/DE
Date of trial registration
26 August 2014

Keywords: Trigeminal neuralgia, Botulinum toxin type A, Prophylactic treatment, Clinical trial, Prospective study, Study protocol

Vol. 122 No. 1 July 2016

The efficacy of botulinum toxin for the treatment of trigeminal and postherpetic neuralgia: a systematic review with meta-analyses

Thomas Shackleton, DDS, MS,[a] Saravanan Ram, DDS, MS,[b] Misty Black, DDS, MS,[a] Jon Ryder, DDS, MS,[a] Glenn T. Clark, DDS, MS,[c] and Reyes Enciso, PhD[d]

Objective. To evaluate the efficacy of a botulinum toxin type A (BoTN-A) in treating trigeminal neuralgia (TN) and postherpetic neuralgia (PHN).
Study Design. Three databases were searched: Medline, Web of Science, and Cochrane Library. The search was restricted to English-language randomized, placebo-controlled trials. Three review authors evaluated the cases for risk of bias.
Results. Six studies were eligible for inclusion. Pooled results showed a difference in post-treatment pain intensity of −3.009 (95% confidence interval −4.566 to −1.453; $P < .001$) in favor of BoTN-A compared with placebo in managing TN or PHN. Of the six studies, five had unclear risk of bias, and one showed high risk.
Conclusions. Although the studies had unclear or high risk of bias, moderate evidence regarding the efficacy of BoTN-A in treating TN and PHN was found. BoTN-A might be an alternative treatment to those patients who are either unable to manage their pain medically or would like adjunct therapy. (Oral Surg Oral Med Oral Pathol Oral Radiol 2016;122:61-71)

Neuralgia is described as pain extending along the course of one or more nerves. Many varieties of neuralgia are distinguished according to the nerves affected, such as the trigeminal, brachial, occipital, and supraorbital nerves, or to the cause, such as postherpetic, anemic, diabetic, gouty, malarial, or syphilitic factors.[1] Pain from neuralgias is often debilitating to those who suffer from it. These patients often suffer for extended periods before any sort of beneficial therapy is suggested.[2] There are two major treatment strategies for neuralgias: pharmacotherapy and neurosurgery. Medical management is the mainstay treatment for most neuralgias, since it generally carries a lower risk compared with major surgical procedures and is suitable for medically compromised patients who are unfit for such surgery.[3] However, side effects from systemic medications, such as ataxia, dizziness, nausea, fatigue, rash, and somnolence, can be problematic and debilitating.

Botulinum toxin type A (BoTN-A) is a potent neurotoxin that blocks acetylcholine release from presynaptic nerve endings by interfering with the activity of SNARE (soluble *N*-ethylamide-sensitive-factor attachment protein receptors) proteins. BoTN-A has been reported to have analgesic effects independent of its action on muscle tone.[4] The most significant results have been observed in patients with neuropathic pain. Neuropathic pain caused by peripheral lesions has been the most widely studied. BoTN-A has shown its efficacy on pain and allodynia in various animal models of inflammatory neuropathic pain.[4] The objective of this review was to determine the efficacy of BoTN-A when used as a treatment in patients suffering from trigeminal neuralgia (TN) or postherpetic neuralgia (PHN).

MATERIALS AND METHODS

This systematic review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[5]

Eligibility criteria

Studies were limited to randomized controlled trials (RCTs) on the efficacy of BoTN-A compared with

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[c]Professor of Dentistry, Program Director, Orofacial Pain, Herman Ostrow School of Dentistry of USC, Los Angeles, CA, USA.
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2212-4403/$ - see front matter
http://dx.doi.org/10.1016/j.oooo.2016.03.003

Statement of Clinical Relevance

In this systematic review, the number of eligible studies was small, and the authors found unclear or high risk of bias in the included studies. However, moderate evidence regarding the efficacy of botulinum toxin A in treating trigeminal and postherpetic neuralgia was found; this evidence provides hope that this may be an alternative treatment for those patients who are either unable to manage their pain medically or would like an adjunct therapy.

Morra *et al. The Journal of Headache and Pain* (2016) 17:63
DOI 10.1186/s10194-016-0651-8

The Journal of Headache and Pain

REVIEW ARTICLE Open Access

Therapeutic efficacy and safety of *Botulinum Toxin A Therapy* in *Trigeminal Neuralgia*: a systematic review and meta-analysis of randomized controlled trials

Mostafa Ebraheem Morra[1†], Ahmed Elgebaly[1†], Ahmed Elmaraezy[1†], Adham M. Khalil[2†], Ahmed M. A. Altibi[3], Tran Le-Huy Vu[4], Mostafa Reda Mostafa[5], Nguyen Tien Huy[6,7*] and Kenji Hirayama[8*]

Abstract

Background: Several different interventions have been examined to alleviate pain and reduce frequency of trigeminal neuralgia (TN) paroxysms. However, some patients continue to have persistent or recurrent painful attacks. Using a systematic review and meta-analysis approach, we aimed to synthesize evidence from published randomized controlled trials (RCTs) regarding safety and efficacy of botulinum toxin type A (BTX-A) as a possible emerging choice of treatment for TN.

Methods: We conducted an electronic search in 10 databases/electronic search engines to access relevant publications. All articles in all languages reporting RCTs on the efficacy and safety of BTX-A in the treatment of TN were included for systematic review and meta-analysis.

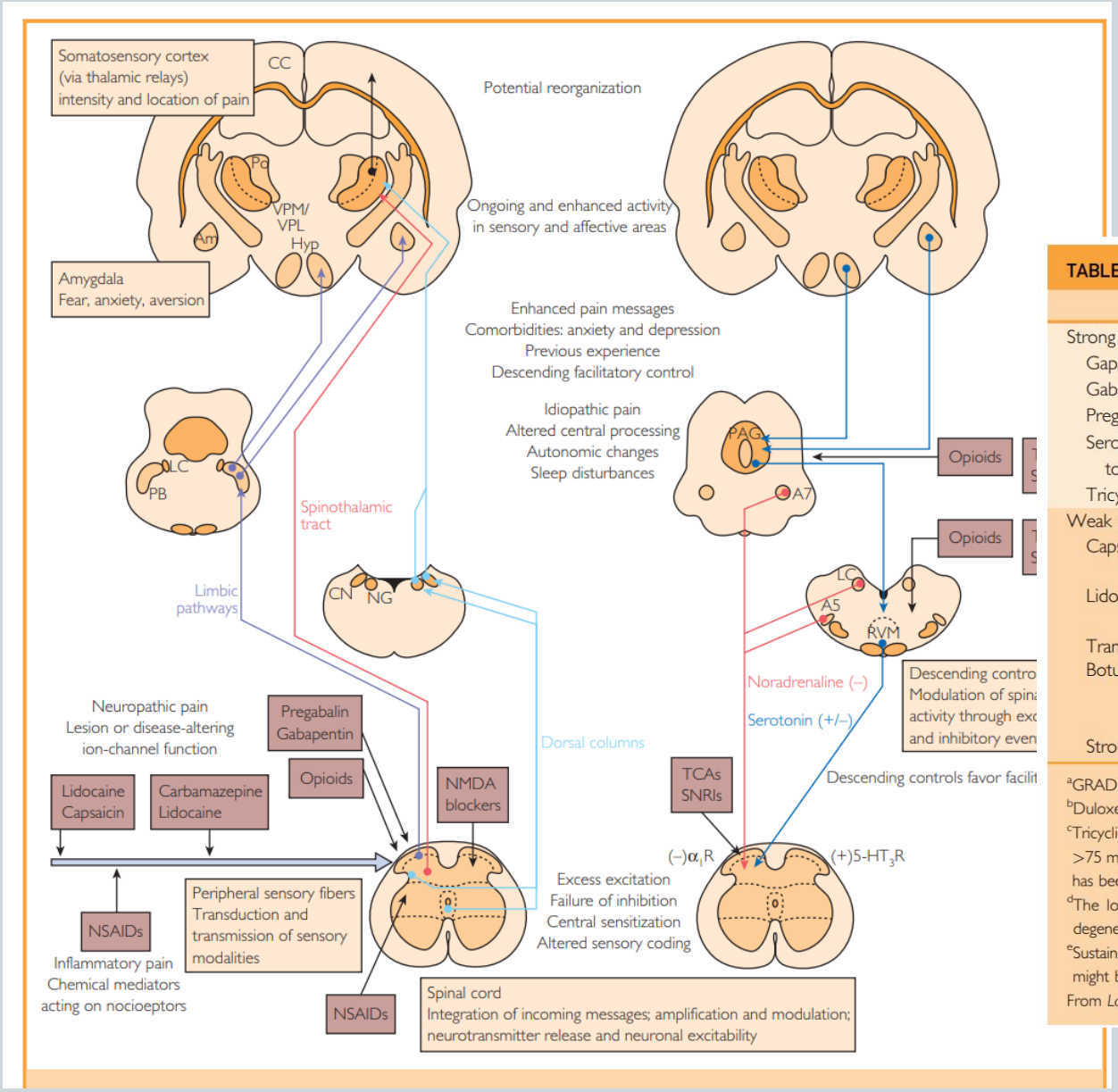
Results: A total of four RCTs (n = 178) were identified for final meta-analysis. The overall effect favored BTX-A versus placebo in terms of proportion of responders (risk ratio RR = 2.87, 95 % confidence interval CI [1.76, 4.69], p <0.0001) with no significant detected heterogeneity (p = 0.31; I^2 = 4 %). Paroxysms frequency per day was significantly lower for BTX-A group (mean difference MD = -29.79, 95 % CI [-38.50,–21.08], p <0.00001) with no significant heterogeneity (p = 0.21; I^2 = 36 %).

Conclusion: Despite limited data, our results suggest that BTX-A may be an effective and safe treatment option for patients with TN. Further larger and well-designed RCTs are encouraged to translate these findings into better clinical outcome and better quality of life for TN patients.

Keywords: Botulinum, BTX-A, Trigeminal neuralgia, Clinical trials, Systematic review, Meta-analysis

Ngeow WC, Nair R Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010 Mar;109(3):e47-50.
Injection of botulinum toxin type A (BOTOX) into trigger zone of trigeminal neuralgia as a means to control pain.

Conventional treatments



SYMPOSIUM ON PAIN MEDICINE

MAYO CLINIC

Neuropathic Pain: Principles of Diagnosis and Treatment

Ian Gilron, MD, MSc, FRCPC; Ralf Baron, MD, PhD; and Troels Jensen, MD, DMSc

From the Departments of Anesthesiology and Perioperative Medicine and Biomedical and Molecular Sciences,

CME Activity

Target Audience: The target audience for *Mayo Clinic Proceedings* is primarily internal medicine physicians and other clinicians who wish to advance

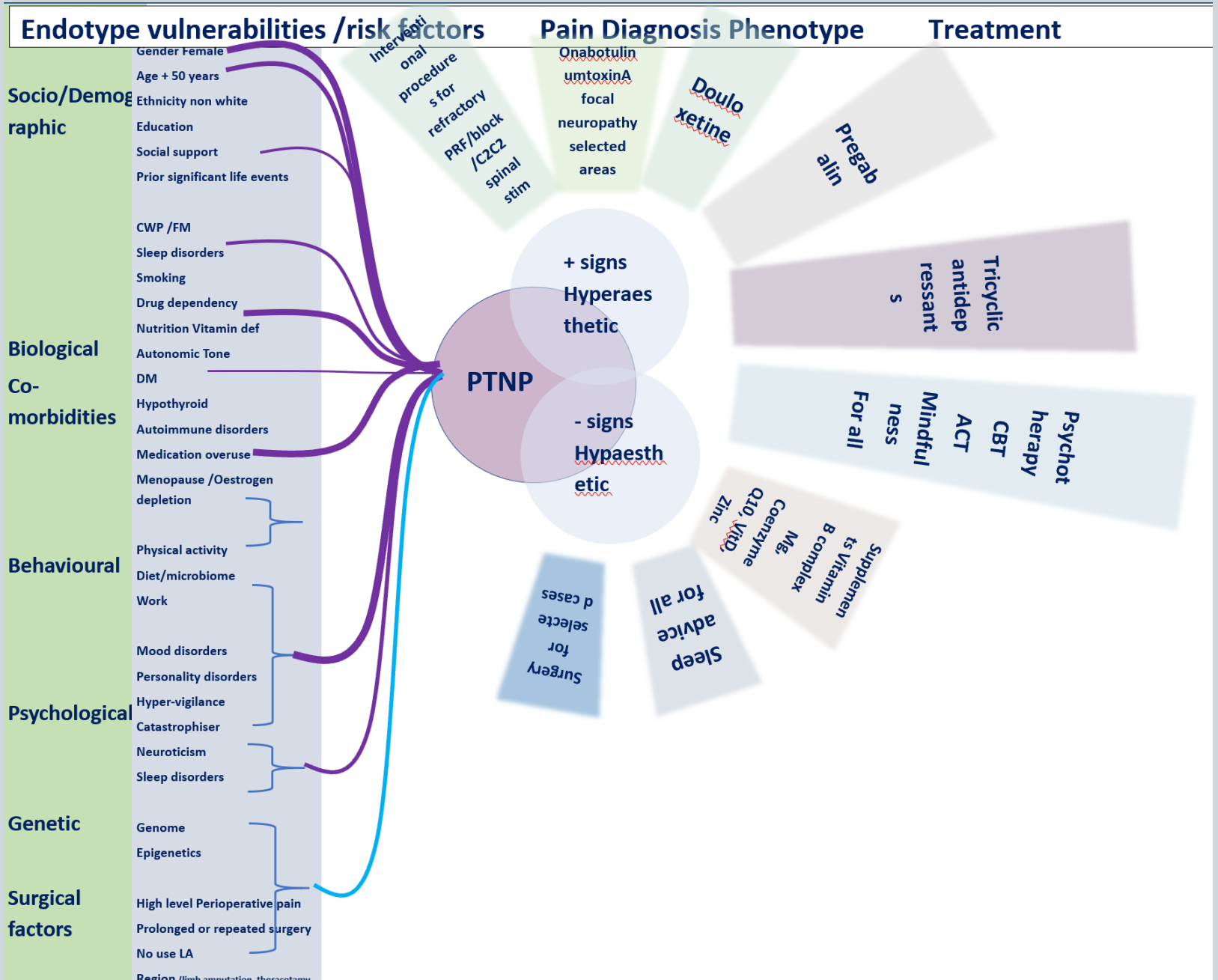
of this information will be published in course materials so that those participants in the activity may formulate their own judgments regarding the presentation.

TABLE 2. Currently Recommended Neuropathic Pain Drugs[a]

Drug	Total daily dose and dose regimen	Recommendations
Strong recommendations for use		
Gapabentin	1200-3600 mg, in 3 divided doses	First line
Gabapentin extended release or enacarbil	1200-3600 mg, in 2 divided doses	First line
Pregabalin	300-600 mg, in 2 divided doses	First line
Serotonin-norepinephrine reuptake inhibitors duloxetine or venlafaxine[b]	60-120 mg, once a day (duloxetine); 150-225 mg, once a day (venlafaxine extended release)	First line
Tricyclic antidepressants	25-150 mg, once a day or in 2 divided doses	First line[c]
Weak recommendations for use		
Capsaicin 8% patches	One to 4 patches to the painful area for 30-60 min every 3 mo	Second line (peripheral neuropathic pain)[d]
Lidocaine patches	One to 3 patches to the region of pain once a day for up to 12 h	Second line (peripheral neuropathic pain)
Tramadol	200-400 mg, in 2 (tramadol extended release) or 3 divided doses	Second line
Botulinum toxin A (subcutaneously)	50-200 units to the painful area every 3 mo	Third line; specialist use (peripheral neuropathic pain)
Strong opioids	Individual titration	Third line[e]

[a]GRADE = Grading of Recommendations Assessment, Development, and Evaluation.
[b]Duloxetine is the most studied, and therefore recommended, of the serotonin-norepinephrine reuptake inhibitors.
[c]Tricyclic antidepressants generally have similar efficacy; tertiary amine tricyclic antidepressants (amitriptyline, imipramine, and clomipramine) are not recommended at doses >75 mg/d in adults aged 65 y and older because of major anticholinergic and sedative adverse effects and potential risk of falls[32]; an increased risk of sudden cardiac death has been reported with tricyclic antidepressants at doses >100 mg/d.[33]
[d]The long-term safety of repeated applications of high-concentration capsaicin patches in patients has not been clearly established, particularly with respect to the degeneration of epidermal nerve fibers, which might be a cause for concern in progressive neuropathy.
[e]Sustained-release oxycodone and morphine have been the most studied opioids (maximum doses of 120 and 240 mg/d, respectively, in clinical trials); long-term opioid use might be associated with abuse, particularly at high doses, cognitive impairment, and endocrine and immunological changes.[34,35]
From *Lancet Neurol*,[71] with permission.

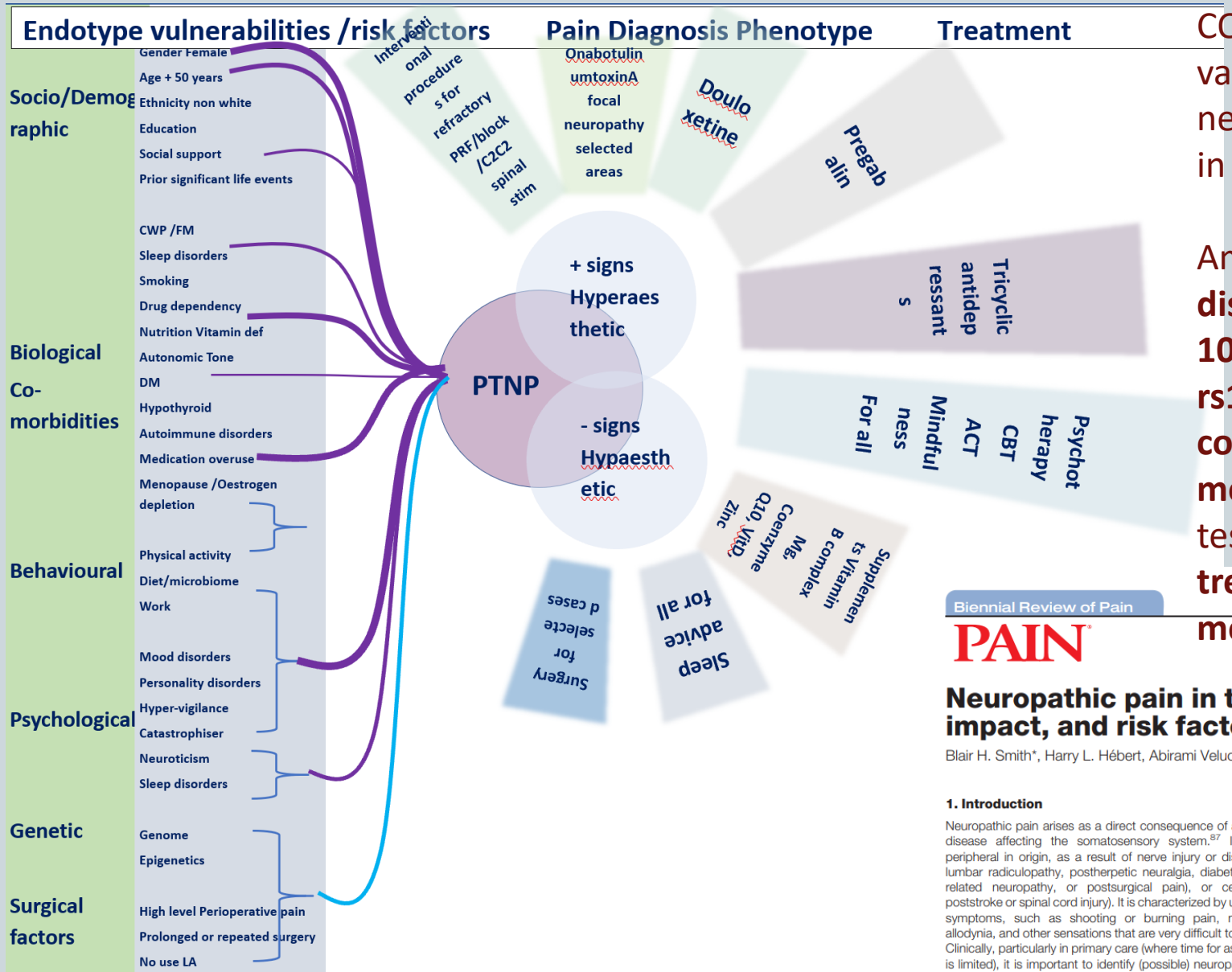
What patient or pain phenotypes that predict outcome of treatment?



Counselling
Medication
Surgery

What patient phenotype predict outcome of treatment?

Genetic predictors for outcome NePain



A recent study investigated the association of COMT, OPRM1, ABCB1, CYP2C19, and CYP2D6 variants with the response to treatment of neuropathic pain with nortriptyline and morphine in 25 Caucasian patients.

Among **34 variants in these genes, they discovered a significant association (P 5 4.89 3 1025) between the carriers of C allele of rs1045642 in ABCB1 and pain relief from combination therapy (nortriptyline and morphine)** after Bonferroni correction for multiple testing, **but no significant association with treatment response to either nortriptyline or morphine alone**.

Biennial Review of Pain
PAIN

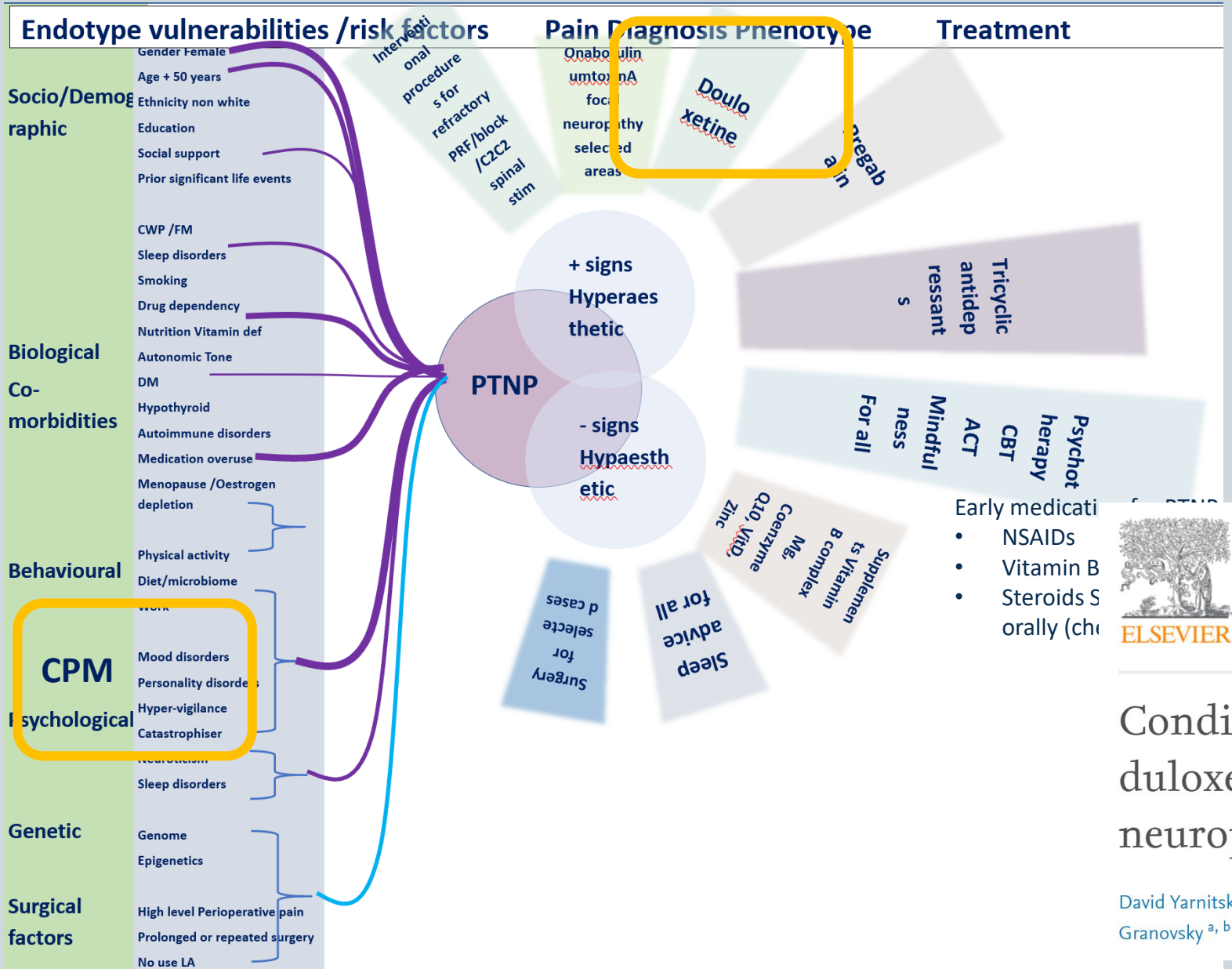
Neuropathic pain in the community: prevalence, impact, and risk factors

Blair H. Smith*, Harry L. Hébert, Abirami Veluchamy

1. Introduction

Neuropathic pain arises as a direct consequence of a lesion or disease affecting the somatosensory system.[87] It can be peripheral in origin, as a result of nerve injury or disease (eg, lumbar radiculopathy, postherpetic neuralgia, diabetic or HIV-related neuropathy, or postsurgical pain), or central (eg, poststroke or spinal cord injury). It is characterized by unpleasant symptoms, such as shooting or burning pain, numbness, allodynia, and other sensations that are very difficult to describe. Clinically, particularly in primary care (where time for assessment is limited), it is important to identify (possible) neuropathic pain, and allow treatment to begin according to an evidence-based neuropathic pain prescribing pathway.[74] Moreover, there is recent and increasing recognition that some classically "non-neuropathic" painful conditions can give rise to symptoms more commonly associated with neuropathic pain, and some evidence that these symptoms respond to "antineuropathic" medicines, such as tricyclic antidepressants and gabapentinoids.[84] For example, a systematic review found that pain was neuropathic in character in 23% of people with knee or hip osteoarthritis,[27] and this was found to be >6 times more likely in those who had experienced knee surgery.[89] Similarly, a Finnish study found that

What patient phenotype predicts outcome of Duloxetine in DM Ne Pain?



Duloxetine improved CPM in diabetic painful neuropathy
And
CPM predicts efficacy of Duloxetine

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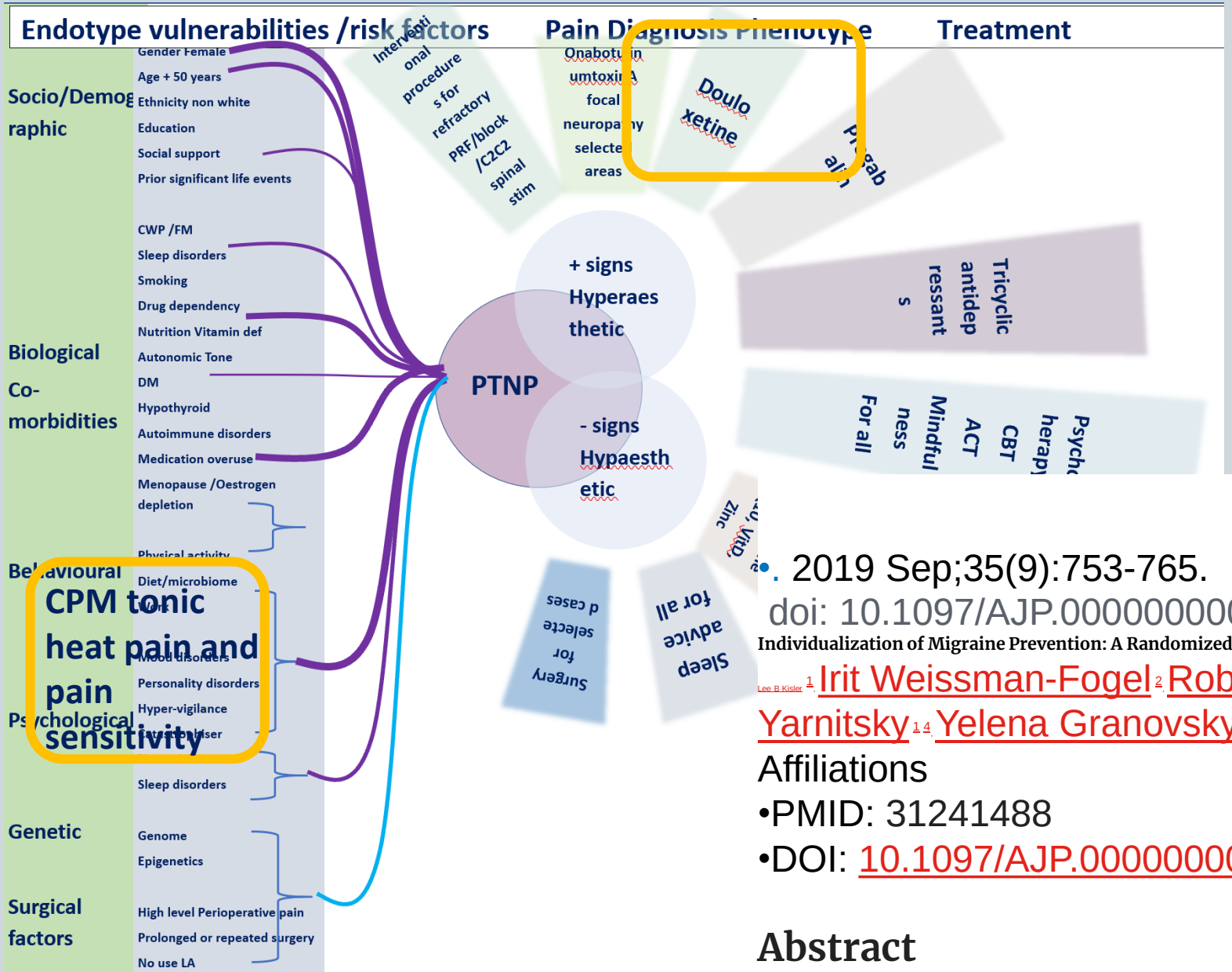
PAIN

Volume 153, Issue 6, June 2012, Pages 1193-1198

Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy

David Yarnitsky [a, b], Michal Granot [c], Hadas Nahman-Averbuch [b], Mogher Khamaisi [d], Yelena Granovsky [a, b]

What patient phenotype predicts outcome of Duloxetine in Migraine?



In the duloxetine group, efficacy of Duloxetine was predicted by higher pretreatment pain ratings for tonic heat pain (P=0.012); greater pain sensitivity at baseline predicted greater percent of migraine improvement in duloxetine (r=0.47; P=0.013),

•. 2019 Sep;35(9):753-765.
doi: 10.1097/AJP.0000000000000739.

Individualization of Migraine Prevention: A Randomized Controlled Trial of Psychophysical-based Prediction of Duloxetine Efficacy

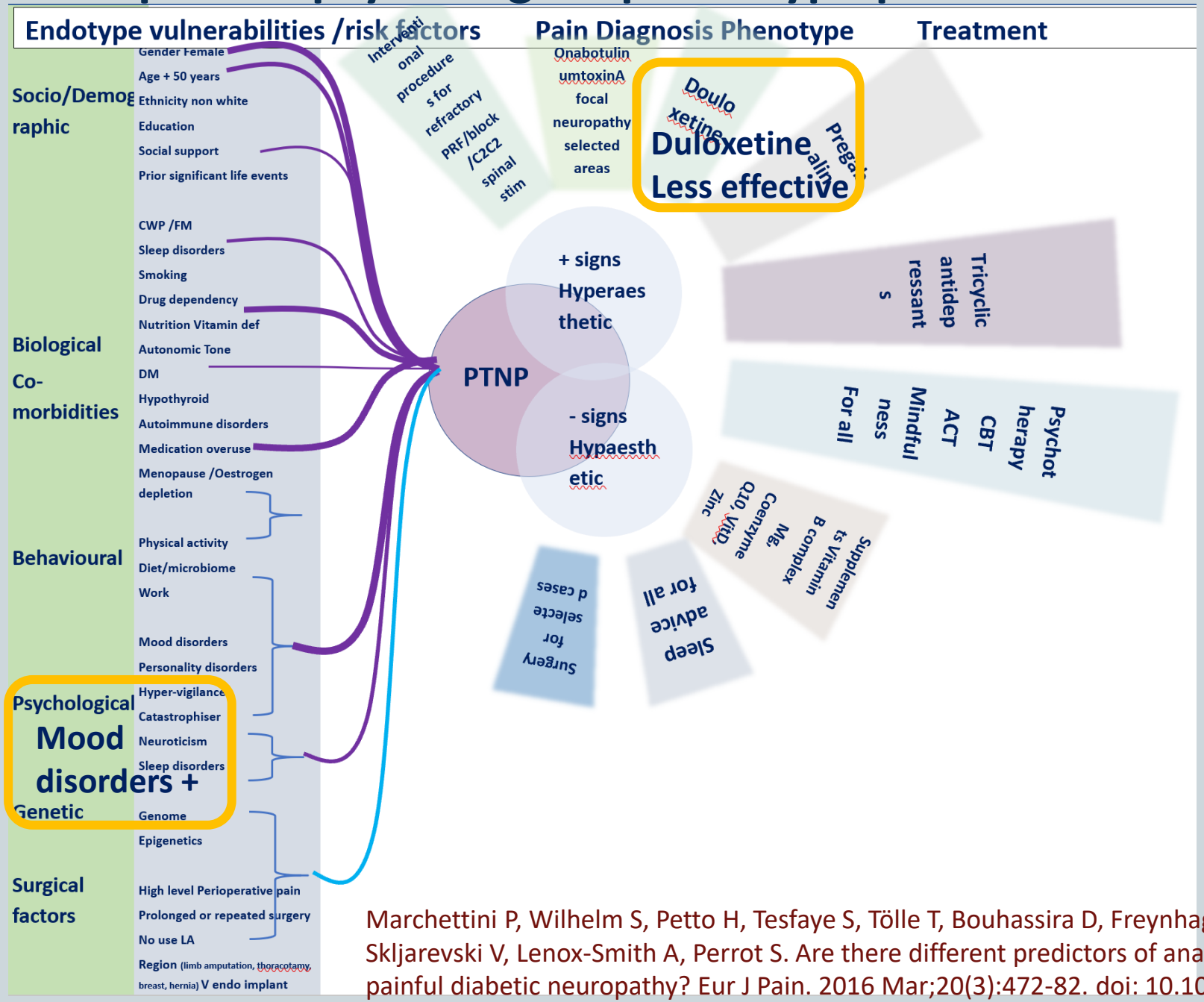
Lee B Kisler [1] Irit Weissman-Fogel [2] Robert C Coghill [3] Elliot Sprecher [4] David Yarnitsky [1 4] Yelena Granovsky [1 4]

Affiliations

•PMID: 31241488
•DOI: 10.1097/AJP.0000000000000739

Abstract

What patient psychological phenotype predicts outcome of Duloxetine in DM Ne Pain



Predictors of analgesic response in Patients with DM NePain

A total of 804 patients with DM NePain

A significant interaction with treatment was observed in the **mood symptom subgroups** with a larger pain reduction in duloxetine-treated patients having no mood symptoms (HADS score <11; -2.33 (duloxetine); -1.52 (pregabalin); p = 0.024]).

No significant interactions between treatment for subgroups by
age (<65 or ≥65 years), gender, baseline pain severity (BPI-MSF), diabetic neuropathy duration (≤2 or >2 years), baseline haemoglobin A1c (HbA1c) (<8% or ≥8%), presence of comorbidities and concomitant medication use.

Duloxetine treatment appeared to be particularly beneficial in DPNP patients having no mood symptoms.

Marchettini P, Wilhelm S, Petto H, Tesfaye S, Tölle T, Bouhassira D, Freynhagen R, Cruccu G, Lledó A, Choy E, Kosek E, Micó JA, Späth M, Skljarevski V, Lenox-Smith A, Perrot S. Are there different predictors of analgesic response between antidepressants and anticonvulsants painful diabetic neuropathy? Eur J Pain. 2016 Mar;20(3):472-82. doi: 10.1002/ejp.763. Epub 2015 Aug 27. PMID: 26311228

What Nepain phenotype predicts outcome of Btx?

Clustering Neuropathic pain presentation

Optimising therapeutic outcome of BtX therapy

Pin point pain (paraesthesia responsive to BtX)

Deep pain responsive to BtX

Elicted pain non repsonsive to BtX

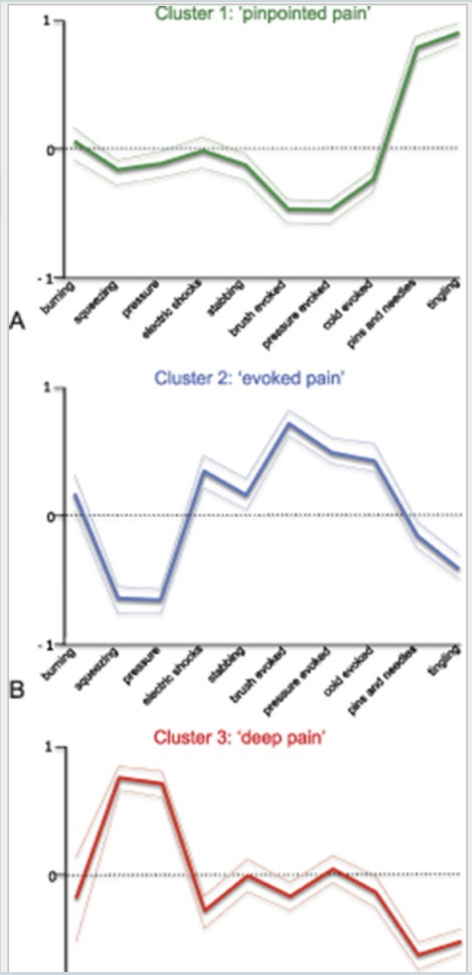


Figure 1.: Description of the 3 clusters of patients with distinct sensory profiles (ie, combinations of symptoms assessed with the 10 neuropathic pain descriptors included in the NPSI). Dashed lines represent confidence intervals (95% CI). (A) Cluster 1, "pinpointed pain," was characterized by above average scores for items relating to paresthesia/dysesthesia (ie, tingling and pins and needles) and below average scores for evoked pain (brush allodynia and pressure allodynia). (B) Cluster 2, "evoked pain," was characterized by above average pain provoked by brushing, provoked by cold or pressure and electric shocks and below average deep pain and paresthesia/dysesthesia. (C) Cluster 3, "deep pain," was characterized by above average pressure and squeezing pain and below average paresthesia/dysesthesia. NPSI, Neuropathic Pain Symptom Inventory.

› Pain. 2021 Apr 1;162(4):1038-1046. doi: 10.1097/j.pain.0000000000002130.

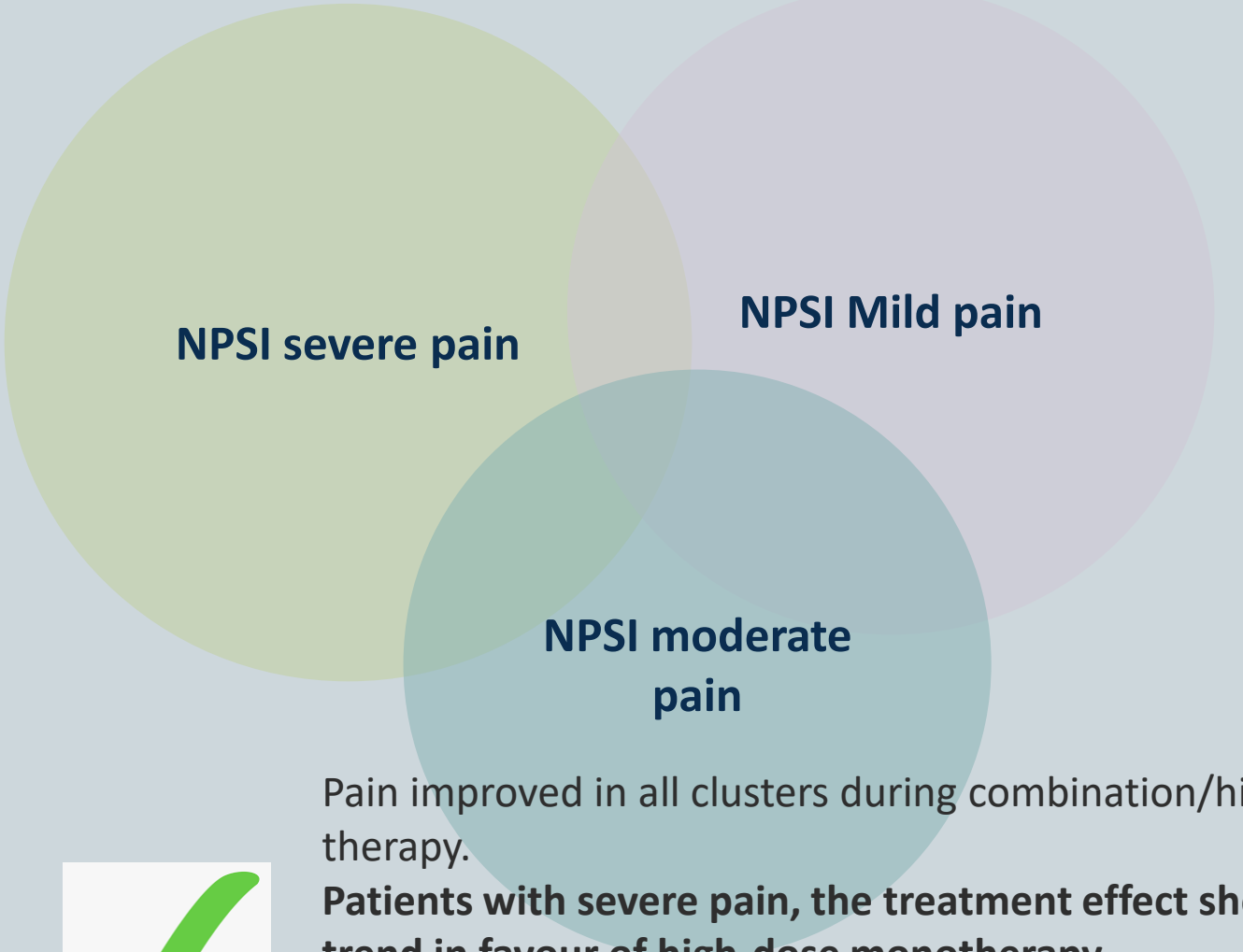
Stratification of patients based on the Neuropathic Pain Symptom Inventory: development and validation of a new algorithm

Didier Bouhassira [1], Samuel Branders [2], Nadine Attal [1], Ana Mercia Fernandes [3], Dominique Demolle [2], Julio Barbour [3], Daniel Ciampi de Andrade [3], Alvaro Pereira [2]

What Nepain phenotype predicts outcome of Duloxetine?

Clustering DM Neuropathic pain presentation

Optimising therapeutic outcome of medication



Randomized Controlled Trial > Pain. 2014 Oct;155(10):2171-9. doi: 10.1016/j.pain.2014.08.020. Epub 2014 Aug 27.

Neuropathic pain phenotyping as a predictor of treatment response in painful diabetic neuropathy: data from the randomized, double-blind, COMBO-DN study

Didier Bouhassira [1], Stefan Wilhelm [2], Alexander Schacht [3], Serge Perrot [4], Eva Kosek [5], Giorgio Cruccu [6], Rainer Freynhagen [7], Solomon Tesfaye [8], Alberto Lledó [9], Ernest Choy [10], Paolo Marchettini [11], Juan Antonio Micó [12], Michael Spaeth [13], Vladimir Skljarevski [14], Thomas Tölle [15]

Affiliations + expand

PMID: 25168665 DOI: 10.1016/j.pain.2014.08.020

Treatment with Duloxetine and or Pregabalin / BPI

Abstract

Sensory profiles are heterogeneous in neuropathic pain disorders, and subgroups of patients respond differently to treatment. To further explore this, patients in the COMBO-DN study were prospectively assessed by the Neuropathic Pain Symptom Inventory (NPSI) at baseline, after initial 8-week therapy with either duloxetine or pregabalin, and after subsequent 8-week combination/high-dose therapy. Exploratory post hoc cluster analyses were performed to identify and characterize potential subgroups through their scores in the NPSI items. In patients not responding to initial 60 mg/d duloxetine, adding 300 mg/d pregabalin for combination treatment was particularly effective regarding the dimensions pressing pain and evoked pain, whereas maximizing the duloxetine dose to 120 mg/d appeared more beneficial regarding paresthesia/dysesthesia. In contrast, adding 60 mg/d duloxetine to 300 mg/d pregabalin in case of nonresponse to initial pregabalin led to numerically higher decreases in all NPSI dimensions/items compared to maximizing the pregabalin dose to 600 mg/d. Cluster analysis revealed 3 patient clusters (defined by baseline scores for the 10 NPSI sensory items) with different pain profiles, not only in terms of overall pain severity, but also across NPSI items. Mean

NEUROPATHIC PAIN SYMPTOM INVENTORY (NPSI)

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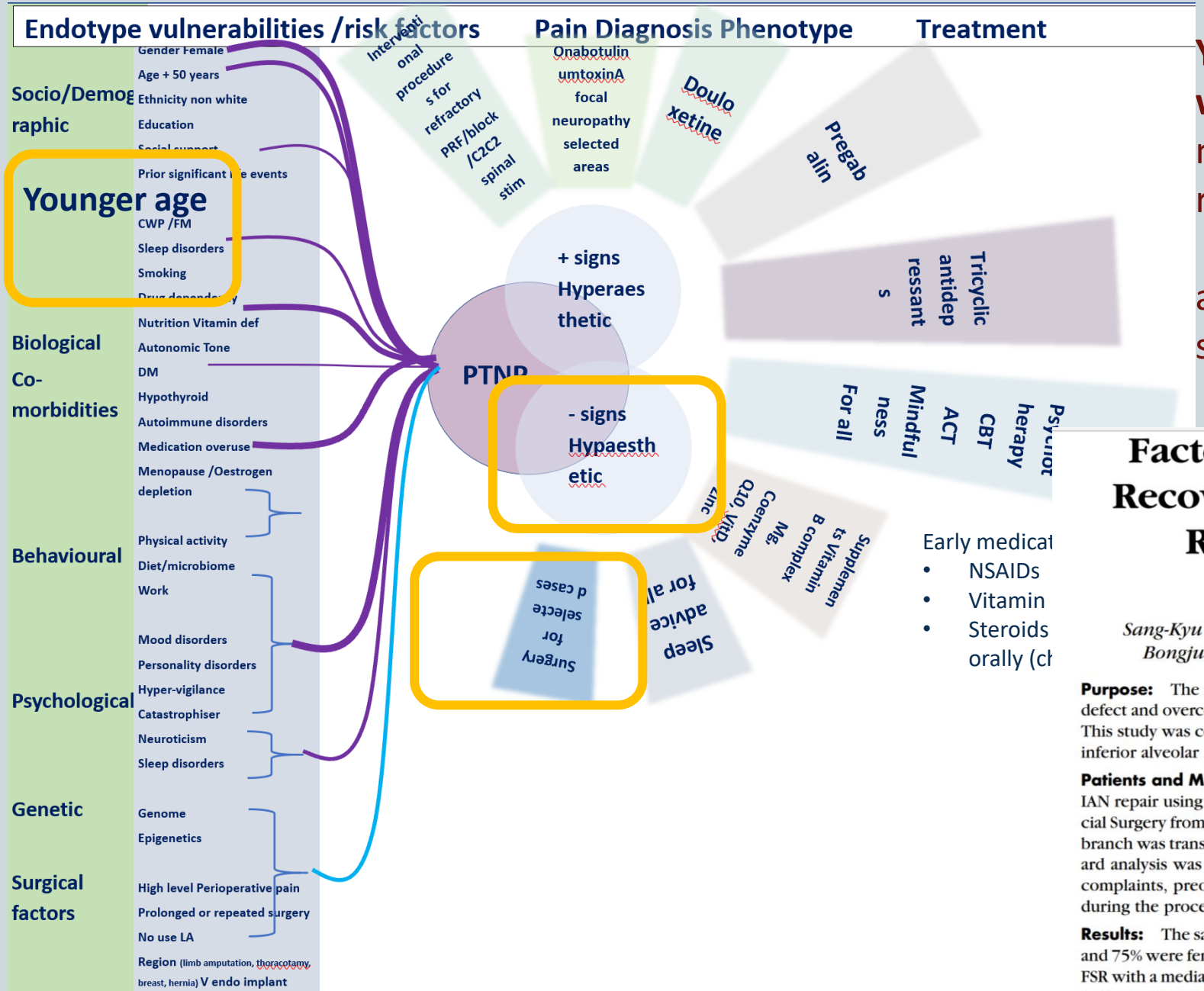
Pain improved in all clusters during combination/high-dose therapy.

Patients with severe pain, the treatment effect showed a trend in favour of high-dose monotherapy

Whereas combination therapy appeared to be more beneficial in patients with moderate and mild pain (not significant).

What patient phenotype predicts outcome of surgery?



Younger patients (P = .041) and patients **without dysesthesia** (P = .019) were more likely to achieve functional sensory recovery (FSR).

Higher proportion of early repair group achieved FSR, although not statistically significant (P = .068).

Factors Affecting Functional Sensory Recovery After Inferior Alveolar Nerve Repair Using the Nerve Sliding Technique

*Sang-Kyu Kang, DDS, *Akram Abdo Almansoori, DDS, PhD, † Yeon-Su Chae, DDS, ‡ Bongju Kim, PhD, § Soung-Min Kim, DDS, PhD, ‖ and Jong-Ho Lee, DDS, PhD ¶*

Purpose: The nerve sliding technique (NST) was introduced for repairing inferior alveolar nerve (IAN) defect and overcoming the disadvantages of conventional surgical treatment methods such as nerve graft. This study was conducted to identify factors associated with functional sensory recovery (FSR) following inferior alveolar nerve repair using the NST.

Patients and Methods: This was a retrospective cohort study including all patients who underwent IAN repair using the NST at Seoul National University Dental Hospital, Department of Oral and Maxillofacial Surgery from February 2009 to March 2020. The damaged part of the IAN was excised, and the incisive branch was transected intentionally to perform direct anastomosis without tension. Cox proportional hazard analysis was utilized to determine the relationships between predictor variables (age, gender, chief complaints, preoperative sensory results, duration from injury to repair, length of nerve tissue resected during the procedure, and neuroma formation) and outcome variable (time to FSR).

Results: The sample was composed of 16 patients with a mean age of 56.1 ± 10.1 years, 25% were males and 75% were females. The mean nerve gap deficit was 7.69 mm (3-15 mm). Ten patients (62.5%) achieved FSR with a median time from operative treatment to FSR of 84.5 days. Dental implant placement was found

Key messages…

Post traumatic neuropathic pain is the most common orofacial neuropathic pain.

Surgical and anatomical risk factors can be mitigated to prevent PTNP and are reported to predict outcome of nerve injury for Trigeminal PTNP

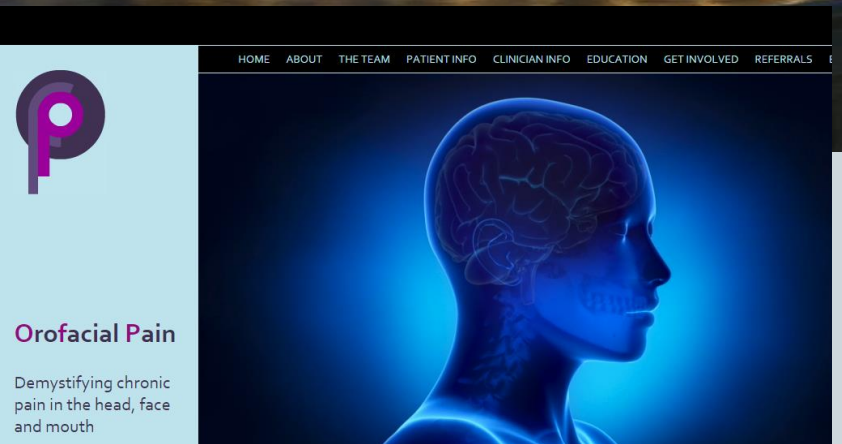
Patient risk factors for PTNP predominantly include age, psychological (mood disorders, personality disorders, hypervigilance, catastrophising, fear of surgery, fear of pain), Understanding these risk factors will assist patient deselection for certain procedures.

However, these factors have not been fully evaluated in trigeminal PTNP yet or for predicting recovery or outcome of PTNP.

Emerging evidence may facilitate 'tailored' management with improved predictable outcomes

Refer to resources at **Trigeminalnerve.org.uk**

Thank you



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http://www.orofacialpain.org.uk

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