

Tooth be or not tooth be

Differential diagnosis of non-odontogenic pain mimicking toothache

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Promoting excellence in Oral Surgery through education, training and research for better patient care




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Orofacial Pain

Demystifying chronic pain in the head, face and mouth

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Orofacialpain.org.uk

Aims & Objectives

- Provide an overview and refresher of Orofacial pain classification and mechanisms.
- Illustrate the variety of diagnoses that can be mistaken for toothache.
- Avoid these diagnostic traps.

TO STAY OUT OF JAIL!



Pain: When poorly managed, is the most common cause for complaints and litigation

Kalenderian E et al have demonstrated that poorly managed perioperative pain is the leading adverse event in routine US dental care. **Patients are most frightened of poorly managed pain and injections**

In Finland a national overview assessing patient complaints about their dental care also report that poorly managed pain was the leading adverse event.

This makes sense, if a patient has an unpleasant experience at the dentist, with either unexpected pain or severe pain during a dental procedure, this may set the basis for the patients to question the quality of other aspects of their care. Thus, patient expectations must be managed, not just in the short term for post-surgical inflammatory pain, but in the context of chronic neuropathic pain if there is risk of nerve injury.



Pixabay royalty free images

Kalenderian E, Obadan-Udoh E, Maramaldi P, Etolue J, Yansane A, Stewart D, White J, Vaderhobli R, Kent K, Hebballi NB, Delattre V, Kahn M, Tokede O, Ramoni RB, Walji MF Classifying Adverse Events in the Dental Office. J Patient Saf. 2017 Jun 30. doi: 10.1097/PTS.0000000000000407. [Epub ahead of print] Maramaldi P, Walji MF, White J, Etolue J, Kahn M, Vaderhobli R, Kwatra J, Delattre VF, Hebballi NB, Stewart D, Kent K, Yansane A, Ramoni RB, Kalenderian E. How dental team members describe adverse events. J Am Dent Assoc. 2016 Oct;147(10):803-11. doi: 10.1016/j.adaj.2016.04.015. Epub 2016 Jun 3 Hiivala N, Mussalo-Rauhamaa H, Tefke HL, Murtomaa H. An analysis of dental patient safety incidents in a patient complaint and healthcare supervisory database in Finland. Acta Odontol Scand. 2016;74(2):81-9. doi: 10.3109/00016357.2015.1042040. Epub 2015 May 13. Hiivala N, Mussalo-Rauhamaa H, Murtomaa H. Can patients detect hazardous dental practice? A patient complaint study. Int J Health Care Qual Assur. 2015;28(3):274-87.

Outline

- Pain
 - The Problem
 - Defns
 - Where is it?
 - What types of pain?
 - What types of patient?
- Differential diagnostic

Review Article

Tooth-Related Pain or Not?

Tara Renton, BDS, MDS, PhD 

Dental pain is the most common acute pain presenting in the orofacial region; however, chronic pain conditions are also frequent and include; temporomandibular joint disorders (TMDs), primary headaches (neurovascular pain), painful post-traumatic trigeminal neuropathy (PPTN) and less commonly referred pain and idiopathic or centralized pain conditions. All of these conditions can mimic toothache and vice versa. Many of these conditions are comorbid with high levels of tension headache and migraine reported in patients with TMD; however, dentists remain unfamiliar with headaches and medics unfamiliar with toothache's multiple presentations. The anatomical complexity of the region, the potential exhaustive differential diagnoses and the multiple siloed training of specialties, leads to incorrect and delayed diagnosis and often results in patients undergoing inappropriate surgical and medical treatments. The continued inappropriate interventions may also complicate the later presentation of the patient with pain, by changing its phenotype, preventing a timely and correct diagnosis. Due to the variable presentation of toothache, which can mimic many different chronic pains including; episodic throbbing pain of migraine, the dull continuous pain of myofascial and arthrogenous TMDs or centralized facial pain, diagnosis can be complex. Neuralgic pain occurs in the dentition in health and with disease, mimicking conditions like PPTN, trigeminal neuralgia (TN), and trigeminal autonomic cephalalgias (TACs), many patients are inappropriately diagnosed and treated, either by general medical practitioners assuming that the neuralgia is due to TN rather than more commonly presenting toothache or by a dentists or other surgeons continuing to treat TN or TACs with routine surgical care. Many patients are prescribed countless courses of antibiotics and undergo multiple surgical interventions simply as a result of poor education due to siloed specialty training. This must be addressed to improve patient safety.

Key words: toothache, headache, temporomandibular disorders, sinusitis, trigeminal nerve injury, neuralgia

(*Headache* 2019;0:1-12)

INTRODUCTION

Poorly diagnosed or managed orofacial is the

significant burden and remains poorly diagnosed and managed due to the siloed training of professionals in

The problem is 'mimicking'

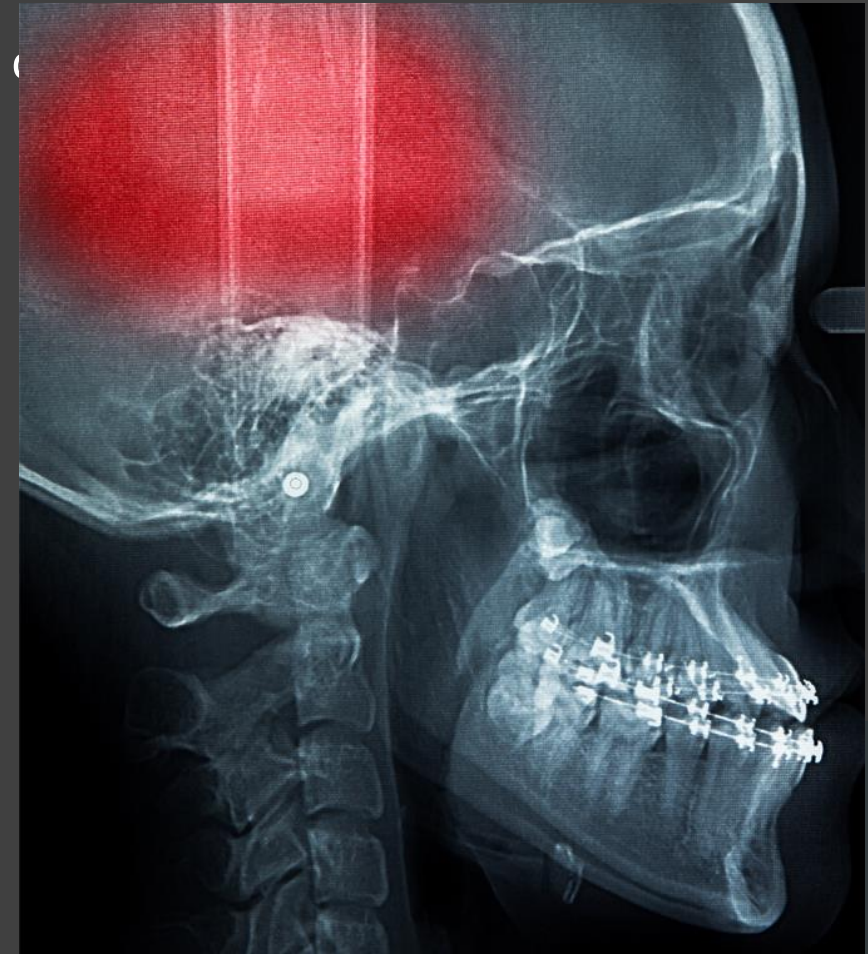


For dentists

- Diagnosing and treating dental pain correctly
- Identifying cancer caused pain and referring appropriately
- **Misdiagnosing non-odontogenic pain as dental pain and then continuing in providing inappropriate dental care**

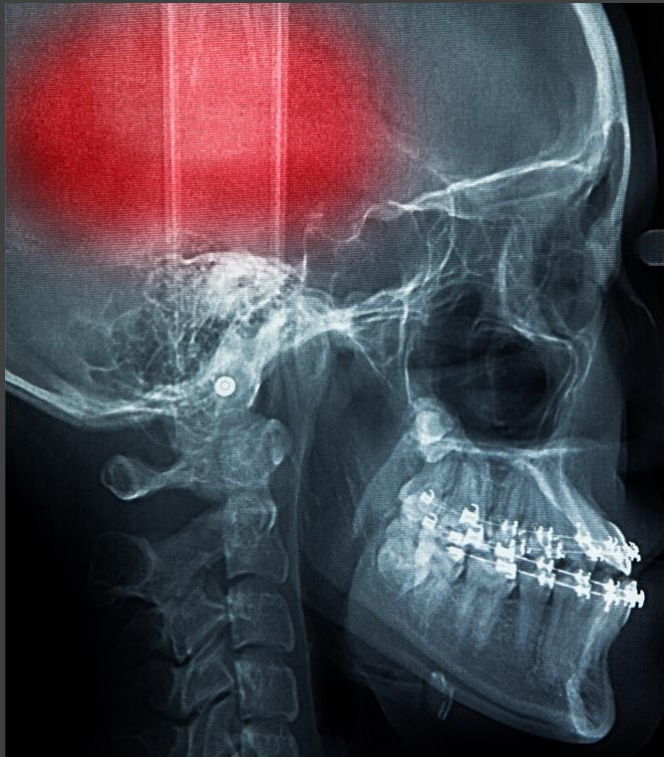
Preventing nerve injuries and related complications

OR?



For non dentists responsibility Neurologists, GMPs, OMFS, ENT surgeons

- Misdiagnosing odontogenic pain as ;
 - Headaches
 - TN
 - TMD
 - Sinusitis



OR?



Never ever discount toothache as the cause!

Is it the teeth?

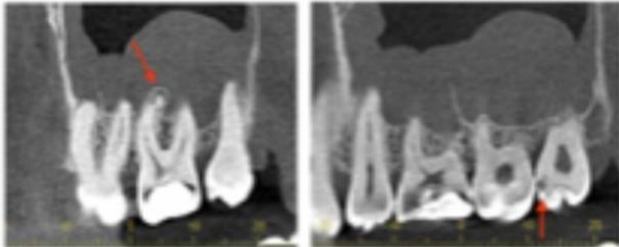
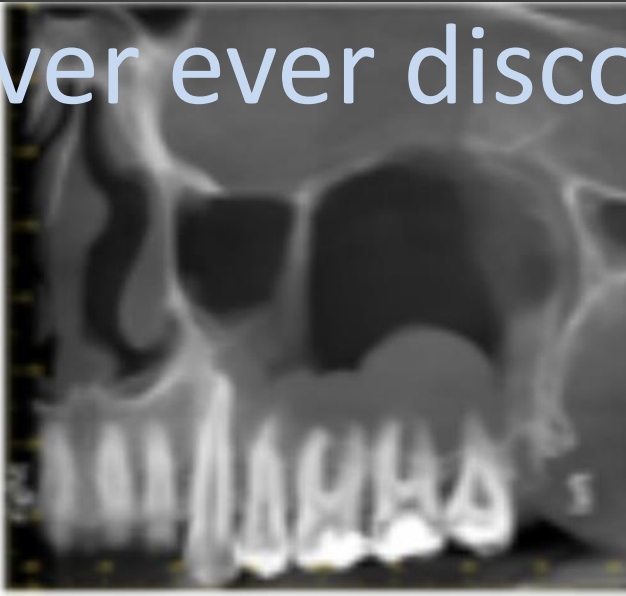


Fig 2. Sagittal views of UL7 and UL8 showing apical PDL widening over UL7 and caries in UL8

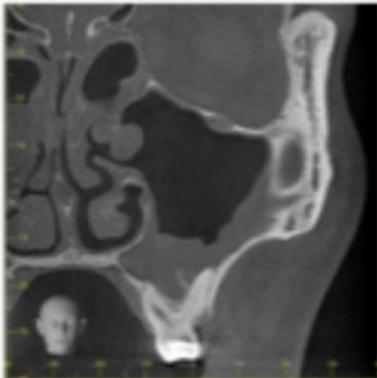


Fig 3. Coronal view of left maxillary sinus

Impression:
1. Early apical periodontitis UL7 - a likely cause of local pain
2. Caries in UL8 - a possible cause of dental pain
3. Chronic rhino sinusitis and left maxillary odontogenic sinusitis - a further probable contributor to pain. An ENT examination, including direct visualisation of the ostio-meatal regions, is recommended.

Please note: Images seen here are for illustrative purposes only and are not 'to scale'.



Never ever discount toothache as the cause!

Is it the teeth?

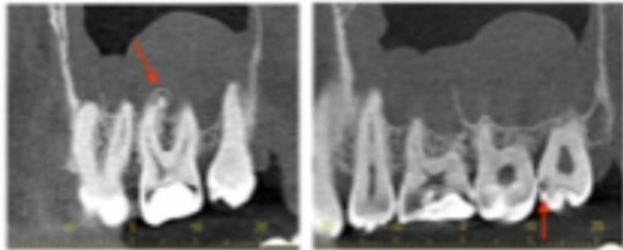
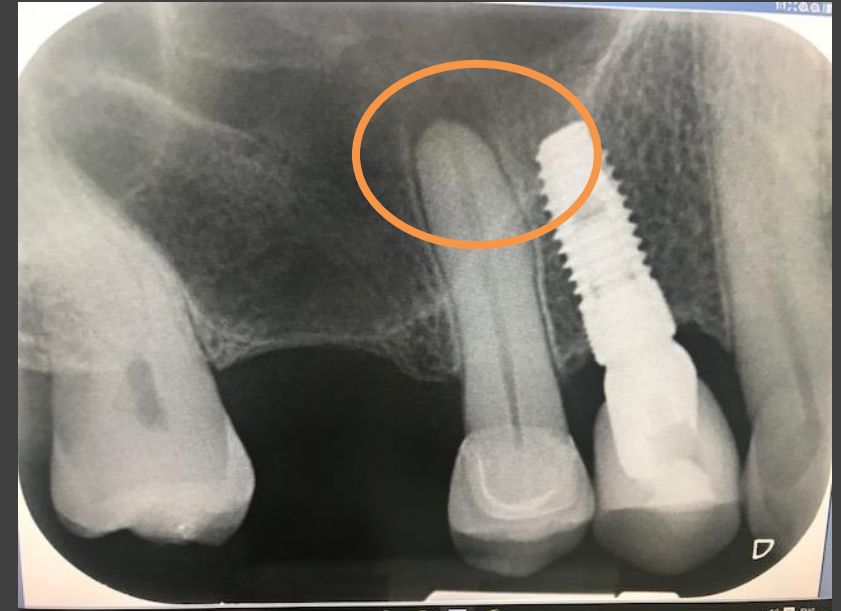


Fig 2. Sagittal views of UL7 and UL8 showing apical PDL widening over UL7 and caries in UL8

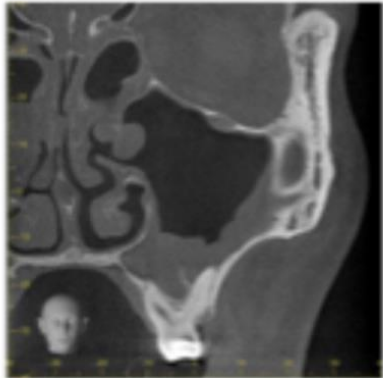


Fig 3. Coronal view of left maxillary sinus

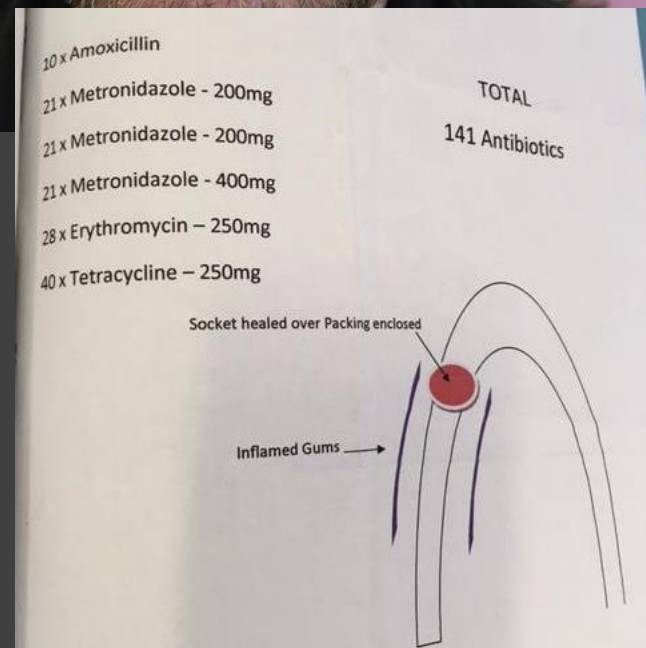
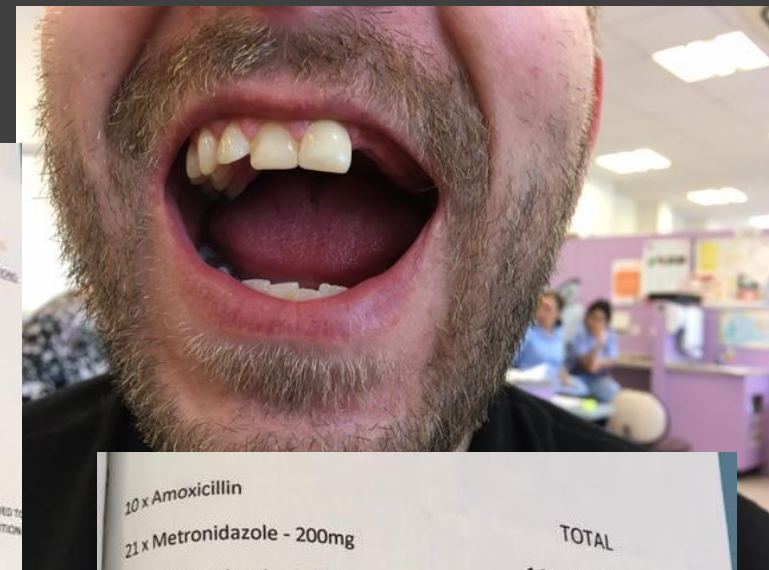
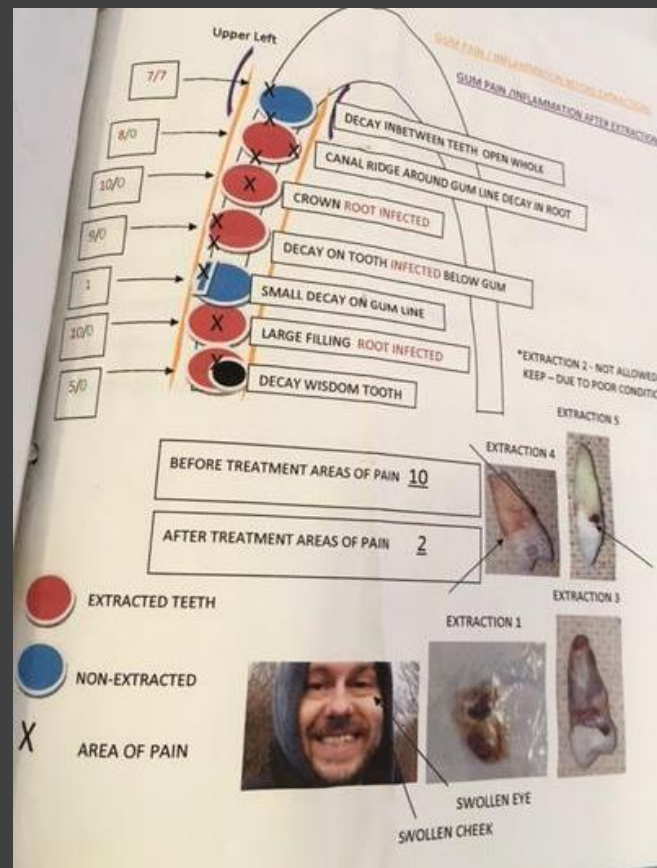
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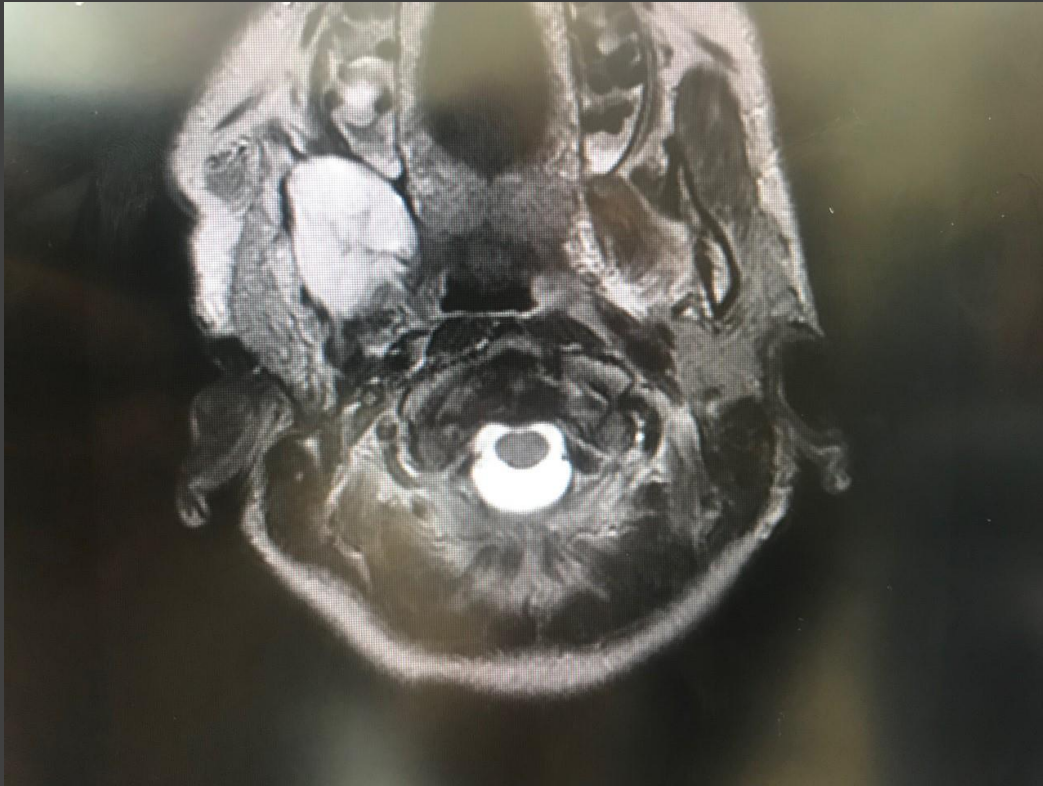
Primary headache treated as sequential toothache



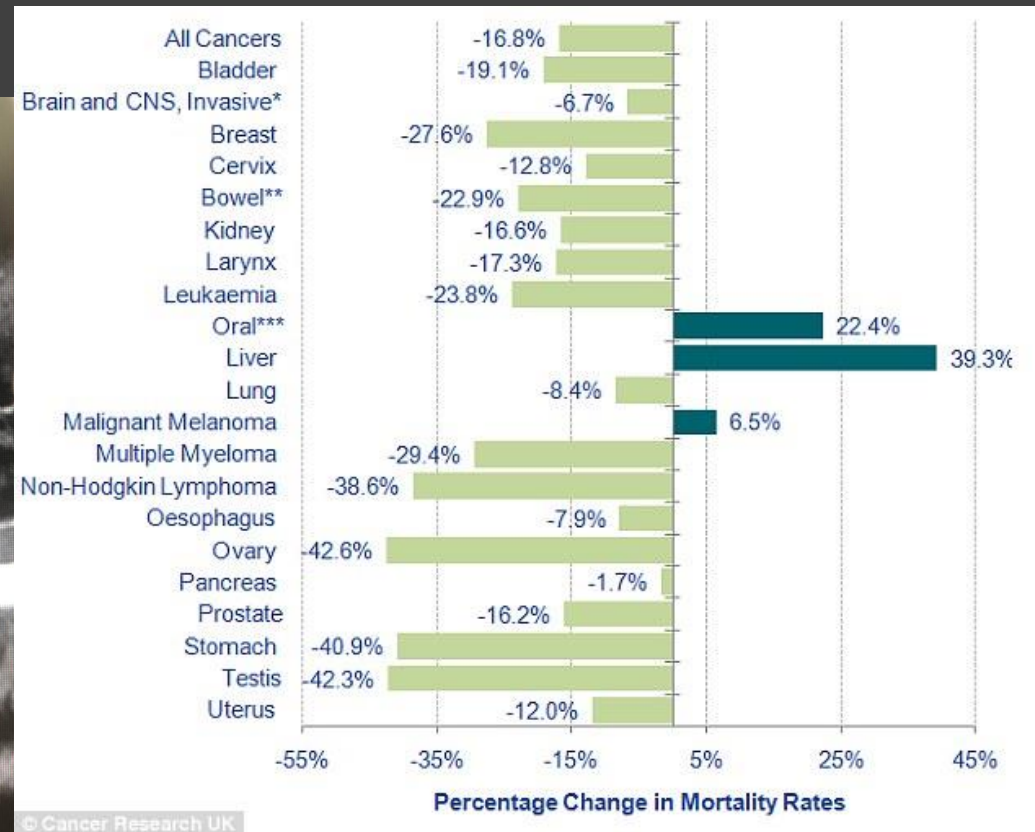
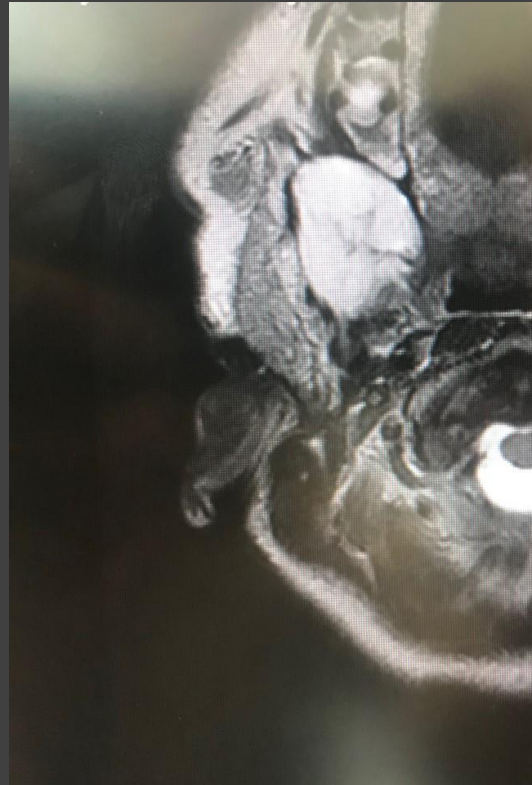
Late diagnosis of Endo PTN causing additional morbidity

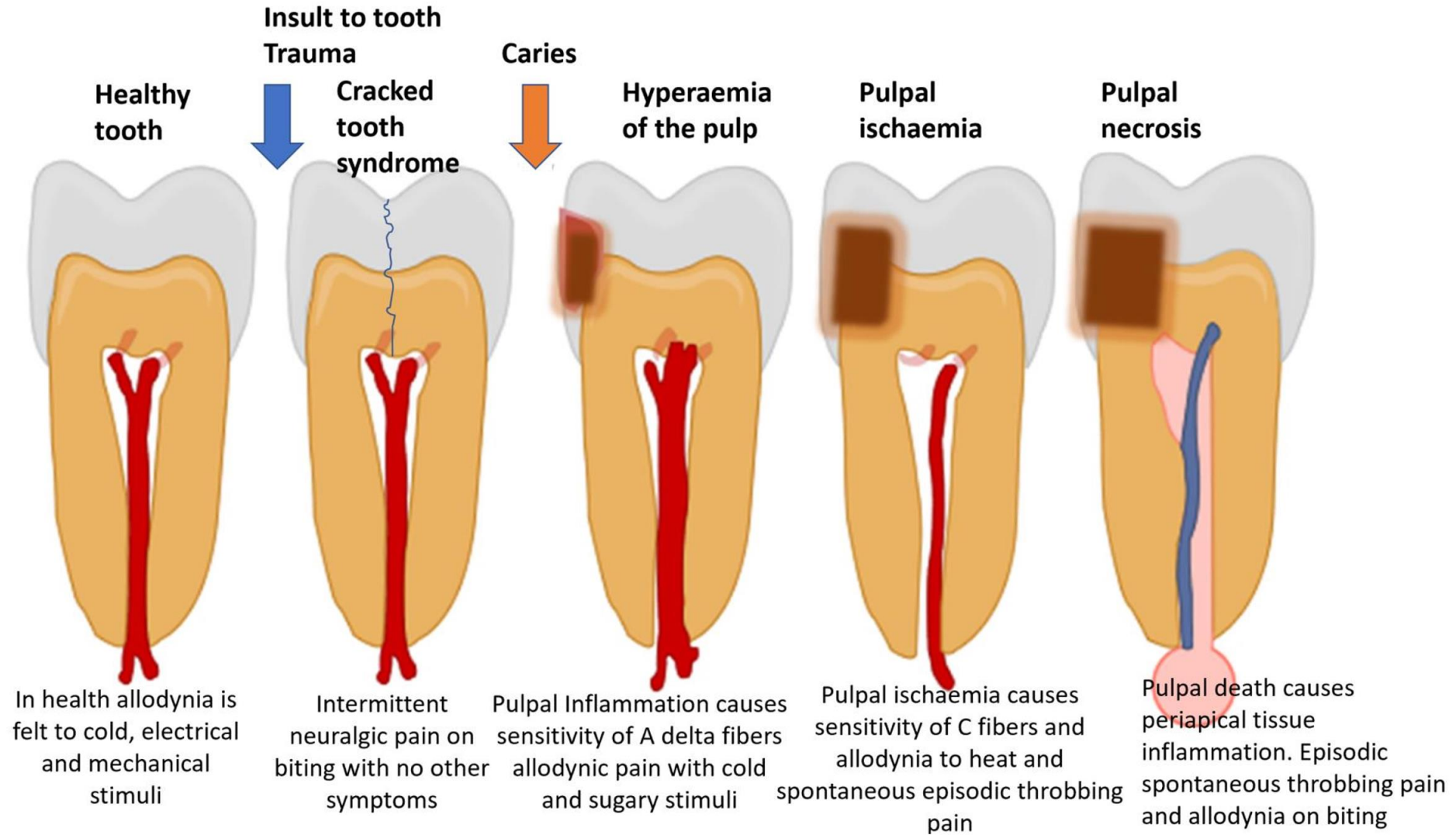


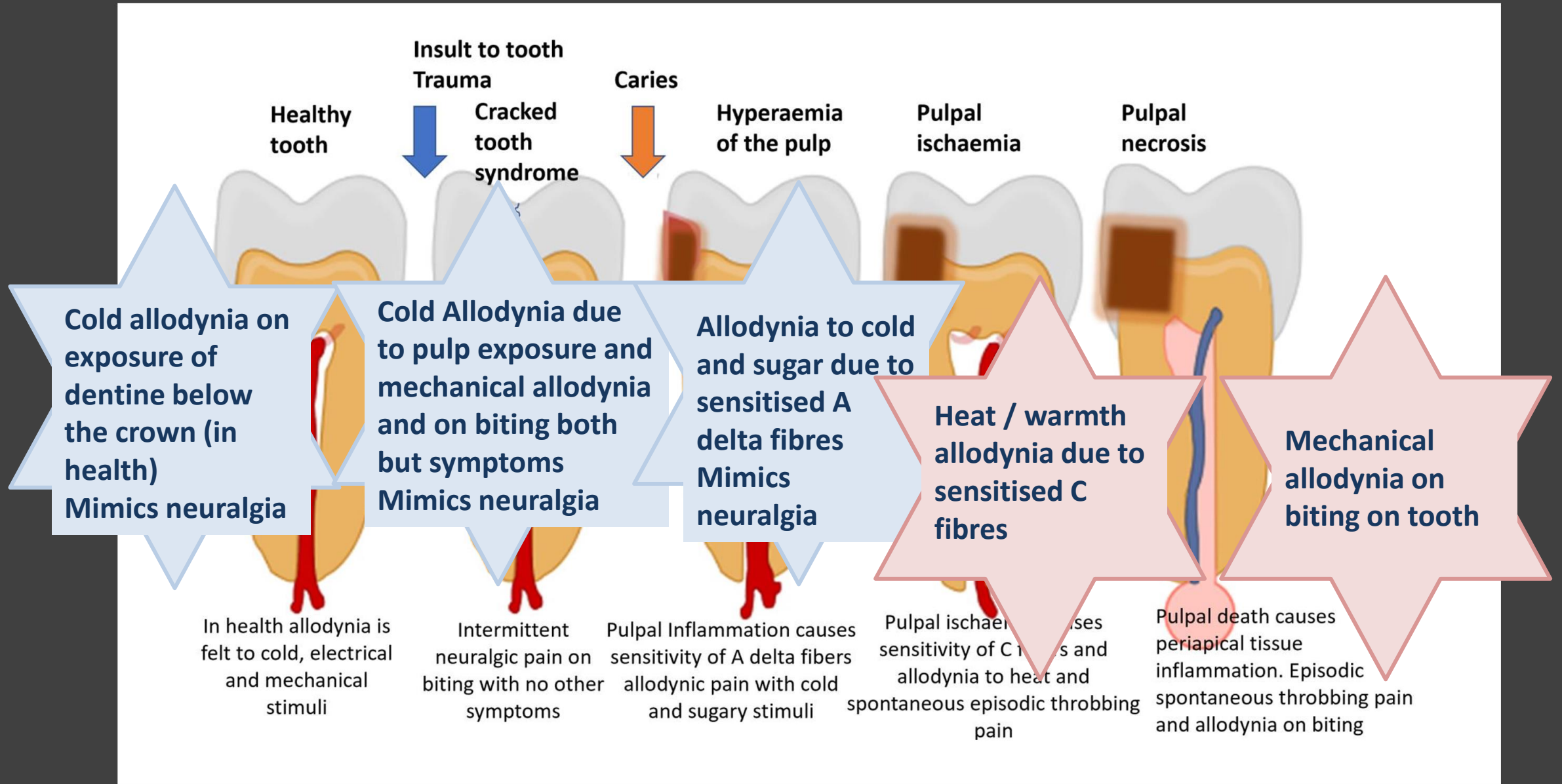
Neoplasia treated as TMD

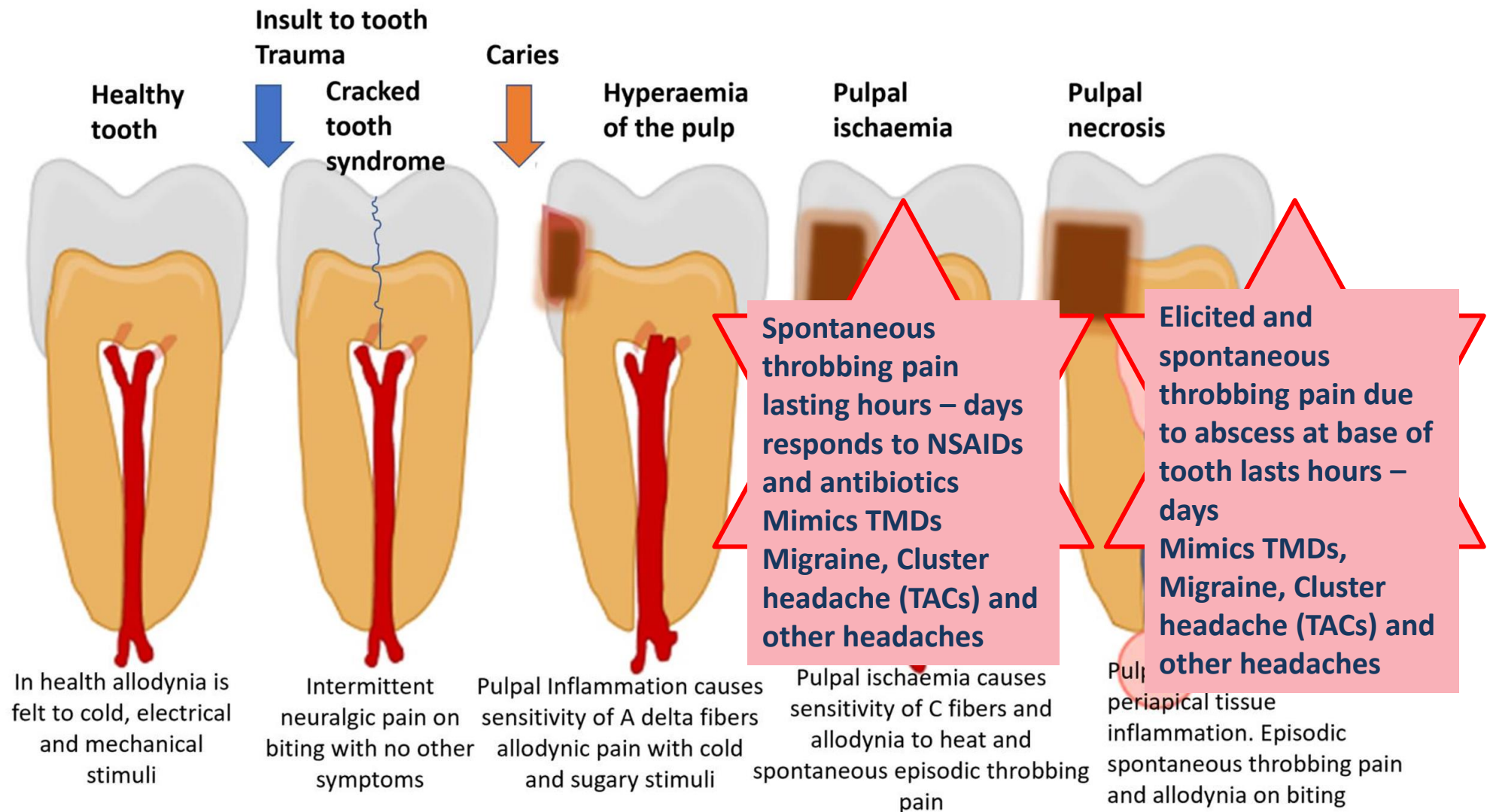


Is it not toothache? Elephant in the room









Outline

- Pain
 - Problem
 - **Defns**
 - Where is it?
 - What types of pain are there?
 - What type of patient is there?
 - What classifications of OFP are there?
- Differential diagnostic OFP diagnosis right

IASP definition of pain

An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage

Pain is a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive and social components (C de C Williams & Craig, in press).

The Trigeminal nerve is 'special'

- **The great protector.....**

Sensory feedback for all cranial functions

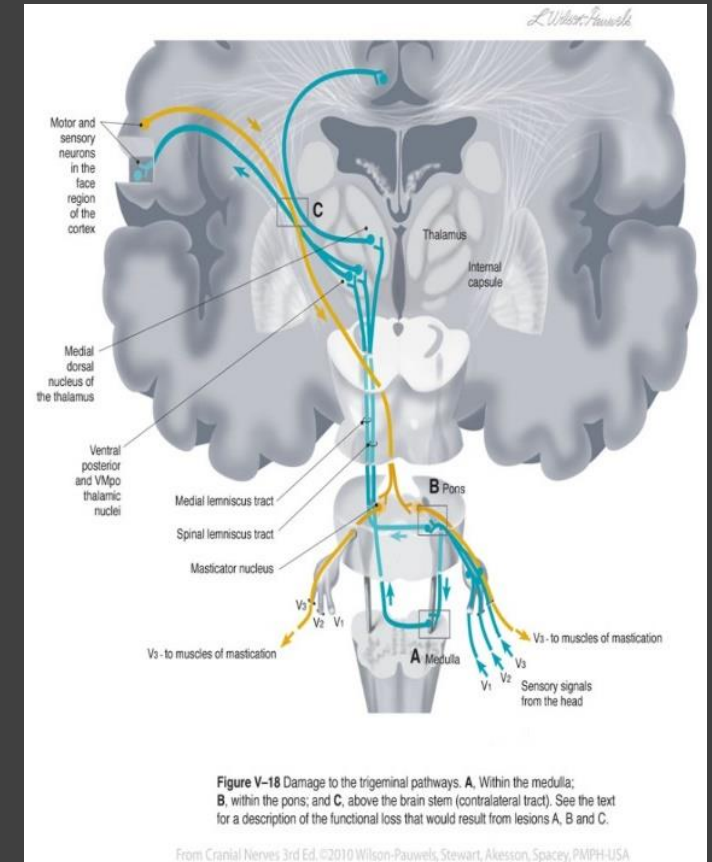
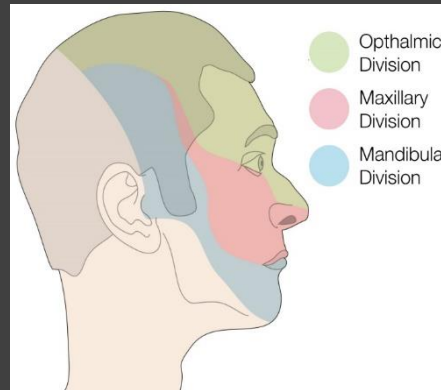
Brains- Consciousness + neural regulation

Breathing

Sight

Smell

Taste

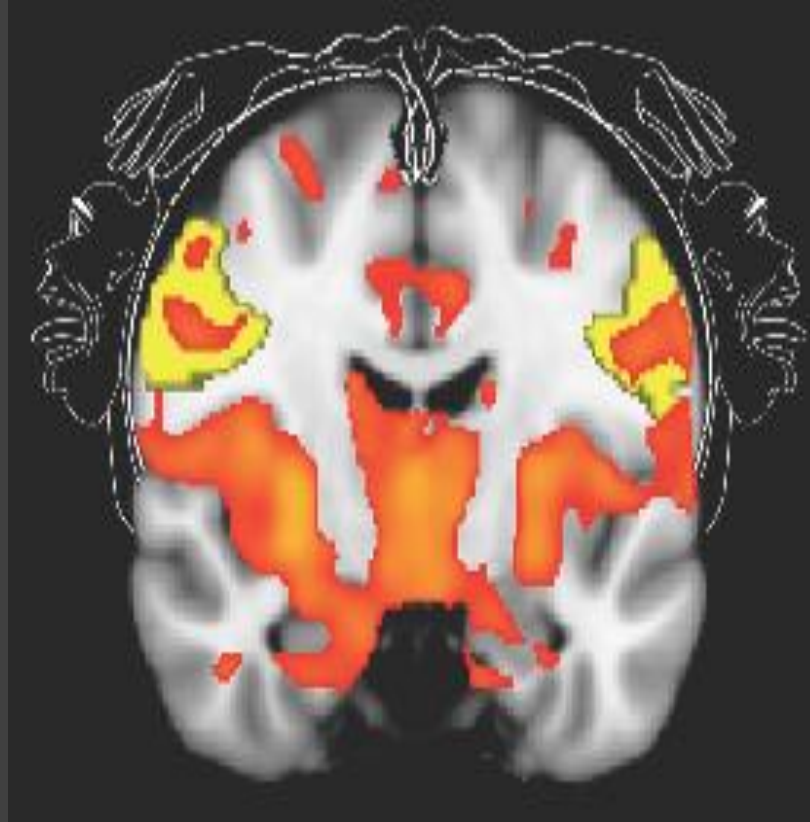


The face...the organ that underpins communication

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Trigeminal nerve



Orange indicates the high level blood flow changes in response to third molar surgical pain

Mostly in the LIMBIC SYSTEM =

Affective and emotional response to pain

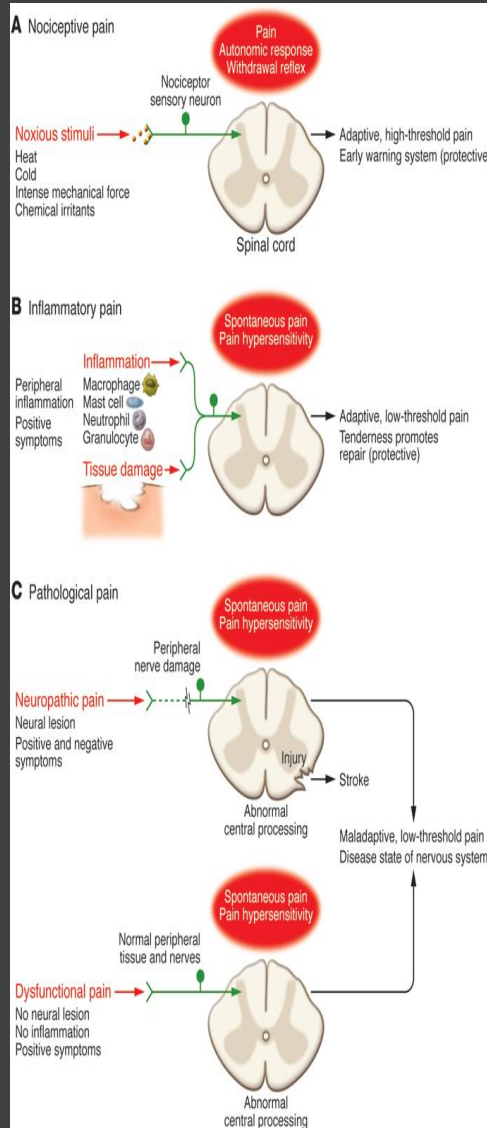
Your patient is programmed to run for the hills!!!!!!!!!!



Outline

- Pain
 - Defns
 - Where is it?
 - **What types of pain are there?**
 - How does it become chronic?
 - What classifications of OFP are there?
- Differential diagnostic OFP diagnosis right
- Management principles

Types of pain



Healthy acute pain

Nociceptive
healthy feeling pain 'pain'

Inflammatory pain
healthy short lived after insult

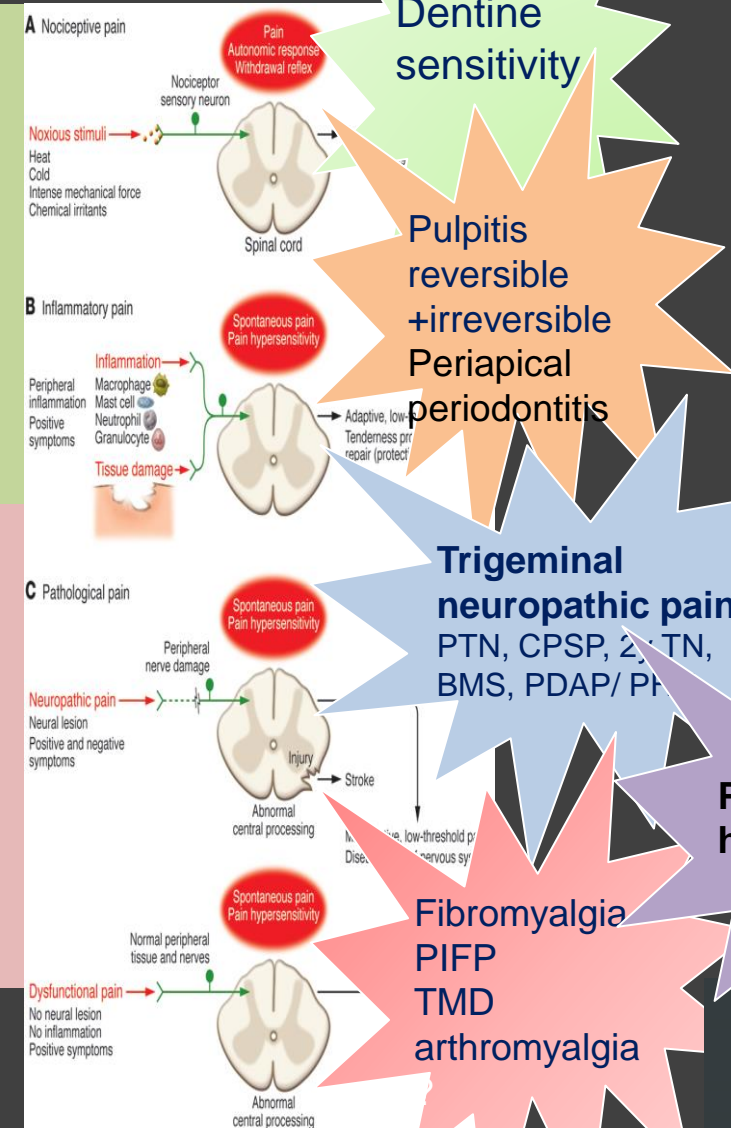
**Chronic pain =
disease of neuromatrix**

Neuropathic pain
Associated with nerve lesion

Dysfunctional or centralised pain
Unknown cause

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

www.trigeminalnerve.org.uk



Dentine sensitivity

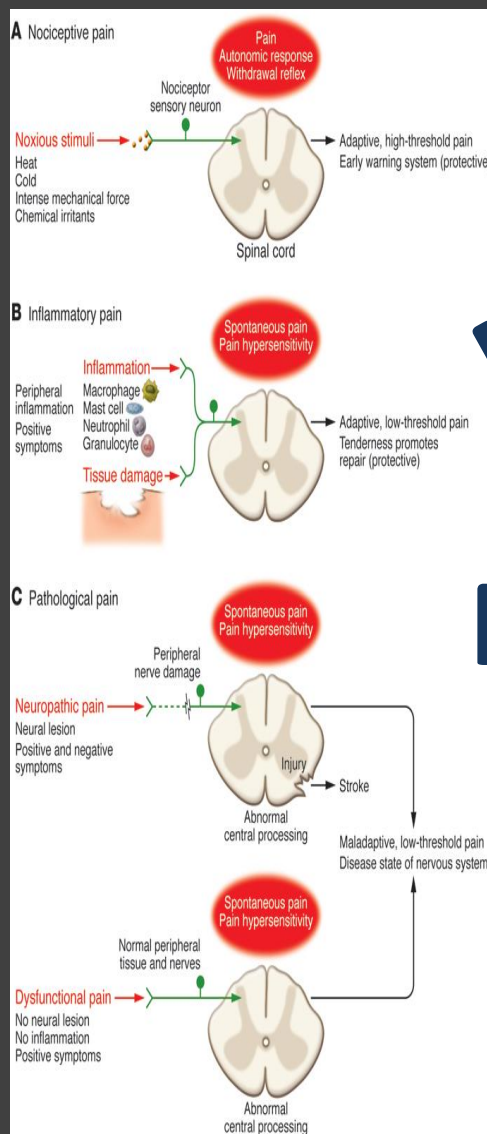
**Pulpitis reversible + irreversible
Periapical periodontitis**

Trigeminal neuropathic pain
PTN, CPSP, 2nd TN, BMS, PDAP/PH

Primary headaches

**Fibromyalgia
PIFP
TMD
arthromyalgia**

Types of pain



Healthy acute pain
Nociceptive
healthy feeling 'pain' pain'

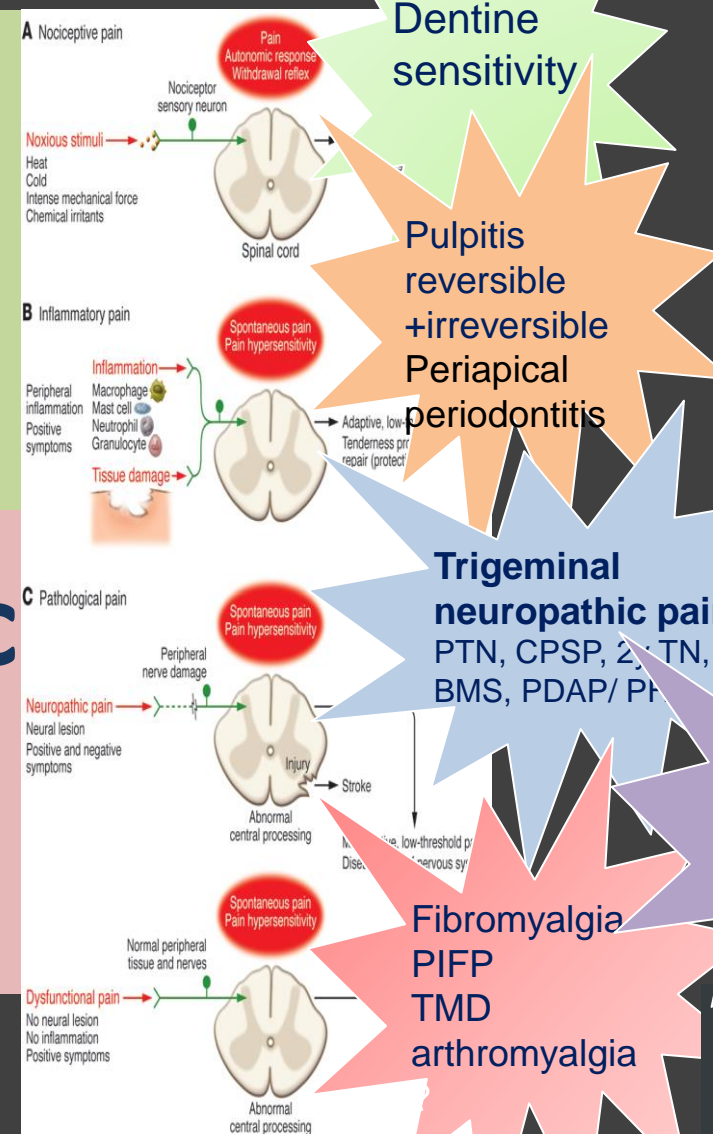
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Dentine sensitivity

Pulpitis reversible + irreversible
Periapical periodontitis

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PTN, CPSP, 2nd TN, BMS, PDAP/ PH

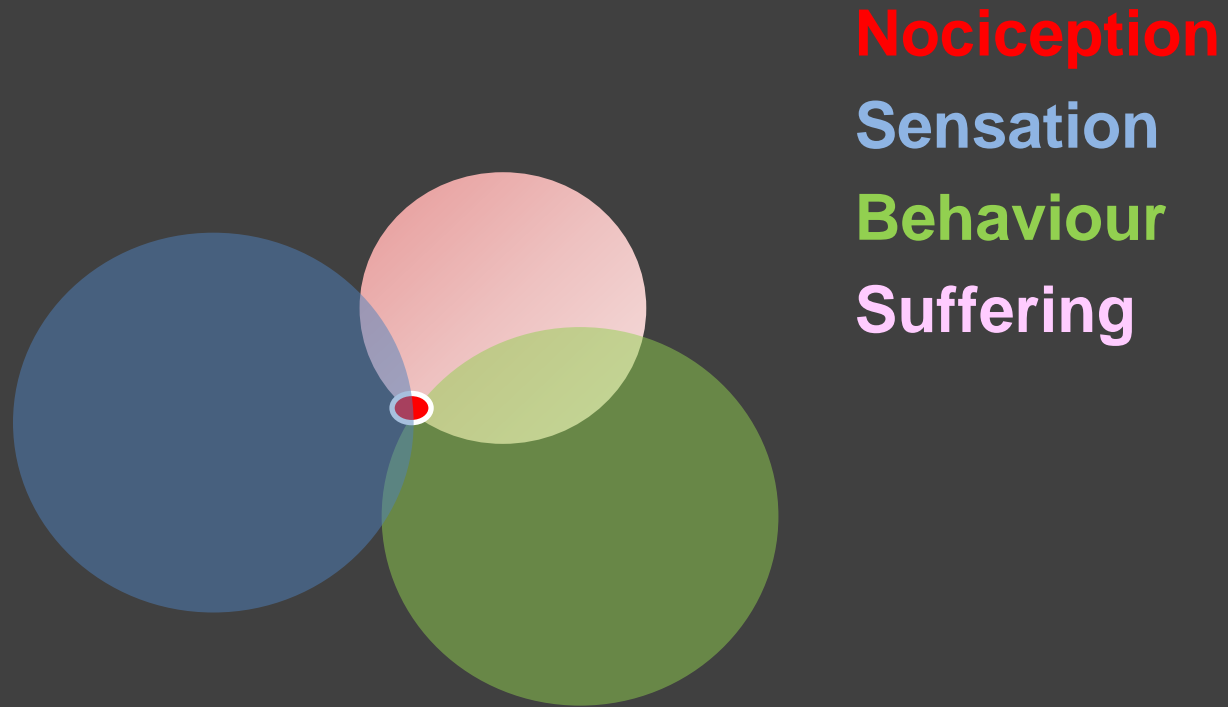
Primary headaches

Fibromyalgia
PIFP
TMD
arthromyalgia

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Type of patient



Type of patient

Nociception

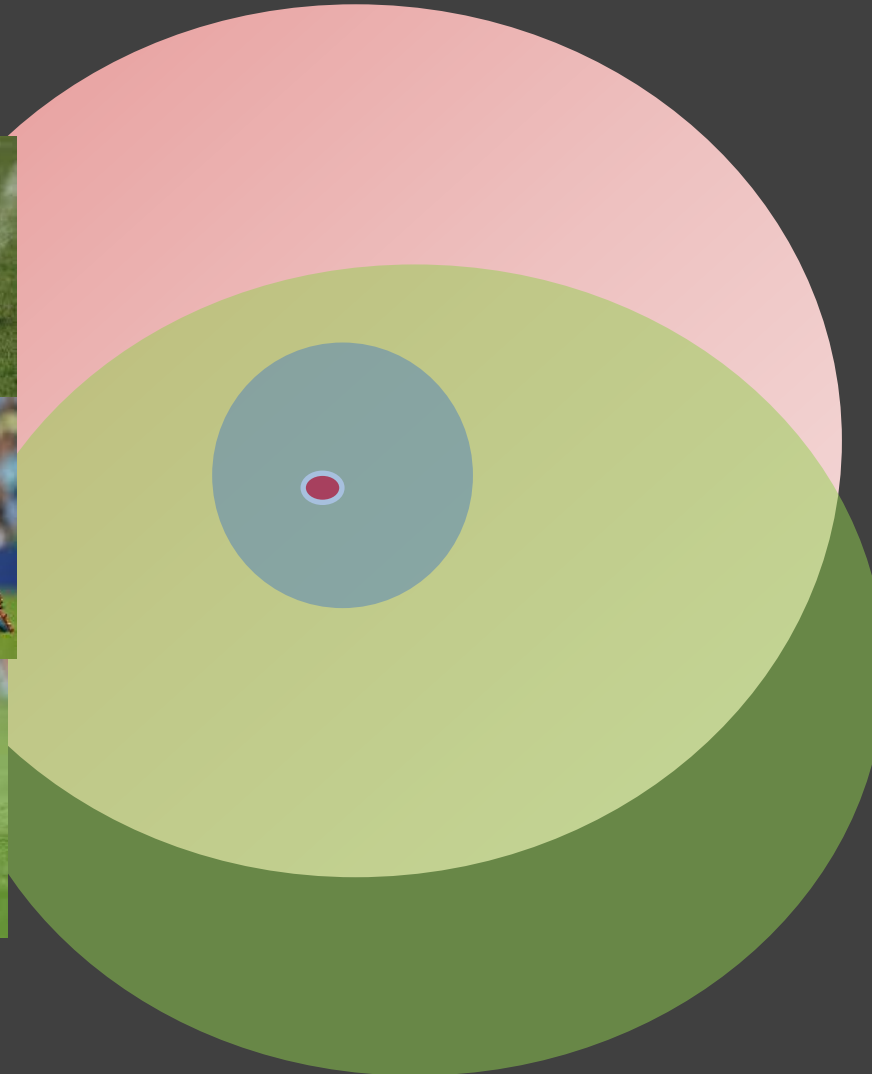
Sensation

Behaviour

Suffering



Type of patient



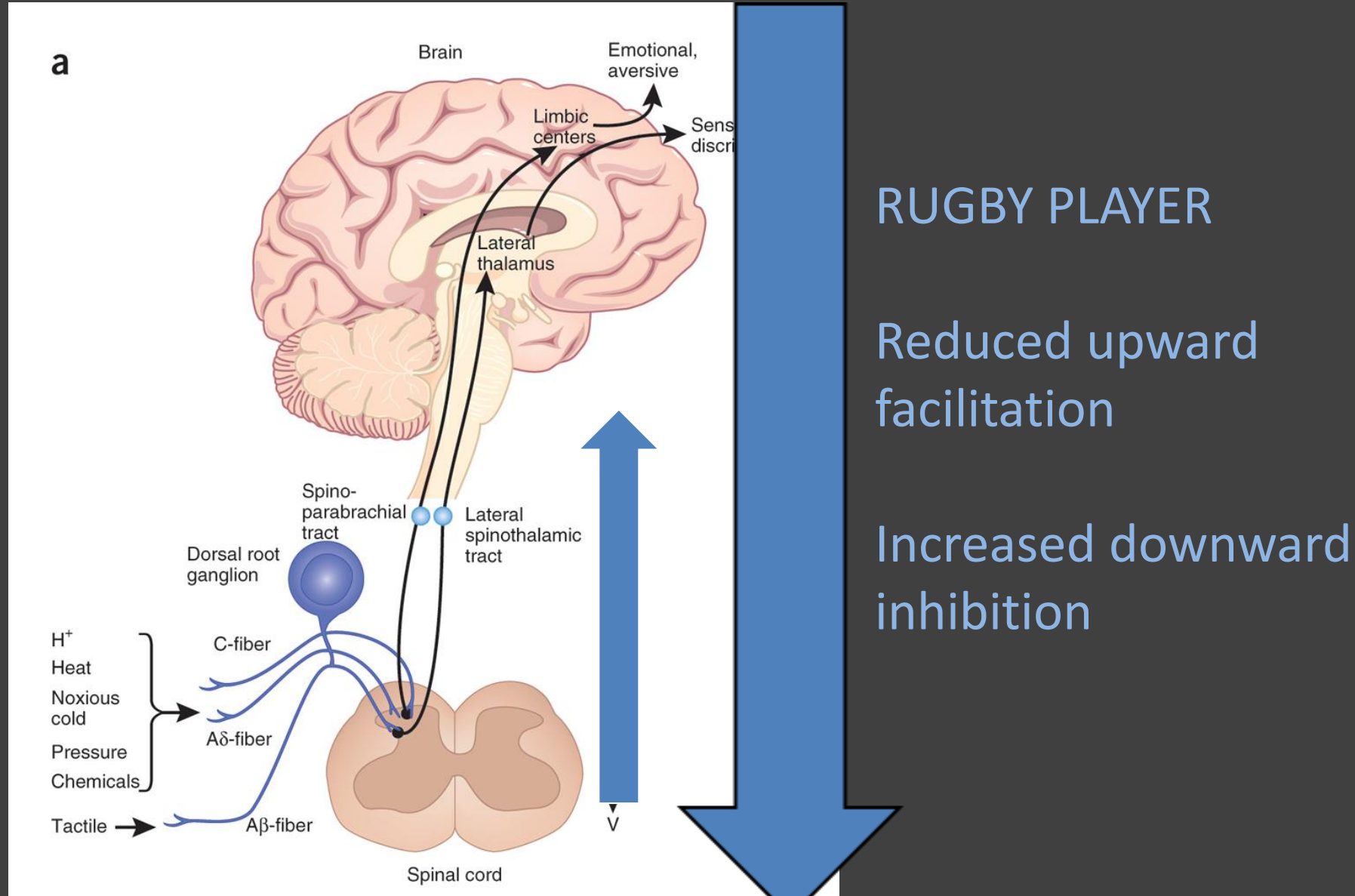
Nociception

Sensation

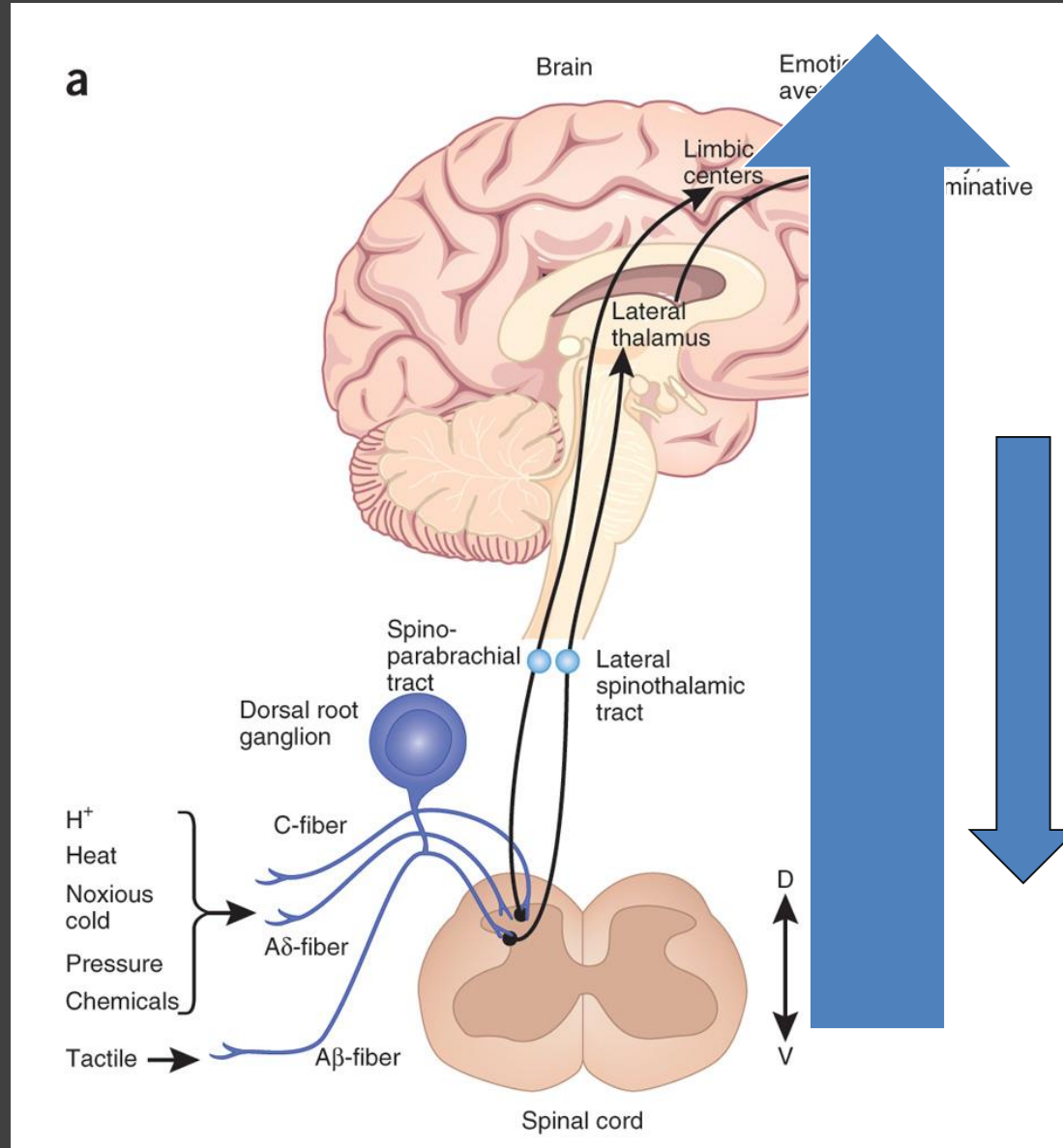
Behaviour

Suffering

Innate GREAT pain Modulation



Innate POOR pain Modulation

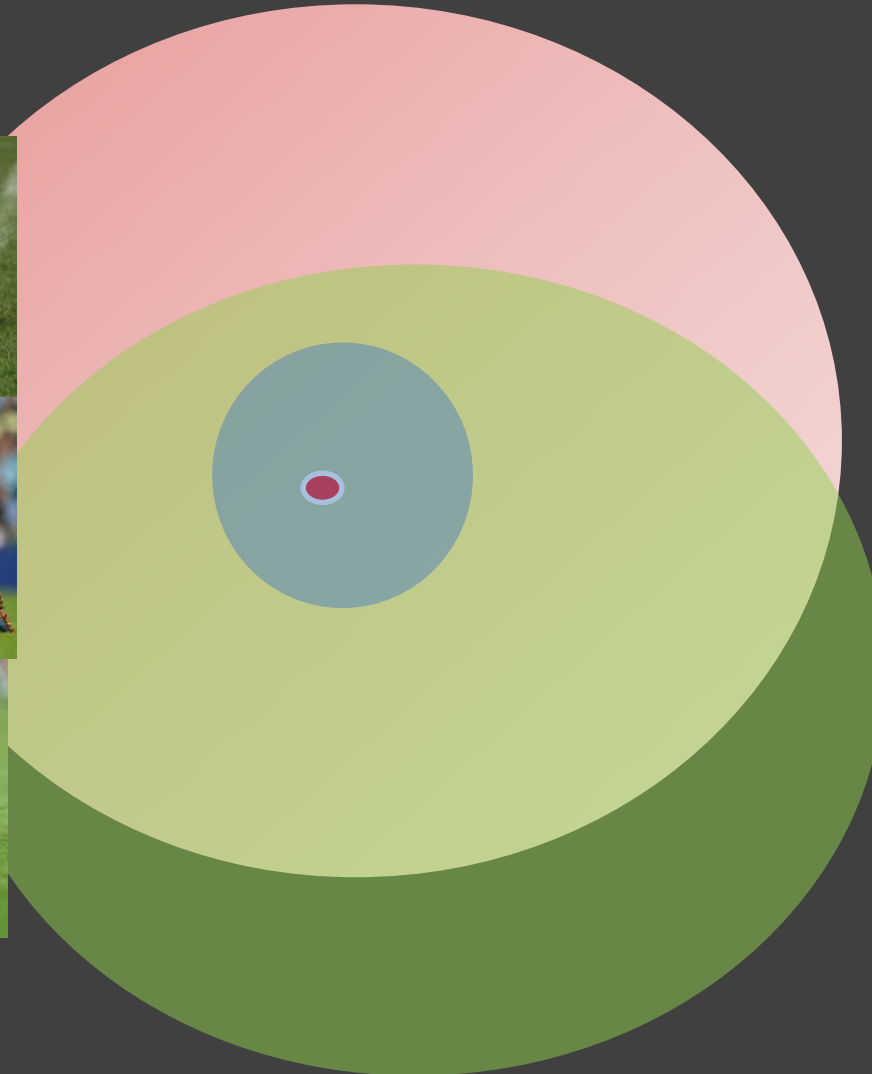


footballer PLAYER

increased upward
facilitation

decreased downward
inhibition

Type of patient



W
I
M
P
S

Types of patient

WW Women
GWAS

II Injury- PTSD
Inhibition is poor
with low pain
modulation

M Mood disorders
Anxiety & Stress

PP Personality
disorders

introspective, catastrophiser and
hypervigilance

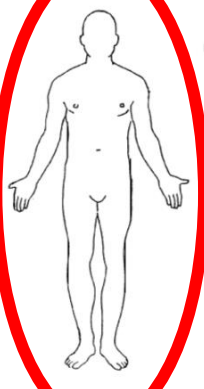
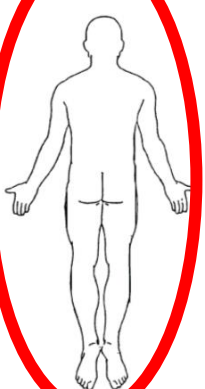
Prior abuse and
neglect

S Sleep deprivation
Stress

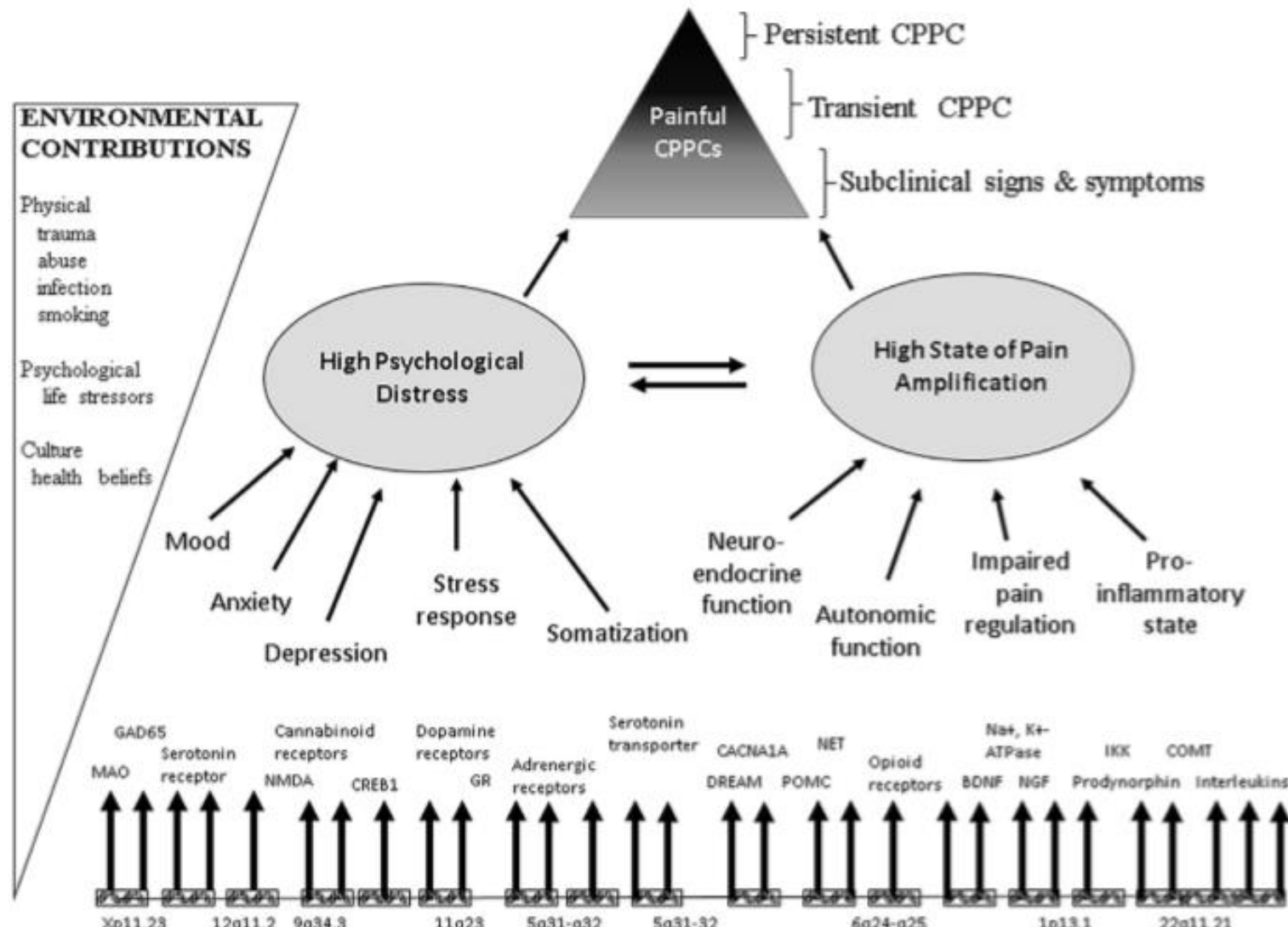


Name: _____ Date: _____

Using the symbols given below, mark the areas on your body where you feel the described sensation. Include all affected areas. Just to complete the picture, draw my face.

Front		Back
	Numbness 	
	Pins and Needles O O O O O	
	Burning XXXXX	
	Stabbing 	
	Ache AAAA	

Determinants for Onset and maintenance of chronic pain=AXIS II

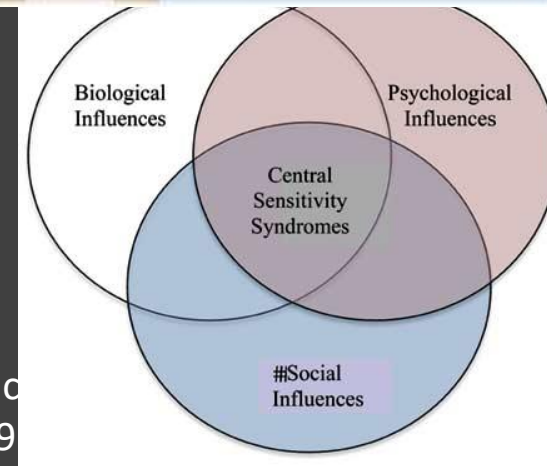
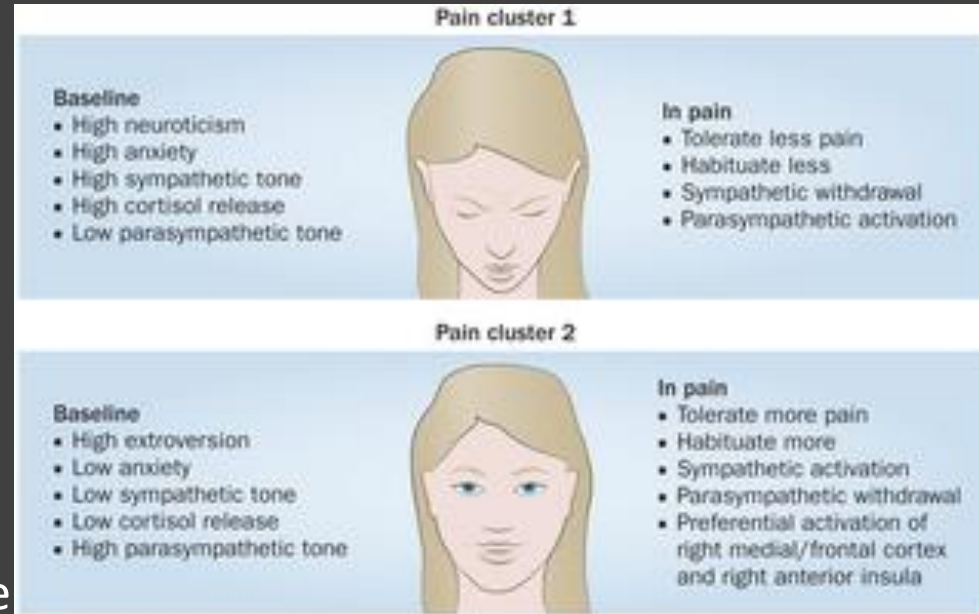


Risk Factors

Psychosocial risk factors predictive of CPSP

- Cognitive
 - Fear of surgery and anxiety
 - Fear of pain
- Personality disorder
 - increased preoperative anxiety
 - Introverted personality
 - Catastrophizing
 - Poor coping skills
 - Hypervigilance state
- Psychological vulnerability – pain re
- Social support
- Solicitous responding
 - Empathetic spouse encouraging negative behaviour
 - Munchausen

Review Katz & Seltzer



Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors. *Expert Rev Neurother.* 2009 May;9(5):723-44. doi: 10.1586/ern.09

Risk Factors

Genetics of pain



- MCR1 Melanocortin 1 receptor def –Mu opoid recepto
- Need 20% 20% more anaesthetic
- Melanocortin-1 Gene for Red Hair

2002 “It does appear that redheads have a significantly different pain threshold and req certain pains,”

2010 Danish study suggests red headed people feel the cold more but could handle eating hot food

An increasing number of studies show that redheads are differently constituted in terms of pain perception and body reactions. Research reveals that redheads:

- are more sensitive to cold
- are less responsive to subcutaneously administered anaesthetics [under the skin]
- suffer more from toothaches and are more frightened of dentists
- are at greater risk of developing sclerosis and endometriosis

Research Reports: Clinical

Fear of Pain Mediates the Association between *MC1R* Genotype and Dental Fear

Journal of Dental Research
2016, Vol. 95(10) 1132–1137
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for Dental Research 2016
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DOI: 10.1177/0022034516661151
jdr.sagepub.com

C.L. Randall^{1,2}, D.W. McNeil^{1,3}, J.R. Shaffer^{1,4}, R.J. Crout^{1,5}, R.J. Weyant^{1,6},
and M.L. Marazita^{1,7}

Abstract

Fear of pain is experienced in acute and chronic pain populations, as well as in the general population, and it affects numerous aspects of the orofacial pain experience, including pain intensity, pain-related disability, and pain behavior (e.g., avoidance). A related but separate construct—dental fear—is also experienced in the general population, and it influences dental treatment-seeking behavior and oral and systemic health. Minimal work has addressed the role of genetics in the etiologies of fear of pain and dental fear. Limited available data suggest that variants of the melanocortin 1 receptor (*MC1R*) gene may predict greater levels of dental fear. The *MC1R* gene also may be etiologically important for fear of pain. This study aimed to replicate the finding that *MC1R* variant status predicts dental fear and to determine, for the first time, whether *MC1R* variant status predicts fear of pain. Participants were 817 Caucasian participants (62.5% female; mean \pm SD age: 34.7 \pm 8.7 y) taking part in a cross-sectional project that identified determinants of oral diseases at the community, family, and individual levels. Participants were genotyped for single-nucleotide polymorphisms on *MC1R* and completed self-report measures of fear of pain and dental fear. Presence of *MC1R* variant alleles predicted higher levels of dental fear and fear of pain. Importantly, fear of pain mediated the relation between *MC1R* variant status and dental fear ($B = 1.60$, 95% confidence interval: 0.281 to 3.056). *MC1R* variants may influence orofacial pain perception and, in turn, predispose individuals to develop fears about pain. Such fears influence the pain experience and associated pain behaviors, as well as fears about dental treatment. This study provides support for genetic contributions to the development/maintenance of fear of pain and dental fear, and it offers directions for future research to identify potential targets for intervention in the treatment of fear of pain and dental fear.

Keywords: orofacial pain/TMD, dental phobia, anxiety, genetics, psychosocial factors, behavioral science

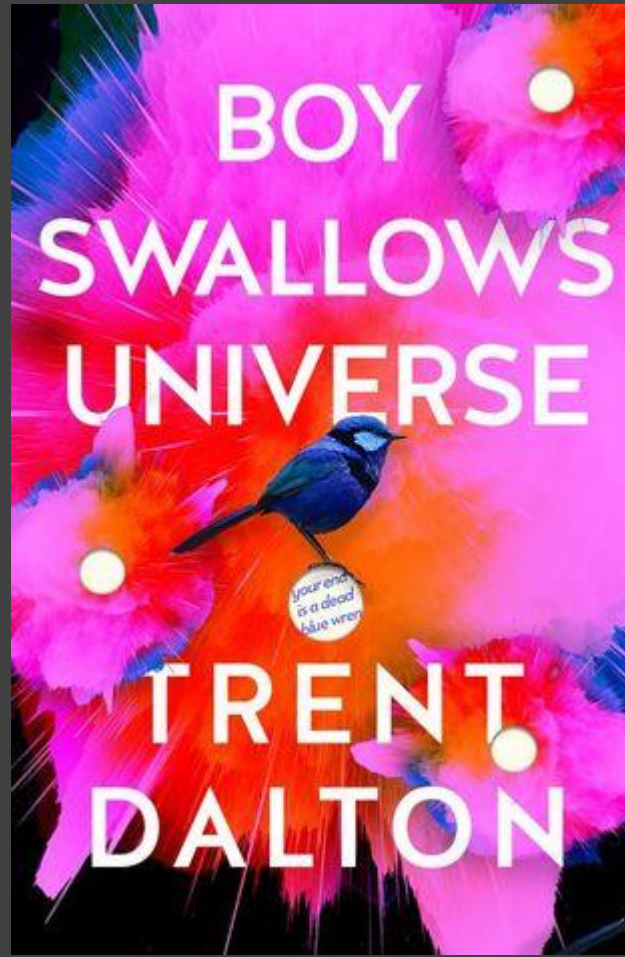
Risk factors

Aetiology centralised pain

- Chronic overlapping pain conditions affects up to 20% of population
- Family history
- 2X more common in women
- **Triggered or exacerbated by stressors**
 - Children born in 1958 who had experienced a motor traffic accident or were institutionalised were 1.5-2X more likely to have chronic widespread pain 42 years later (Jones et al 2007 ACR meeting)
 - Peripheral pain syndromes (RA OA SLE) (Clauw D et al JCR 1997)
 - Physical trauma (McBeth 2006 ACR meeting)
 - Post deployment (Clauw D et al J Occup environ Med 2003 Oct 45(10) 1040-8)
 - Infections (Abin et al Sem Arthritis Rheum 2009)
 - Psychological distress
- Genetics

Clauw JAMA 2014 Clauw et al Neuromodulation 1997; 4:134-153; McClean SA et al Med Hypotheses 2004; 63:653-658

Past life events.....



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- Pain
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 - **What classifications of OFP are there?**
- Differential diagnostic OFP diagnosis right

Classifications of OFP

- Woda et al 2005
- IASP Int Assoc Study of Pain
- ICHD-3 Beta - The International Classification of Headache Disorders
- American Association of Orofacial Pain (AAOP)
- Research Diagnostic Criteria for TMD
- AXES I and II

Pain. 2005 Aug;116(3):396-406.

Towards a new taxonomy of idiopathic orofacial pain.

Woda A¹, Tubert-Jeannin S, Bouhassira D, Attal N, Fleiter B, Goulet JP, Greteau-Richard C, Navez ML, Picard P, Pionchon P, Albuissou E.

Author information

Abstract

There is no current consensus on the taxonomy of the different forms of idiopathic orofacial pain (stomatodynia, atypical odontalgia, atypical facial pain, facial arthromyalgia), which are sometimes considered as separate entities and sometimes grouped together. In the present prospective multicentric study, we used a systematic approach to help to place these different painful syndromes in the general classification of chronic facial pain. This multicenter study was carried out on 245 consecutive patients presenting with chronic facial pain (>4 months duration). Each patient was seen by two experts who proposed a diagnosis, administered a 111-item questionnaire and filled out a standardized 68-item examination form. Statistical processing included univariate analysis and several forms of multidimensional analysis. Migraines (n=37), tension-type headache (n=26), post-traumatic neuralgia (n=20) and trigeminal neuralgia (n=13) tended to cluster independently. When signs and symptoms describing topographic features were not included in the list of variables, the idiopathic orofacial pain patients tended to cluster in a single group. Inside this large cluster, only stomatodynia (n=42) emerged as a distinct homogenous subgroup. In contrast, facial arthromyalgia (n=46) and an entity formed with atypical facial pain (n=25) and atypical odontalgia (n=13) could only be individualised by variables reflecting topographical characteristics. These data provide grounds for an evidence-based classification of idiopathic facial pain entities and indicate that the current sub-classification of these syndromes relies primarily on the topography of the symptoms.



AMERICAN ACADEMY
OF OROFACIAL PAIN

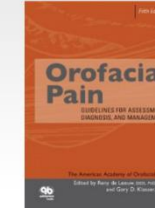


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The Fifth Edition of The AAOP Guidelines is now available



The AAOP is proud to announce that the fifth edition of the AAOP Guidelines edited by Remy de Leeuw and Gary Klasser, and with contributions from several AAOP members, has been published and is available for just \$48 at [Quantessence Publishing](http://www.aaop.org/content.aspx?page_id=2&club_id=508439&module_id=127004). This state of the

http://www.aaop.org/content.aspx?page_id=2&club_id=508439&module_id=127004



IHS CLASSIFICATION ICHD-3 BETA

IASP
International Association for the Study of Pain
Working together for pain relief

World Health Organization
The IASP is an NGO in official relationship with the WHO

The proposed classification of chronic headache and orofacial pain for ICD-11

Peter Svensson*, Rafael Benoliel, Stefan Evers, Shu-Jiun Wang, Antonia Barke
& the IASP Task Force Chronic Pain Classification for ICD-11*

Background

- Chronic primary headache has a major impact on activities and participation in day-to-day life including mobility, occupational activities, the activities and social participation. Headache and migraine are listed by the WHO among the top 10 of most disabling conditions worldwide.
- Chronic orofacial pain (OFP) also has a significant impact on activities and participation in day-to-day life, in particular social participation, mobility and occupational activities, the activities, socialization, and eating.

Definition of Chronic Headache and/or OFP

- Chronic primary headache or OFP is defined as headache or OFP that occurs on at least 150 of the days during at least three months.
- Chronic primary headache or OFP is multifactorial: biological, psychological, and social factors contribute to the pain syndrome. The diagnosis is representative independently of identified biological or psychological contributors unless another diagnosis would better account for the persisting symptoms.
- Other chronic headache or OFP diagnoses to be considered are listed under chronic secondary headache and OFP.
- The duration of pain per day is at least 4 hours (expressed as several shorter attacks per day occur).

Headache and OFP at a glance

- Pain disorders involving different types of headache and OFP

Chronic Headache and/or OFP

Categorized as chronic primary pain in the relevant section:

- Chronic primary headache and/or OFP
 - Chronic migraine
 - Chronic tension-type headache
 - Signs of autonomic dysregulation (NHS)
 - Chronic temporomandibular disorder (NHS)
 - Chronic neuralgia
 - Chronic myofascial pain with referral
 - Chronic neuropathic
 - Chronic burning mouth
 - Chronic primary orofacial pain
- Persistent dentonocisor pain
- Chronic orofacial pain
- Other chronic primary headache and/or OFP
- Chronic primary headache and/or OFP unspecified

Categorized as chronic secondary headache and orofacial pain in the relevant section:

- Chronic secondary headache and/or OFP
 - attributed to trauma or injury to the head and/or neck
 - attributed to stroke or cerebrovascular disorder
 - attributed to non-vascular intracranial disorder
 - attributed to substance or its withdrawal
 - attributed to infection
 - attributed to disorder of homeostasis or their treatment
 - attributed to disorder of the circulatory, endocrine, immune, nervous, genital, and musculoskeletal systems
 - attributed to mental and behavioral disorder
 - Chronic orofacial pain
 - Chronic headache/orofacial neuropathic pain
 - trigeminal neuropathic
 - Other cranial neuropathic
 - attributed to chronic secondary temporomandibular disorder
 - Other chronic secondary headache and/or OFP
 - Chronic secondary headache and/or OFP unspecified

Detailed description

Chronic primary headache and/or OFP

- Chronic primary headache or OFP may manifest at any age and largely depends on the specific symptoms and the response to the treatment. The term 'chronic' is defined as occurring on at least 150 days per year.
- Chronic migraine**
- Chronic tension-type headache**
- Signs of autonomic dysregulation (NHS)**
- Chronic temporomandibular disorder (NHS)**
- Chronic neuralgia**
- Chronic myofascial pain with referral**
- Chronic neuropathic**
- Chronic burning mouth**
- Chronic primary orofacial pain**

Persistent dentonocisor pain

Chronic orofacial pain

Other chronic primary headache and/or OFP

Chronic primary headache and/or OFP unspecified

Chronic secondary headache and/or OFP

- attributed to trauma or injury to the head and/or neck
- attributed to stroke or cerebrovascular disorder
- attributed to non-vascular intracranial disorder
- attributed to substance or its withdrawal
- attributed to infection
- attributed to disorder of homeostasis or their treatment
- attributed to disorder of the circulatory, endocrine, immune, nervous, genital, and musculoskeletal systems
- attributed to mental and behavioral disorder
- Chronic orofacial pain
- Chronic headache/orofacial neuropathic pain
 - trigeminal neuropathic
 - Other cranial neuropathic
- attributed to chronic secondary temporomandibular disorder
- Other chronic secondary headache and/or OFP
- Chronic secondary headache and/or OFP unspecified

Expected outcome

- The new chronic pain classification for ICD-11 including chronic primary and secondary headache and OFP is expected to increase awareness in this area and research and thereby to improve diagnosis, treatment, and management of these conditions.

References

- Woda A, Tubert-Jeannin S, Bouhassira D, Attal N, Fleiter B, Goulet JP, Greteau-Richard C, Navez ML, Picard P, Pionchon P, Albuissou E. Towards a new taxonomy of idiopathic orofacial pain. Pain. 2005 Aug;116(3):396-406.

Task Force Members

Chairman

Members

Observers

PART III

Neuropathies & Facial Pains

Neuropathic pain of the head is caused by a lesion or disease of the somatosensory nervous system. Neuralgias are characterized by pain in the distribution of a nerve or nerves

<https://www.ichd-3.org/>



Classifications of OFP

- Woda et al 2005
- IASP Int Assoc Study c
- ICHD-3 Beta - The I
- Classification of Head
- American Association of O
- (AAOP)
- Research Diagnostic C
- AXES I and II

Pain. 2005 Aug;116(3):396-406.

Towards a new taxonomy of idiopathic orofacial pain.

Woda A¹, Tubert-Jeannin S, Bouhassira D, Attal N, Fleiter B, Goulet JP, Greteau-Richard C, Navez ML, Picard P, Pionchon P, Albuissou E.

Author information

Abstract

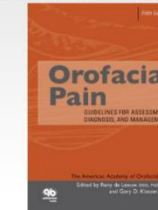
There is no current consensus on the taxonomy of the different forms of idiopathic orofacial pain (stomatodynia, atypical odontalgia, atypical facial pain, facial arthromyalgia), which are sometimes considered as separate entities and sometimes grouped together. In the present prospective multicentric study, we used a systematic approach to help to place these different painful syndromes in the general classification of chronic facial pain. This multicenter study was carried out on 245 consecutive patients presenting with chronic facial pain (>4 months duration). Each patient was seen by two experts who proposed a diagnosis, administered a 111-item questionnaire and filled out a standardized 68-item examination form. Statistical processing included univariate analysis and several forms of multidimensional analysis. Migraines (n=37), tension-type headache (n=26), post-traumatic neuralgia (n=20) and trigeminal neuralgia (n=13) tended to cluster independently. When signs and symptoms describing topographic features were not included in the list of variables, the idiopathic orofacial pain patients tended to cluster in a single group. Inside this large cluster, only stomatodynia (n=42) emerged as a distinct homogenous subgroup. In contrast, facial arthromyalgia (n=46) and an entity formed with atypical facial pain (n=25) and atypical odontalgia (n=13) could only be individualised by variables reflecting topographical characteristics. These data provide grounds for a evidence-based classification of idiopathic facial pain entities and indicate that the current sub-classification of these entities relies primarily on the topography of the symptoms.



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www.aaop.org/content.aspx?page_id=2

3439&module_id=127004

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CLASSIFICATION ICHD-3 BETA

IASP **World Health Organization**

The IASP is an NGO in official relationship with the WHO

The proposed classification of chronic headache and orofacial pain for ICD-11

Peter Svensson*, Rafael Benoliel, Stefan Evers, Shu-Jiun Wang, Antonia Barke & The IASP Task Force Chronic Pain Classification for ICD-11*

Background

- Chronic primary headache has a major impact on activities and participation in day-to-day life including mobility, interpersonal relations, the activities and social participation. Headache and migraine are listed by the WHO among the top 10 of most disabling conditions worldwide.
- Chronic orofacial pain (OFP) also has a significant impact on activities and participation in daily life, in interpersonal relations, the activities, socialization, and eating.

Definition of Chronic Headache and/or OFP

- Chronic primary headache or OFP is defined as headache or OFP that occurs on at least 105 of the days during at least three months.
- Chronic primary headache or OFP is multifactorial: biological, psychological, and social factors contribute to the pain syndrome. The diagnosis is representative independently of identified biological or psychological contributors unless another diagnosis would better account for the persisting symptoms.
- Other chronic headache or OFP diagnoses to be considered are listed under chronic secondary headache and OFP.
- The duration of pain per day is at least 4 hours (superimposed on several shorter attacks per day occur).

Headache and OFP at a glance

- For brevity, the following different types of headache and OFP are listed:

Chronic Headache and/or OFP

Categorized as chronic primary pain in the relevant section:

1. Chronic primary headache and/or OFP
 - 1.1 Chronic migraine
 - 1.2 Chronic tension-type headache
 - 1.3 Chronic orofacial neuropathic pain (CN)
 - 1.4 Chronic temporomandibular disorder (TMD)
 - 1.5 Chronic stomatodynia
 - 1.6 Chronic arthromyalgia
 - 1.7 Chronic burning mouth
 - 1.8 Chronic primary orofacial pain
- 1.9 Persistent denture-related pain
2. Chronic secondary headache and/or OFP
 - 2.1 Other chronic primary headache and/or OFP
 - 2.2 Other chronic primary headache and/or OFP unspecified
3. Chronic secondary headache and/or OFP
 - 3.1 attributed to trauma or injury to the head and/or neck
 - 3.2 attributed to cranial or cervical vascular disorder
 - 3.3 attributed to non-vascular intracranial disorder
 - 3.4 attributed to substance or its withdrawal
 - 3.5 attributed to infection
 - 3.6 attributed to disorder of homeostasis or their treatment
 - 3.7 attributed to disorder of the circulatory, lymphatic, endocrine, immune, genetic, and metabolic systems
 - 3.8 attributed to mental and behavioral disorder
 - 3.9 Chronic orofacial pain
 - 3.10 Chronic headache/orofacial neuropathic pain
 - 3.11 attributed to chronic secondary temporomandibular disorder
 - 3.12 Other chronic secondary headache and/or OFP
 - 3.13 Chronic secondary headache and/or OFP unspecified

Detailed description

Chronic primary headache or OFP may manifest at any age and largely depends on the specific migraines and the response to the treatment. The most frequent symptoms are recurrent attacks of moderate to severe pain.

Chronic primary headache or OFP

- 1. Chronic primary headache or OFP is characterized by recurrent attacks of moderate to severe pain.
- 2. The attacks are recurrent and last for at least 4 hours.
- 3. The attacks are not caused by any other disorder.
- 4. The attacks are not caused by any other disorder.
- 5. The attacks are not caused by any other disorder.
- 6. The attacks are not caused by any other disorder.
- 7. The attacks are not caused by any other disorder.
- 8. The attacks are not caused by any other disorder.
- 9. The attacks are not caused by any other disorder.
- 10. The attacks are not caused by any other disorder.

Chronic secondary headache and/or OFP

- 1. Chronic secondary headache and/or OFP is characterized by recurrent attacks of moderate to severe pain.
- 2. The attacks are recurrent and last for at least 4 hours.
- 3. The attacks are not caused by any other disorder.
- 4. The attacks are not caused by any other disorder.
- 5. The attacks are not caused by any other disorder.
- 6. The attacks are not caused by any other disorder.
- 7. The attacks are not caused by any other disorder.
- 8. The attacks are not caused by any other disorder.
- 9. The attacks are not caused by any other disorder.
- 10. The attacks are not caused by any other disorder.

Neuropathies & Facial Pains

Neuropathic pain of the head is caused by a lesion or disease of the somatosensory nervous system. Neuralgias are characterized by pain in the distribution of a nerve or nerves

<https://www.ichd-3.org/>

Classification OFP Draft ICOP

International Classification of Orofacial Pain

ICOP

Version 1.0 beta

2019

Orofacial pain associated with dentoalveolar structures

Orofacial pain associated with regional muscles

Orofacial pain associated with disorders of the TMJ

Orofacial pain associated with lesion/disorders of the cranial nerves and other regional nerves

Orofacial pain resembling presentation of primary headaches

Idiopathic orofacial pain

Psychological assessment

Members of individual classification working groups in alphabetical order other than chair.

1. Orofacial pain associated with disorders of dentoalveolar and associated structures

Maria Pigg, Sweden (Chair); Alan Law, USA; Donald Nixdorf, USA; Tara Renton, UK; Yair Sharav, Israel

2. Orofacial pain associated with regional muscles

Peter Svensson, Denmark (Chair); Malin Ernberg, Sweden; Chris Peck, Australia

3. Orofacial pain associated with disorders of the TMJ

Per Alstergren, Sweden (Chair); Ghabi Kaspo, USA; Frank Lobbezoo, Netherlands; Ambra Michelotti, Italy

4. Orofacial pain associated with lesion/disorders of the cranial nerves and other regional nerve structures

Lene Baad-Hansen, Denmark (Chair); Eli Eliav, USA; Yoshiki Imamura, Japan

5. Orofacial pain resembling presentations of Primary Headaches

Rafael Benoliel, USA (Chair); Paulo Conti, Brazil; Arne May, Germany

6. Idiopathic orofacial pain

Thomas List, Sweden (Chair); Justin Durham, England; Jean-Paul Goulet, Canada; Satu Jääskeläinen, Finland

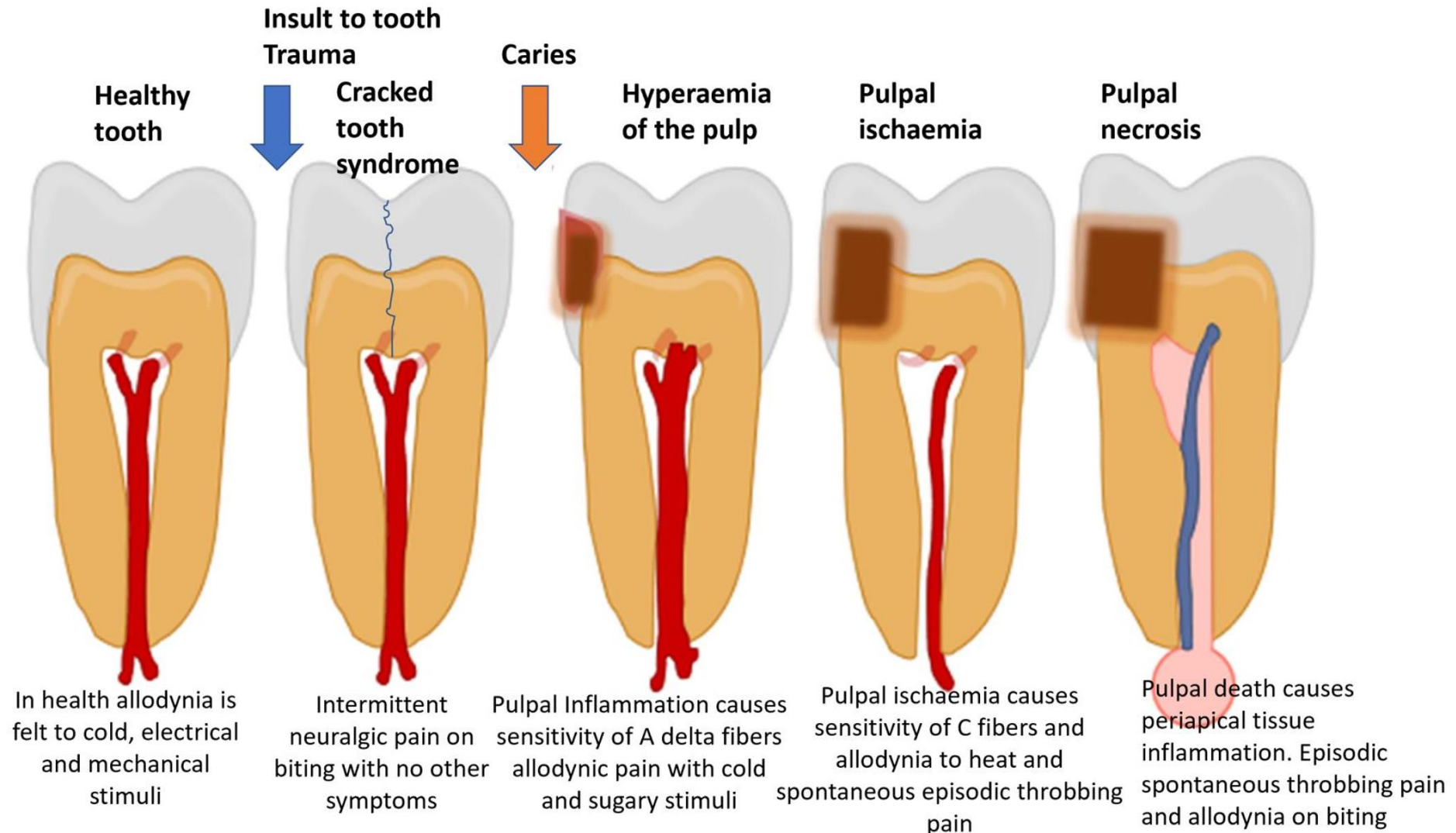
7. Psychosocial Assessment

Richard Ohrbach, USA

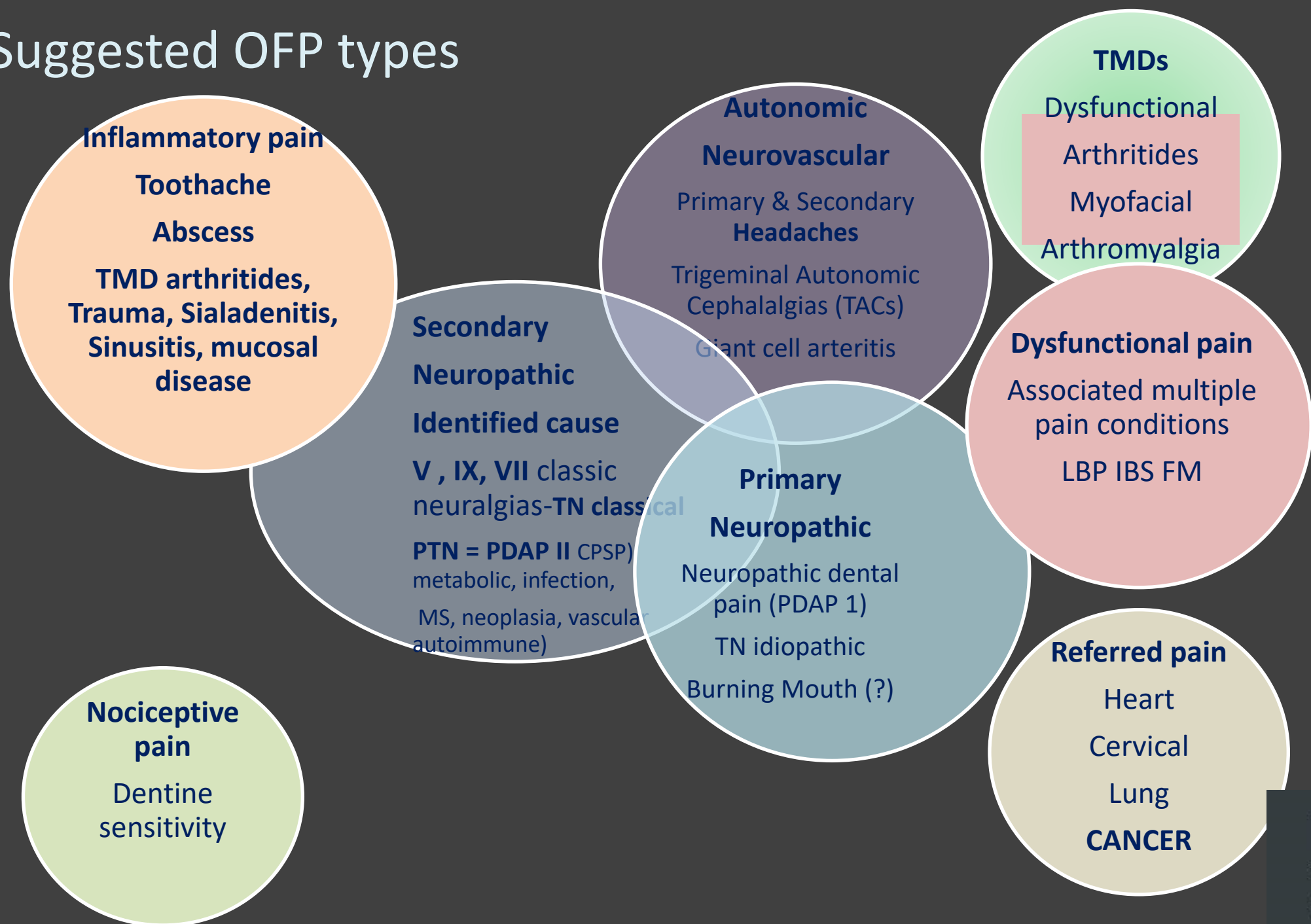
Outline

- Pain
 - Problem
 - Defns
 - Where is it?
 - What types of pain are there?
 - What type of patient is there?
 - What classifications of OFP are there?
- **Differential diagnostic toothache versus chronic orofacial pains**

The multiple 'faces' of toothache



Tara's Suggested OFP types



Inflammatory pain

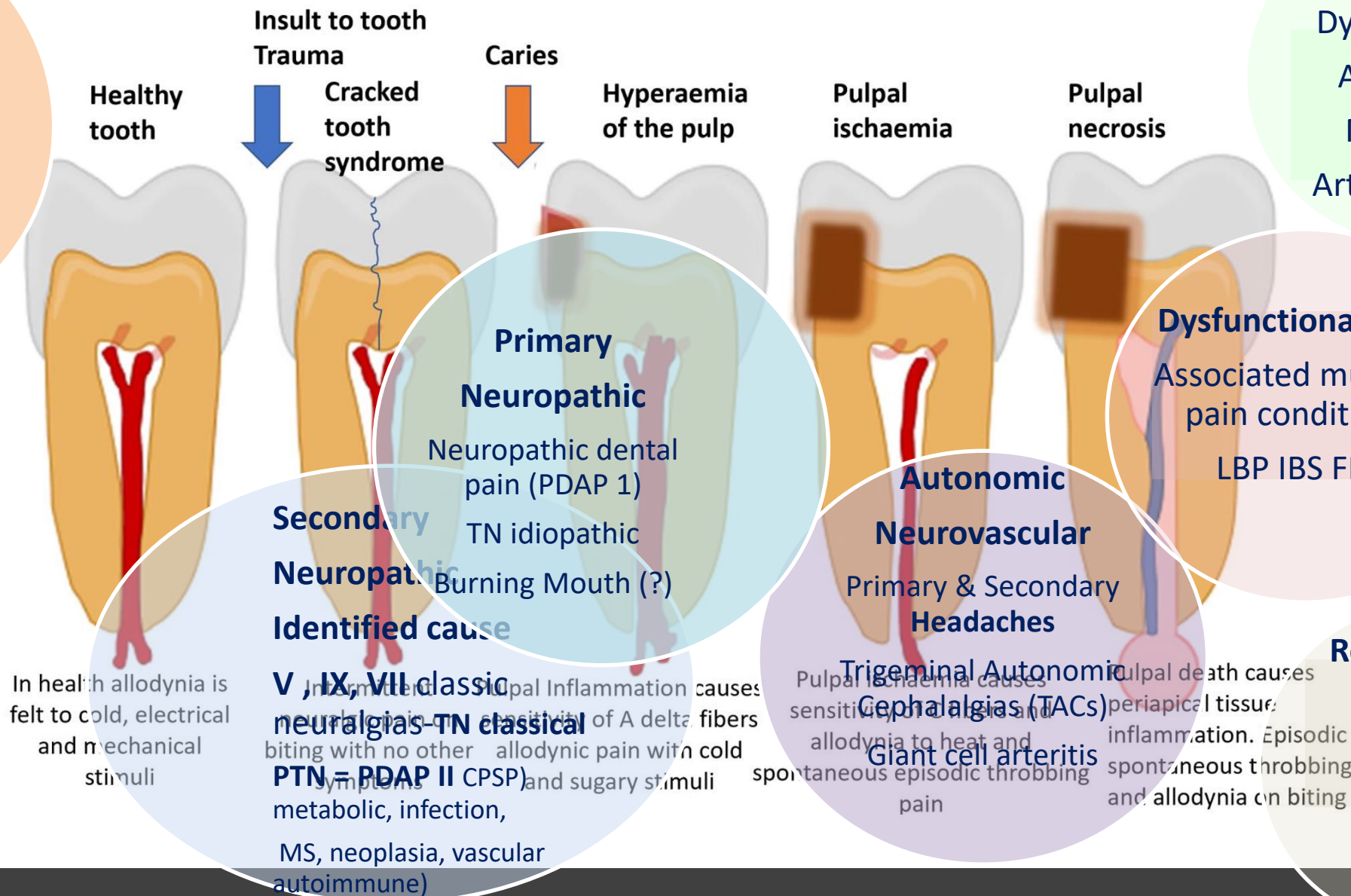
Toothache

Abscess

TMD arthritides,
trauma, Sialadenitis,
Sinusitis, mucosal
disease

Nociceptive pain

Dentine
sensitivity



TMDs

Dysfunctional
Arthritides
Myofacial
Arthromyalgia

Dysfunctional pain

Associated multiple
pain conditions
LBP IBS FM

Referred pain

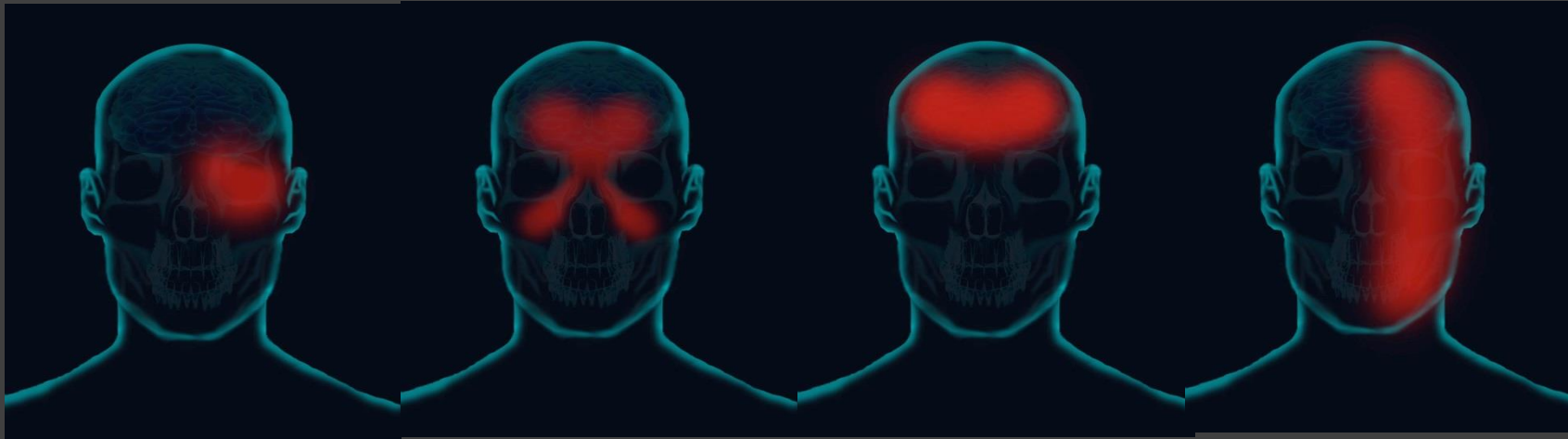
Heart
Cervical
Lung
CANCER

SOCRATES

- Site
- Onset
- Character
- Radiation
- Associated factors
- Timing
- Severity

What are the differentiators?

Site of pain?



Onset ?

- Possible physical injury
 - Surgery
 - Trauma
 - Dental treatment Significant life event
- Significant life event
 - Death of a spouse or close relative
 - History of Abuse or Neglect

Radiation ?

More common in

- headaches
neurovascular pain
- joint pain
- referred pain

Character of pain = descriptors?

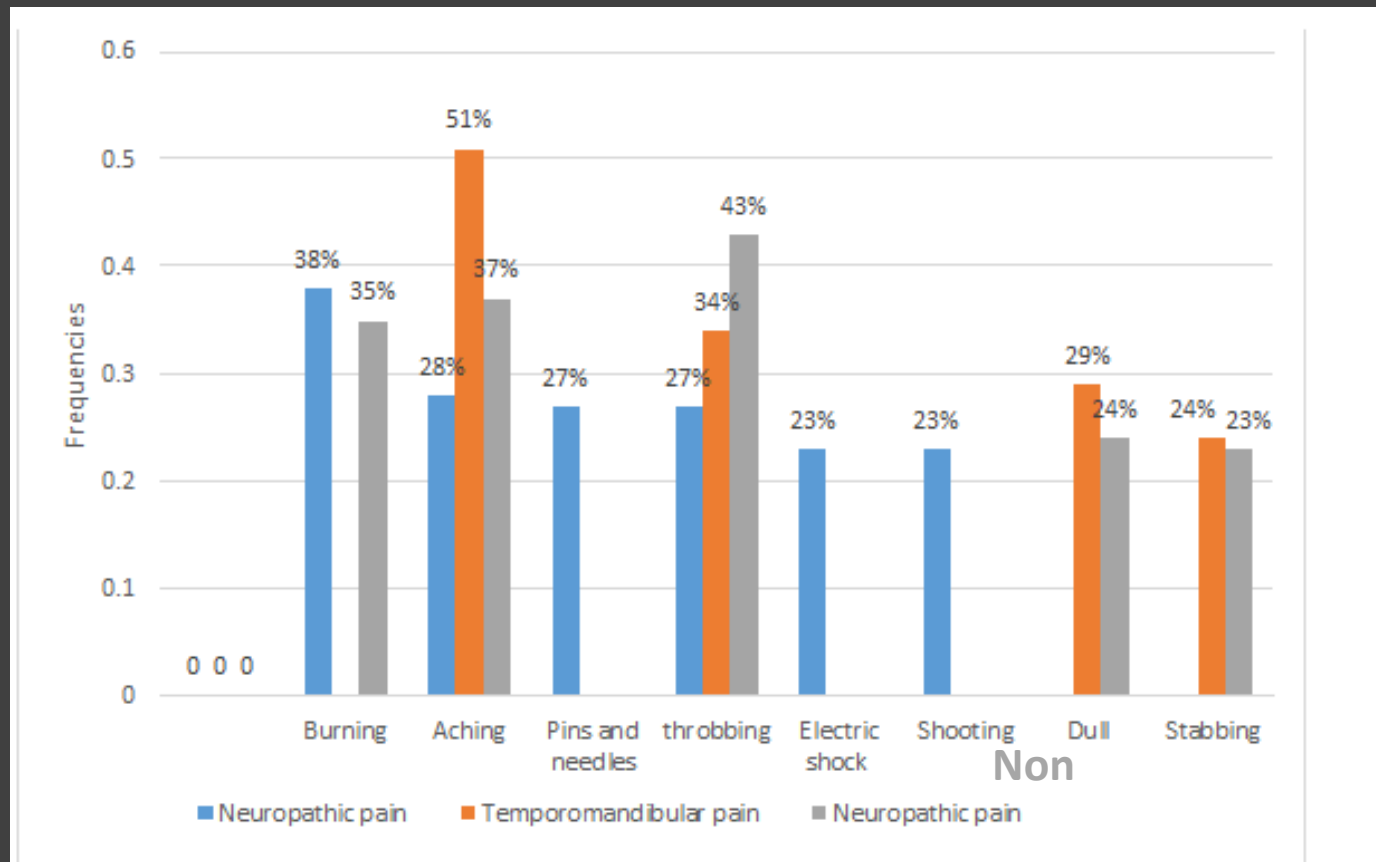


Figure: 3 Report of pain descriptors in patients with neuropathy, TMD and neurovascular pain

Biggest differentiators?

Non response to dental treatment Non dentists

Associated factors dentists Always ask for headache history

- Migrainous
 - Photophobia-need darkness
 - Phonophobia- need quiet
 - Aura
 - Unable to move head during attacks
 - Nausea vomiting
 - Paraesthesia / numbness
 - Cant brush hair
- Autonomic
 - Unilateral
 - Redness of eye
 - Tearing
 - Nasal congestion
 - Cheek redness
 - Paraesthesia / numbness
 - Meiosis
 - Ptosis
 - Worse exercise alcohol
 - Cannot stay still during attack
 - Hypothalamic behaviour

Exacerbating / relieving factors?

- Does not respond to anti inflammatory analgesics
 - Paracetamol
 - Ibuprofen
 - Or antibiotic course for infection
- Absent or less in mornings
- Worse with stress, tiredness, illness
- Not present at night
- Minimised on holiday

IS NOT inflammatory pain

Consider neuropathic pain

Assessment

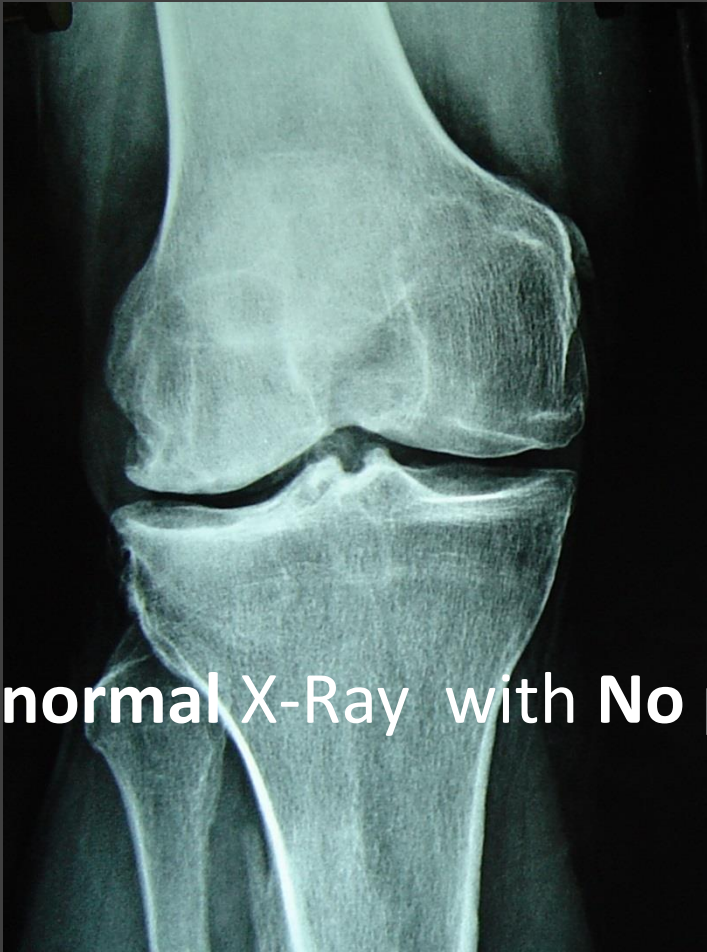
- History-listen
 - History-listen
 - History-listen
 - History-listen
 - Other pains
 - Chronic widespread pain
 - Headaches
 - Family history of HAs or pain
 - Sleep quality
 - Prior abuse / neglect
 - Axis II Psychological factors
 - Function
- Investigations
 - Haematological
 - Radiological
 - Other
 - Nerve conduction tests
 - US
 - QST
 - Previous Medication

William Osler



Listen to the patient and they will tell you their diagnosis

You cannot diagnose pain on a radiograph!!!!

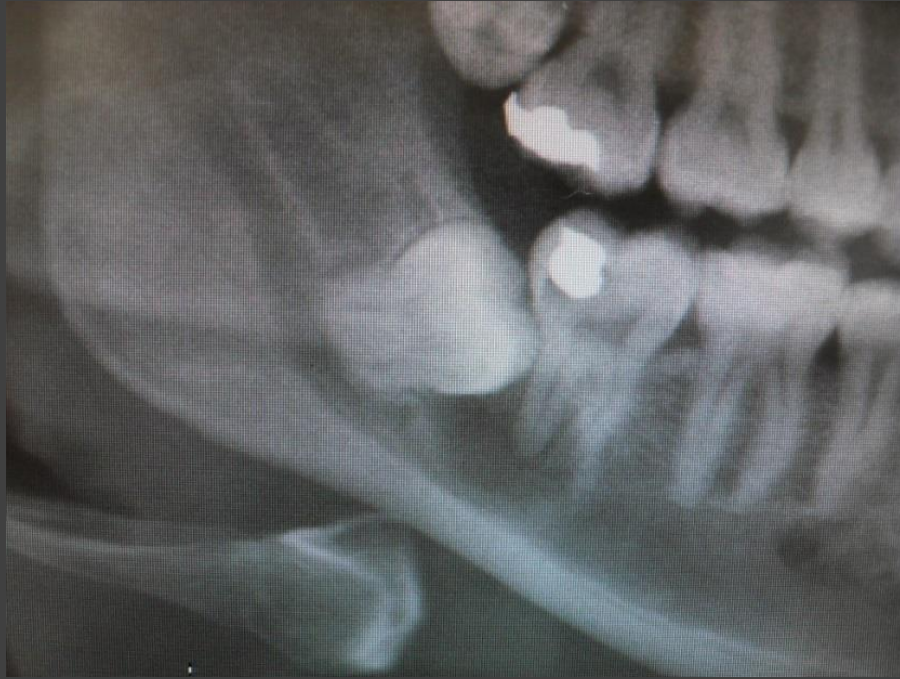


30-40% abnormal X-Ray with No pain

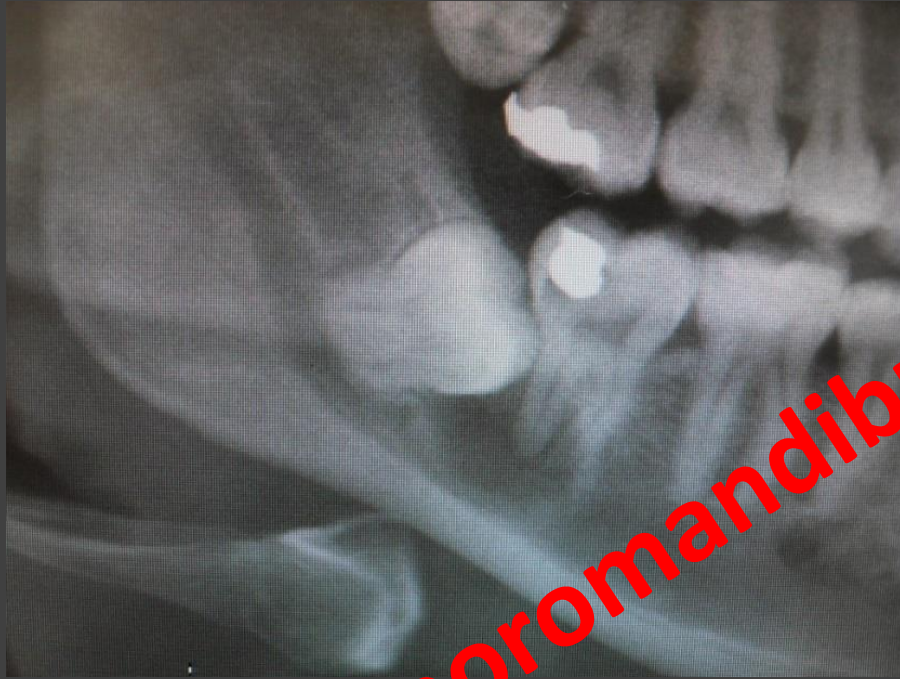


15-20% normal X-Ray with pain

Why its important to get the diagnosis right.....

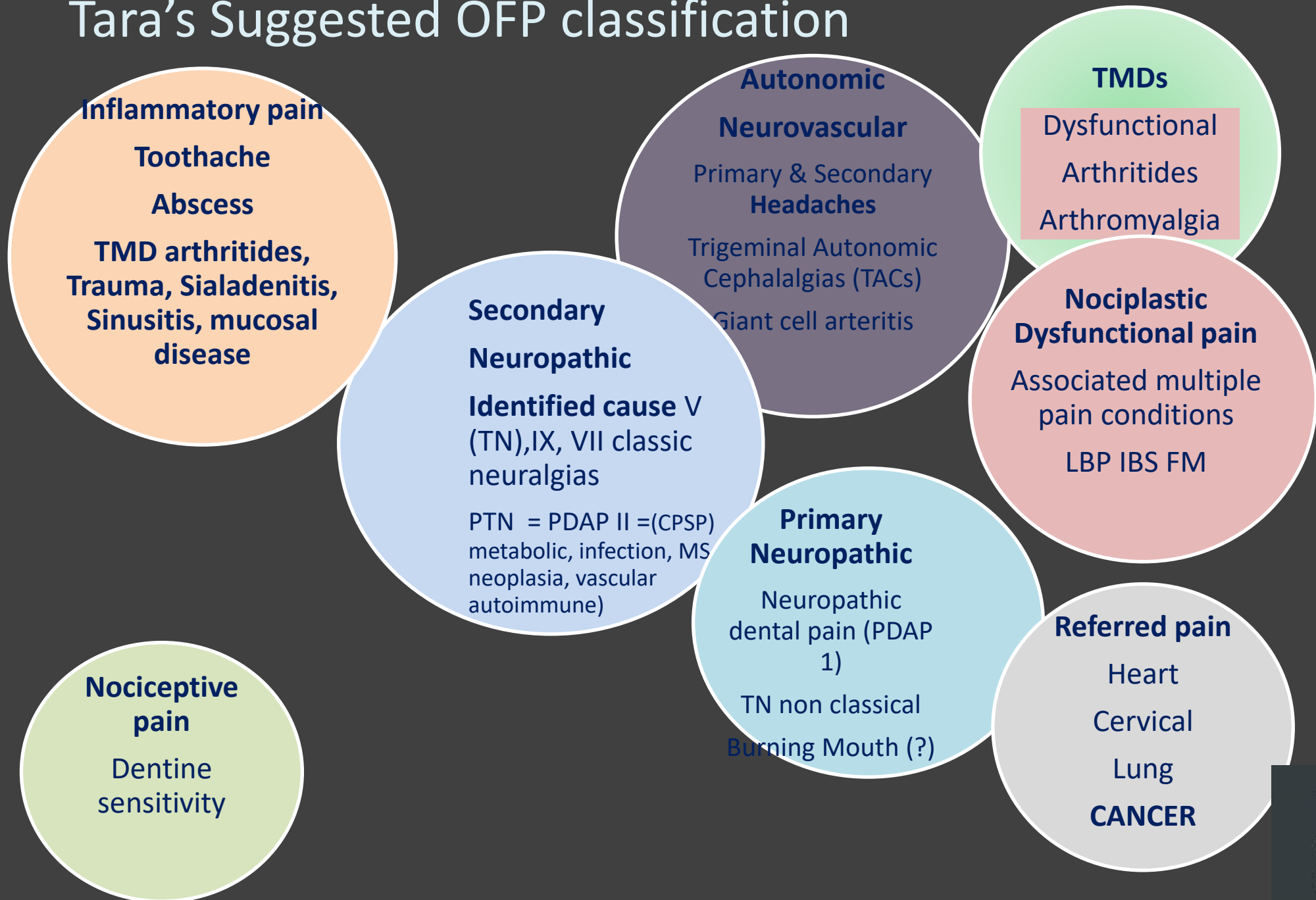


Why its important to get the diagnosis right.....



Temporomandibular joint disorder

Tara's Suggested OFP classification



Never ever underestimate toothache mimickery!

Inflammatory pain

Toothache

Abscess

TMD arthritides,
trauma, Sialadenitis,
Sinusitis, mucosal
disease

TMDs

Dysfunctional

Arthritides

Myofacial

Arthromyalgia

Healthy
tooth

Insult to tooth
Trauma

Cracked
tooth
syndrome

Caries

Hyperaemia
of the pulp

Pulpal
ischaemia

Pulpal
necrosis

**Primary
Neuropathic**

Neuropathic dental
pain (PDAP 1)

**Secondary
Neuropathic**
TN idiopathic
Burning Mouth (?)

Identified cause

V, IX, VII classic
neuralgias-TN classical

PTN = PDAP II CPSP)
metabolic, infection,
MS, neoplasia, vascular
autoimmune)

In health allodynia is
felt to cold, electrical
and mechanical
stimuli

Intermittent
neuralgic pain on
biting with no other
symptoms

Pulpal inflammation causes
sensitivity of A delta fibers
allodynic pain with cold
and sugary stimuli

**Autonomic
Neurovascular**

Primary & Secondary
Headaches

Trigeminal Autonomic
Cephalalgias (TAGs)

Giant cell arteritis
Pulpal ischaemia causes
sensitivity of C fibers and
allodynia to heat and
spontaneous episodic throbbing
pain

**Nociplastic/Dysfun
ctional pain**

Associated multiple
pain conditions

LBP IBS FM

Referred pain

Heart

Cervical

Lung

CANCER

**Nociceptive
pain**

Dentine
sensitivity

In health

In relation to dental innovation.....
Allodynia is NORMAL!
But not anywhere else in the body!

Nociceptive pain
Dentine sensitivity



Dentine sensitivity causing ALLODYNIA in

- Attrition....tooth against tooth wear
- Abrasion....over brushing
 - (hard tooth brush, wrong technique, abrasive tooth paste)
- Erosionacid erosion of enamel and dentine
 - Fruit juice just before or after brushing, anorexia, GORD

Convergence = Referred (heterotopic) pain

- As with all maps there are other paths that are possible to take to your destination:

Convergence

- Using the analogy of a walking map, it is possible to explain the phenomenon of convergences. There are other paths that may get you to the same destination on your map and some of these other paths may even cross the main path to your chosen destination. On your way to your chosen destination you could, therefore, get confused and change direction/path but end up at the same destination.
- The analogy above is known as 'convergence'. The difference between the analogy above and convergence in the brain is that the brain struggles to tell which area the impulse is originally from. This can result in the phenomenon of referred pain where the brain interprets a pain as coming from one area because of convergence, but actually the pain is from elsewhere.

Referred pain

Heart

Cervical

Lung

CANCER

Heart attack pain due to vagus nerve

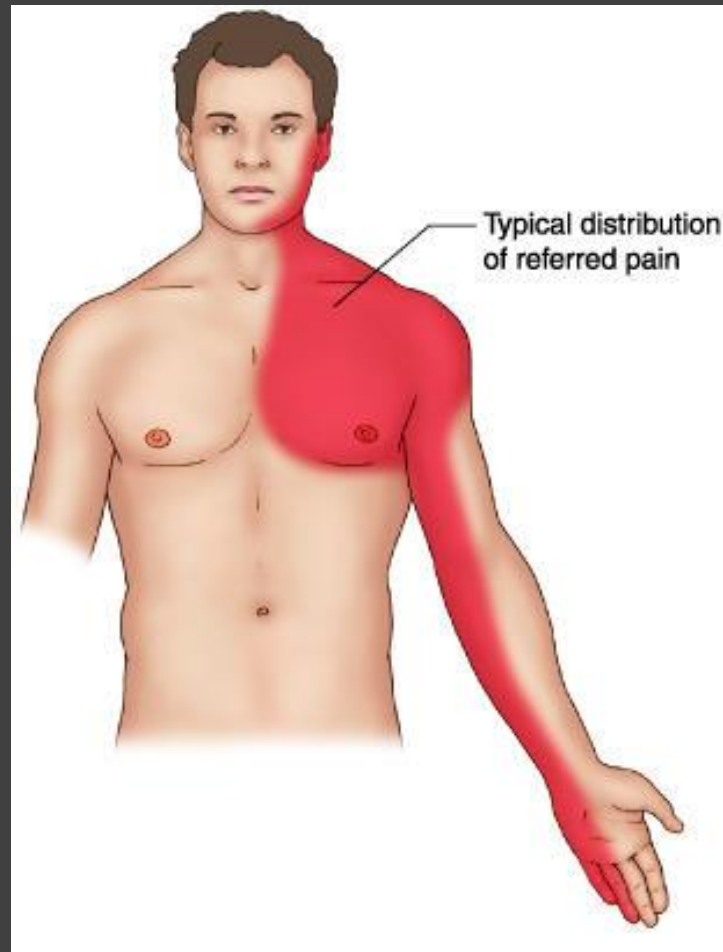
Referred pain

Heart

Cervical

Lung

CANCER



Facial pain due to cervical referred pain

Referred pain

Heart

Cervical

Lung

CANCER



The elephant in the room

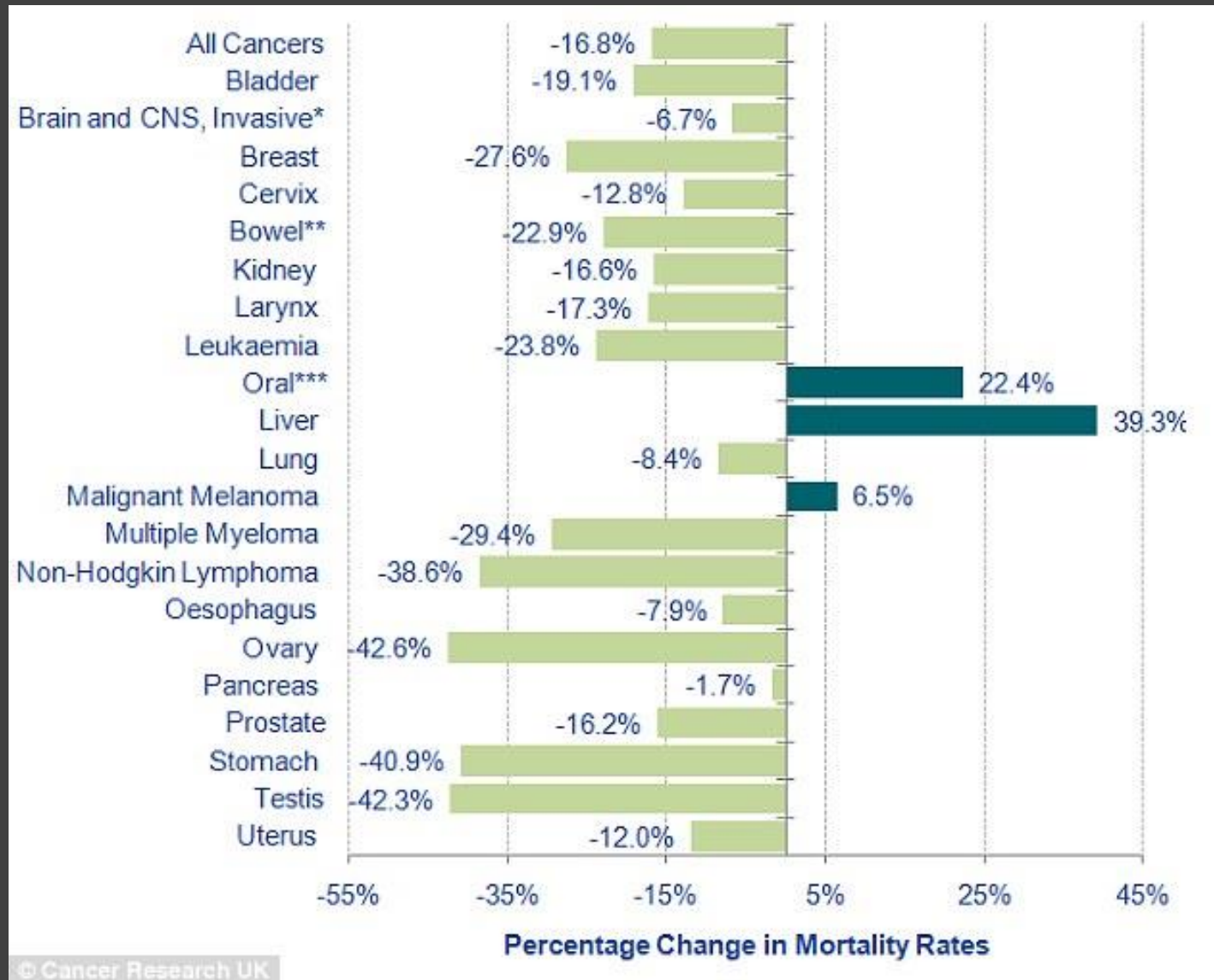
Referred pain

Masseteric
muscle, Cardiac,
Cervical, Lung

CANCER



Hepatocellular, melanoma and Oropharyngeal Ca



Red flags of malignancy

• Over 50 years
• Previous history of Carcinoma
• Smoking /alcohol/ Betel nut/ Pan
• Night fevers
• Weight loss
• Blood loss/ anaemia

NHS 2 (NICE 3) weeks
Referral pathway

• Recent onset
• Rapid growth
• Neuropathy - sensory or motor
• Resorption of adjacent structures
• Localised mobility of teeth
• Progressive trismus
• Persistent painless ulcer
• Lymphadenopathy painless persistent
• Lack of response to conventional treatments:
– Antibiotics
– Endodontic surgery

Definition Types of Temporomandibular disorders

Diagnostic Criteria

- TMJ RDC now DC
 - Degenerative joint disease
 - Arthritides
 - +/-pain OA, RA, Reactive
 - Myalgia or arthralgia
 - Muscle or joint pain
 - Myofascial
 - Internal derangements
 - Disc displacement with or without reduction (with or without open or closed locking)
 - subluxation

– Headache attributable to TMD
<http://www.iadr.org/INFORM/DC-TMD>

Degenerative
Myofacial pain
Arthro/myalgia
DDWOR /DDWR
subluxation
Headache



HHS Public Access

Author manuscript

J Oral Facial Pain Headache. Author manuscript; available in PMC 2015 June 23.

Published in final edited form as:

J Oral Facial Pain Headache. 2014 ; 28(1): 6–27.

Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: Recommendations of the International RDC/TMD Consortium Network* and Orofacial Pain Special Interest Group†

Eric Schiffman, DDS, MS [Associate]
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Department of Oral Diagnostic Sciences
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Edmond Truelove, DDS, MSD [Professor]
Department of Oral Medicine School of Dentistry
USA

John Look, DDS, PhD [Senior Researcher]
Department of Diagnostic and Biological Sciences



International Network for Orofacial Pain and Related Disorders Methodology
A Consortium Focused On Clinical Translation Research

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TMD ASSESSMENT/DIAGNOSIS

DC-TMD

Diagnostic Criteria for Temporomandibular Disorders (2014)

Overview

The Diagnostic Criteria for Temporomandibular Disorders (DC/TMD), by Schiffman et al, are available in the [Journal of Oral & Facial Pain and Headache, 2014](#). The DC/TMD is intended for use in both clinical settings and applied research settings. Schiffman et al describe the rationale and methodology underlying the changes from the RDC/TMD to the DC/TMD. The extensive development process can be explored in

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– Headache attributable to TMD

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Myofacial pain
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TMD & comorbid multiple pain conditions

No. of Comorbid Pain Conditions*	Population (Millions)	People (Millions), N	Percentage of Population	Odds Ratio	95% CI†
0	118.4	1.3	1.1%	Referent	
1	57.1	2.0	3.6%	3.2	2.6, 4.0
2	29.8	3.0	10.1%	9.8	7.7, 12.4
3 or 4	21.9	5.1	23.4%	26.5	21.2, 33.0
Total	227.2	11.5	5.1%		

*1) Severe headache/migraine, 2) neck pain, 3) low back pain, and 4) 2 or more painful joints.

†95% Confidence limits for the odds ratio.

For the current report, we analyzed the NHIS data set from the 2009 survey, restricting the analysis to people aged 18 years or older. Case definitions were therefore on the basis of a positive response to each of the self-reported questions about pain in the back, head, neck,

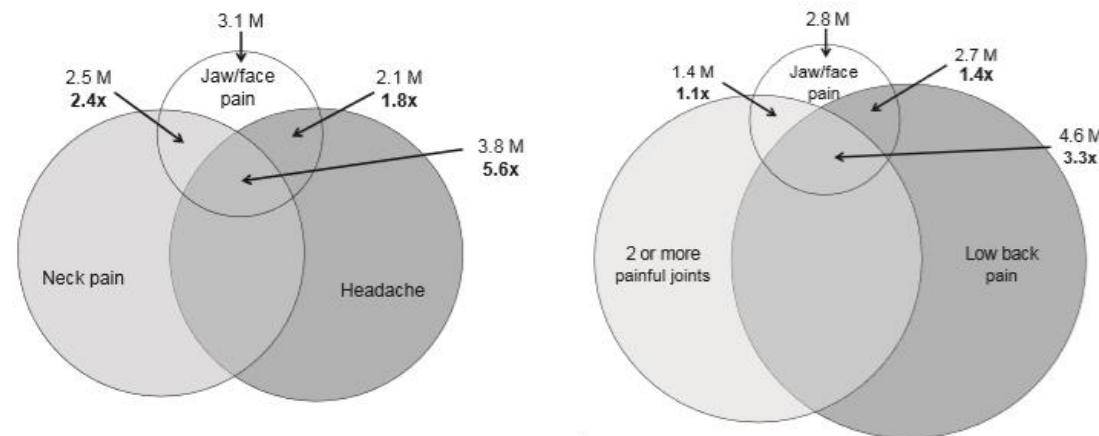


Figure 2. Venn diagram depicting overlap of jaw/face pain and other painful conditions, US adults, 2009. Source: the authors' analysis of the 2009 National Health Interview Survey.

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Available online at www.jpain.org and www.sciencedirect.com

Overlapping Chronic Pain Conditions: Implications for Diagnosis and Classification



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Abstract: There is increasing recognition that many if not most common chronic pain conditions are heterogeneous with a high degree of overlap or coprevalence of other common pain conditions along with influences from biopsychosocial factors. At present, very little attention is given to the high degree of overlap of many common pain conditions when recruiting for clinical trials. As such, many if not most patients enrolled into clinical studies are not representative of most chronic pain patients. The failure to account for the heterogeneous and overlapping nature of most common pain conditions may result in treatment responses of small effect size when these treatments are administered to patients with chronic overlapping pain conditions (COPCs) represented in the general population. In this brief review we describe the concept of COPCs and the putative mechanisms underlying COPCs. Finally, we present a series of recommendations that will advance our understanding of COPCs.

Perspective: This brief review describes the concept of COPCs. A mechanism-based heuristic model is presented and current knowledge and evidence for COPCs are presented. Finally, a set of recommendations is provided to advance our understanding of COPCs.

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TMD mimicking dental pain

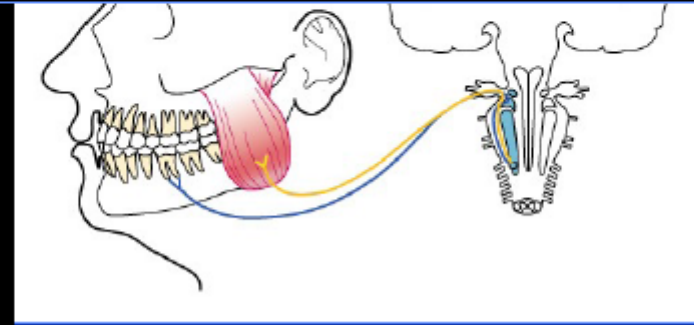
- Referral of pain from masseter to maxillary and mandibular molar teeth

TMDs
Dysfunctional
Arthritides
Myofacial
Arthromyalgia

Convergence & Referred Pain

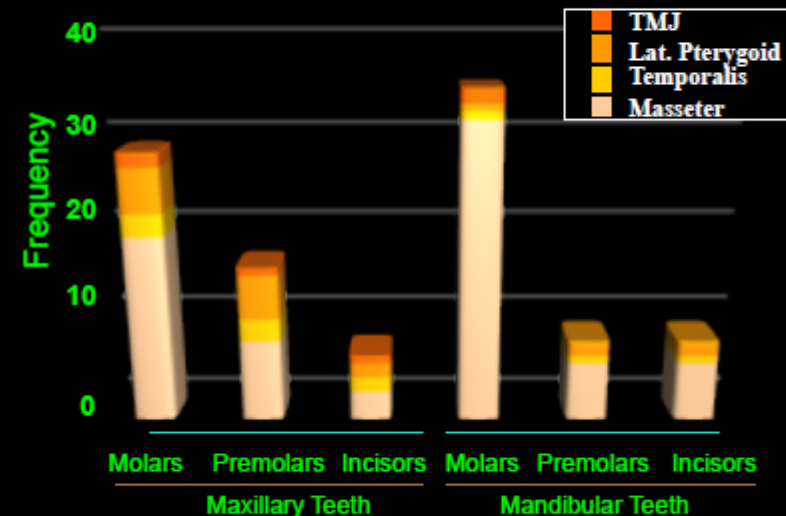
The "Site" of pain perception is Different from the "Origin" of nociceptor activation

Local Anesthetic Blocks and Local Stimulation (eg, palpation) can distinguish "site" from "origin"



Seltzer & Hargreaves, in: Seltzer & Bender's Dental Pulp, 2002

Frequency of Pain Referral to Teeth



Wright JADA 131:1307, 2000

N = 230

What are the management steps for a painful TMD?

Explanation, Reassurance, Motivation
& Behavioural Mx

Pain Reduction

Regain Function

Review & Future Prevention

Check out comorbid

1. headaches especially migraine
2. other pain conditions back or joint or neck pain
3. Exclude hypermobility
4. Habits caffeine and nicotine and sleeping on front

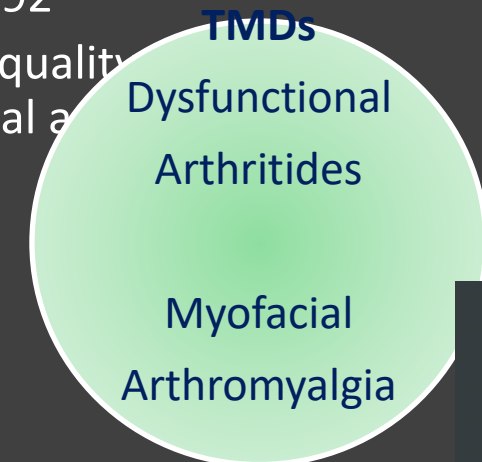
TMDs

Dysfunctional
Arthritides
Myofacial
Arthromyalgia

TMD Cochrane reviews

- **NO OCCLUSAL THERAPIES**
- **DENTAL INTERVENTION IS NOT INDICATED**
- Koh H, Robinson PG Occlusal adjustment for treating and preventing temporomandibular joint disorders. J Evid Based Dent Pract. 2006.
- Al-Ani MZ Stabilisation splint therapy for temporomandibular pain dysfunction syndrome. Evid Based Dent. 2004;5(3):65-6.
- Koh H, Robinson PG Occlusal adjustment for treating and preventing temporomandibular joint disorders. J Oral Rehabil. 2004 Apr;31(4):287-92
- Bessa-Nogueira RV, Vasconcelos BC, Niederman R The methodological quality of systematic reviews comparing temporomandibular joint disorder surgical and non-surgical treatment. BMC Oral Health. 2008 Sep 26;8:27

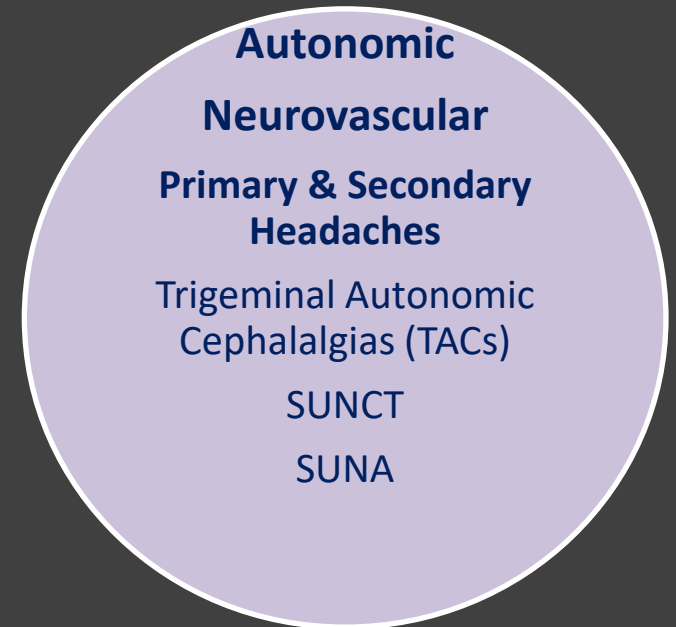
NO EVIDENCE !



Neurovascular



- Exclude sinister headaches 1%
 - » >50 yrs Tumour 1%
 - » Subarachnoid haemorrhage - recent trauma LoC
- Tensions type headaches
 - 30-78% population -Highest socioeconomic impact*
 - At least 10 episodes occurring <1 day a month on average
 - Infrequent episodes lasting from 30 minutes to 7 days
 - Typically bilateral
- Medication over use headaches **30-78%**
- Migraine 10-17%
 - Five or more lifetime headache attacks lasting 4-72 hours each and symptom-free between attacks
 - moderate to severe pain, unilateral +/- aura visual signs
- Trigeminal autonomic cephalalgias
 - Cluster headaches 5% - SUNCT, SUNA, PH, HC
 - Male:female ratio 4:1 to 20:1 / 30yrs +
 - Severe episodic pain lasting 15-180 minutes
 - Unilateral Orbital, supraorbital or temporal
 - 8x a day to every other day for a period of 2 -12 weeks



Migraine can mimic toothache

Migraine it's the same nerve!

What's in a name?

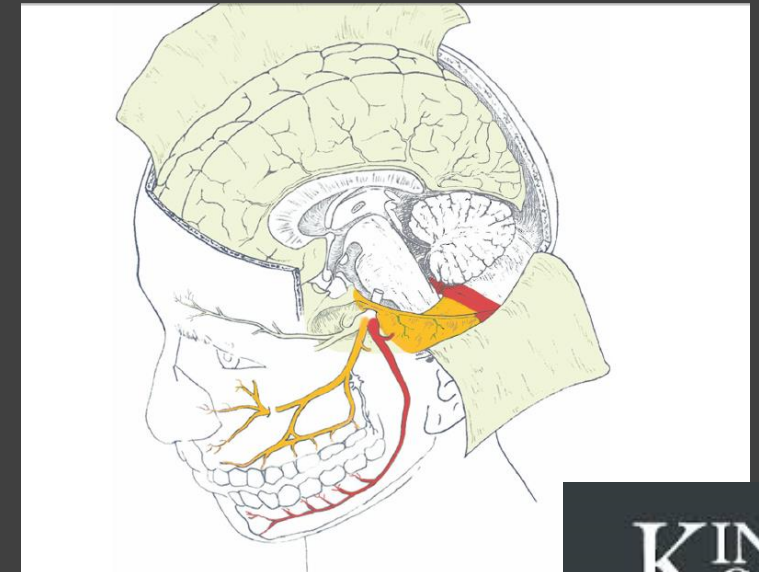
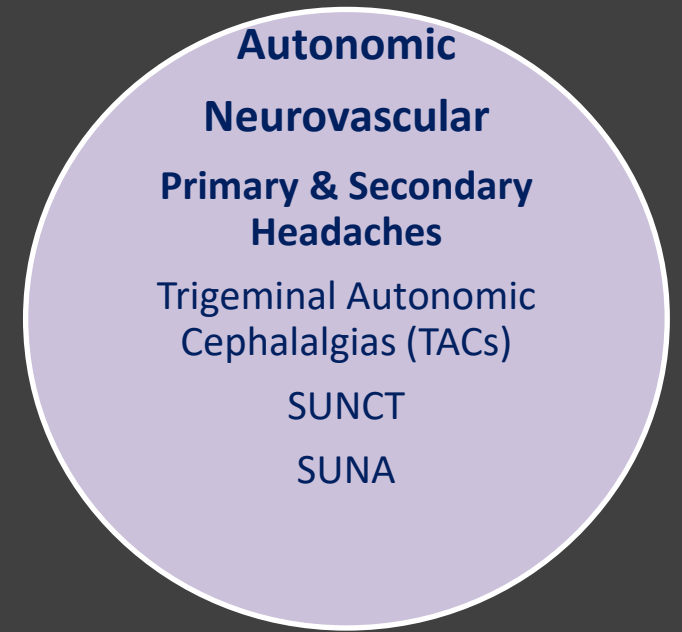
- Facial Migraine
- Below orbito-meatal migraine
- Neurovascular orofacial pain
- Headache attributed to facial pain (ICHD3)

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



Case Series of Four Different Headache Types Presenting as Tooth Pain
Aurelio A. Alonso, DDS and Donald R. Nixdorf, DDS, MS**

How has this approach changed our practice?

- Overall, 639 patients attended the service;
- 315 in 2013-2015 and 324 in 2016-2017.
- In 2013-2015, there were increased rates of diagnoses related to neurovascular (27.5% vs. 19.0%; $P=.012$) and musculoskeletal pain (36.9% vs. 26.0%; $P=.003$) in the 2016-2017 cohort and decreased rates of neuropathic (55.6% vs. 70.2%; $P<.001$) and atypical/idiopathic pain (1.3% vs. 5.4%; $P=.003$) diagnoses.
- There was a trend towards an increased rate of comorbid diagnoses (26.3% vs. 20.3%; $P=.077$), especially those relating to headache conditions.
- The findings suggest that introduction of a specialist headache neurologist into the OFP clinic widened its remit of assessment, increasing recognition of (co-morbid) neurovascular-related pain and decreasing atypical/idiopathic pain diagnoses in patients with complex OFP

Int J Oral Maxillofac Surg. 2019 Jul;48(7):924-929. doi: 10.1016/j.ijom.2018.11.002. Epub 2018 Dec 13.

Changing face of orofacial pain: The diagnostic impact of working with Neurology on an orofacial pain clinic.

Karamat A¹, Smith JG², Lambrou G³, Renton T⁴.

Author information

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Abstract

This study assessed the impact of collaborative working with a headache neurologist on diagnoses of patients attending orofacial pain (OFP) clinic. Patient diagnostic data was collected from adult patients attending an Orofacial Pain Service from January 2013 to January 2017. A liaison headache neurologist was appointed late 2015; OFP clinics were co-run with the neurologist specialist thereafter. Overall, 639 patients attended the service; 315 in 2013-2015 and 324 in 2016-2017. Compared to 2013-2015, there were increased rates of diagnoses related to neurovascular (27.5% vs. 19.0%; $P=.012$) and musculoskeletal pain (36.9% vs. 26.0%; $P=.003$) in the 2016-2017 cohort and decreased rates of neuropathic (55.6% vs. 70.2%; $P<.001$) and atypical/idiopathic pain (1.3% vs. 5.4%; $P=.003$) diagnoses. There was a trend towards an increased rate of comorbid diagnoses (26.3% vs. 20.3%; $P=.077$), especially those relating to headache conditions. The findings suggest that introduction of a specialist headache neurologist into the OFP clinic widened its remit of assessment, increasing recognition of (co-morbid) neurovascular-related pain and decreasing atypical/idiopathic pain diagnoses in patients with complex OFP. The increase rate of musculoskeletal pain diagnosis in the later cohort is likely attributable to service expansion and normalisation of diagnostics reportedly seen in other OFP services. Statement of clinical relevance: Orofacial pain is a complex diagnosis, it requires a multidisciplinary approach that includes neurological input.

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TAC or toothache?

Familiarise yourself with TAC conditions

Patient seen by our neurology team

The most common diagnosis made in the Clinic was TACs (42 %), followed by migraine (34 %) and post-traumatic trigeminal neuropathy (11%).

TACs are the most common diagnosis made in our Multidisciplinary Orofacial Pain clinic. The data stress the importance of a multidisciplinary team approach to seeing these complex patients.

V2 Migraine and TACs are probably most 'persistent idiopathic facial pains'



Trigeminal autonomic cephalalgias

- Cluster headache
- Sudden Onset unilateral conjunctival irritation (SUNCT)
- Hemicranial continua
- Paroxysmal Hemicrania

Autonomic

Neurovascular

Primary & Secondary Headaches

Trigeminal Autonomic Cephalalgias (TACs)

SUNCT

SUNA

How has this changed our practice?

- Clinic letters from the initial consultation and subsequent follow up reviews of the 142 patients, who were seen in the tertiary Multidisciplinary Orofacial Pain clinic between January 2015 until January 2018 were reviewed as a clinical audit
- The most common diagnoses were possible
 - trigeminal autonomic cephalalgia (n = 62, 44%),
 - migraine (n = 38, 27%)
 - painful post-traumatic trigeminal neuropathy (n = 17, 12%).
- The most common trigeminal autonomic cephalalgia diagnosis was hemicrania continua (n = 13, 9%), which is higher than the reported prevalence in neurology and headache clinics.
- This study demonstrates the importance of a multidisciplinary approach to diagnosing complex orofacial pain patients and the importance of awareness of primary headache disorders, in particular trigeminal autonomic cephalalgias, thereby reducing unnecessary diagnostic delays or procedures.

Wei et al. *The Journal of Headache and Pain*
<https://doi.org/10.1186/s10194-019-1019-7>

(2019) 20:69

The Journal of Headache
and Pain

RESEARCH ARTICLE

Open Access

Trigeminal autonomic cephalalgias presenting in a multidisciplinary tertiary orofacial pain clinic



D. Y. Wei¹ , D. Moreno-Ajona¹ , T. Renton² and P. J. Goadsby^{1,3*}

Abstract: Orofacial pain may have a variety of causes and offers a significant clinical challenge for its diagnosis and management.

Objective: To assess the headache disorders presenting in a tertiary multidisciplinary orofacial pain clinic, after dental causes have been excluded.

Methods: Clinic letters from the initial consultation and subsequent follow up reviews of the 142 patients, who were seen in the tertiary Multidisciplinary Orofacial Pain clinic between January 2015 until January 2018 were reviewed as a clinical audit.

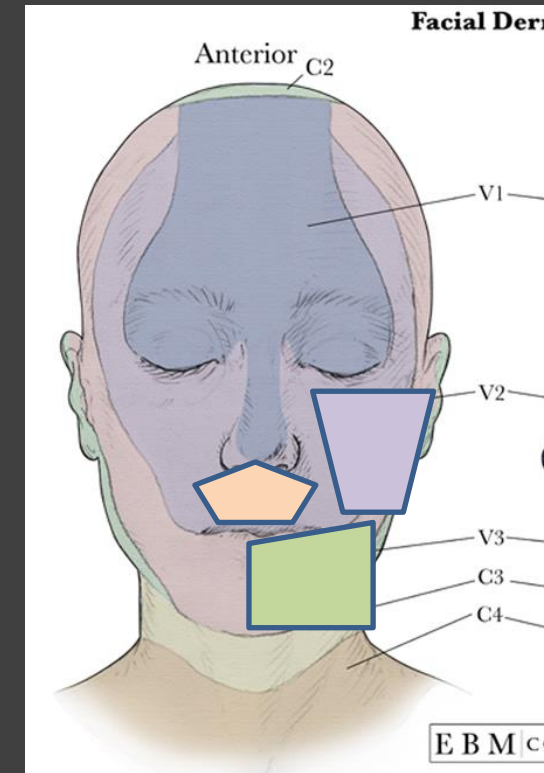
Results: The most common diagnoses were possible trigeminal autonomic cephalalgia (n = 62, 44%), migraine (n = 38, 27%) and painful post-traumatic trigeminal neuropathy (n = 17, 12%). The most common trigeminal autonomic cephalalgia diagnosis was hemicrania continua (n = 13, 9%), which is higher than the reported prevalence in neurology and headache clinics.

Conclusion: This study demonstrates the importance of a multidisciplinary approach to diagnosing complex orofacial pain patients and the importance of awareness of primary headache disorders, in particular trigeminal autonomic cephalalgias, thereby reducing unnecessary diagnostic delays or procedures.

Keywords: Orofacial pain, Trigeminal autonomic cephalalgias, Hemicrania continua

TAC OR toothache?

- Patients with TACs consult;
 - 34-45% dentists
 - 27-33% ENT
 - > 15% of PH patients have pain similar to dental pain
- Average 4.3 physicians consulted
- 4% have sinus surgery
- Most common misdiagnosis
 - Migraine 45%
 - TTH 16%
 - Sinusitis 23%
 - Dental 23%
 - TN 16%
 - Klapper et al 2000; van Viet et al 2003; Bahca and Goadsby 2004; Larner al 2009
 - 2008; vanAlboom et al 2009
- Regions of orofacial region most affected by Neurovascular pain
Premaxilla 30%, V2 17%, V3 31%
- Age of onset 21 years and 51 years
- Duration 9-16 hours
 - Benoliel R et al Cephalalgia 2008



Autonomic

Neurovascular

Primary & Secondary
Headaches

**Trigeminal Autonomic
Cephalalgias (TACs)**

SUNCT

SUNA

Toothache or secondary neuropathic pain?

Peripheral

- Post traumatic neuropathy (Same as PDAP II , PPTTN, Chronic post surgical pain)
 - Mechanical Trauma, surgery
 - Chemo therapy
 - Radiation
 - Thermal
- Non traumatic lesioned
 - **Burning mouth DISORDER**

Central

- V ,IX, VII classic neuralgias
- For example-secondary Trigeminal neuralgia
 - MS, vascular compromise
 - Space occupying lesions
 - Stroke
 - Intracranial bleed

Identified cause Neuropathic

Central or peripheral

Post traumatic or lesioned

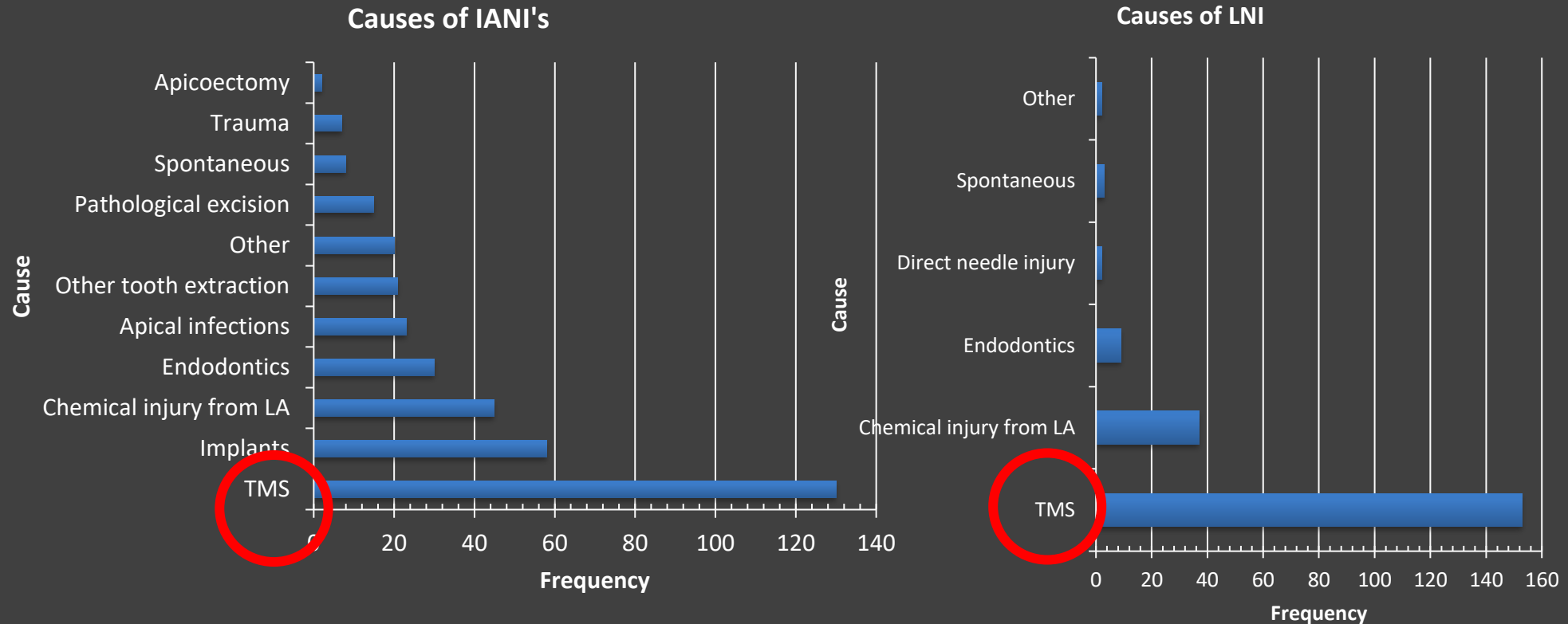
CV (TN),IX, VII classic neuralgias-
TN classical

PDAP II

Ne pain/PTN (CPSP) metabolic, infection,
MS, neoplasia, vascular autoimmune)

Post traumatic neuropathy (n=1331 patients)

- 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])



Assessment of neuropathic area

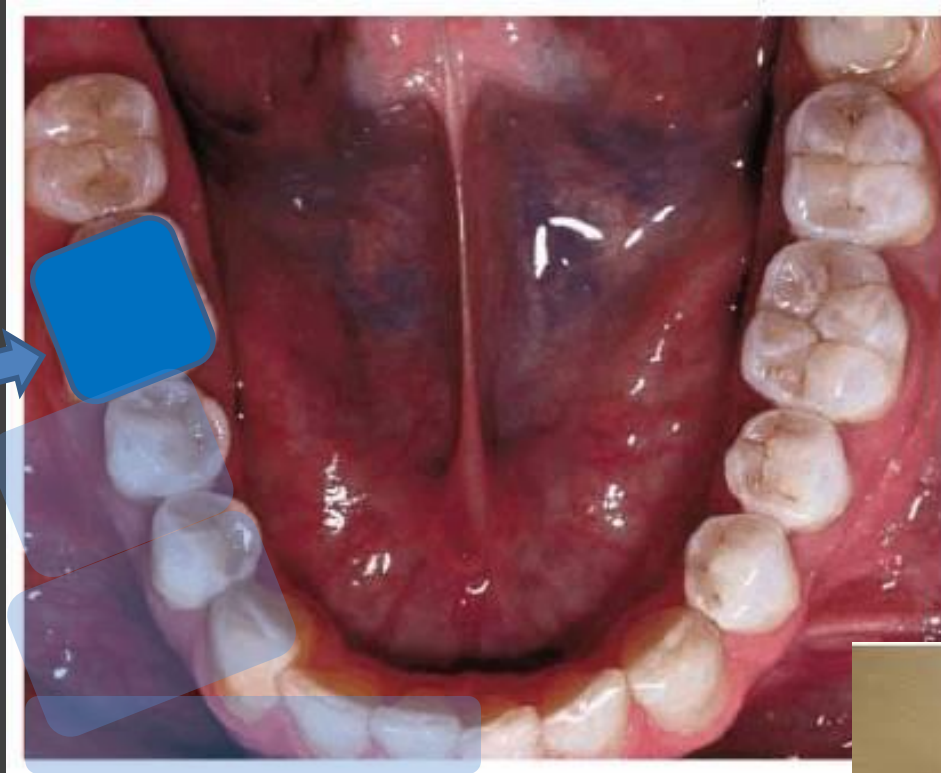
Know your anatomy!

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



Stratification of orofacial pain patients?

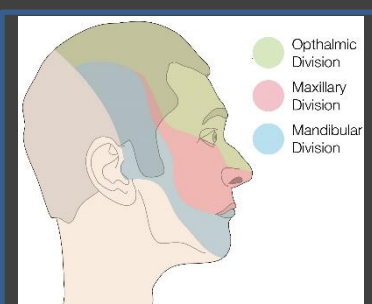
Outcomes: More accurate diagnosis, prognosis and treatment choice



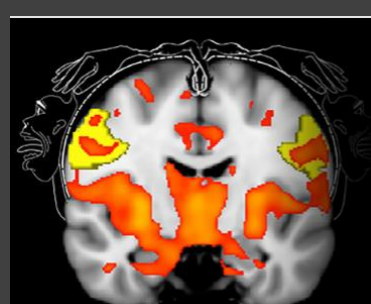
Clinical
disease or lesion,
neurological deficits,
family history



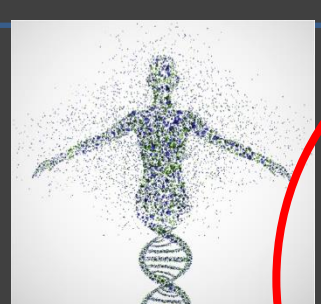
**Psychological
medical /
Co-morbidities**



Sensory Profile
Pain quality, Qual and
Quant sensory testing



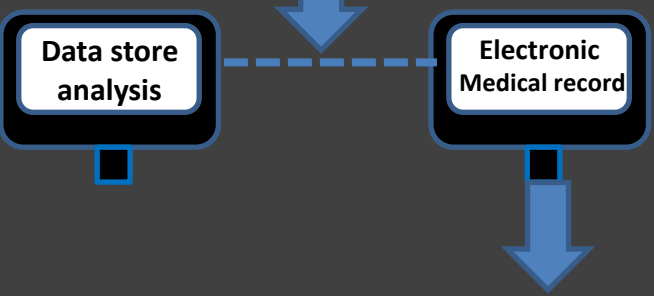
Physiological
Electrophysiology
Functional imaging



Molecular Profile
OMICs
Genome, proteome,
metabolome



Big Data
Machine learning and Ai
to improve diagnosis and
clustering for treatment



678 patients to date



Prof David Bennett


Machine learning on large patient datasets

- 1331/1500 trigeminal nerve injury patients
 - Collaboration with University of Leuven
 - Frederic Van der Cruyssen
 - Constantis Politis
 - Reinhilde Jacobs
- 600/1500 orofacial pain patients
 - Aalia Karamat MPhil student
 - Jared Smith Health psychologist

Got a big data headache?

Enterprise-grade Hadoop can ease the pain

Data scientists translate business problems into data analysis. In today's world of high-volume, fast-moving data and complex integration and architecture challenges, that's not easy. Here's how IBM® BigInsights™ for Apache Hadoop helps put data scientists' minds at ease with analytics and performance designed for enterprise-scale workloads.



The infographic shows a silhouette of a human head in profile, facing left. Inside the head, there are several colored circles and icons representing different data science concepts: a red circle with a question mark and a person icon labeled 'Analytics'; a blue circle with a person icon labeled 'Business insight'; a yellow circle with a bar chart icon labeled 'Data accuracy'; and a green circle with a speedometer icon labeled 'Speed & scale'. Lines connect these circles, suggesting a flow or relationship between the concepts.

Analytics

The IBM BigInsights Data Scientist module accelerates data science with advanced analytics to extract valuable insights from Hadoop. Big R statistical analysis and distributed frames allow data scientists to use the entire Hadoop cluster. Stable machine learning algorithms are optimized for Hadoop. Text analytics extract insight from unstructured data with existing tooling so analytic applications don't have to be developed from scratch.

Business insight

The BigInsights Analyst module lets data scientists use their existing skills to find data across the organization and visualize it without extra coding. IBM BigSheets is a spreadsheet-style data manipulation and visualization tool that gives business users direct access to data through a recognizable interface. IBM-designed Big SQL offers HDFS caching and high availability benefits as well as query optimization—without forcing data scientists to learn a new skillset.

Spark

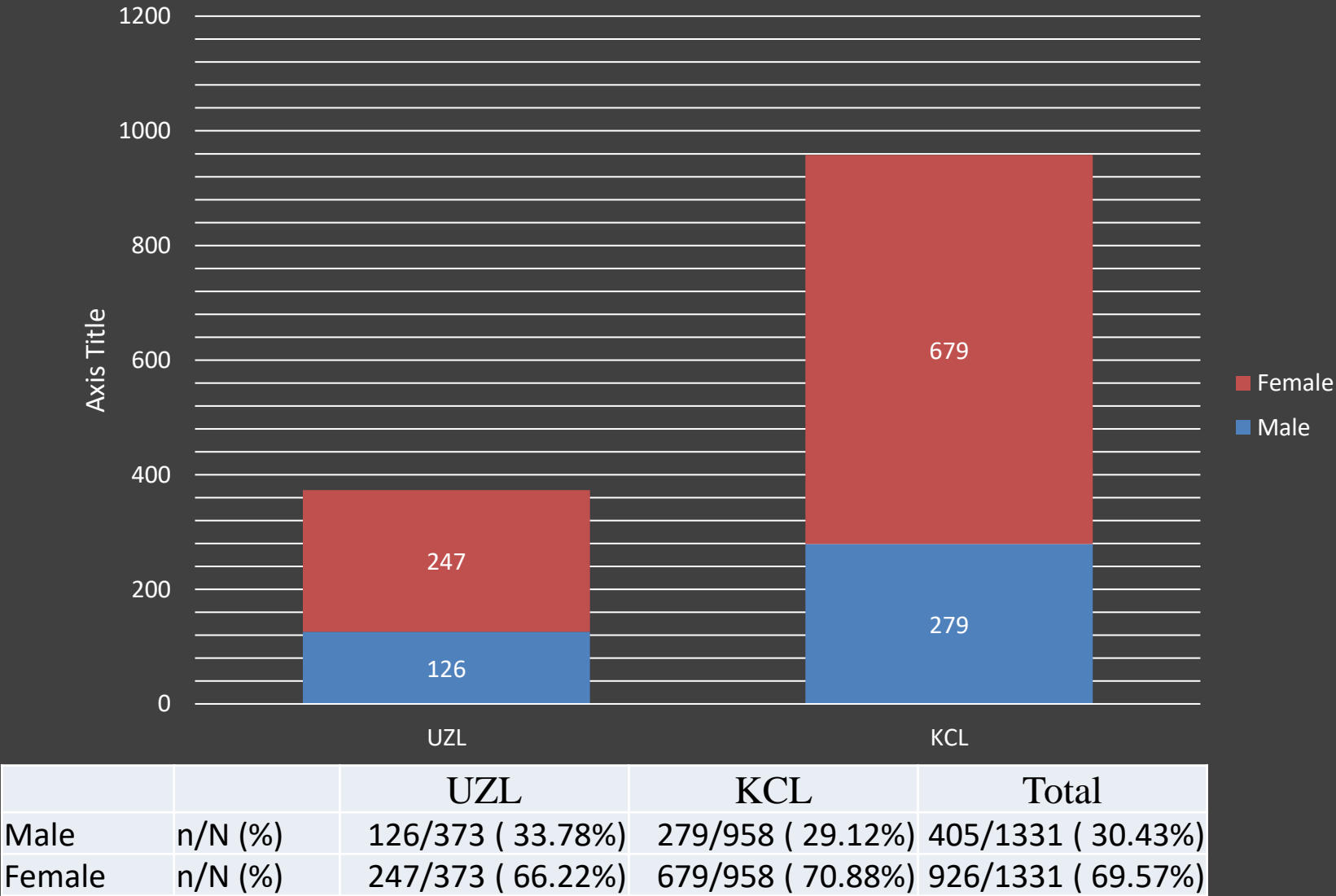
BigInsights 4.0 includes Apache Spark 1.2.1, which is a key capability for advanced Hadoop and Data Scientist users. Spark helps data scientists to do in-memory distributed computation, driving dramatic performance increases. BigInsights 4.0 with Spark accelerates emerging capabilities for streaming, SQL, machine learning & graph processing. It simplifies developer experience, leveraging Java, Python & Scala languages.

Data accuracy Speed & scale

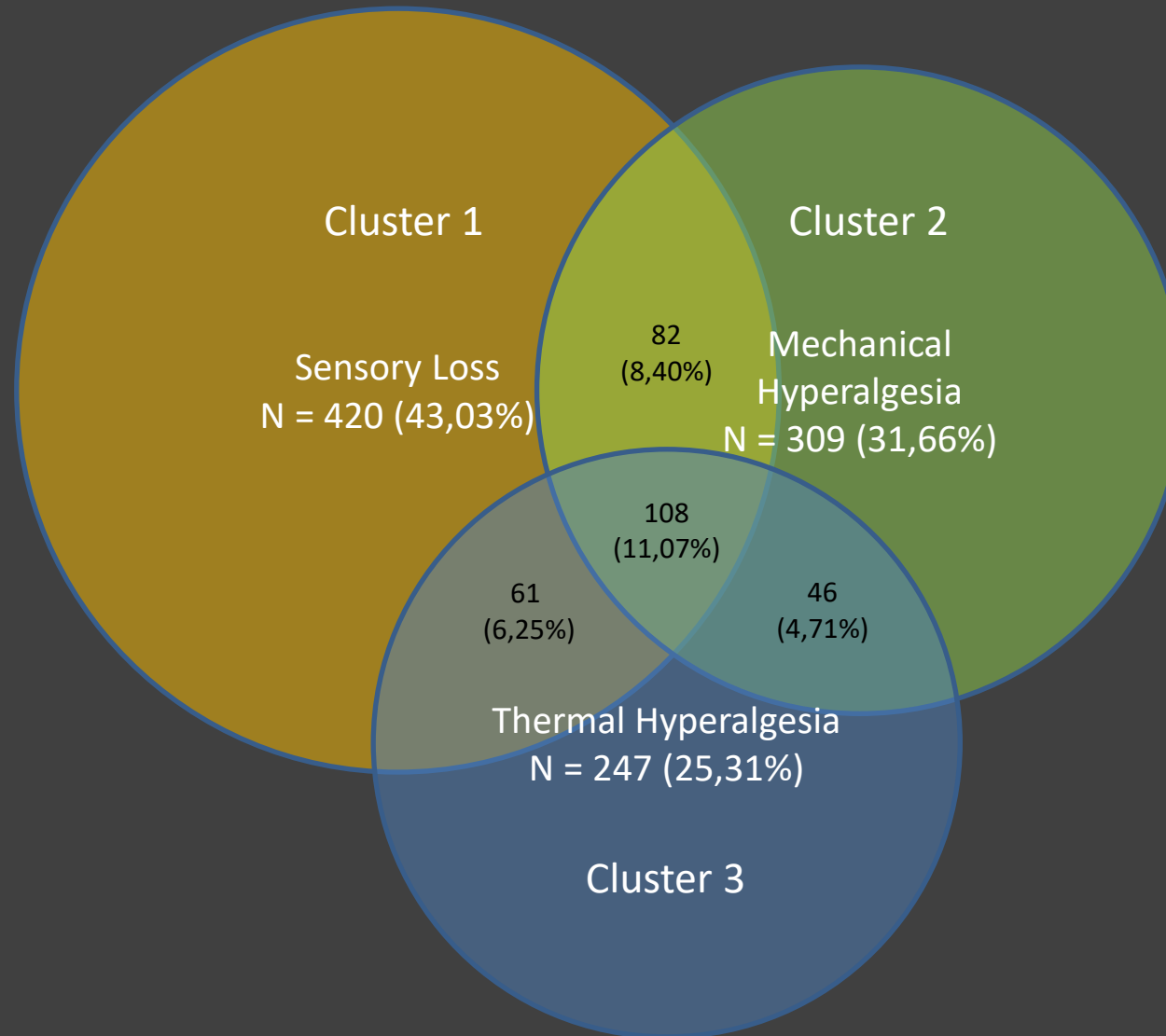
The IBM BigInsights Enterprise Management module helps ensure the scalability, performance and security of Hadoop clusters. For example, multi-tenant scheduling and multi-instance support enhance scalability and performance by allowing multiple installs of BigInsights on the same cluster with data isolation and resource sharing.

1331 Trigeminal nerve injury patients

Sample size, Male/female ratio



Clustering of Sensory Profiles (N = 976)



Spearman Correlation Matrix Sensory Profile & Treatments

P	SL-P	SL+P	MH	TH	MH+SL+P	TH+SL+P	MH+TH	MH+TH+SL+P	
		Cluster 1	Cluster 2	Cluster 3	Cluster 1+2	Cluster 1+3	Cluster 2+3	Cluster 1+2+3	
,084	-,129	-,062	,146	,079	,096	,041	,034	-,017	NSAID
,023	-,118	-,057	,227	,089	,098	,036	,043	-,040	Paracetamol
-,012	-,013	,051	,062	-,022	,054	-,031	-,027	-,022	Corticosteroids
-,076	,000	,205	,008	-,007	,086	-,016	-,029	-,080	VitaminB
,146	-,197	-,056	,201	,100	,069	,027	,069	-,052	TCA
,068	-,095	-,063	,119	,105	,077	,003	,056	-,039	Opioids
,039	-,069	-,027	,123	,004	,035	,008	,045	-,015	SSRI
,233	-,193	-,079	,152	,061	,029	-,005	,080	-,043	Anti-epileptics
,110	-,125	-,077	,277	,009	,027	-,034	,032	-,030	Benzodiazepines
,051	-,064	-,008	,042	,004	,087	,040	,008	-,024	Antibiotics
,083	-,062	-,034	,061	-,018	,027	,007	,015	-,009	Capsaicin
,025	-,037	-,031	,033	,063	,076	-,015	-,013	-,020	LidocainPatch
-,018	,002	,010	-,010	-,003	,002	,133	-,036	,003	CBT

Box/number in bold: $P < 0.05$

A negative value means negative correlated

A positive value means positive correlated

A value of zero means no correlation

0,00-0,19: very weak correlation

0,20-0,39: weak

0,40-0,59: moderate

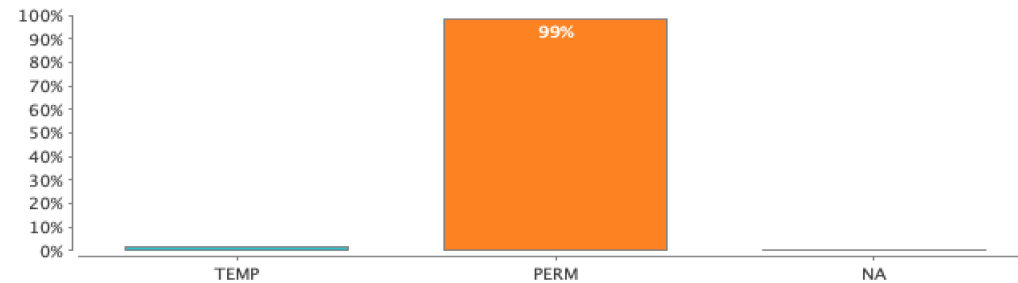
0,60-0,79: strong

0,80-1,00: very strong

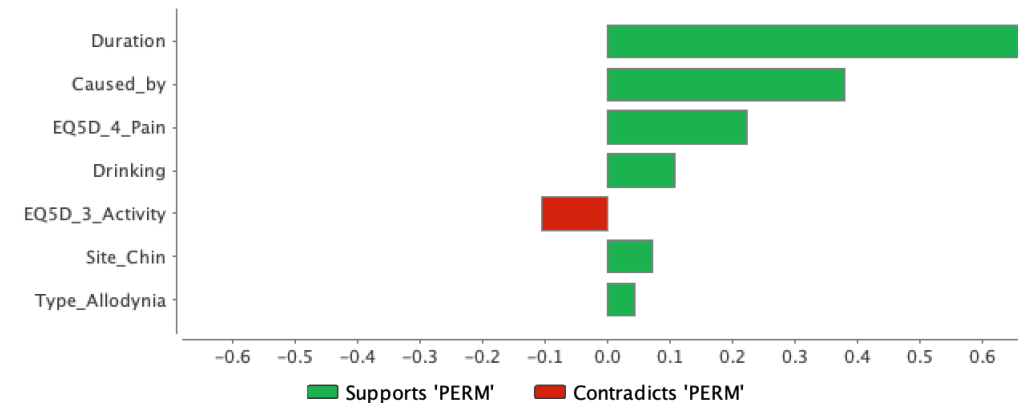
P: pain, SL: sensory loss, MH: mechanical hyperalgesia, TH: thermal hyperalgesia

Prediction Model RapidMiner (generalized linear model)

Most Likely: **PERM**



Important Factors for **PERM**



Agreed national core data for OFP history

Axis 1 and Axis 2

- Prof Justin Durham
- Prof Joanna Zakzrewska

SmartSurvey

Dashboard My Surveys Libraries Support Account Upgrade

CURRENT SURVEY:
• Copy of Consent and Self report for Pain presentat...

Design Collect Results

Survey Design Design Theme Settings Organise Options

Title: Copy of Consent and Self report for Pain presentation

+ Insert Page Here

1. Add Question Here

We are looking forward to meeting you

You have been referred to the orofacial pain service and we would like to ask you some questions

We understand that you are likely to be suffering from oral and/or facial pain and you have an appointment with specialist orofacial pain clinics at King's College Hospital Dental Institute.

Survey: Copy of Consent and Self report for Pain presentat...

Navigate: -- Select Page -- Top Preview Survey

Q19

Please select diagram that most accurately represent where your pain is

☐ Dental region in the lower jaw ☐ Temple ☐ Top of head

☐ Dental region in upper jaw side ☐ Forehead ☐ Back of head

ID: 7837893

Edit Question
Copy Question
Move Question
Skip Logic
Delete Question

Axis 2 Assessment of preceding and injury related psychological problems

- All patients:
 - EQ-5D
 - GAD7 generalised anxiety disorder
 - PHQ9 Patient Health Questionnaire
 - PHQ 15 MULTIDIMENSIONAL SCALE OF PERCEIVED SOCIAL SUPPORT
 - GCPS
 - SF-MPQ-2 Short-form McGill Pain Questionnaire-2
 - PAIN DETECT PAIN QUESTIONNAIRE No pain
 - BPI Facial pain
 - CPSI (sleep)
 - ES-R (abuse)
- Dash board with red flags suicidal thoughts/ depression, anxiety and somatic disorders



Severe Anxiety
Probable Major depression
Somatic disorder
PTSD
Likely NP

Integrating Mental & Physical healthcare:
Research, Training & Services

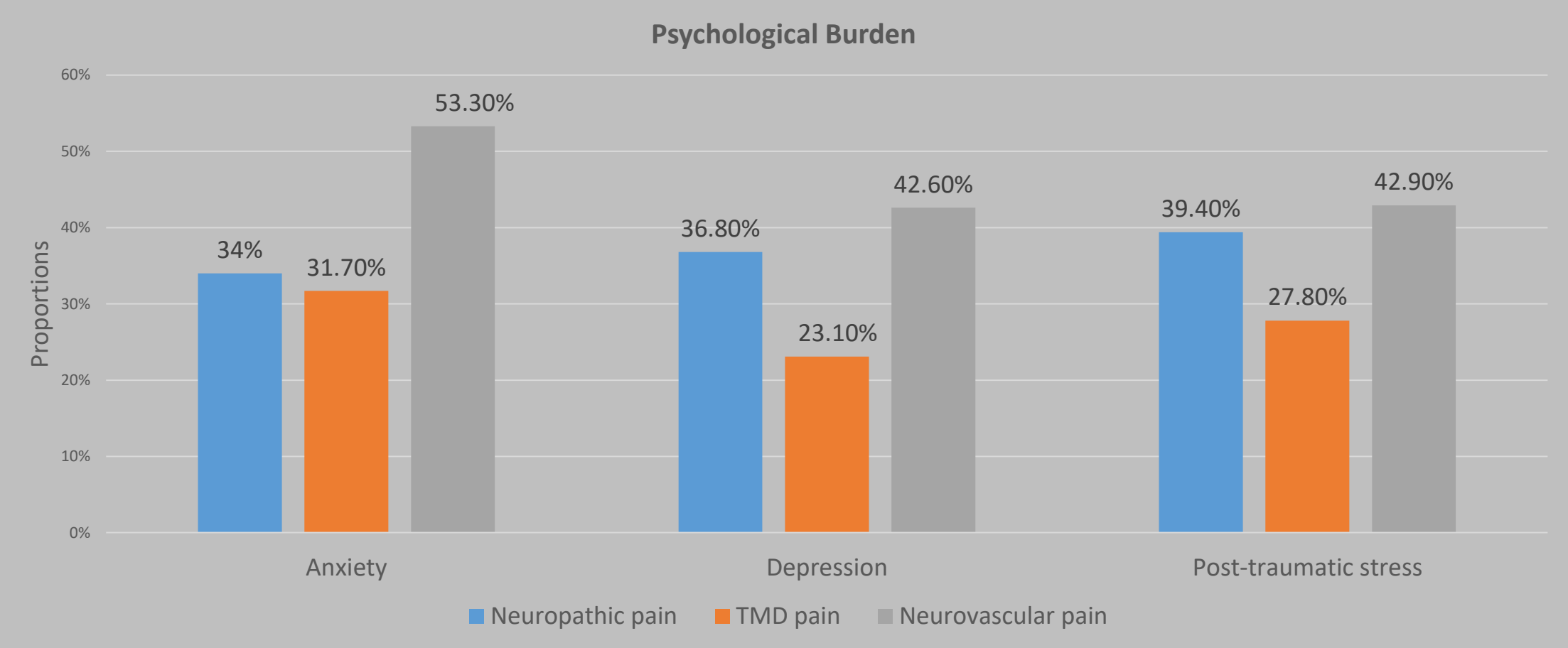


Integrating Mental & Physical healthcare: Research, Training & Services (IMPARTS) is an initiative funded by King's Health Partners to integrate mental and physical healthcare in research, training and clinical services at Guy's, St Thomas's and King's College Hospitals, as well as South London and Maudsley NHS Foundation Trust.

Find out more in our IMPARTS video below:

Psychological burden of orofacial pain (n=600)

Dr Aalia Karamat PhD unpublished





The psychosocial impact of orofacial pain in trigeminal neuralgia patients: a systematic review

L.N. Melek¹, M. Devine², T. Renton²



Psychological impact of orofacial neuropathic and non-neuropathic pain: a systematic review

Karamat A, Smith JG, Melek L, Renton T. J Orofac Pain 2019 In Press

Abstract

Aims: This systematic review aims to explore the psychological function in patients with neuropathic and non-neuropathic orofacial pain conditions. **Methods:** A systematic online search of Medline (PubMed) and Ovid databases was performed from 2006-2016. Observational studies, including cross-sectional, case-control and case-series and longitudinal prospective studies were included. Search strategy was restricted to studies in English with patients aged 18 years and older. Seventy-five articles were selected. The standardised PRISMA checklist was used to report studies for this review. Due to heterogeneity across studies, it was not possible to perform meta-analyses. **Results** showed that moderate to severe depression (25.7%~46.7%) and anxiety (51.2%~54.3%) were commonly observed in patients with chronic orofacial pain (COFP) and closely linked to pain severity. Comorbid conditions, such as chronic degenerative disorders, migraines or adverse life events increased the likelihood of psychological dysfunction in individuals. Females were more likely affected than males. **Conclusion:** Assessment of (Axis II) psychological impact of orofacial pain predominantly focused on TMDs and rarely on other conditions including neuropathic or neurovascular pain conditions. More research is needed to evaluate the psychological impact of multiple orofacial pain conditions in an individual, pre-condition psychological morbidity, the influence of social factors and delay in identifying psychological dysfunction.

Key words: Orofacial pain, Neuropathic/Non-neuropathic pain, TMD, Anxiety, Depression

J Orofac Pain. 2013 Fall;27(4):293-303. doi: 10.11607/jop.1056.

The psychosocial and affective burden of posttraumatic neuropathy following injuries to the trigeminal nerve.

Smith JG, Elias LA, Yilmaz Z, Barker S, Shah K, Shah S, Renton T.

Abstract

AIMS: To explore the impact of trigeminal nerve injuries on quality of life, including the effect of pain on psychological and affective function.

METHODS: An observational, cross-sectional survey design was employed. Fifty-six patients with inferior alveolar nerve injury (IANI) and 33 patients with lingual nerve injury (LNI) completed standardized self-report measures of pain intensity, pain catastrophizing, self-efficacy to cope with pain, and mood, in addition to generic and oral health-related quality of life (HRQoL) indicators. The impact of pain severity on these aspects of psychosocial function was examined. Summary statistics were calculated for all measures and compared with norms or values of other relevant studies, when available, using t tests. The impact of pain severity on these aspects of psychosocial function was examined using analysis of variance and hierarchical multivariate regression models.

RESULTS: The majority of patients reported pain associated with their nerve injury (86%). Nerve injury had a significant impact on all investigated domains, and this was closely linked with reported pain levels. Patients with severe pain showed particularly elevated levels of depression and pain catastrophizing, as well as substantially reduced HRQoL and coping efficacy levels. Pain intensity level was a significant predictor in all models except anxiety, uniquely contributing between 17% and 26% of variance to the prediction of pain catastrophizing, depression, coping efficacy, and generic and oral HRQoL.

CONCLUSION: Traumatic injury to the trigeminal nerve is associated with a substantial patient burden, particularly in patients who experience severe neuropathic pain as part of their condition. These findings highlight the need to identify, develop, and evaluate more effective treatments for neuropathic pain in trigeminal nerve injury that will not only provide clinically meaningful reductions in pain but also improve patients' quality of life.

2.2. Psychological impact of patients with neuropathic, musculoskeletal and neurovascular orofacial pain

Smith JG, Karamat A, Renton T

Invited paper Journal of Oral Pathology & Medicine Sept 2019

2.2.1. Abstract

Introduction: Orofacial pain (OFP) is an unpleasant sensation in the area of the face. It is commonly prevalent and produces significant level of disability and distress. Management of

orofacial pain is complex and requires a multidisciplinary approach

Aims: This study aims to evaluate the psychological impact of chronic orofacial pain (COFP)

through existing standardised questionnaires and to assess the contribution of psychological

function of neuropathic, musculoskeletal (TMD), neurovascular orofacial pain using

standardised questionnaires incorporated in (IMPARTS) Integrating Mental and Physical

healthcare: Research, Training and Services. **Methodology:** Patients between the ages of 18-

80 years were recruited from the OFP clinic at Kings College Hospital London. Their

demographic details were noted and psychological questionnaires were administered.

According to their responses, psychological impact of OFP was assessed. **Results:** A total of

319 patients were recruited. Two hundred and thirty five (73.6%) patients were females and

84(26.3%) were males. Mean age was 48.98 years (age range from 20-80 years). Psychological

questionnaires were filled by 189 (59.2%) patients. Almost 40% of individuals did not

complete the questionnaires for reasons such as; questionnaires lost in the post, few individuals

refuse to complete and others reported that questionnaire set was lengthy and tedious.

Neuropathic pain; (Post traumatic neuropathic pain was identified in 149 (46.7%) cases,

trigeminal neuralgia in 20 (6.2%), burning mouth syndrome in 6 (1.8%) cases).

Temporomandibular disorders pain (TMD); were reported by 112 (35.1%) cases.

Neurovascular pain; (migraine was identified in 44 (13.7%) cases, headache in 34 (10.6%)

cases, trigeminal autonomic cephalalgia in 9 (2.80%) cases). Dysfunctional pain; (Persistent

Toothache or Non traumatic

Secondary neuropathic pain mimicking toothache

Nutritional deficiencies

Fe, Ferritin, Zinc, Magnesium,
Vit B complex, D, E

Malignancy

Compression by a space occupying lesion
centrally or peripherally NEOPLASIA

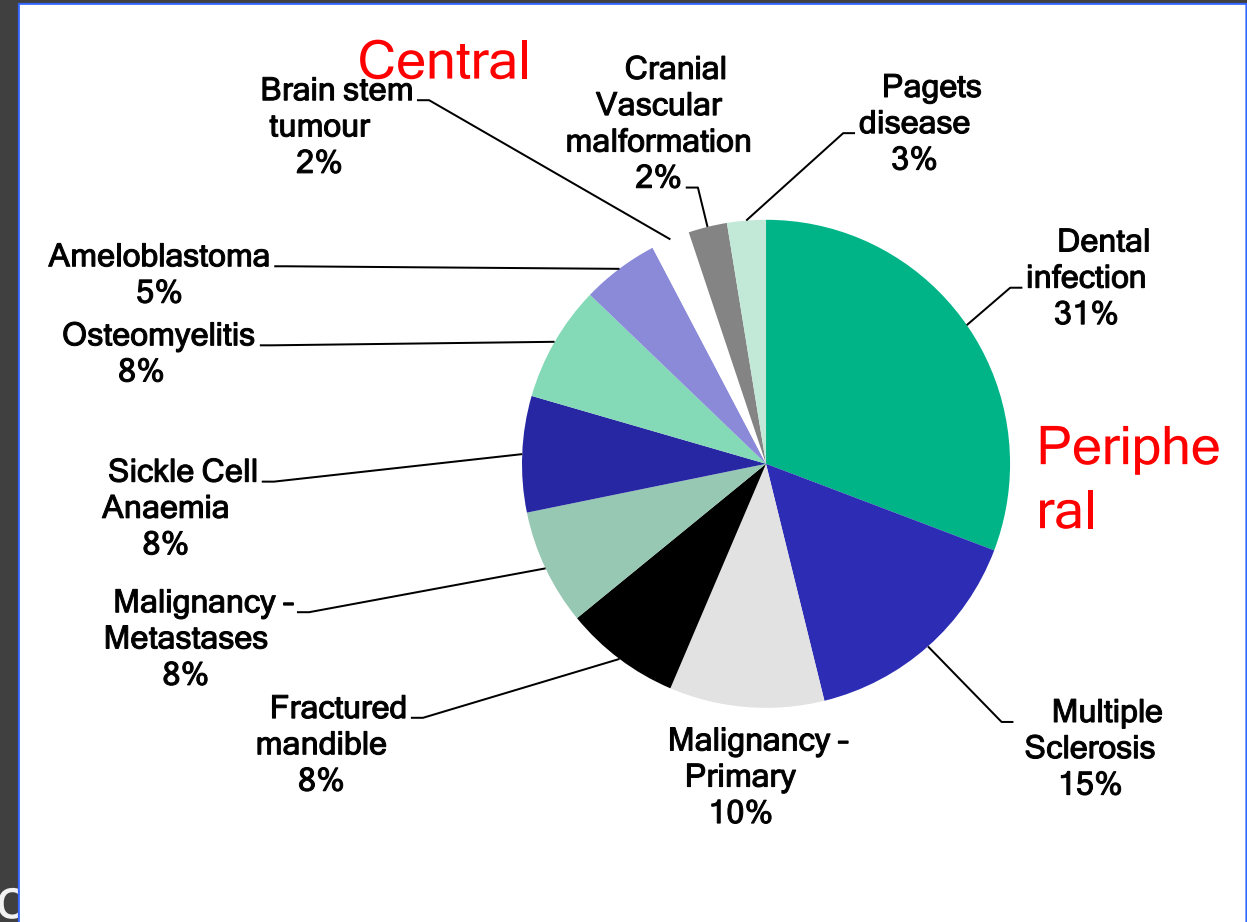
Metabolic Acromegaly, Hormonal neuropathy
(Hypothyroidism, Diabetes),
Infarction (sickle cell hypoxic neural damage,
giant cell arteritis)

Demyelination (Multiple sclerosis)

Infection Post viral neuropathy, Bacterial, Leprosy

Toxic Heavy metal poisoning (lead, mercury)
radiation, thermal, chemotherapy, drugs

Auto immune problems: Lupus, Rheumatoid



Trigeminal Neuralgia

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”.

13. Painful lesions of the cranial nerves and other facial pain

13.1 Pain attributed to a lesion or disease of the trigeminal nerve

13.1.1 Trigeminal neuralgia

13.1.1.1 Classical trigeminal neuralgia

13.1.1.1.1 Classical trigeminal neuralgia, purely paroxysmal

13.1.1.1.2 Classical trigeminal neuralgia with concomitant continuous pain

13.1.1.2 Secondary trigeminal neuralgia

13.1.1.2.1 Trigeminal neuralgia attributed to multiple sclerosis

13.1.1.2.2 Trigeminal neuralgia attributed to space-occupying lesion

13.1.1.2.3 Trigeminal neuralgia attributed to other cause

13.1.1.3 Idiopathic trigeminal neuralgia

13.1.1.3.1 Idiopathic trigeminal neuralgia, purely paroxysmal

13.1.1.3.2 Idiopathic trigeminal neuralgia with concomitant continuous pain

13.1.2 Painful trigeminal neuropathy

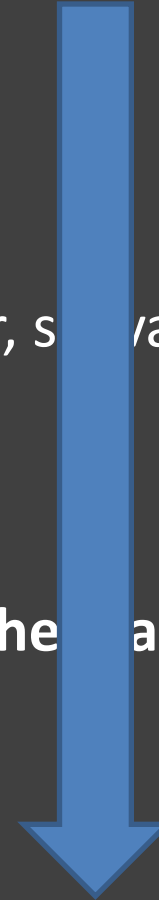
Causes of 'neuralgia' in the trigeminal system

Most common

- Toothache
- TMD
- Post traumatic neuropathy
- Non dental pathology-cysts, SOLs, sinus, ear, salivary

○ Least common

- Secondary peripheral painful neuropathies
 - PHN getting rarer
- **Trigeminal autonomic cephalalgia (Cluster headache)**
 - **SUNCT, SUNA, HC ,PH**
- Trigeminal neuralgia
- IX neuralgia
- Nervous intermedius neuralgia



Central causes Ne Pain

Classical TN + vasc comp

- vascular compression

Multiple sclerosis

- MRI plaques

Stroke

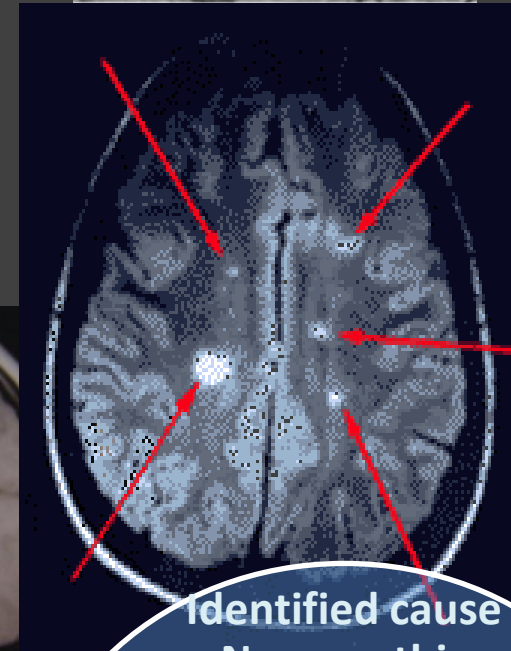
Vasculitis

Central viral infection

Tumours

- Cervical pathology

**RED
FLAGS?**

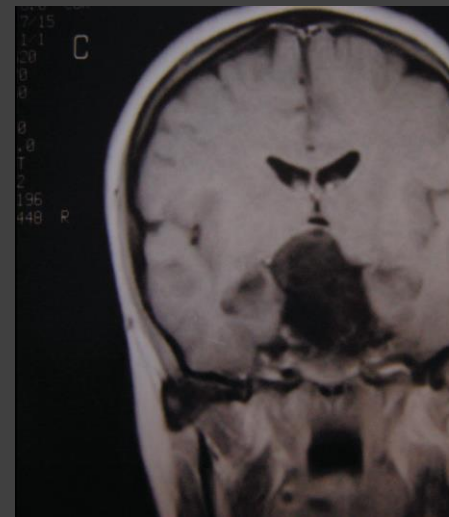


**Identified cause
Neuropathic**

Central or peripheral
Post traumatic or lesioned

CV (TN), IX, VII classic
neuralgias-TN classical

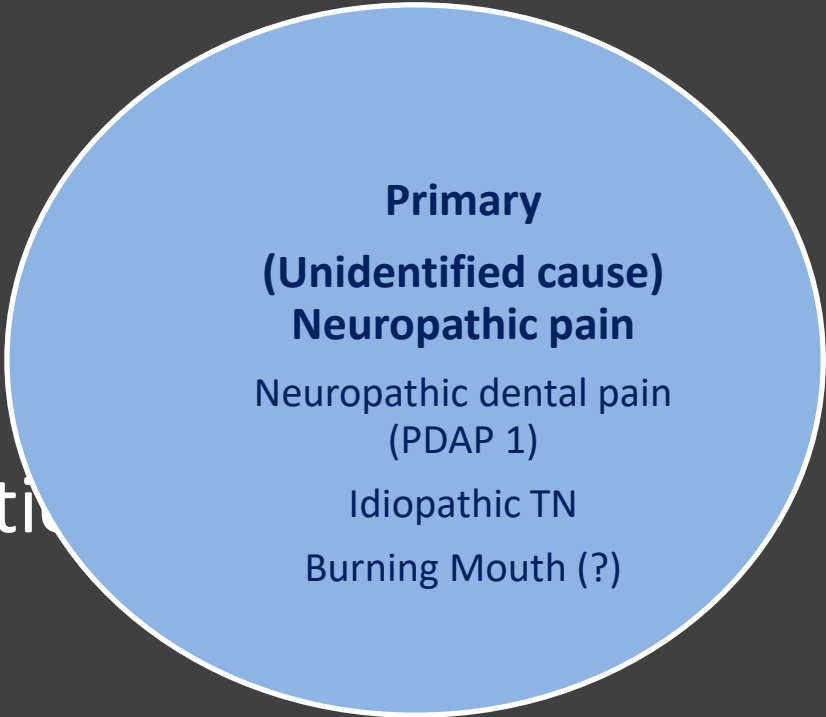
PDAP II



Neuropathic pain or toothache?
Centralised pain /
Idiopathic neuropathic pain

Congenital neuropathic pain conditions

- ~~Burning Mouth Syndrome~~
- Idiopathic Trigeminal neuralgia
- Primary neuropathic pain in intraoral region
 - Pre TN
 - Pre Tic
 - Persistent dentoalveolar pain
 - PDAP 1
 - OLD TERMS -Phantom tooth pain, Atypical odontalgia



Primary
(Unidentified cause)
Neuropathic pain
Neuropathic dental pain
(PDAP 1)
Idiopathic TN
Burning Mouth (?)

Centralised pain states Nociceptive pain CWP, FM?

Persistent idiopathic facial pain (extra or intra oral) ~~atypical facial pain~~

- Most common and costly illness in humans
- Used to be termed idiopathic or somatisation
- Characterised by;
 - Chronic overlapping conditions-multisystem illness typically begins in childhood or young adult hood
 - Chronic pain or discomfort in several body regions
 - TMD, IBS, Migraine, back pain, Tension headaches, interstitial dry eye disease (NIH PA 14-244)
 - Multiple other somatic disorders of CNS origin
 - Fatigue, sleep disorder, mood, memory
 - By stressful trigger
 - Abuse and neglect in childhood
 - Post deployment Gulf war syndrome
 - Post infection (Lyme disease chronic EBV)
 - Post emotional trauma Death of spouse

Dysfunctional pain

Associated multiple
pain conditions

LBP IBS FM



Never ever underestimate toothache mimickery!

Inflammatory pain

Toothache

Abscess

TMD arthritides,
trauma, Sialadenitis,
Sinusitis, mucosal
disease

TMDs

Dysfunctional

Arthritides

Myofacial

Arthromyalgia

Healthy
tooth

Insult to tooth
Trauma

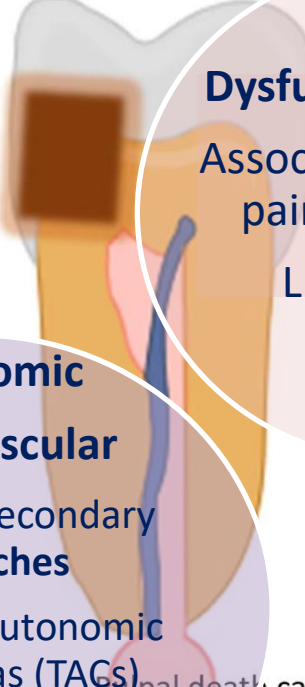
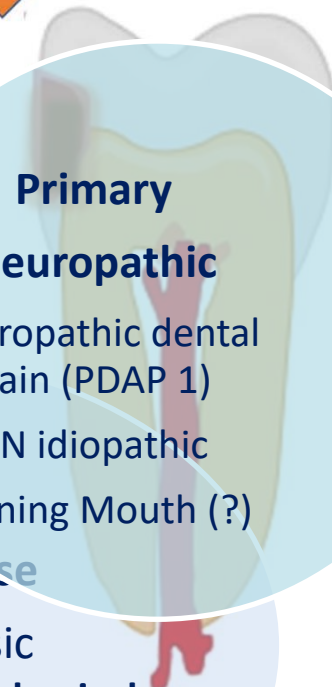
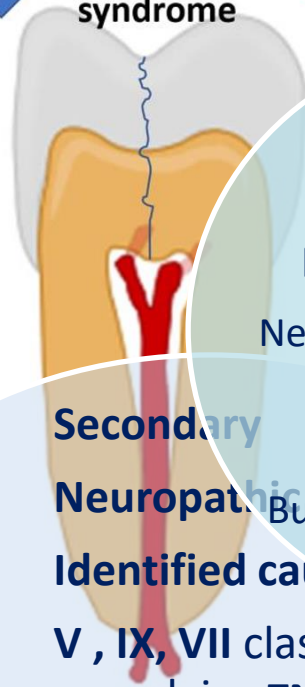
Caries

Hyperaemia
of the pulp

Pulpal
ischaemia

Pulpal
necrosis

Cracked
tooth
syndrome



**Primary
Neuropathic**

Neuropathic dental
pain (PDAP 1)

Secondary

Neuropathic

Identified cause

V, IX, VII classic
neuralgias-TN classical

PTN = PDAP II CPSP)
metabolic, infection,
MS, neoplasia, vascular
autoimmune)

Intermittent
neuralgic pain on
biting with no other
symptoms

Pulpal inflammation causes
sensitivity of A delta fibers
allodynic pain with cold
and sugary stimuli

**Autonomic
Neurovascular**

Primary & Secondary
Headaches

Trigeminal Autonomic
Cephalalgias (TAGs)

Giant cell arteritis
Pulpal ischaemia causes
sensitivity of C fibers and
allodynia to heat and
spontaneous episodic throbbing
pain

Dysfunctional pain

Associated multiple
pain conditions

LBP IBS FM

Referred pain

Heart

Cervical

Lung

CANCER

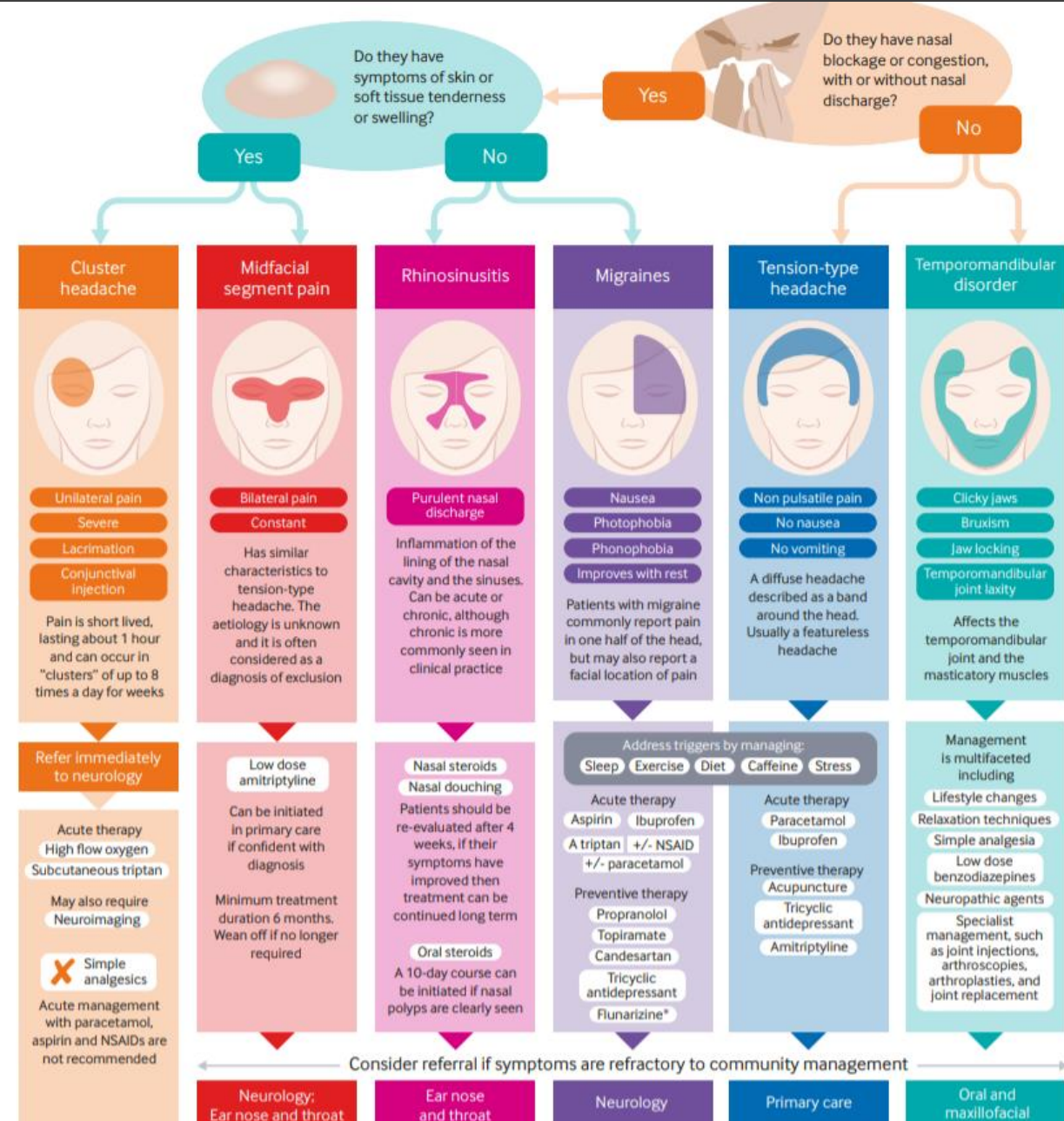
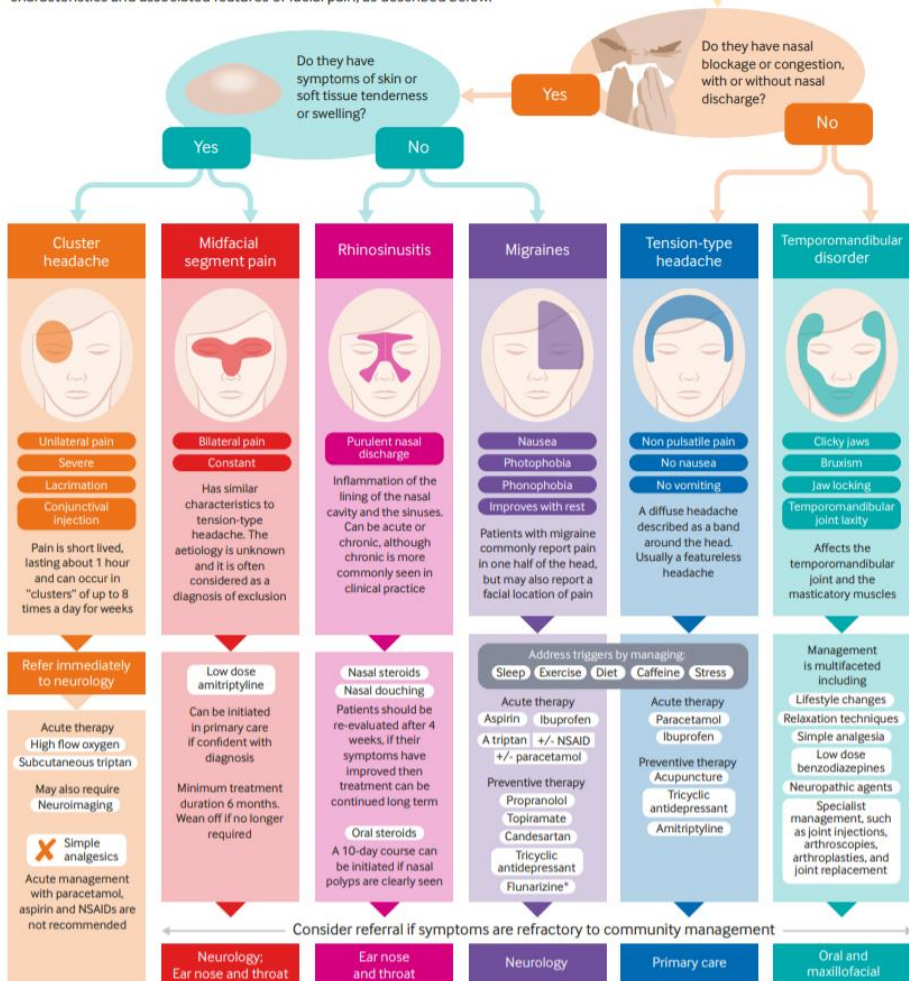
**Nociceptive
pain**

Dentine
sensitivity

In health allodynia is
felt to cold, electrical
and mechanical
stimuli

Identification and initial management

Chronic orofacial pain (lasting more than 12 weeks) can be debilitating for patients. After this time, primary care treatments have often been exhausted, and referral is an obvious next step. However, many cases are incorrectly attributed to rhinosinusitis, which can lead to inappropriate referrals and delay for patients. A more accurate diagnosis may be performed by focusing on the characteristics and associated features of facial pain, as described below.



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The good physician treats the disease; the great physician treats the patient who has the disease.

William Osler

1849-1919





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Orofacial Pain

Demystifying chronic
pain in the head, face
and mouth

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APPLIED EVIDENCE

Zeroing in on the cause of your patient's facial pain

J Fam Pract. 2015 September;64(9):524-526,528-531B

By [Feras Ghazal, DDS](#); [Mohammed Ahmad, MD](#); [Hussein Elrawy, DDS](#); [Tamer Said, MD](#)

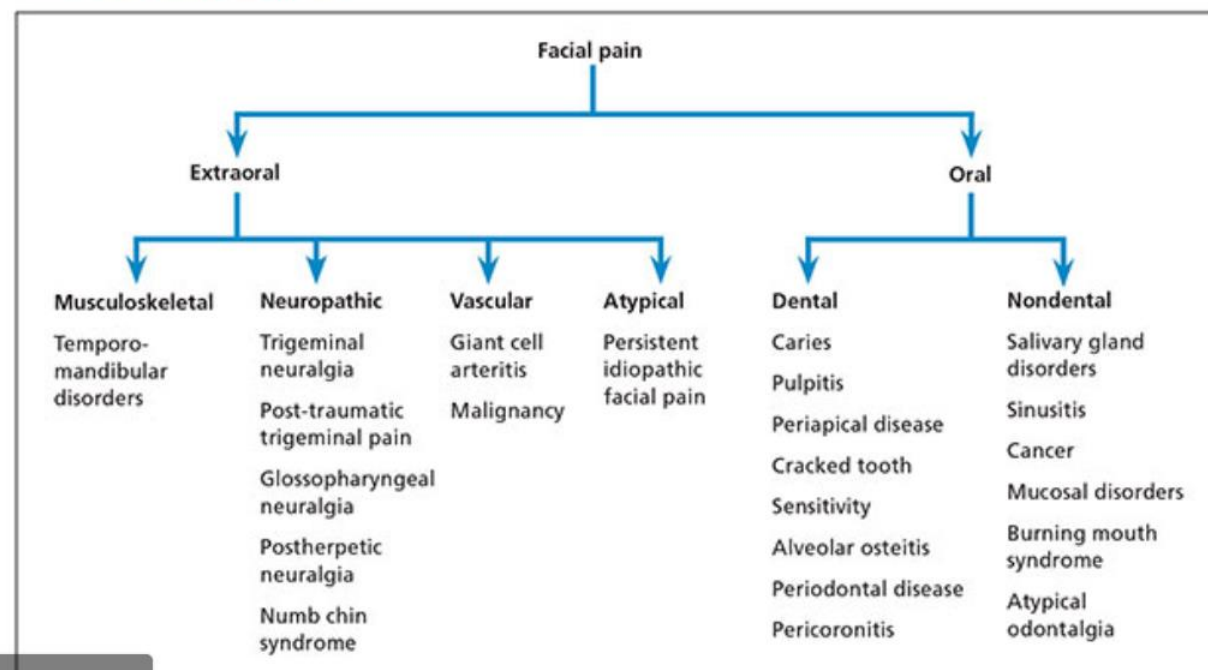
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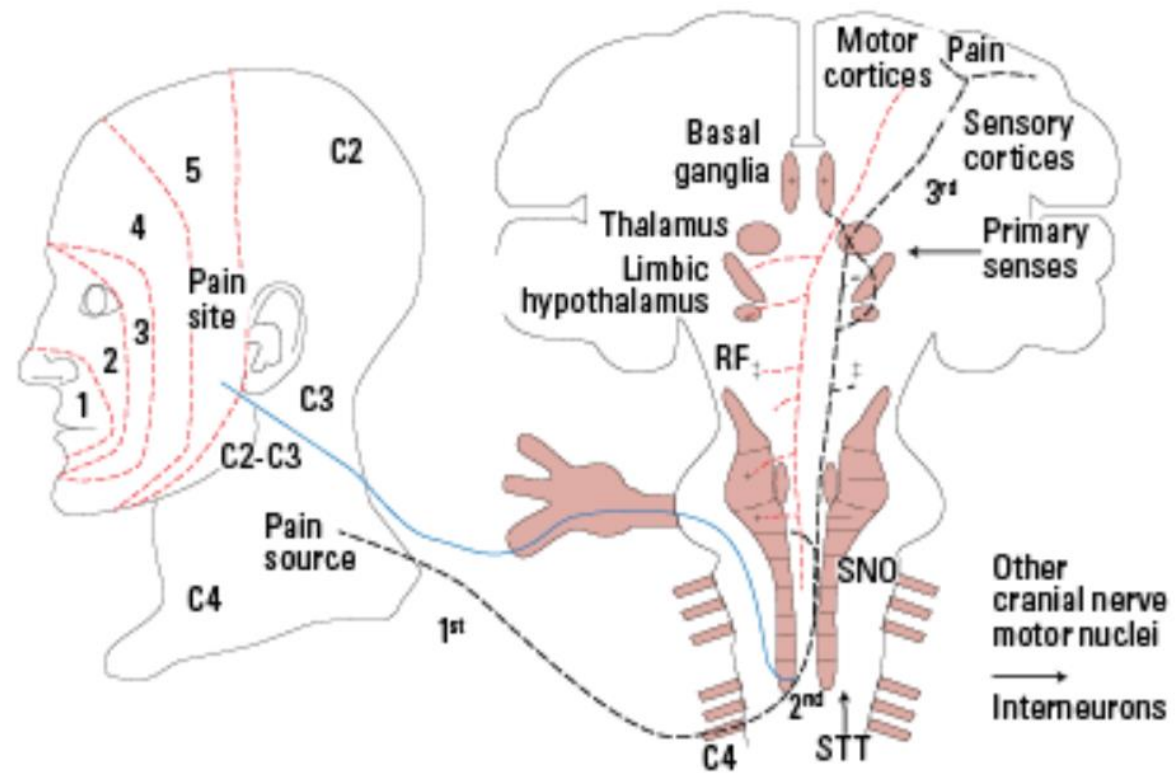
THE JOURNAL OF
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PRACTICE**

The overlapping characteristics of facial pain can make it difficult to pinpoint the cause. This article, with a handy at-a-glance table, can help.

FIGURE

Causes of facial pain





Analgesic	Analgesic and/or Hyperalgesic	Hyperalgesic
<p>Opioid system</p> <p>↓ Responsivity to opioids</p>	<p>Monoaminergic - Serotonin</p> <p>↓ Serotonin 1A receptor sensitivity</p> <p>↑ Extracellular serotonin in basal forebrain</p> <p>↑ Plasma serotonin metabolites</p>	<p>Adenosine signaling</p> <p>↑ Adenosine (A2A receptor mediated)</p>
<p>Monoaminergic - Dopamine</p> <p>↓ Dopamine D2 receptor activity</p>	<p>HPA axis</p> <p>↑ Cortisol (indirect effects on pain through interplay with immune system)</p>	<p>Nitric oxide signaling</p> <p>↑ NO in basal forebrain, PAG, cortex</p>
<p>Monoaminergic - Norepinephrine</p> <p>↑ Norepinephrine transporter mRNA in LC, norepinephrine levels in blood</p>		<p>Immune system</p> <p>↑ Prostaglandins (PGE2)</p> <p>↑ Cytokines (IL-1, IL-6, TNF)</p>
<p>Orexin signaling</p> <p>↓ Orexin-A in hypothalamus, plasma, bone marrow</p> <p>↑ Orexin-A in hypothalamus, LC, cortex, CSF</p>		
<p>Melatonin</p> <p>↓ Melatonin levels in blood (mediated through light exposure at night)</p>		
<p>Endocannabinoids</p> <p>↑ Endocannabinoids in blood</p>		

System/mediator property:



Analgesic



Analgesic/hyperalgesic



Hyperalgesic

Effect of sleep deficiency on system/mediator:

↑ Activating

↓ Deactivating