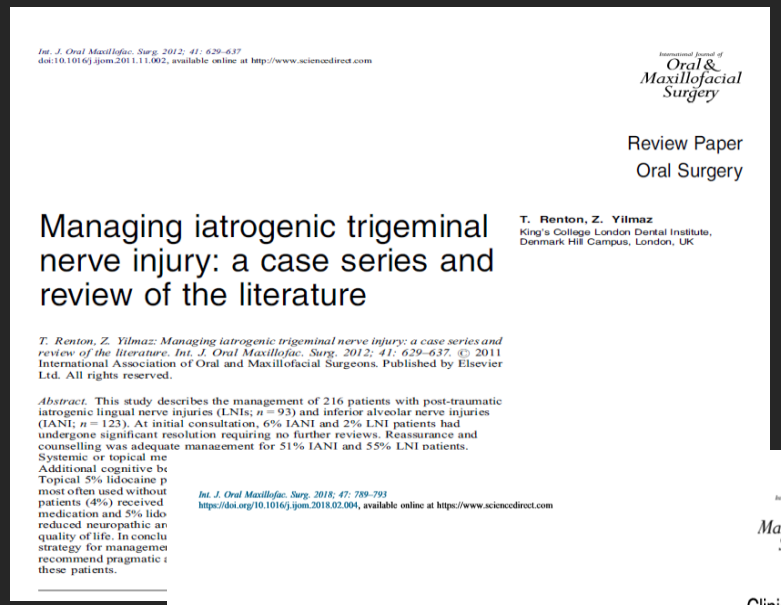
Management of nerve injury

Tara.renton@kcl.ac.uk

Management of dentistry related nerve injury

- **Prevention is best!**
- **Treatment must depend upon the mechanism and duration of nerve injury**
- **Holistic approach**
- Treat
  - *Pain*
  - *Functional disability*
  - *Psychological impact*
- Counselling
  - *Reaffirm nerve injury is permanent*
  - *Be honest with the patient*
  - *Reassurance and explanation*
- Medical for pain +/- depression
  - *Topical*
  - *Systemic*
- Surgical
- **Remove implant or Endo within 30 hours**



Int. J. Oral Maxillofac. Surg. 2012; 41: 629–637
doi:10.1016/j.ijom.2011.11.002, available online at http://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

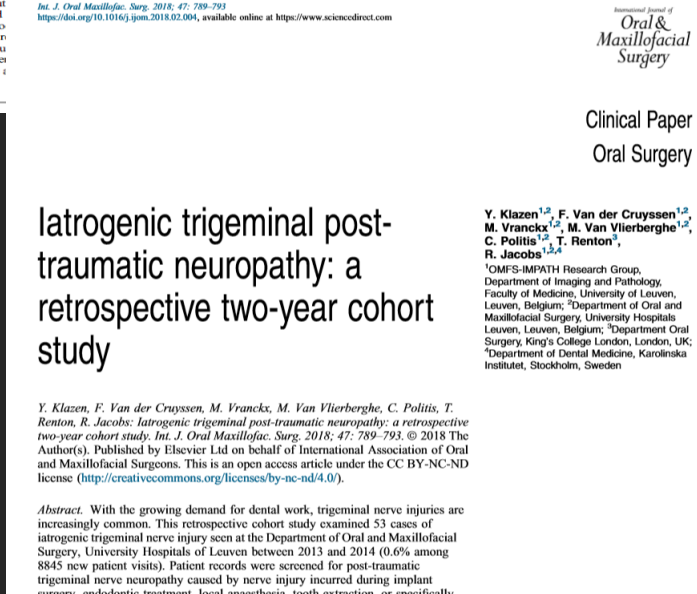
Review Paper
Oral Surgery

Managing iatrogenic trigeminal nerve injury: a case series and review of the literature

T. Renton, Z. Yilmaz
King's College London Dental Institute, Denmark Hill Campus, London, UK

T. Renton, Z. Yilmaz: Managing iatrogenic trigeminal nerve injury: a case series and review of the literature. Int. J. Oral Maxillofac. Surg. 2012; 41: 629–637. © 2011 International Association of Oral and Maxillofacial Surgeons. Published by Elsevier Ltd. All rights reserved.

Abstract. This study describes the management of 216 patients with post-traumatic iatrogenic lingual nerve injuries (LNIs; $n = 93$) and inferior alveolar nerve injuries (IANI; $n = 123$). At initial consultation, 6% IANI and 2% LNI patients had undergone significant resolution requiring no further reviews. Reassurance and counselling was adequate management for 51% IANI and 55% LNI patients. Systemic or topical me
Additional cognitive b
Topical 5% lidocaine p
most often used without
patients (4%) received
medication and 5% lido
reduced neuropathic an
quality of life. In conclu
strategy for managemer
recommend pragmatic
these patients.



Int. J. Oral Maxillofac. Surg. 2018; 47: 789–793
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International Journal of Oral & Maxillofacial Surgery

Clinical Paper
Oral Surgery

Iatrogenic trigeminal post-traumatic neuropathy: a retrospective two-year cohort study

Y. Klazen[1,2], F. Van der Cruyssen[1,2], M. Vranckx[1,2], M. Van Vlierberghe[1,2], C. Politis[1,2], T. Renton[3], R. Jacobs[1,2,4]
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Y. Klazen, F. Van der Cruyssen, M. Vranckx, M. Van Vlierberghe, C. Politis, T. Renton, R. Jacobs: Iatrogenic trigeminal post-traumatic neuropathy: a retrospective two-year cohort study. Int. J. Oral Maxillofac. Surg. 2018; 47: 789–793. © 2018 The Author(s). Published by Elsevier Ltd on behalf of International Association of Oral and Maxillofacial Surgeons. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Abstract. With the growing demand for dental work, trigeminal nerve injuries are increasingly common. This retrospective cohort study examined 53 cases of iatrogenic trigeminal nerve injury seen at the Department of Oral and Maxillofacial Surgery, University Hospitals of Leuven between 2013 and 2014 (0.6% among 8845 new patient visits). Patient records were screened for post-traumatic trigeminal nerve neuropathy caused by nerve injury incurred during implant

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International Journal of Oral & Maxillofacial Surgery

Clinical Paper
Oral Surgery

Treatment modalities and risk factors associated with refractory neurosensory disturbances of the inferior alveolar nerve following oral surgery: a multicentre retrospective study

T. Hasegawa[1], S. I. Yamada[2], N. Ueda[3], S. Soutome[4], M. Funahara[2], M. Akashi[1], S. Furuno[5], H. Miyamoto[6], S. Hayashida[2], R. Amano[7], K. Mori[6], Y. Kojima[7], H. Kurita[2], T. Kirita[3], M. Umeda[4], Y. Shibuya[5], S. Fujita[6], T. Komori[1] Japanese Study Group of Cooperative Dentistry with Medicine (JCDM)
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T. Hasegawa, S.I. Yamada, N. Ueda, S. Soutome, M. Funahara, M. Akashi, S. Furuno, H. Miyamoto, S. Hayashida, R. Amano, K. Mori, Y. Kojima, H. Kurita, T. Kirita, M. buya, S. Fujita, T. Komori: Treatment modalities and risk factors refractory neurosensory disturbances of the inferior alveolar nerve urgery: a multicentre retrospective study. Int. J. Oral Maxillofac. Surg. 801. © 2017 International Association of Oral and Maxillofacial Surgeons. lsevier Ltd. All rights reserved.

e research has been conducted into hypoesthesia, and no studies have risk factors for refractory hypoesthesia and compared treatment e purpose of this multicentre retrospective cohort study was to relationships between various risk factors, treatment modalities, and oesthesia. Risk factors for refractory hypoesthesia after oral surgery l using univariate and multivariate analysis. To minimize the associated with a retrospective data analysis, a propensity score erformed between the medication and non-medication groups h group). Moderate or severe hypoesthesia (odds ratio 13.42) and no tration of ATP/vitamin B12 (odds ratio 2.28) were significantly refractory hypoesthesia. In the propensity score analysis, the of refractory hypoesthesia in the medication group was lower than -medication group ($P < 0.001$). This study demonstrated the lationships between various risk factors, treatment modalities, and oesthesia. Moderate or severe hypoesthesia and no or late of ATP/vitamin B12 were significantly associated with refractory Therefore, clinicians should consider these risk factors and initiate inistration of ATP/vitamin B12 in cases of hypoesthesia.

Key words: neurosensory deficit; extraction; treatment; hypoesthesia.

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We do know that
Surgery alone is not enough!

Zuniga JR, Renton T. J Neurol Neuromed (2016) 1(7): 10-14
www.jneurology.com

J Neurology Neuromedicine
www.jneurology.com
Journal of Neurology & Neuromedicine

Mini Review Open Access

Managing post-traumatic trigeminal neuropathic pain: is surgery enough?

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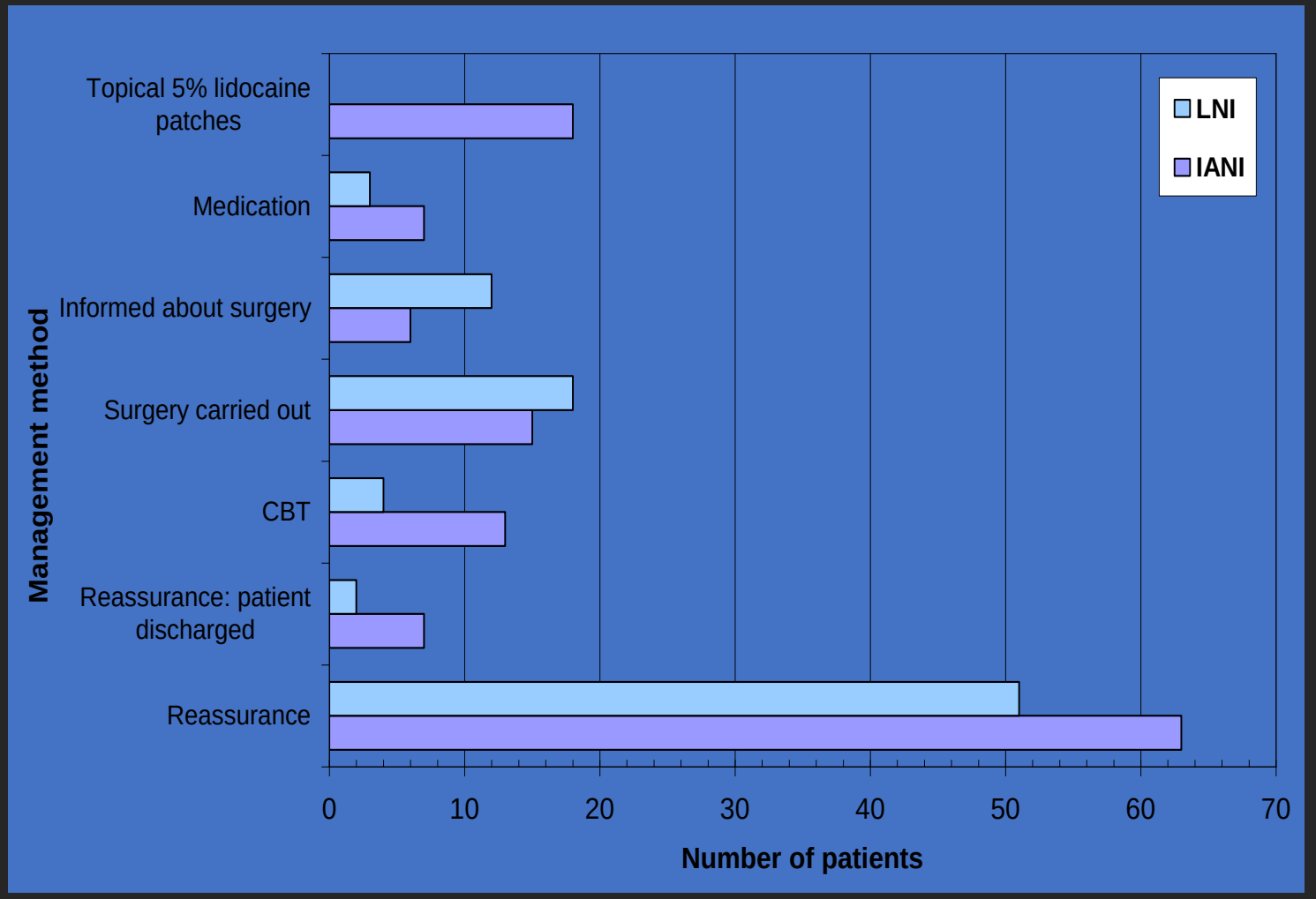
Keywords:
Trigeminal Nerve
Neuropathic Pain
Trigeminal Nerve Microsurgery

ABSTRACT

In the absence of effective non-surgical methods to permanently resolve neuropathic pain involving the lip, chin, or tongue following inferior alveolar and/or lingual nerve injury, microsurgery of these nerves has been a recommended modality. In two ambispective clinical trials, we demonstrated that phenotypic differences exist between individuals with neuropathic pain and those without neuropathic pain of the trigeminal nerve. In those without neuropathic pain before microsurgery there was a 2% incidence of neuropathic pain after microsurgery whereas there was a 67% incidence of neuropathic pain after microsurgery, some reporting an increase in pain levels, when neuropathic pain was present before microsurgery. The recurrence of neuropathic pain after trigeminal microsurgery is likely multifactorial and might not depend on factors that normally affect useful or functional sensory recovery in those who have no neuropathic pain. These results indicate that the understanding of post-traumatic trigeminal neuropathic pain is incomplete. Predictive outcomes of treatment will probably improve when the etiology is better defined to allow mechanistic or target-/site-specific treatment. Until then, non-surgical treatment for post-traumatic trigeminal neuropathic pain remains a safer option. Risk factors have been identified for patients developing chronic post -surgical pain due to post-traumatic neuropathy. These include psychological, medical, and age related factors. The best management may lie in preoperative screening and avoidance of elective surgery for high risk

Response to treatment is multi modal



A small percentage of IANI patients (4%) received a combination of therapies involving CBT, surgery, medication and 5% lidoca

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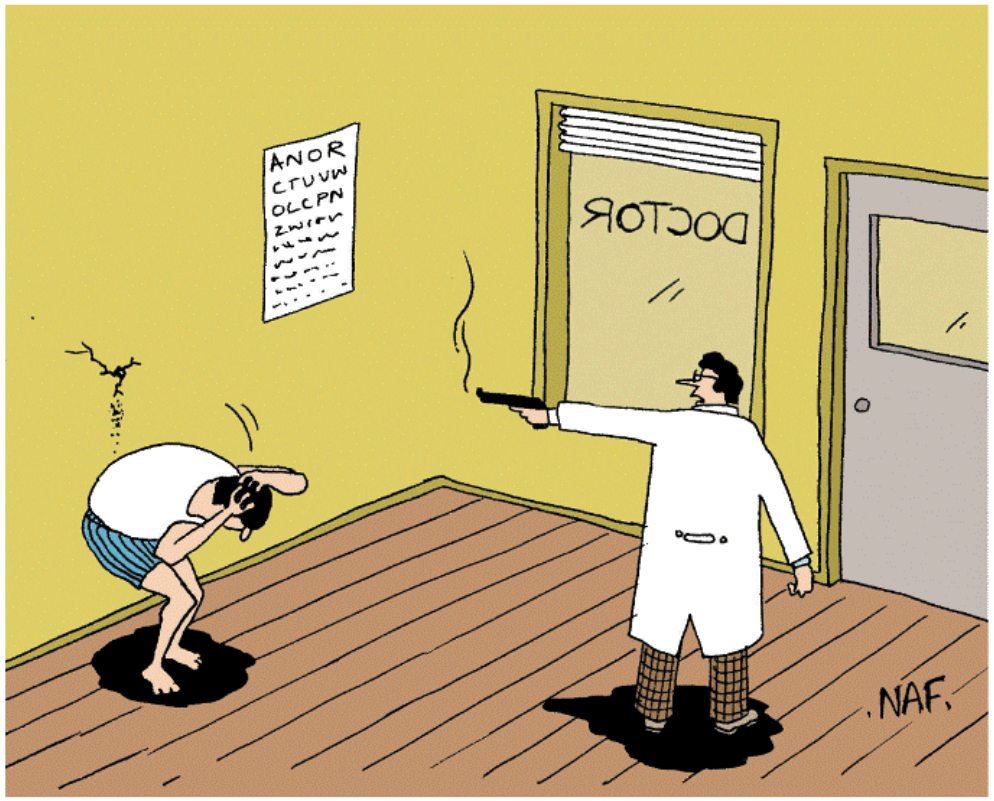
What are we trying to treat?

- The patient with the nerve injury
- Impact of nerve injury include;
  - Pain, numbness and or altered sensation
  - Functional difficulties
  - Psychological impact
- These result in changed behaviours, anxiety depression, anger, frustration and PTSD
- Management Strategies
  - Understanding and acknowledging their problem. Providing realistic prognosis and possible management strategies
  - Pain ‘relief’
  - Behavioural techniques to assist the patient in adapting to new self (both functional and psychological)

CLINICAL ASSESSMENT
Mechanosensory assessment



"Your reflexes seem fine Mr Hart"

The purpose of this study was to determine the statistical efficacy of the clinical neurosensory test using surgical findings as the "gold" standard, and to determine whether a correlation existed between the sensory impairment score obtained by preoperative testing and the degree of nerve injury found at surgery.

The positive predictive and negative predictive values for LN-injured patients were 95% and 100%, respectively. The positive predictive and negative predictive values for IAN patients were 77% and 60%, respectively.

There were statistically **significant differences in the distribution of age, duration of injury, cause of injury, presence of neuropathic pain, presence of trigger pain, and degree of injury between the IAN and LN patient populations**.

There was a statistically significant positive relationship found between the sensory impairment score and the degree of nerve injury.

No complicated tests!

Zuniga JR, Meyer RA, Gregg JM, Miloro M, Davis LF.The accuracy of clinical neurosensory testing for nerve injury diagnosis. J Oral Maxillofac Surg. 1998 Jan;56(1):2-8.

Presentation of persistent PTNP (n=525) Renton et al unpublished

- **Onset of neuropathy +/- pain correlates with intervention surgery or local anaesthetic**
  - LNI patients (mean age 38.4 years [range 20-64]
    Male:Female ratio 37:63%
  - IANI patients (mean age 43.2 years [range 22-85];
    Male:Female ratio 27:70%

  Referral from:
  - General dental practitioner LNI = 40%/IANI = 51%
  - Specialist LNI = 50% IANI = 32%
- **Reported extreme pain during surgery 48%**
- **Reported high level pain post surgically 56%**
- IANI related to;
  - Third molar surgery 60%
  - Implant 14%
  - LA 16%
  - Endo 8%
  - Periapical infections 1%
  - Facial electrolysis 1%
- LNIs related to;
  - TMS 75%
  - LA 21%

Pain descriptors

Presenting with neuropathic pain 70%

Functionality

Significantly daily functional impact 65% with pain

Psychologically (PTSD in 68% of patients) impact especially with pain 62%

Neuropathy 100%

Dermatome: The neuropathic area varied between 5-100% of the affected dermatome (intra- and/or extra-orally).

Hypoeasthetic or **Hyperaesthetic**

Mechanical allodynia 70%

Mechanical Hyperalgesia 48%

Cold allodynia in IANI pts 87%

CBT			
		Subjective Function	
	Neuropathic Area (%)	Min	Max
Extraorally	70 (2-100)	3.1 (0-10)	8.8 (1-30)
Intraorally	66 (0-100)	2.3 (0-5)	10.5 (6-12)
Versatis			
		Subjective Function	
	Neuropathic Area (%)	Min	Max
Extraorally	68 (8-100)	1.75 (1-2)	9.6 (4-12)
Intraorally	69 (0-100)	4.0 (4)	10.0 (6-12)

Table 1: Summary of Neuropathic Area Affected and Subjective Function (SF). Hypersensitivity to touch is indicated by a subjective function (SF) value of above 10, as a value of 10 indicates

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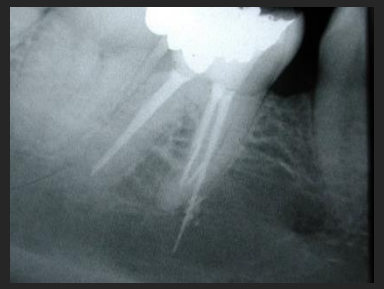
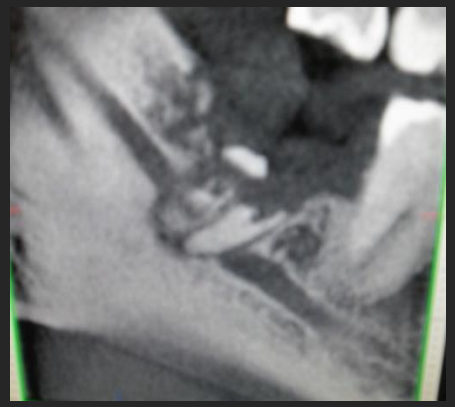
You cannot ‘see’ nerves on radiographs just the canals and foramina……

but CBCT may be useful for post wisdom tooth surgery and confirmed nerve injury

ADDITIONAL INVESTIGATIONS POSSIBLE BIOMARKERS?

Radiology Post surgical radiographs (panoral for wisdom teeth and LCPA for endo Nis) are required to confirm causality though mainly a clinical diagnosis





Use plain film only
CBCT -unnecessary irradiation of the patient
Provides no further information and does not change treatment unless M3M nerve injury to exclude roots displaced into submandibular or sublingual space

Post surgical CBCTs only required for M3M Inferior alveolar nerve injury

Additional tests
Neurosensory
- **Mechanosensory**
- **QST**
- **Blink reflex**

Diagnostic Lidocaine blocks
Psychological

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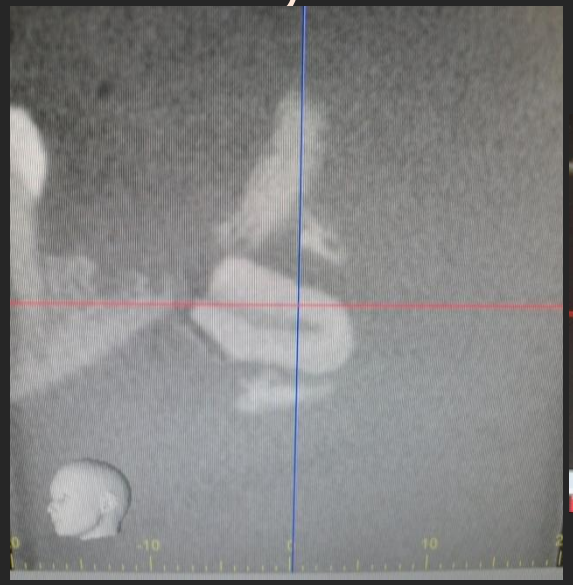
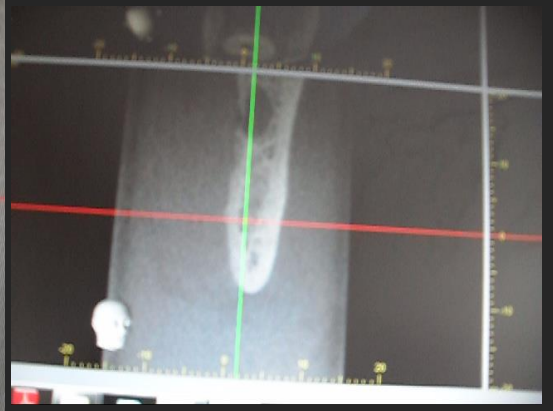
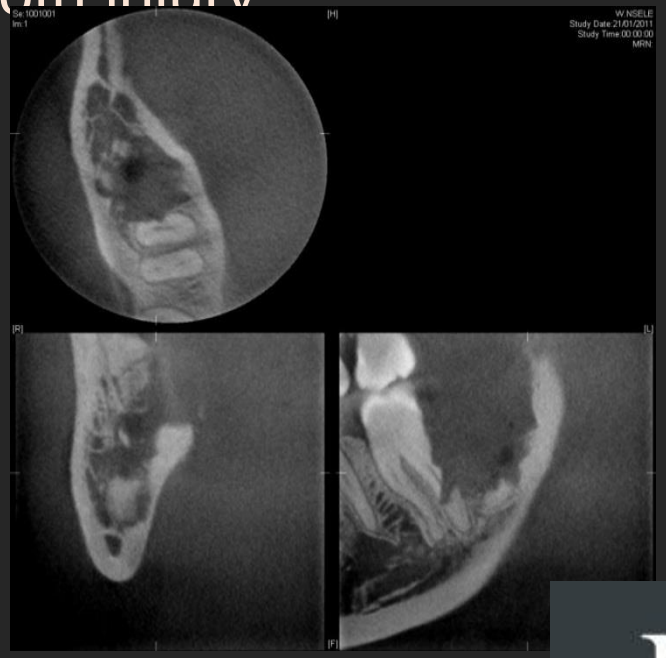
IMAGING Inferior alveolar nerve injury (IANI)

WHEN IS CBCT INIDICATED POST NERVE INJURY?

Retained roots? In submandibular space?
CBCT may be useful for post wisdom tooth injury







MRI neuroradiography>>>>>>>>>>>>>>>>>>>

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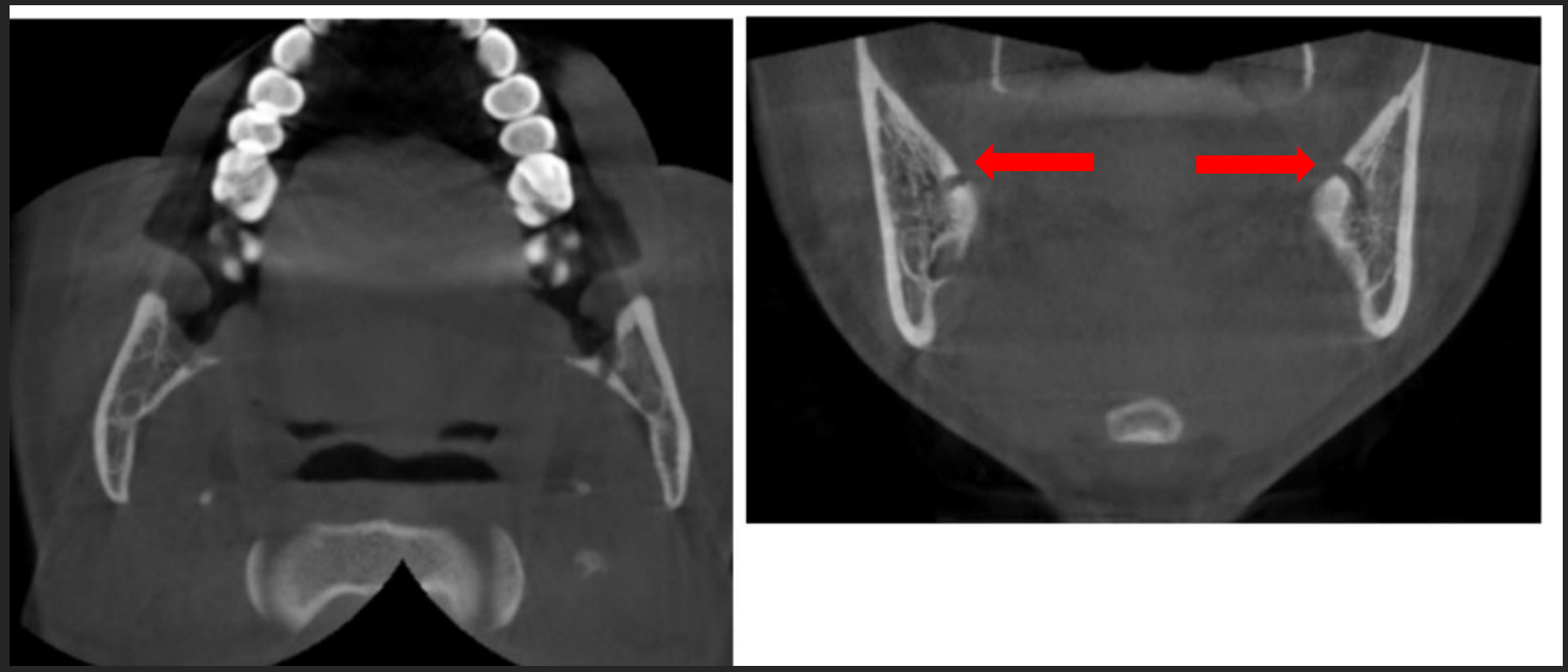
IMAGING Lingual nerve injury (LNI)
CBCT early post op detection of Lingual plate damage



CBCT MAY BE USEFUL WITH CLINICAL CONFIRMATION OF LINGUAL NEUROPATHY USEFUL TO ESTABLISH IF LINGUAL PLATE DAMAGE INDICATES URGENT NEED FOR LINGUAL NERVE EXPLORATION AND REPAIR CBCT DEMONSTRATING BILATERAL BUR PERFORATION OF LINGUAL PLATE POST TMS (COURTESY OF TONY POGREL)

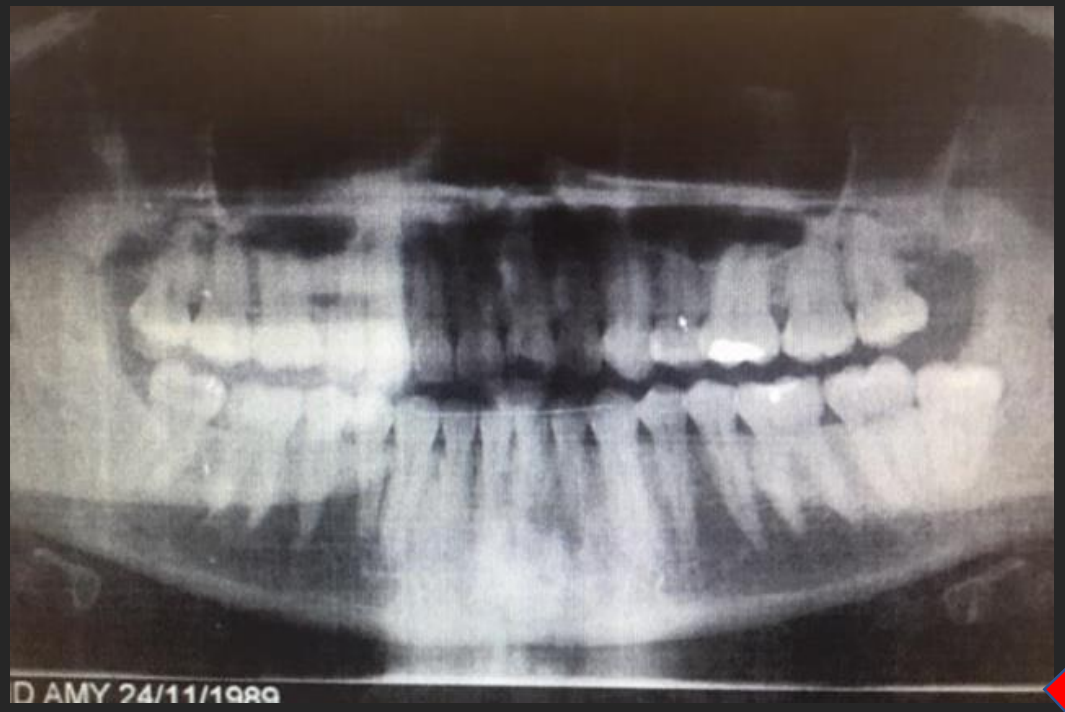
Recent Case Pre op findings

Dense left sided hypoaesthetic neuropathy LN (M3M surgery 3 weeks ago)

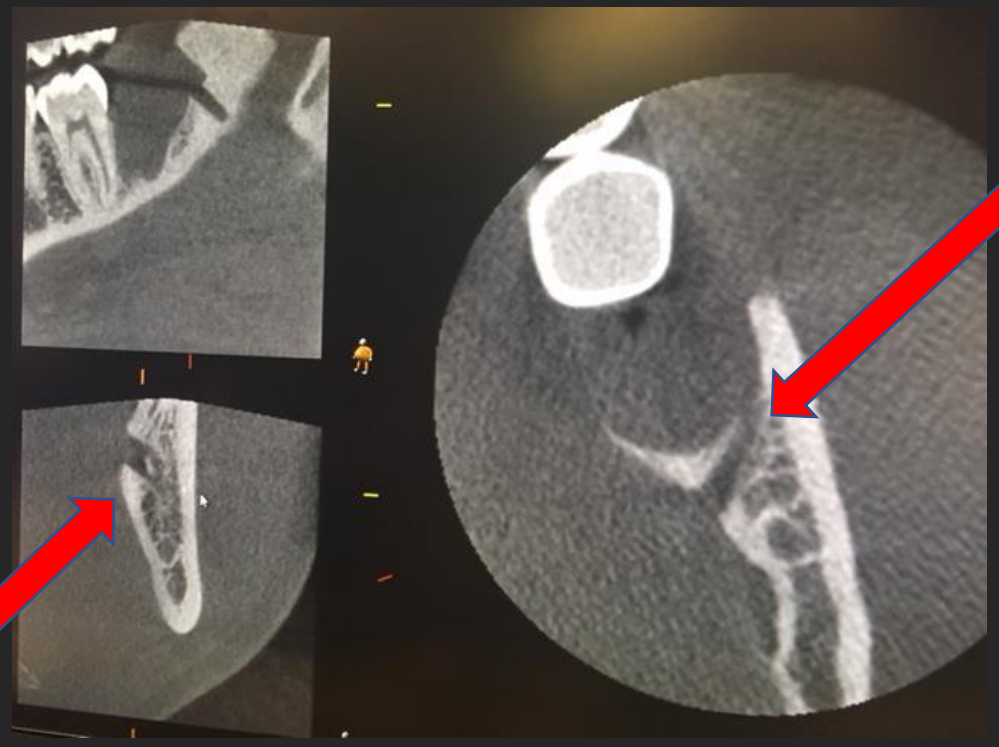
c/o numbness with occ spontaneous paraesthesia, functional difficulty speaking and eating.

mechanosensory sf 2/10, no SB detection or LT

Preop DPT



CBCT taken 14/08/18



Management of PTPN

Cause and duration

URGENT treatment < 30 hours

- Any known or Suspected nerve trauma
- Implants
- Endodontics (neuropathy may develop 2-3 days post treatment)

- **Within 2 weeks**
- Buccal approach causing Lingual nerve
- Inferior alveolar nerve injuries related to third molar surgery

- **> 2 weeks**
- Not ideal

Wait for resolution

- Lingual nerve injuries related to LINGUAL ACCESS third molar surgery (consider explore @ 12 weeks)
- LA
- Trauma
- Orthognathic

Consent patient properly…forearmed is for warned
Risk assessment in planning
Check on patients post operatively HOMECHECK
Acknowledge problem
No sit and WAIT !!!!!
You MUST reassure your patient but don't give them false expectations!
Seek advice- Trigeminalnerve.org.uk- Medication and REFERRAL

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Psychological consequences

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.

40% of patients display PTSD

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.

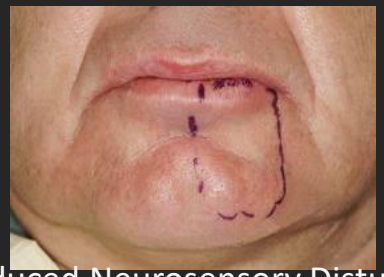
RESULTS: The majority of patients reported pain associated with their nerve injury (86%). Nerve injury had a significant impact on all investigated domains, and this was closely linked with reported pain levels. Patients with severe pain showed particularly elevated levels of depression and pain catastrophizing, 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.

PMID: 24171179 [PubMed - indexed for MEDLINE]

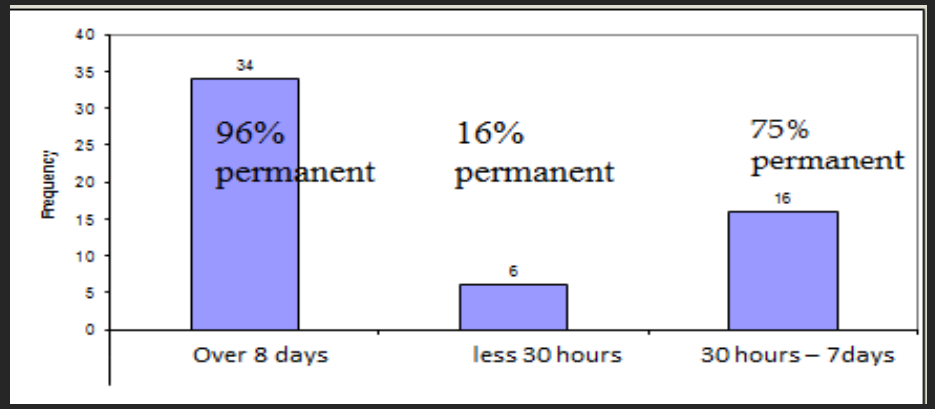
Acute surgical intervention

- **Acute management < 30 hours (delayed onset neuropathy)**
  - (LA IDB lasts 3 hours and 25minutes)
  - Check on Patient after 6 hours (Home check)
  - IAN NEUROPATHY? (extreme pain/ mixed symptoms large neuropathic area)
    - Yes
  - Consult patient, check for area of neuropathy and signs of nerve injury
    - Confirmed
  - **<u>Remove IMPLANT OR Endo / tooth < 30 hours with neuropathy</u>**
  - + High dose oral NSAIDs (600-800mgs Ibuprofen PO QDS)
  - Prednisolone 5 day step down does 50-40-30-20-10mg PO
  - Vitamin B Complex?
  - (check medical history!)
  - Review



Only use plain films

Removing implant or endo filled tooth < 30 hours does Improve NI resolution

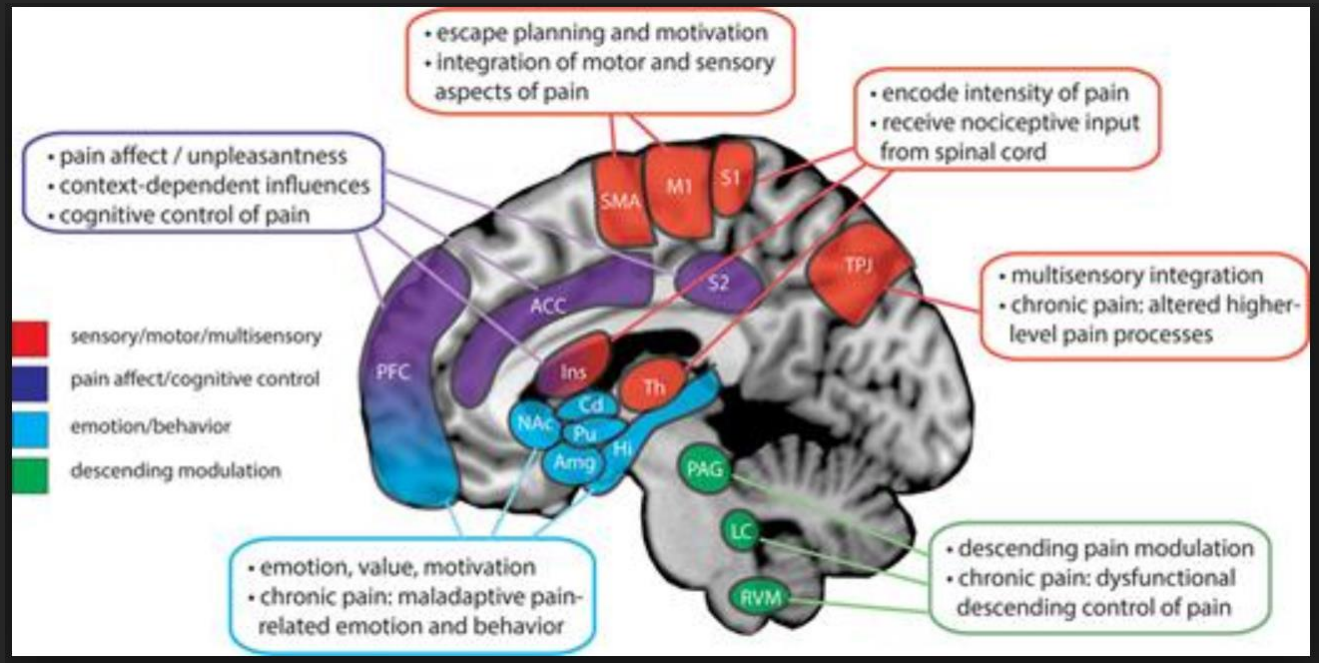


Bhavsar I, Khalaf M, Ferrin J, Al-Sabbagh M. Resolution of Implant-Induced Neurosensory Disturbance: A Procedural Failure. Implant Dent. 2015 Dec;24(6):735-41.
Khawaja N, Renton T. Case studies on **implant removal** influencing the resolution of inferior alveolar **nerve injury**. Br Dent J. 2009 Apr 11;206(7):365-70

Central changes after peripheral nerve injury

Central changes increased with catastrophising

- CPSP likely due to biological and psychological factors. Here, we tested the hypotheses that
- **high Pain Catastrophizing Scale (PCS) scores at the time of injury and repair are associated with pain**
- cold sensitivity after 1-year recovery
- **insula gray matter changes reflect the course of injury and improvements over time.**
- **pain catastrophizing trended toward predicting cold pain thresholds at time 2, and at time 1 cortical thickness of the right insula was reduced**.
- At time 2, chronic pain was related to the time 1 pain-PCS relationship and cold sensitivity, pain catastrophizing correlated with cold pain threshold, and insula thickness reversed to control levels.
- This study highlights the interplay between **personality, sensory function, and pain in patients following PNI and repair**. The PCS-pain association suggests that a focus on affective or negative components of pain could render patients vulnerable to chronic pain. Cold sensitivity and structural insula changes may reflect altered thermosensory or sensorimotor awareness representations.



Goswami R Anastakis DJ Katz J, Davis KD. A longitudinal study of pain, personality, and brain plasticity following peripheral nerve injury. Pain. 2016 Mar;157(3):729-39.

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Amplified parabrachial nucleus activity in a rat model of trigeminal neuropathic pain

Olivia Uddin[a,b,1], **Paige Studlack**[a,b,1], **Titilola Akintola**[a], **Charles Raver**[a], **Alberto Castro**[a,b], **Radi Masri**[b,c], and **Asaf Keller**[a,b,*]

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[c]Department of Advanced Oral Sciences and The
Dentistry, 650 W. Baltimore St, Baltimore, MD 21

Abstract

The parabrachial (PB) complex mediates both asc
pain modulatory information in the affective/emo
hyperactivity influences chronic pain behavior af
induction of neuropathic pain using the chronic c
ION) model, rats displayed spontaneous markers
beyond the receptive field of the injured nerve. Pl
displayed amplified activity, manifesting as signi
compared to shams. These findings suggest that c
hyperactivity.

Keywords

Chronic pain; Affective pain; Facial grimace; Chr

Experimental Brain Research (2018) 236:1357–1368
https://doi.org/10.1007/s00221-018-5226-2

RESEARCH ARTICLE

Face sensorimotor cortex undergoes neuroplastic changes in a rat model of trigeminal neuropathic pain

Dongyuan Yao[1,2] · **Barry J. Sessle**[2]

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Abstract

Trigeminal nerve injury can result in neuropathic pain behavior and alterations in motor function, but it is unclear if such injury produces neuroplastic alterations in face sensorimotor cortex that could contribute to the alterations in motor function. Therefore, this study aimed to determine if trigeminal nerve injury in a rat neuropathic pain model induces neuroplastic changes in jaw and tongue motor representations in face sensorimotor cortex in association with facial nociceptive behavior. Right infraorbital nerve transection was performed in adult male Sprague–Dawley rats; sham-operated rats served as controls. Nociceptive behavior was assessed by testing facial mechanical sensitivity pre-operatively and post-operatively (1–28 days). Intracortical microstimulation was also applied post-operatively in a series of microelectrode penetrations to map jaw and tongue motor representations in the face sensorimotor cortex by analyzing anterior digastric and genioglossus electromyographic activities evoked by microstimulation at histologically verified sites in face primary somatosensory cortex (face-SI) as well as face primary motor cortex (face-MI). Compared to sham, infraorbital nerve injury induced a significant (2-way repeated-measures analysis of variance, $P<0.001$) bilateral decrease in facial mechanical threshold that lasted up to 28 days post-operatively. Nerve injury also induced a significant bilateral decrease compared to sham ($P<0.05$) in the number of anterior digastric and/or genioglossus sites in face-MI and in face-SI. These findings indicate that trigeminal nerve injury induces neuroplastic alterations in jaw and tongue motor representations in face sensorimotor cortex that are associated with facial nociceptive behavior and that may contribute to sensorimotor changes following trigeminal nerve injury.

Research Paper

PAIN

Reversal of insular and microstructural nerve abnormalities following effective surgical treatment for trigeminal neuralgia

Danielle D. DeSouza[a,b], Karen D. Davis[a,b,c,*], Mojgan Hodaie[a,b,c]

Abstract

Classical trigeminal neuralgia (TN) is a severe neuropathic facial pain disorder commonly associated with neurovascular compression at the trigeminal nerve root entry zone (REZ). Neurosurgical interventions can relieve TN pain, but the mechanisms underlying these effects are unknown. We determined whether the abnormalities we previously reported at the REZ of TN patients using diffusion tensor imaging (DTI) and brain gray matter (GM) analyses resolve after effective neurosurgical treatment. Twenty-five patients who underwent either microvascular decompression surgery or Gamma Knife radiosurgery for right-sided TN had magnetic
treatment and were compared with age-matched controls. Cortical thickness and voxel-
ain GM we previously reported as abnormal in TN. White matter metrics of fractional
fusivities (MD, RD, and AD, respectively) were extracted bilaterally from each trigeminal
spread GM abnormalities including thinner ventral anterior insula (vAI) cortex, and REZ
d higher MD, RD, and AD) compared with controls. We considered a 75% reduction in
as the only GM region that normalized toward the level of healthy controls after effective
reversed FA, MD, RD, and AD abnormalities and was correlated with pain relief after
t treatment can effectively resolve pain by normalizing REZ abnormalities, which may
es should consider DTI as an adjunct to assess the patient outcome and subtle

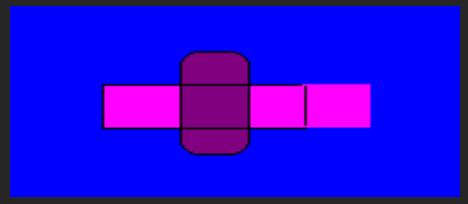
ent, Pain, MRI, DTI, Neurosurgery

Nerve exploration what do we find?

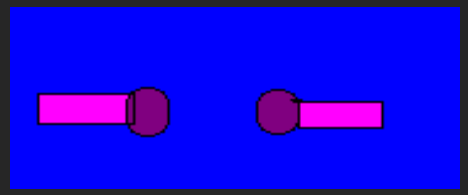
- Exploration

- Decompression

- Neuroma in continuity (NIC) excision and re-approximation



- End neuromata EN) excision and re-approximation with minimal tension



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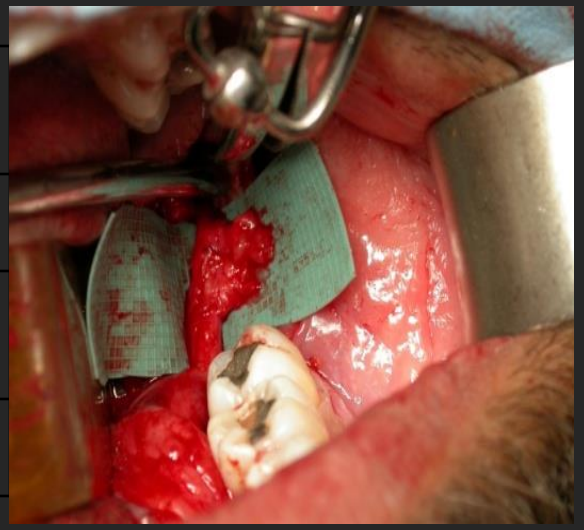
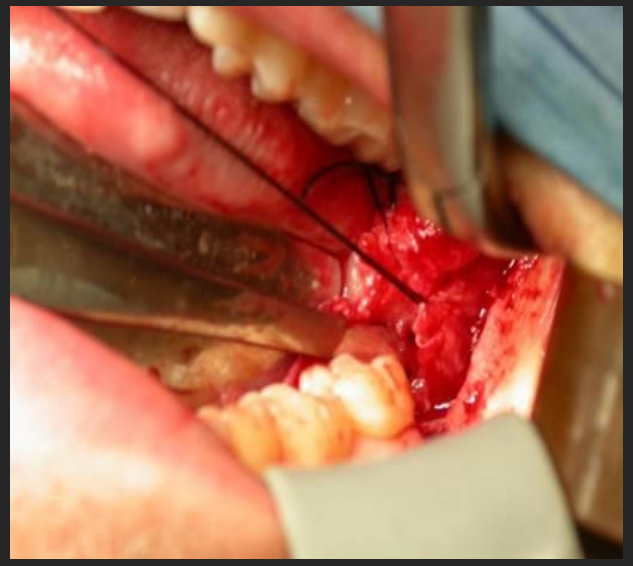
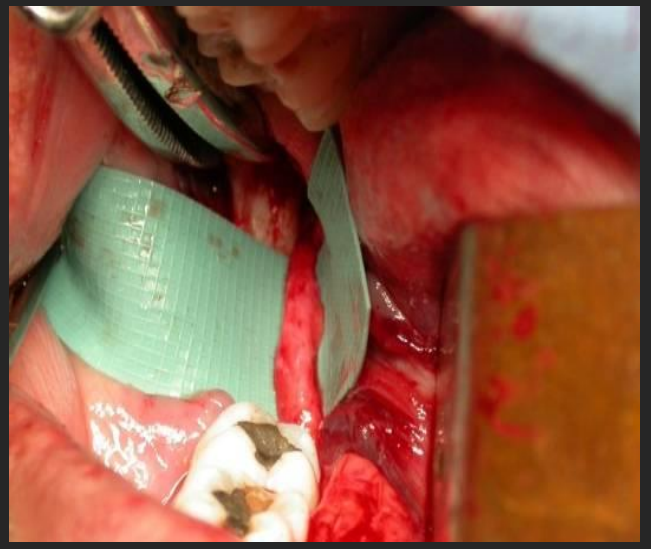
Key surgical procedures carried out for LNI patients

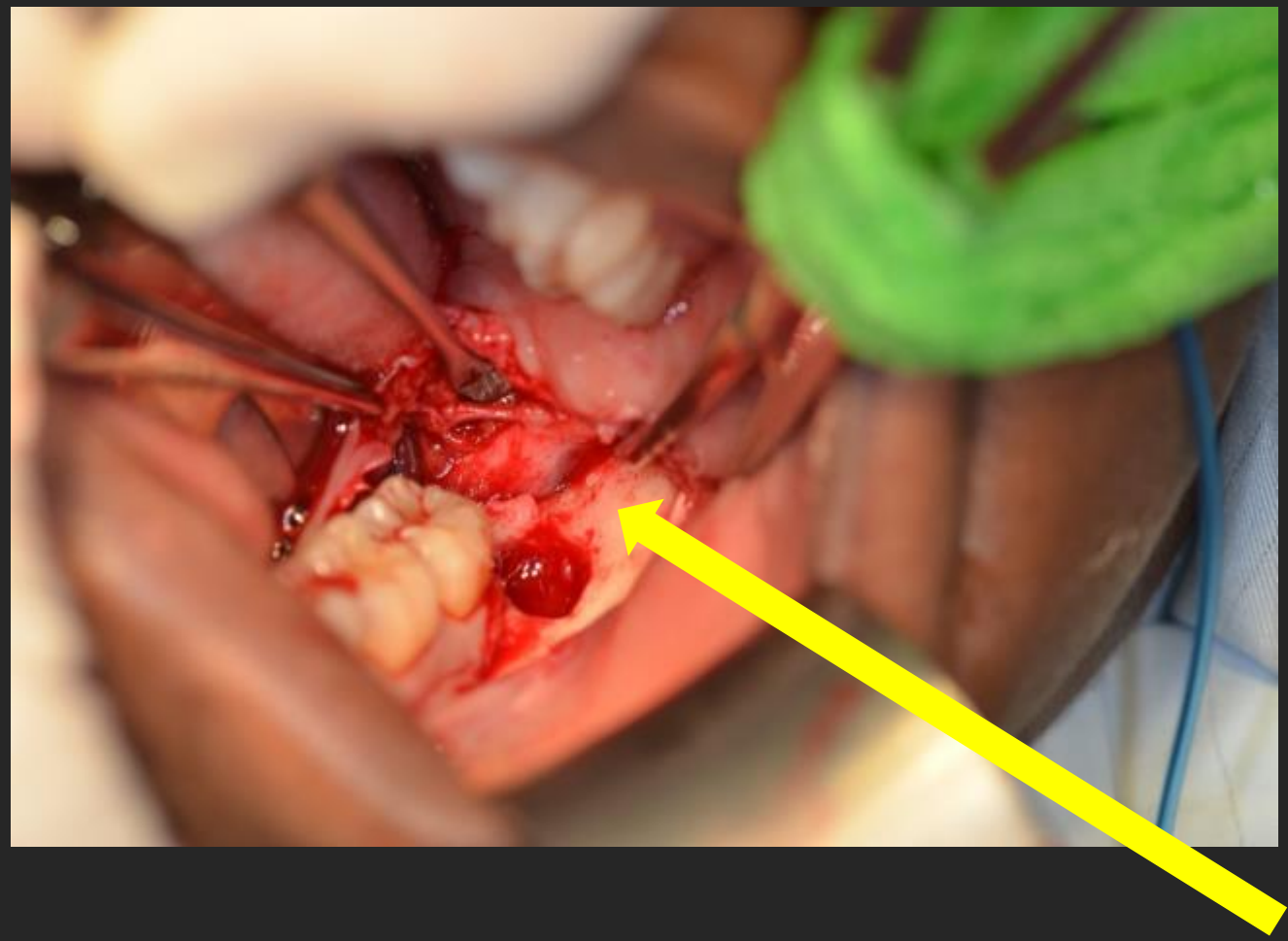
Procedure	Number of patients
Exploration and decompression	28
Release of scar tissue, excision of neuroma and re-anastimosis of the nerve	7
Nerve appears normal	2







Findings during lingual nerve exploration .....we can see damaged lingual plates

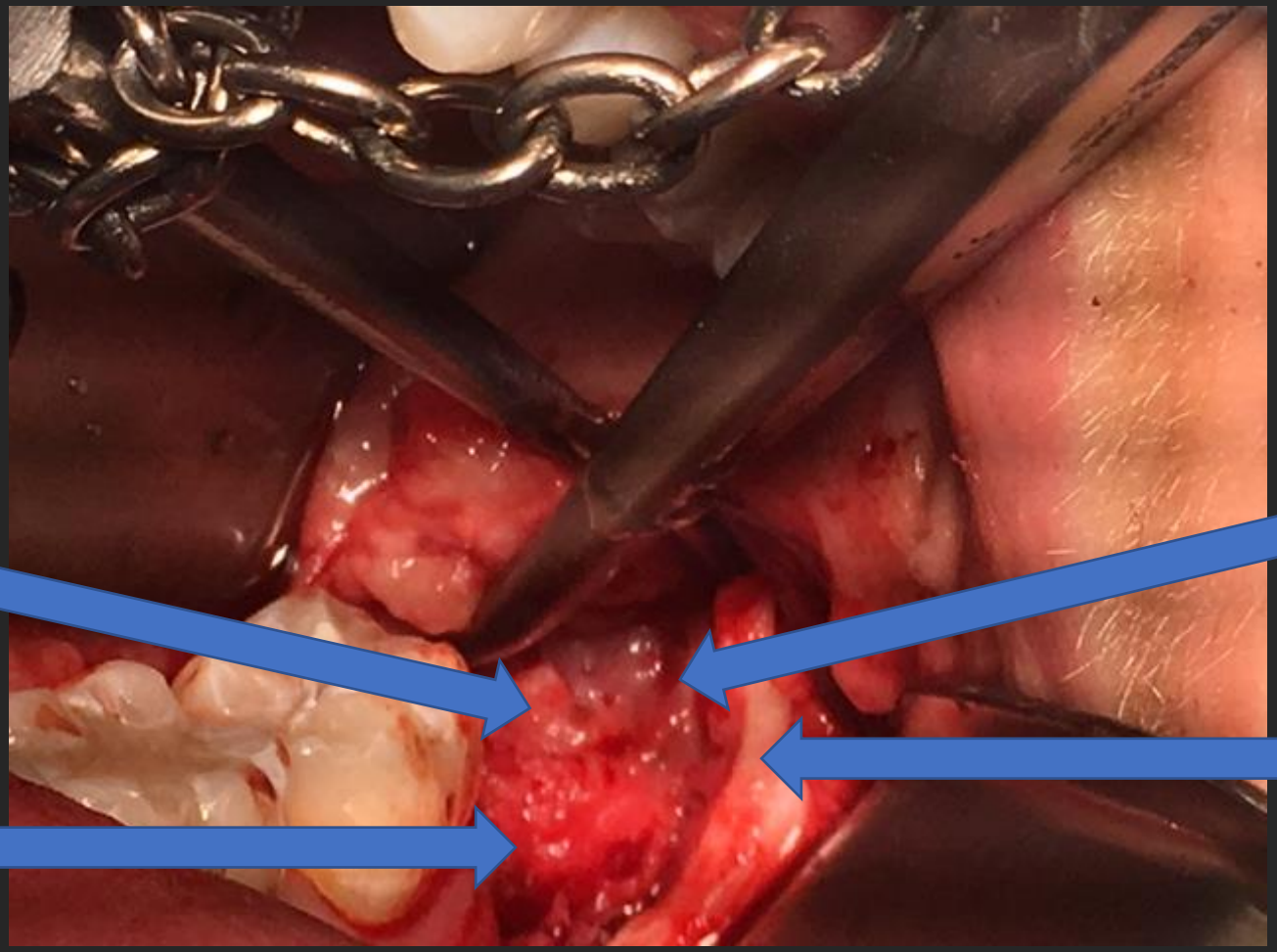


Damaged Lingual plate can be detected by CBCT scanning early post surgically

Allowing for earlier lingual nerve exploration and repair if necessary

ONLY wait for 12 weeks for resolution associated ONLY with lingual access surgery NOT Buccal access surgery

Operative findings lingual nerve injury 22/8/18



Sharp ledge bone with defect caused by previous surgery into lingual space

Granulation tissue in healing socket

Nerve tissue pulled into socket

Exposed buccal bone illustrating healing socket margin

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Edorium J Surg 2015;2:12–15.
www.edoriumjournalofsurgery.com

EDITORIAL OPEN ACCESS

Inferior alveolar nerve injuries and impacted lower third molars: The importance of third dimension

József Szalma

One of the most frequent oral surgical intervention is the removal of impacted wisdom-teeth. Inferior alveolar nerve (IAN) injury is a possible and unpleasing complication of surgical removal of impacted lower third molars. The incidence of irreversible injuries according to literature is usually below 1%, but reversible injuries are reported between 0.4–8.4% [1].

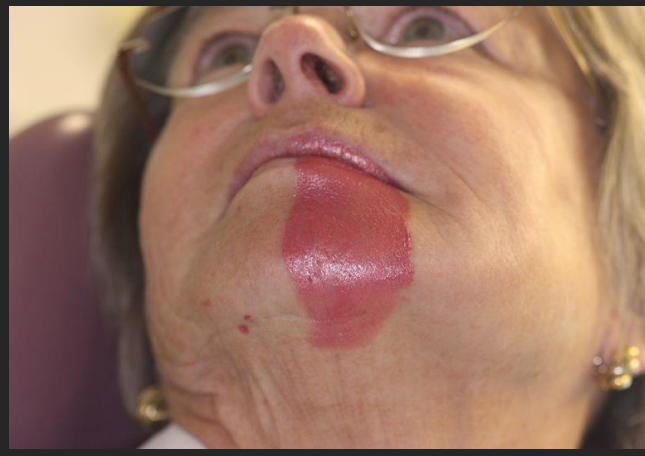
Anesthesia or paresthesia of the lower lip (consequent mental nerve sensory function disturbance) can significantly change patients' quality of life. Missing or reduced sensory innervation of the lower lip causes difficulties during eating and drinking, and uncontrolled bite trauma of the soft tissues is more frequent.

To predict "high-risk" cases more accurately or to try to avoid nerve injuries, several diagnostic and

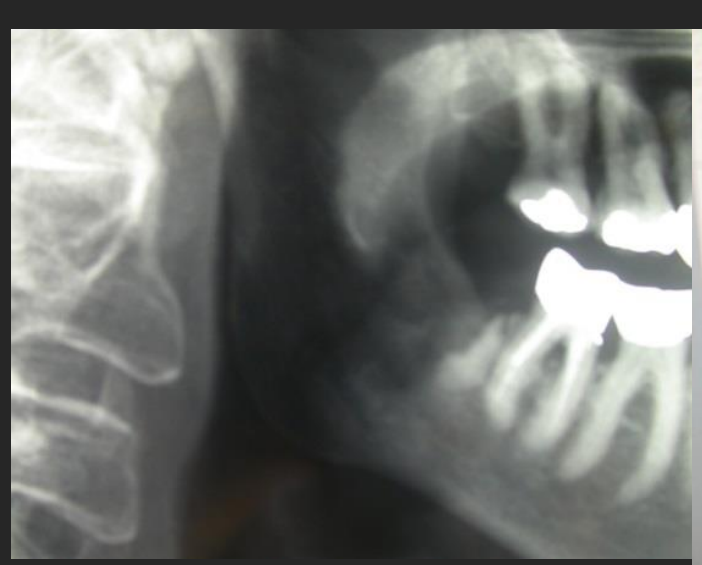
as the neurovascular bundle can "vibrate together" with piezoelectric-tips avoiding irreversible injury) when bone removal is necessary near to the IAN at the apical region of third molars.

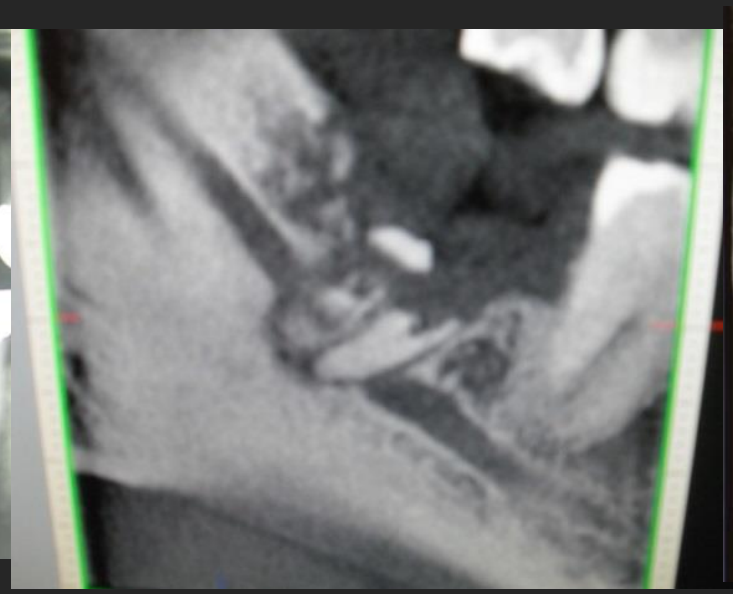
Diagnostic efforts include the analysis of two dimensional (panoramic radiography, periapical-, occlusal radiographs, vertical tube shifting technique) and three dimensional imaging methods such as computed tomography (CT) scan, cone beam CT magnetic resonance imaging (MRI) sc and limitations of specific and non-sp signs indicating intimate connections molar and the IAN are well investigat panoramic radiography, however the can carry several times important additi

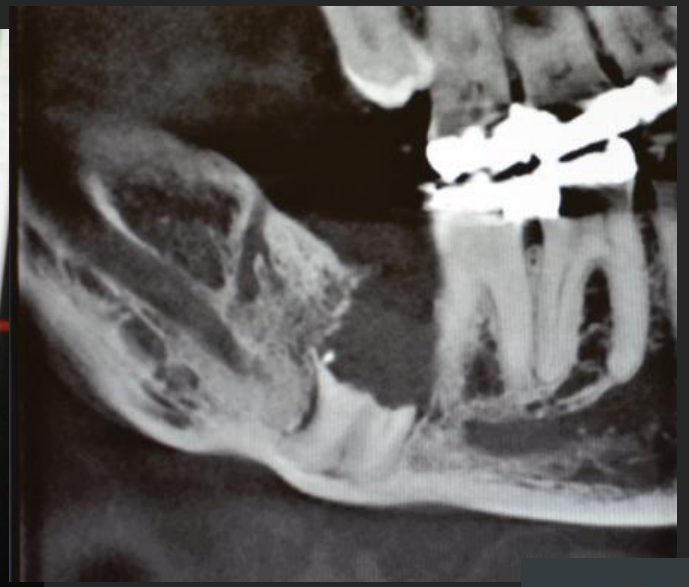
Inferior alveolar nerve injury



If DPT illustrates retained roots or compressed inferior dental canal (IDC) the CBCT useful to assess root position/ displacement and IDC structure **consider early exploration**







A Survey of the Opinion and Experience of UK Dentists: Part 2: Risk Assessment Strategies and the Management of Iatrogenic Trigeminal Nerve Injuries Related to Dental Implant **Surgery**.
Yilmaz Z, Ucer C, Scher E, Suzuki J, Renton T. Implant Dent. 2017 Apr;26(2):256-262. doi: 10.1097/ID.0000000000000545

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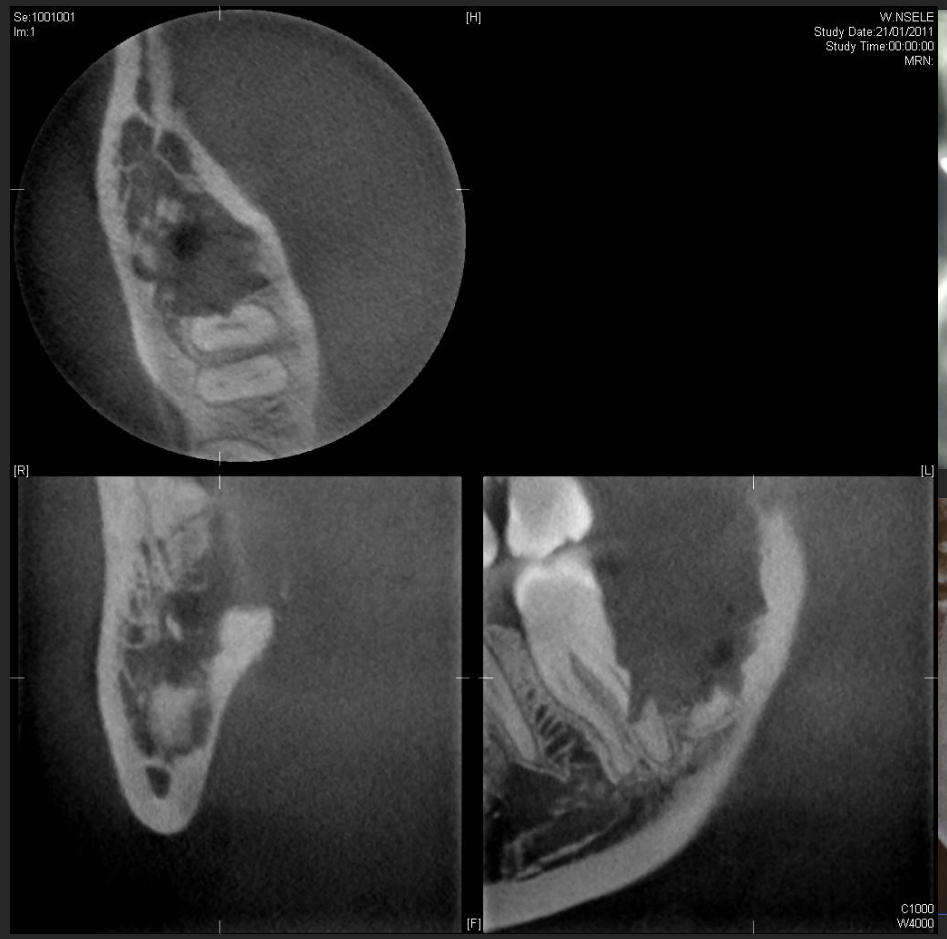
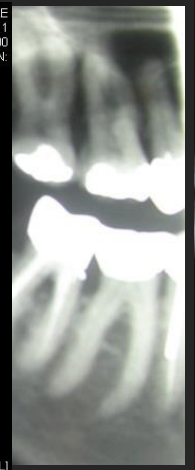
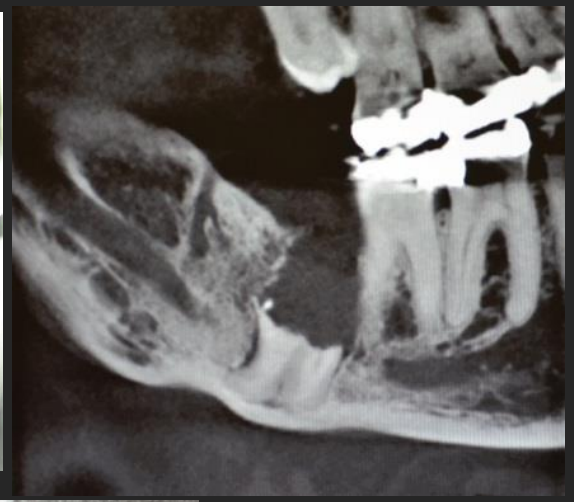
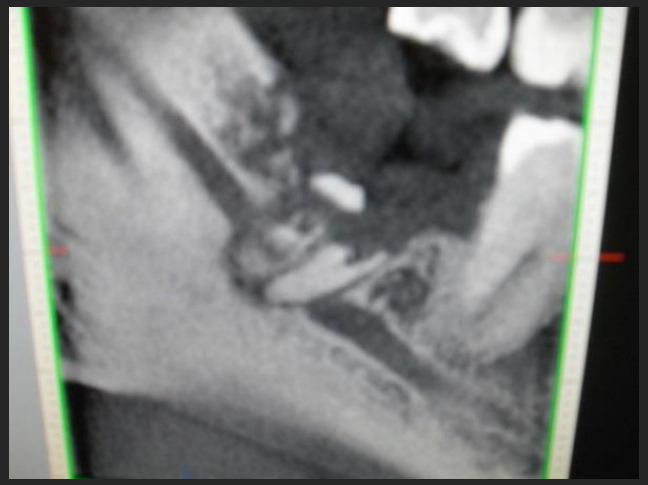
Inferior alveolar nerve injury with root retention

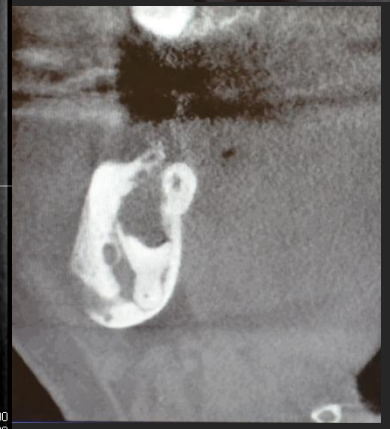
CBCT useful for risk assessment of nerve injury on removing roots and provides evidence for earlier nerve exploration











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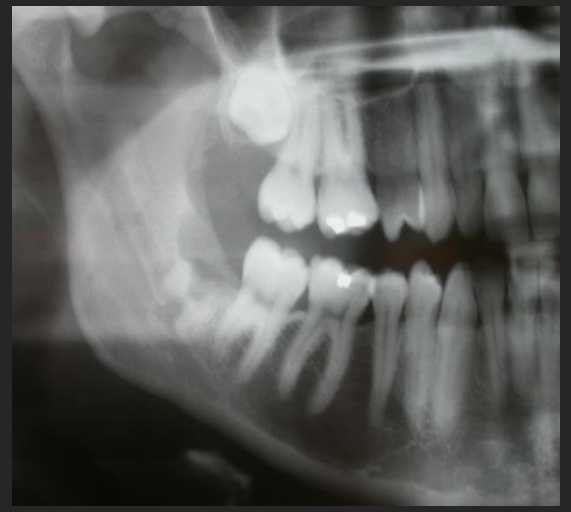
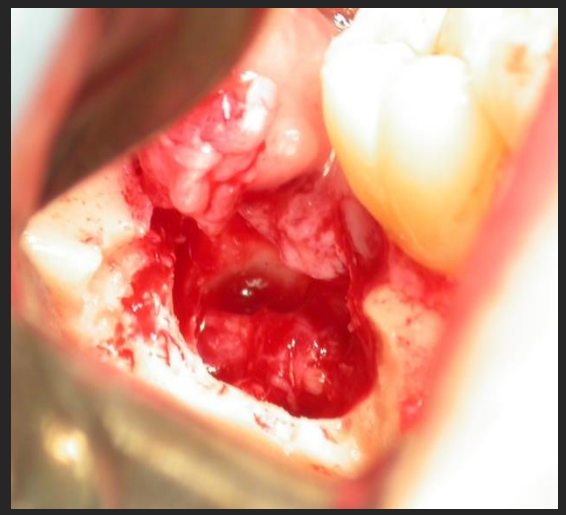
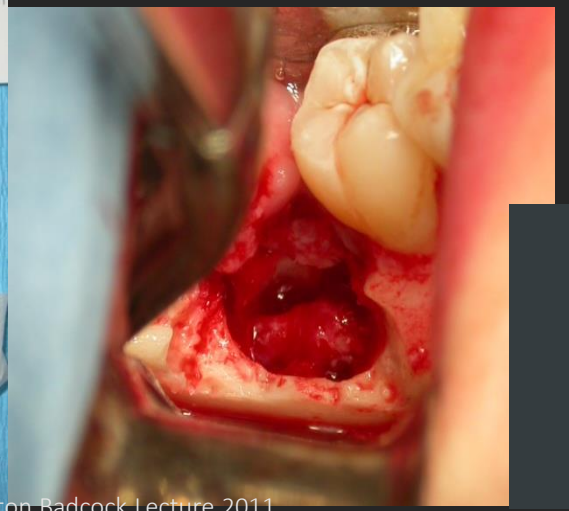
Early surgical intervention for patients IANI (< 2 weeks)

Procedure	Number of patients
Exploration and debridement	1
Exploration and decompression	8
Exploration and removal of roots and decompression	12
Excision of neuroma and reanastamosis of the nerve	3
Extraction of infected retained root and re-anastomosis of the nerve,	1







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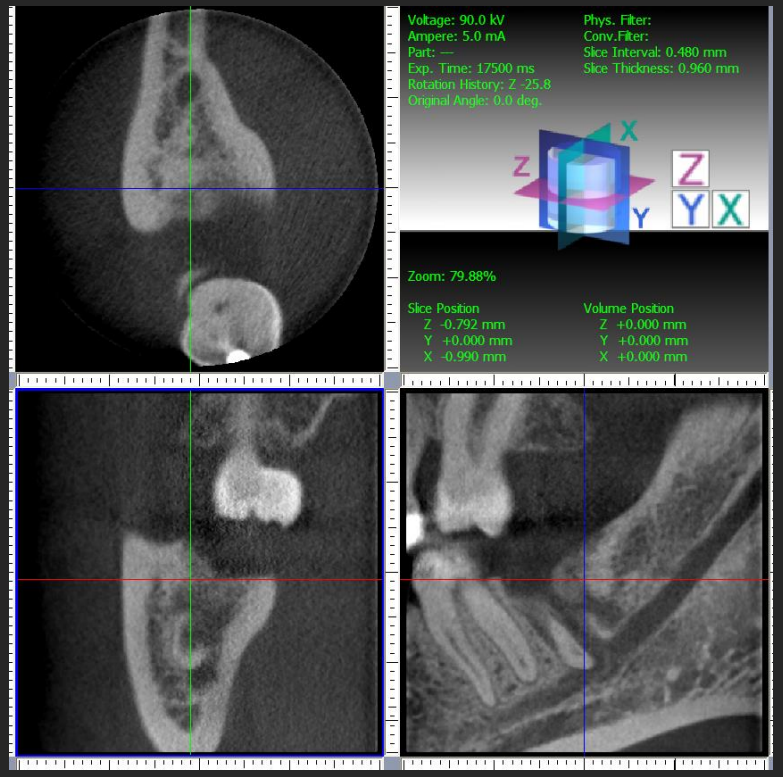
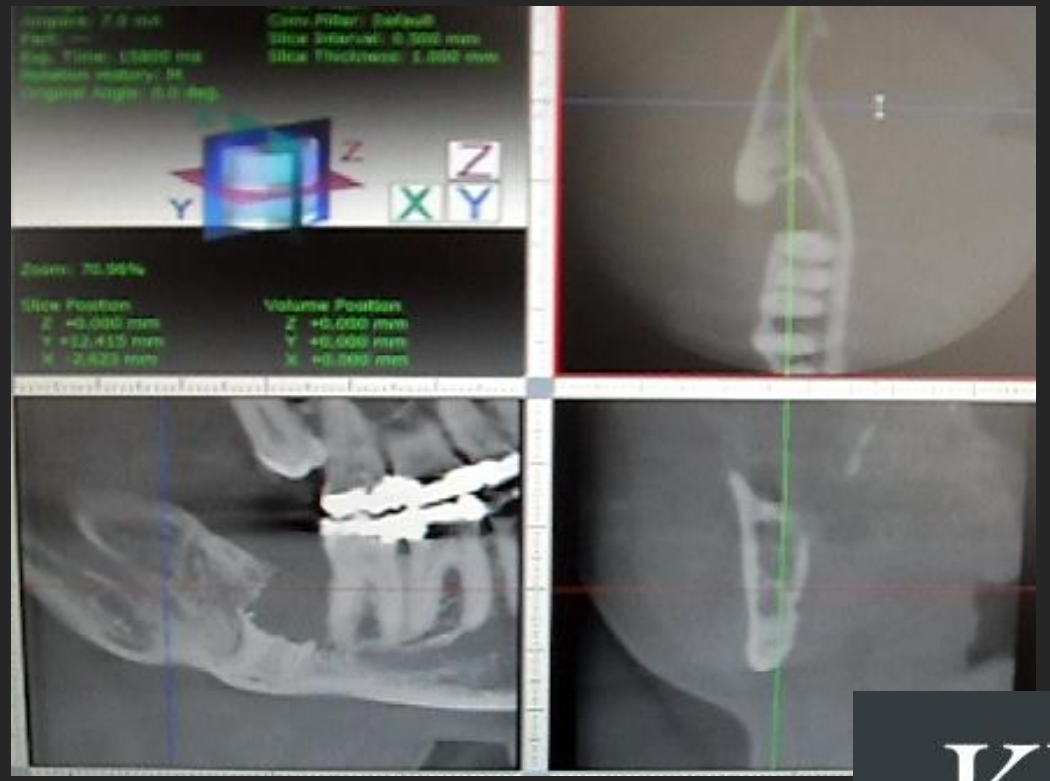
Late management of inferior alveolar nerve injury

Root retention with persistent
Chronic infection-external draining sinus (20 years post surgical) Plan surgical approach





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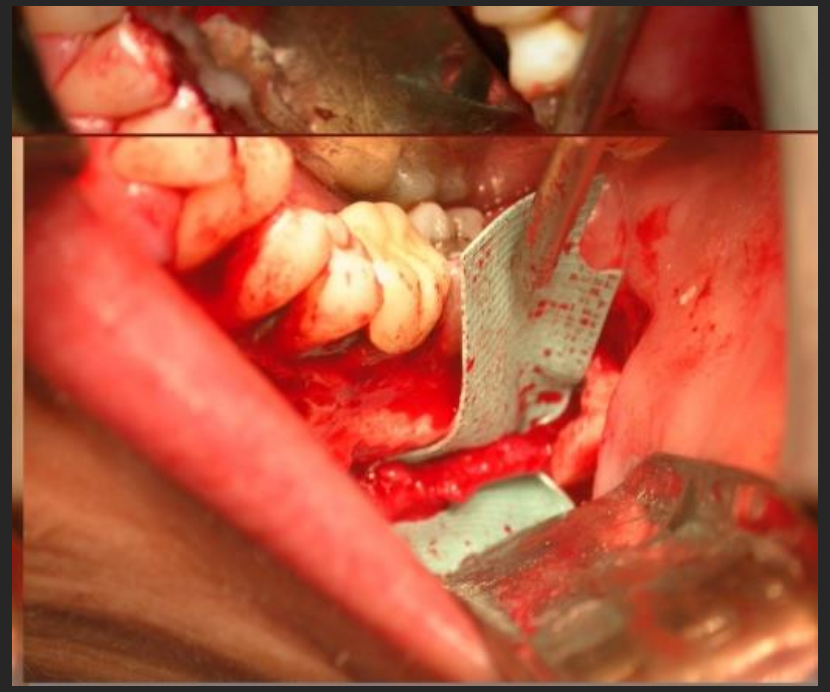
Late management of inferior alveolar nerve injury

If injury is > 36 hours days old or more

Manage therapeutically

- Surgery - removal of implant **doesn't work**
- Reassure patient
  - Psychological support
- Pain management **Medical management**
  - Topical Lidocaine patches, Capsaicin, Amitriptyline
  - Systemic Pregabalin / Tricyclic antidepressants



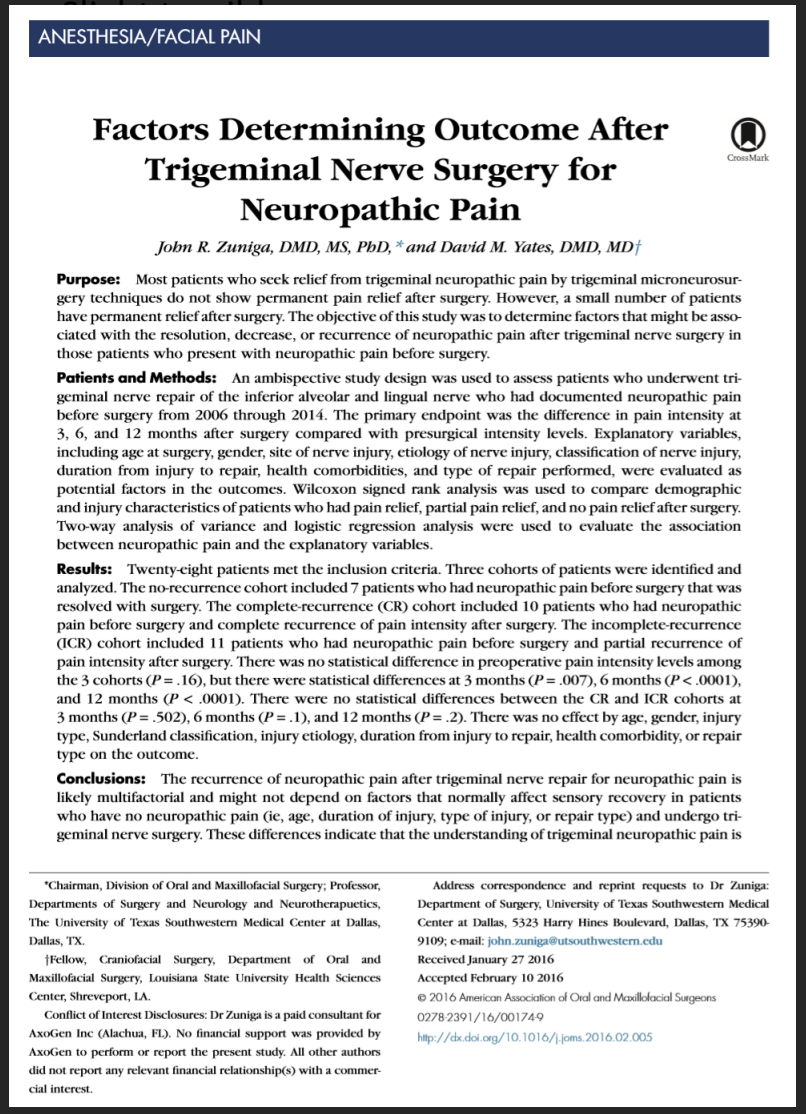
Rodriquez-Lozano F, Sanchez-Perez A, Moya-Villaescusa MJ, Rodriguez-Lozano A, Saez-Yuguero MR. Neuropathic orofacial pain after dental implant placement: review of the literature and case report. OOOE 2010; **109:** e8-e12. Renton T, Yilmaz Z. Profiling of patients presenting with posttraumatic neuropathy of the trigeminal nerve. J Orofac Pain. 2011 Fall;25(4):333-44. Renton T, Dawood A, Shah A, Searson L, Yilmaz Z. Post-implant neuropathy of the trigeminal nerve. A case series. Br Dent J. 2012 Jun 8;212(11):E17. doi: 10.1038/sj.bdj.2012.497

However Neuropathic pain does not respond to surgery

Surgical impact on NP

Lingual nerve repair and recurrence of neuropathic pain

27 patients Various procedures



ANESTHESIA/FACIAL PAIN

Factors Determining Outcome After Trigeminal Nerve Surgery for Neuropathic Pain

John R. Zuniga, DMD, MS, PhD, and David M. Yates, DMD, MD†*

Purpose: Most patients who seek relief from trigeminal neuropathic pain by trigeminal microneurosurgery techniques do not show permanent pain relief after surgery. However, a small number of patients have permanent relief after surgery. The objective of this study was to determine factors that might be associated with the resolution, decrease, or recurrence of neuropathic pain after trigeminal nerve surgery in those patients who present with neuropathic pain before surgery.

Patients and Methods: An ambispective study design was used to assess patients who underwent trigeminal nerve repair of the inferior alveolar and lingual nerve who had documented neuropathic pain before surgery from 2006 through 2014. The primary endpoint was the difference in pain intensity at 3, 6, and 12 months after surgery compared with presurgical intensity levels. Explanatory variables, including age at surgery, gender, site of nerve injury, etiology of nerve injury, classification of nerve injury, duration from injury to repair, health comorbidities, and type of repair performed, were evaluated as potential factors in the outcomes. Wilcoxon signed rank analysis was used to compare demographic and injury characteristics of patients who had pain relief, partial pain relief, and no pain relief after surgery. Two-way analysis of variance and logistic regression analysis were used to evaluate the association between neuropathic pain and the explanatory variables.

Results: Twenty-eight patients met the inclusion criteria. Three cohorts of patients were identified and analyzed. The no-recurrence cohort included 7 patients who had neuropathic pain before surgery that was resolved with surgery. The complete-recurrence (CR) cohort included 10 patients who had neuropathic pain before surgery and complete recurrence of pain intensity after surgery. The incomplete-recurrence (ICR) cohort included 11 patients who had neuropathic pain before surgery and partial recurrence of pain intensity after surgery. There was no statistical difference in preoperative pain intensity levels among the 3 cohorts ($P = .16$), but there were statistical differences at 3 months ($P = .007$), 6 months ($P < .0001$), and 12 months ($P < .0001$). There were no statistical differences between the CR and ICR cohorts at 3 months ($P = .502$), 6 months ($P = .1$), and 12 months ($P = .2$). There was no effect by age, gender, injury type, Sunderland classification, injury etiology, duration from injury to repair, health comorbidity, or repair type on the outcome.

Conclusions: The recurrence of neuropathic pain after trigeminal nerve repair for neuropathic pain is likely multifactorial and might not depend on factors that normally affect sensory recovery in patients who have no neuropathic pain (ie, age, duration of injury, type of injury, or repair type) and undergo trigeminal nerve surgery. These differences indicate that the understanding of trigeminal neuropathic pain is

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†Fellow, Craniofacial Surgery, Department of Oral and Maxillofacial Surgery, Louisiana State University Health Sciences Center, Shreveport, LA.

Conflict of Interest Disclosures: Dr Zuniga is a paid consultant for AxoGen Inc (Alachua, FL). No financial support was provided by AxoGen to perform or report the present study. All other authors did not report any relevant financial relationship(s) with a commercial interest.

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If surgical reconstruction is used to treat allodynia, this often results in a decrease of complaints but symptoms almost never completely resolve.[10] Zuniga[26] reported only 3% of patients with neuropathic pain before surgery will completely recover following surgery. Occasionally, reconstruction can worsen complaints.[9,26]

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Conclusions: The recurrence of neuropathic pain after trigeminal nerve repair for neuropathic pain is likely multifactorial and might not depend on factors that normally affect sensory recovery in patients who have no neuropathic pain (ie, age, duration of injury, type of injury, or repair type) and undergo tri-

Medical management- Pain medication

- **Acute phase**
  - Step down steroids prednisolone 50/40/30/20/10 mg over 5 day
  - Vitamin B complex including Riboflavin 300mg daily 3 months
  - NSAIDs
- **Late phase**
- **Neuralgic pain**
  - Neurontin (Lyrica) Pregabalin
  - Gabapentin
  - Oxcarbazepine
- **Burning chronic pain**
  - SNRIs
  - TCAs Nortriptyline > Amitriptyline
- 15% Pts persisted with systemic meds
- 18% IANI used topical medication

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

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

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

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

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

Conflicts of interest

NA has served on the advisory boards or speakers panels of Astellas Pharma, Adir Servier, Eli Lilly, Grunenthal, Johnson and Johnson, Sanofi Pasteur Merieux and Pfizer and has been investigator of studies sponsored by Astellas, Grunenthal and Astra Zeneca. RB has received grant/research support from Pfizer, Genzyme, Grünenthal, German Federal Ministry of Education and Research (BMBF): German Research Network on Neuropathic Pain, NoPain system biology and German Research Foundation (DFG). He has received speaker honorarium from Pfizer, Genzyme, Grünenthal, Mundipharma, Sanofi Pasteur, Medtronic, Eisai, Lilly, Boehringer Ingelheim, Astellas, Desitin, Teva Pharma, Bayer-Schering, MSD and served as consultant for Pfizer, Genzyme, Grünenthal, Mundipharma, Allergan, Sanofi Pasteur, Medtronic, Eisai, Lilly, Boehringer Ingelheim, Astellas, Novartis, Bristol-Myers Squibb, Biogenidec, AstraZeneca, Merck, Abbvie. RHD has received research grants from US Food and Drug Administration and US National Institutes of Health, and compensation for activities involving clinical trial research methods from Acorda, Adynxx, Allergan, Analgesic Solutions, Anika, Astellas, AstraZeneca, Avanir, Axsome, Bayer, Biogen, Bioness, Bristol-Myers Squibb, Cardiome, Centrexion, Charleston, Chromocell, Collegium, Concert, Daiichi Sankyo, Depomed, Depuy, Eli Lilly, Epicept, Flexion, Genzyme, Glenmark, Inhibitex, Johnson & Johnson, Lpath, Medicinova, Merck, Metys, MMS Holdings, Nektar, Neura, NeurogesX, Olatec, Ono, Periphagen, Pfizer, Phillips, Phosphagenics, Prolong, Q-Med, QRx Pharma, Regenesis, Relmada, Sanofi-Aventis, Salix, Smith & Nephew, Sorrento, Spinifex, Takeda, Taris, Teva, Theravance, and Xenon. NBF has received speaker's honorarium from Pfizer, Grunenthal, and Norpharma, research grant from Grünenthal, and consultancy fee from Astellas. MH has received honoraria from Eli Lilly, Janssen-Cilag, MSD, Mundipharma, Orion, Sanofi-Aventis for lecture, honoraria from Pfizer, Allergan, Astellas for lecture and consulting and honoraria from Abbvie for consulting TSJ have received honoraria from Pfizer, Grünenthal, Astellas, Orion and Sanofi Pasteur as speaker, advisory Board participant or grant. PK has served on advisory board for Reckitt Benckizer, and received speakers' honoraria from Pfizer. KL has received travel grants from Pfizer and Astellas. EM reports grants from Richard Saltonstall Charitable Foundation, USA, during the conduct of the study. AM has received speaker's honorarium from Pfizer, speaker's honorarium and consultancy fees from Eli Lilly and Grünental and research grant from Grünenthal. SNR has served on the advisory boards of Purdue Pharma, QRx pharma, Salix Pharmaceuticals, and Shionogi. ASCR has share options in Spinifex Pharmaceuticals. He undertakes consulting for Imperial College Consultants, and has received fees from Spinifex Pharmaceuticals, Astellas, Servier, Allergan, Asahi Kasei, and Medivir. Through EuroPain, ASCR's laboratory has received funding for research studentships from Pfizer and Astellas. Other recent or current grant/studentship funding for ASCR's laboratory are: Wellcome Trust (London Pain Consortium), Dunhill Medical Trust, NC3Rs, Westminster Medical School Research Trust, International Association for the Study of Pain, National Institute of Academic Anaesthesia, Derek Butler Trust, Medical Research Council Industrial, Biotechnology and Biological Sciences Research Council and Pfizer/Christian-Albrechts University of Kiel (Neuropain). ASCR is a member of the England and Wales Joint Committee on Vaccinati
and other from Afferent Pharmaceuticals, Centrexion, Nektar The
Biogen IDEC outside the submitted work. PS has a patent System
resonance spectroscopy, US Patent 08755862 issued. BHS has co
grants from Pfizer to support epidemiological research. MW repo
Modulations, Depomed and Inergetics. RB, NBF, KL, TSJ and A
industry members of this are: Astra Zeneca, Pfizer, Esteve, UCB-
Ingelheim, Astellas, Abbott and Lundbeck. The other authors hav

Contributors

NA, NF, SH, KL, and EM did the search and extracted data. NF
NA and NF drafted the manuscript and the tables. PH, MR, PS a
members contributed to the guidelines in formulating the recomm
external reviewers contributed to the final text version.

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

American Society Neurology recommendations

- Medical management of neuropathic pain

	Recommended drugs and doses and other treatments	Drugs and other treatments not recommended
Level A	Pregabalin, 300–600 mg/d	Oxcarbazepine
Level B	• Gabapentin, 900–3600 mg/d • Sodium valproate, 500–1200 mg/d • Venlafaxine, 75–225 mg/d • Duloxetine, 60–120 mg/d • Amitriptyline, 25–100 mg/d • Dextromethorphan, 400 mg/d • Morphine sulfate, titrated to 120 mg/d • Tramadol, 210 mg/d • Oxycodone, mean of 37 mg/d, maximum of 120 mg/d • Capsaicin cream, 0.075% 4 times daily • Isosorbide dinitrate spray • Electrical stimulation, percutaneous nerve stimulation, 3–4 wk	• Lamotrigine • Lacosamide • Clonidine • Pentoxifylline • Mexiletine • Magnetic field treatment • Low-intensity laser therapy • Reiki therapy

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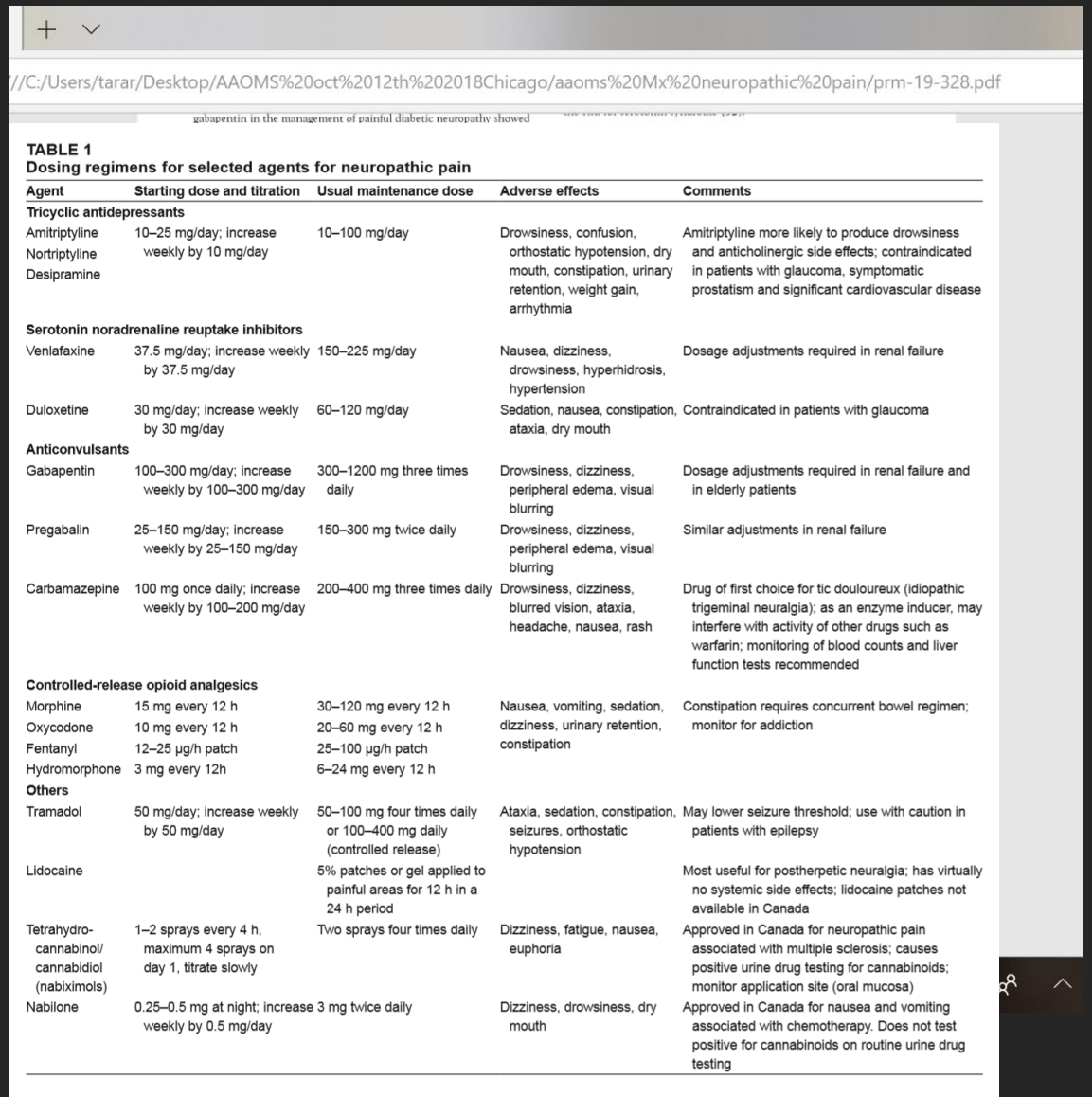
Canadian Pain society recommendations
Medical management of neuropathic pain



//C:/Users/tarar/Desktop/AAOMS%20oct%2012th%202018Chicago/aaoms%20Mx%20neuropathic%20pain/prm-19-328.pdf

gabapentin in the management of painful diabetic neuropathy showed

TABLE 1
Dosing regimens for selected agents for neuropathic pain

Agent	Starting dose and titration	Usual maintenance dose	Adverse effects	Comments
Tricyclic antidepressants				
Amitriptyline Nortriptyline Desipramine	10–25 mg/day; increase weekly by 10 mg/day	10–100 mg/day	Drowsiness, confusion, orthostatic hypotension, dry mouth, constipation, urinary retention, weight gain, arrhythmia	Amitriptyline more likely to produce drowsiness and anticholinergic side effects; contraindicated in patients with glaucoma, symptomatic prostatism and significant cardiovascular disease
Serotonin noradrenaline reuptake inhibitors				
Venlafaxine	37.5 mg/day; increase weekly by 37.5 mg/day	150–225 mg/day	Nausea, dizziness, drowsiness, hyperhidrosis, hypertension	Dosage adjustments required in renal failure
Duloxetine	30 mg/day; increase weekly by 30 mg/day	60–120 mg/day	Sedation, nausea, constipation, ataxia, dry mouth	Contraindicated in patients with glaucoma
Anticonvulsants				
Gabapentin	100–300 mg/day; increase weekly by 100–300 mg/day	300–1200 mg three times daily	Drowsiness, dizziness, peripheral edema, visual blurring	Dosage adjustments required in renal failure and in elderly patients
Pregabalin	25–150 mg/day; increase weekly by 25–150 mg/day	150–300 mg twice daily	Drowsiness, dizziness, peripheral edema, visual blurring	Similar adjustments in renal failure
Carbamazepine	100 mg once daily; increase weekly by 100–200 mg/day	200–400 mg three times daily	Drowsiness, dizziness, blurred vision, ataxia, headache, nausea, rash	Drug of first choice for tic douloureux (idiopathic trigeminal neuralgia); as an enzyme inducer, may interfere with activity of other drugs such as warfarin; monitoring of blood counts and liver function tests recommended
Controlled-release opioid analgesics				
Morphine	15 mg every 12 h	30–120 mg every 12 h	Nausea, vomiting, sedation, dizziness, urinary retention, constipation	Constipation requires concurrent bowel regimen; monitor for addiction
Oxycodone	10 mg every 12 h	20–60 mg every 12 h		
Fentanyl	12–25 µg/h patch	25–100 µg/h patch		
Hydromorphone	3 mg every 12h	6–24 mg every 12 h		
Others				
Tramadol	50 mg/day; increase weekly by 50 mg/day	50–100 mg four times daily or 100–400 mg daily (controlled release)	Ataxia, sedation, constipation, seizures, orthostatic hypotension	May lower seizure threshold; use with caution in patients with epilepsy
Lidocaine		5% patches or gel applied to painful areas for 12 h in a 24 h period		Most useful for postherpetic neuralgia; has virtually no systemic side effects; lidocaine patches not available in Canada
Tetrahydro-cannabinol/ cannabidiol (nabiximols)	1–2 sprays every 4 h, maximum 4 sprays on day 1, titrate slowly	Two sprays four times daily	Dizziness, fatigue, nausea, euphoria	Approved in Canada for neuropathic pain associated with multiple sclerosis; causes positive urine drug testing for cannabinoids; monitor application site (oral mucosa)
Nabilone	0.25–0.5 mg at night; increase weekly by 0.5 mg/day	3 mg twice daily	Dizziness, drowsiness, dry mouth	Approved in Canada for nausea and vomiting associated with chemotherapy. Does not test positive for cannabinoids on routine urine drug testing

CONSENSUS STATEMENT

Pharmacological management of chronic neuropathic pain: Revised consensus statement from the Canadian Pain Society

DE Moulin MD, A Boulanger MD, AJ Clark MD, H Clarke MD PhD, T Dao DMD PhD, GA Finley MD, A Furlan MD PhD, I Gilron MD MSc, A Gordon MD, PK Morley-Forster MD, BJ Sessle MDS PhD, P Squire MD, J Stinson RN PhD, P Taenzer PhD, A Velly DDS PhD, MA Ware MD, EL Weinberg MD, OD Williamson MBBS

DE Moulin, A Boulanger, AJ Clark, et al. Pharmacological management of chronic neuropathic pain: Revised consensus statement from the Canadian Pain Society. Pain Res Manag 2014;19(6):328-335.

BACKGROUND: Neuropathic pain (NeP), redefined as pain caused by a lesion or a disease of the somatosensory system, is a disabling condition that affects approximately two million Canadians.
OBJECTIVE: To review the randomized controlled trials (RCTs) and systematic reviews related to the pharmacological management of NeP to develop a revised evidence-based consensus statement on its management.
METHODS: RCTs, systematic reviews and existing guidelines on the pharmacological management of NeP were evaluated at a consensus meeting in May 2012 and updated until September 2013. Medications were recommended in the consensus statement if their analgesic efficacy was supported by at least one methodologically sound RCT (class I or class II) showing significant benefit relative to placebo or another relevant control group. Recommendations for treatment were based on the degree of evidence of analgesic efficacy, safety and ease of use.
RESULTS: Analgesic agents recommended for first-line treatments are gabapentinoids (gabapentin and pregabalin), tricyclic antidepressants and serotonin noradrenaline reuptake inhibitors. Tramadol and controlled-release opioid analgesics are recommended as second-line treatments for moderate to severe pain. Cannabinoids are now recommended as third-line treatments. Recommended fourth-line treatments include methadone, anticonvulsants with lesser evidence of efficacy (eg, lamotrigine, lacosamide), tapentadol and botulinum toxin. There is support for some analgesic combinations in selected NeP conditions.
CONCLUSIONS: These guidelines provide an updated, stepwise approach to the pharmacological management of NeP. Treatment should be individualized for each patient based on efficacy, side-effect profile and drug accessibility, including cost. Additional studies are required to examine head-to-head comparisons among analgesics, combinations of analgesics, long-term outcomes and treatment of pediatric, geriatric and central NeP.

Key Words: *Analgesic agents; Neuropathic pain; Randomized controlled trials*

La prise en charge pharmacologique de la douleur neuropathique chronique : une déclaration de consensus révisée de la Société canadienne de la douleur

HISTORIQUE : La douleur neuropathique (DNe), redéfinie comme une douleur causée par une lésion ou une maladie du système somatosensoriel, est un trouble invalidant dont sont affligés environ deux millions de Canadiens.
OBJECTIF : Examiner les essais aléatoires et contrôlés (EAC) et les analyses systématiques liées à la prise en charge pharmacologique de la DNe pour préparer une déclaration de consensus révisée, fondée sur des faits probants, à l'égard de sa prise en charge.
MÉTHODOLOGIE : Les EAC, les analyses systématiques et les lignes directrices sur la prise en charge pharmacologique de la DNe ont été évaluées lors d'une réunion de consensus en mai 2012, puis mises à jour en septembre 2013. Les médicaments étaient recommandés dans le document de consensus si leur efficacité analgésique était soutenue par au moins une EAC solide sur le plan méthodologique (classe I ou II), qui démontrait des avantages marqués par rapport à un placebo ou à un autre groupe témoin pertinent. Les recommandations thérapeutiques reposaient sur la qualité des preuves d'efficacité analgésique, d'innocuité et de facilité d'utilisation.
RÉSULTATS : Les analgésiques recommandés pour le traitement de première intention sont les gabapentinoïdes (gabapentine et prégabaline), les antidépresseurs tricycliques et les inhibiteurs spécifiques du recaptage de la sérotonine et de la noradrénaline. Le tramadol et les opioïdes à libération contrô
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Neuropathic pain (NeP) has been redefined as pain caused by a lesion or a disease of the somatosensory system, and may be generated by either the peripheral or central nervous system, or both

newe
higher rate of 4% to 8% (6,7), which suggest that approximately two million Canadians experience this disabling condition. Even

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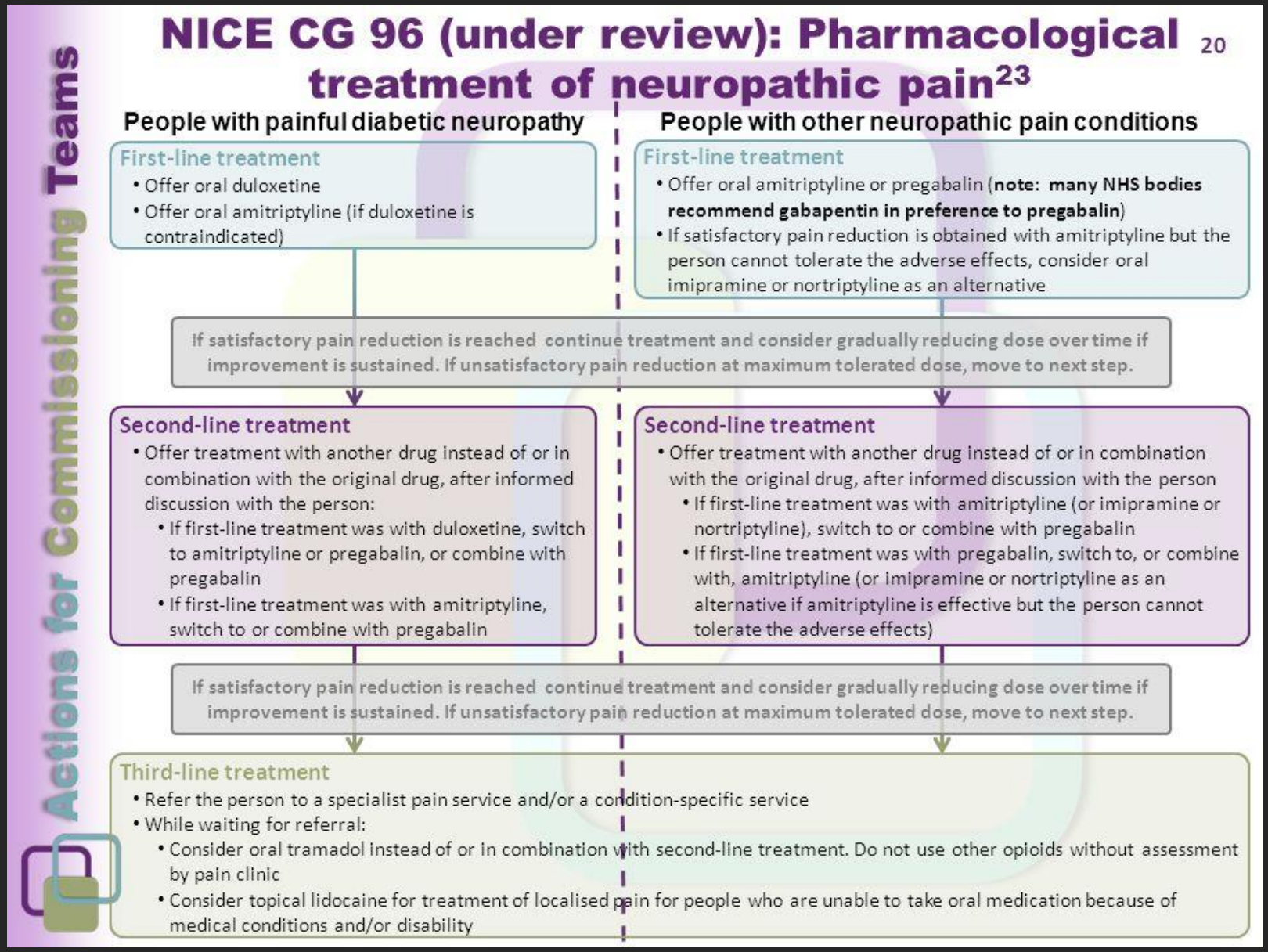
National Institute Clinical excellence (NICE) NHS recommendations Guidance for prescribing for adult neuropathic pain



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Go to drugs

Nortriptyline (TCA) (10-40mgs nocte)

Lyrica Pregabalin (25mgs nocte / BD)

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

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

Actions for Commissioning Teams

21

Pregabalin or gabapentin?

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

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Side effects and compliance

only 11% of PTNP patients continue with medication

TABLE 4

MOST COMMON ADVERSE SNRI DRUG REACTIONS[1-4]

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

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

SNRI=serotonin norepinephrine reup

Shelton RC. *Primary Psychiatry.* Vol

Common side effects associated with tricyclic antidepressants

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

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

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

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

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

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

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Medical Trigeminal Ne pain management

Grade A for TN (Tegretol)
Grade B for BMS (Nortriptyline & clonazepam)
limited for other conditions

Alonso-Ezpeleta O, Martín PJ, López-López J, Castellanos-Cosano L, Martín-González J, Segura-Eg JJ. Pregabalin in the treatment of inferior alveolar n paraesthesia following overfilling of endodontic sea Clin Exp Dent. 2014 Apr 1;6(2):e197-202.

CASE REPORT

Inferior alveolar nerve injury resulting from overextension of an endodontic sealer: non-surgical management using the GABA analogue pregabalin

1. J. López-López[1],
2. A. Estrugo-Devesa[1],
3. E. Jané-Salas[1] and
4. J. J. Segura-Egea[2]

Article first publish

DOI: 10.1111/j.136

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Issue

International End

López-López J, Estrugo-Devesa A, Jané-Salas E, Segura-Egea JJ Infe alveolar nerve injury resulting from overextension of an endodontic management using the GABA analogue pregabalin. Int Endod J. 2012 doi: 10.1111/j.1365-2591.2011.01939.x. Epub 2011 Aug 23.

AIM:To describe a case of endodontic sealer (AH Plus) penetration within the after root canal treatment with resolution of pain and paraesthesia after a nc including treatment with prednisone and pregabalin.
SUMMARY:A 37-year-old woman underwent root canal treatment of the left molar tooth. Postoperative periapical radiographs revealed the presence of r sealer in the mandibular canal. The day after, the patient reported severe pa paraesthesia/anaesthesia in the region innervated by the left inferior alveola Diagnosis of injury to the inferior alveolar nerve because of extrusion of AH The non-surgical management included 1 mg kg(-1) per day prednisone, two regimen on a daily basis, and 150 mg per day pregabalin, two doses per day progress with periodic follow-up visits. One month after the incident, the sig were gone.
KEY LEARNING POINTS: This case illustrates the care required when performing root canal treatment, especially when the root apices are in close proximity to the inferior alveolar nerve canal. The complete resolution of paraesthesia and the control of pain achieved in

Haviv Y, Zadik Y, Sharav Y, Benoliel R. Painful traumatic trigeminal neuropathy: an open study on the pharmacotherapeutic response to stepped treatment. J Oral Facial Pain Headache. 2014 Winter;28(1):52-60. doi: 10.11607/jop.1154.

AIMS: To evaluate pharmacotherapeutic success in patients with painful traumatic trigeminal neuropathy (PTTN) and to identify patient or pain characteristics that may predict treatment outcome.

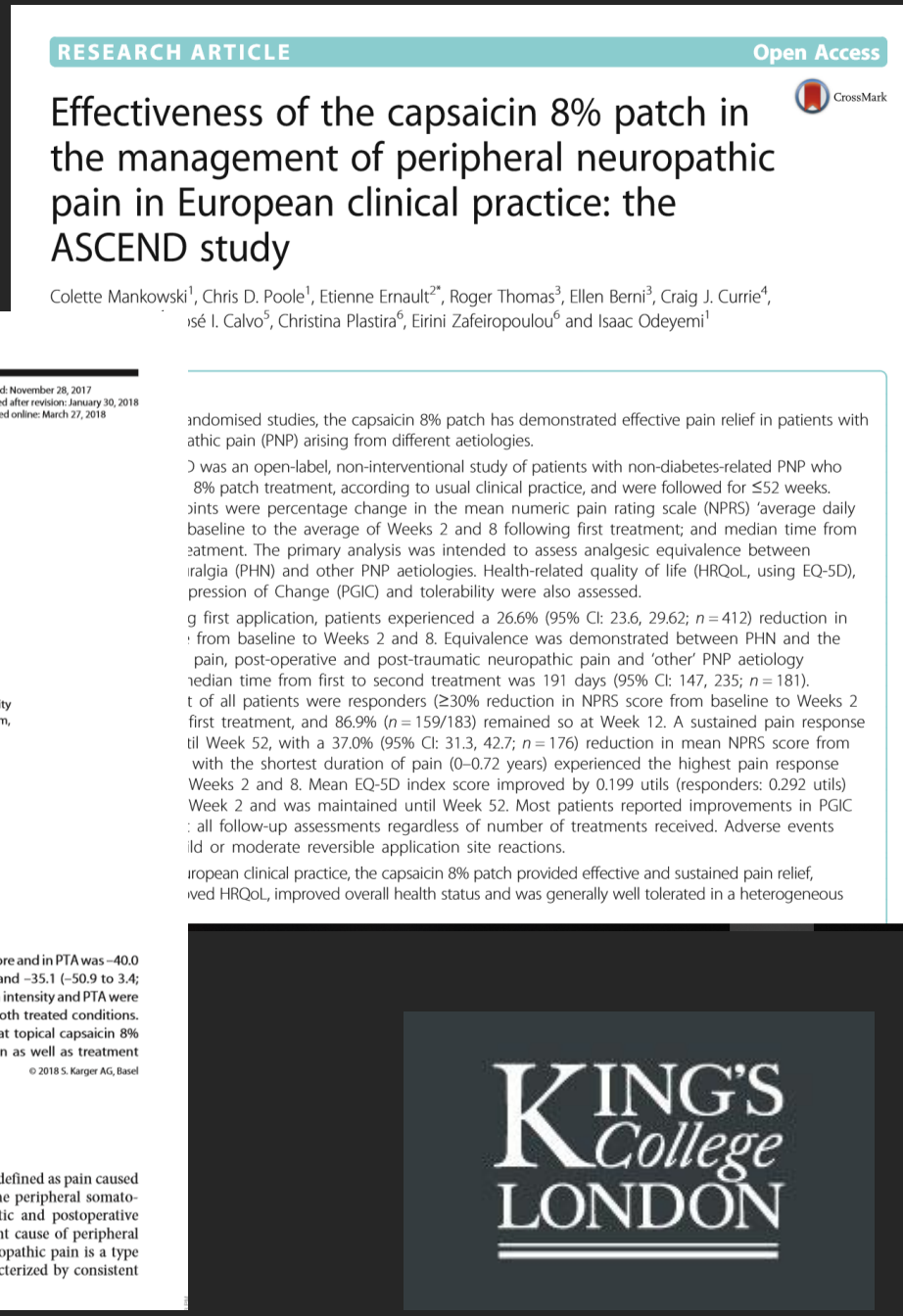
METHODS: Pharmacotherapy was instituted for PTTN patients and was based on widely accepted protocols fo neuropathic pain and conducted in an open fashion. Outcome was assessed by employing prospective diaries recording pain intensity measured with an 11-point (0 to 10) verbal pain score (VPS). Individual characteristics in the patients and their influence on outcome were analyzed. Treatment results in the PTTN patients were compared with those in classical trigeminal neuralgia (CTN) patients, who were used as a comparative cohort. Data were analyzed with a Pearson chi-square test for nominal variables and with an independent samples t test or analysis of variance for continuous variables.

RESULTS: A total of 145 patients were included: 91 with PTTN and 54 with CTN. In PTTN patients, 11% had ≥ 50% reduction in pain intensity. Higher VPS scores in the PTTN patients were associated with a significantly reduced response to therapy (P = .03). No other pain-related or demographic parameters were associated with treatment outcome in the PTTN patients. Also the response rate of PTTN patients was significantly inferio to that of CTN patients, 74.1% of whom attained a significant reduction in pain intensity (P < .001).

CONCLUSION: This study underpins the poor pharmacotherapeutic prognosis of PTTN. The results support findings on neuropathic pain in other sites and point to the need for further research and reexamination of current PTTN treatment protocols.

Capsaicin patches

- Grade evidence for other PTNs
- Low evidence for PPTTN



RESEARCH ARTICLE Open Access

Effectiveness of the capsaicin 8% patch in the management of peripheral neuropathic pain in European clinical practice: the ASCEND study

Colette Mankowski[1], Chris D. Poole[1], Etienne Ernault[2*], Roger Thomas[3], Ellen Berni[3], Craig J. Currie[4], ...sé I. Calvo[5], Christina Plastira[6], Eirini Zafeiropoulou[6] and Isaac Odeyemi[1]

...ndomised studies, the capsaicin 8% patch has demonstrated effective pain relief in patients with ...athic pain (PNP) arising from different aetiologies.

...) was an open-label, non-interventional study of patients with non-diabetes-related PNP who ... 8% patch treatment, according to usual clinical practice, and were followed for ≤52 weeks. ...oints were percentage change in the mean numeric pain rating scale (NPRS) 'average daily ...baseline to the average of Weeks 2 and 8 following first treatment; and median time from ...eatment. The primary analysis was intended to assess analgesic equivalence between ...uralgia (PHN) and other PNP aetiologies. Health-related quality of life (HRQoL, using EQ-5D), ...pression of Change (PGIC) and tolerability were also assessed.

...g first application, patients experienced a 26.6% (95% CI: 23.6, 29.62; $n = 412$) reduction in ... from baseline to Weeks 2 and 8. Equivalence was demonstrated between PHN and the ... pain, post-operative and post-traumatic neuropathic pain and 'other' PNP aetiology ...edian time from first to second treatment was 191 days (95% CI: 147, 235; $n = 181$). ...t of all patients were responders (≥30% reduction in NPRS score from baseline to Weeks 2 ... first treatment, and 86.9% ($n = 159/183$) remained so at Week 12. A sustained pain response ...til Week 52, with a 37.0% (95% CI: 31.3, 42.7; $n = 176$) reduction in mean NPRS score from ... with the shortest duration of pain (0–0.72 years) experienced the highest pain response ...Weeks 2 and 8. Mean EQ-5D index score improved by 0.199 utils (responders: 0.292 utils) ...Week 2 and was maintained until Week 52. Most patients reported improvements in PGIC ... all follow-up assessments regardless of number of treatments received. Adverse events ...ild or moderate reversible application site reactions.

...uropean clinical practice, the capsaicin 8% patch provided effective and sustained pain relief, ...ved HRQoL, improved overall health status and was generally well tolerated in a heterogeneous

Pharmacology

Original Paper

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Efficacy Analysis of Capsaicin 8% Patch in Neuropathic Peripheral Pain Treatment

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Keywords
Capsaicin · Allodynia · Analgesic affect · Peripheral neuropathic pain

Abstract
Background/Aims: Several guidelines for neuropathic pain management and various effective drugs are available; however, neuropathic pain remains undertreated. This retrospective study aimed to evaluate the efficacy of topical capsaicin 8% in peripheral neuropathic pain in a routine clinical setting. ***Methods:*** Therapeutic efficacy was evaluated through pain intensity, using numerical pain rating scale at baseline and 7–14 days after each treatment, and using pain treatment area (PTA) assessed immediately before each treatment. ***Results:*** A total of 43 patients with either postherpetic neuralgia or post-traumatic/post-surgical neuropathic pain were enrolled. The median percentage reduction in numerical pain rating scale score and in PTA was −40.0 (−50.0 to −33.3; 95% CI, bootstrap) and −35.1 (−50.9 to 3.4; 95% CI, bootstrap), respectively. Pain intensity and PTA were equally improved and reduced in both treated conditions. ***Conclusion:*** This study suggests that topical capsaicin 8% reduces peripheral neuropathic pain as well as treatment pain area.

Introduction

Peripheral neuropathic pain is defined as pain caused by a lesion or disease affecting the peripheral somatosensory system [1]. Post-traumatic and postoperative nerve injuries represent a frequent cause of peripheral neuropathic pain. Localized neuropathic pain is a type of neuropathic pain that is characterized by consistent

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Botulinum toxin A

High level evidence for

- diabetic neuropathic pain
- Migraine
- Limb amputation pain

- Low evidence PPTTN
- Emerging evidence for TN

Disease-a-Month 62 (2016) 353–357

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Botulinum toxin for chronic pain conditions

Rachel Kermen, MD

Introduction

Botulinum neurotoxin (BoNT), derived from *Clostridium botulinum*, a Gram-positive anaerobic bacterium, was first used for therapeutic purposes in 1980 for treatment of strabismus. Since that time, its use has expanded for a multitude of cosmetic and therapeutic indications. There are seven BoNT serotypes of which there are currently four BoNT versions available in the United States, onabotulinumtoxinA (Botox), abobotulinumtoxinA (Dysport), incobotulinumtoxin A (Xeomin), and rimabotulinumtoxinB (Myobloc). The list of FDA approved indications for BoNT has grown over the years with BoNT-A (Botox) having the most approved indications, including cervical dystonia, severe primary axillary hyperhidrosis, strabismus, blepharospasm, neurogenic detrusor overactivity, chronic migraine, upper limb spasticity, as well as additional cosmetic uses. Currently, only one primary pain disorder, chronic migraine, has FDA approval (BoNT-A). [illegible] research exploring the use of BoNT for other chronic pain disorders, i[illegible] pain, intra-articular pain, myofascial pain, and complex regional pain sy[illegible]

BoNT mechanism of action and rationale for use in chronic pain co[illegible]

The primary mechanism of action of BoNT is blockage of ac[illegible] transmitter release from the presynaptic nerve at the neuromuscular j[illegible] contraction of the muscle fiber, causing involuntary muscle relaxation and above a certain threshold, muscle weakness and paralysis. This effect is temporary with recovery occurring

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Botoxin A
Grade B for TN but low evidence for PTN

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

TRIALS

STUDY PROTOCOL Open Access

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

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Abstract

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

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

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

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

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

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

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

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

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

MATERIALS AND METHODS

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

Eligibility criteria

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

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2212-4403/$ - see front matter
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Statement of Clinical Relevance

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

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

The Journal of Headache and Pain

REVIEW ARTICLE Open Access

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

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Abstract

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

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

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

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

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

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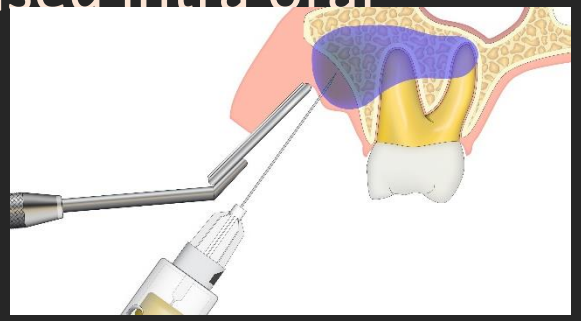
Ngeow WC, Nair R Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010 Mar;109(3):e47-50.
Injection of botulinum toxin type A (BOTOX) into trigger zone of trigeminal neuralgia as a means to control pain.

Pre Botox LA injections for focal neuropathic pain

Lidocaine 2% (1:80K epinephrine) 1-2mls infiltrations
positive response prerequisite for BTX treatment but not predictive

PDAP 1 or primary localised intra oral Ne Pain



- 7 patients
- Mean age 55yrs
- 60% Female
- Site
  - 40% mandibular posterior molar region
  - 40% posterior maxillary molar region
  - 20% anterior maxilla
- Response rate
  - Complete 3 (1 hour-30days)
  - Partial 2
  - None 2

PPTTN localised intra oral Ne Pain

- 18 patients
- Mean age 42 yrs
- 75% female
- Site
  - 15% mandibular posterior molar region
  - 5% posterior maxillary molar region
  - 80% anterior maxilla
- Response rate
  - Complete 14 (duration 1 hour -42 days)
  - Partial 2
  - None 2

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Interventional pain management includes;

- **Peripheral stimulation**
  - Superficial sessional neurostimulation
- **Central Neurostimulation/ neuromodulation**
  - SPG - Ganglia implanted neurostimulation
  - TG Pulsed Radiofrequency
  - Spinal cord stimulation (not for OFP)
  - Deep brain stimulation
  - Transmagnetic stimulation

ABLATIVE TECHNIQUES

Gasserian Ganglion interventions
- Radiofrequency ablation
- Thermocoagulation
- Balloon compression
- Glycerolysis
- Cryosurgery

Sphenopalatine ganglion injections

Stereotactic radiosurgery

Gamma knife may be indicated If there is medical contraindications to MVD

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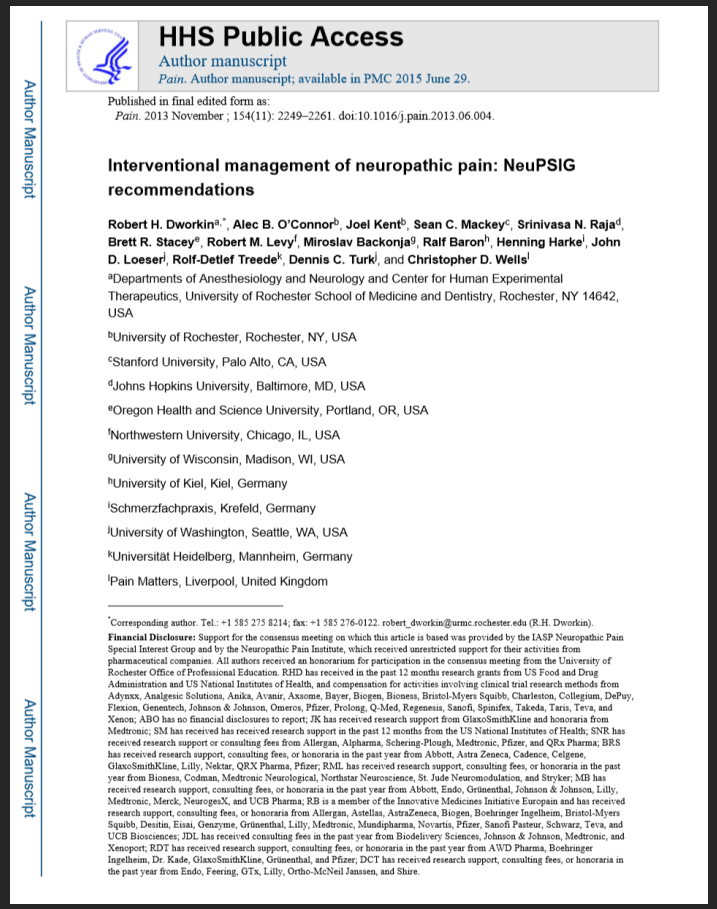
IASP Neuropathic SIG Recommendations interventional procedures for Ne Pain



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Interventional management of neuropathic pain: NeuPSIG recommendations

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Neuropathic pain (NP) is often refractory to pharmacologic and non-interventional treatment. On behalf of the International Association for the Study of Pain Neuropathic Pain Special Interest Group (NeuPSIG),

Ne pain due to

- peripheral and central NP conditions
- herpes zoster and postherpetic neuralgia (PHN)
- painful diabetic and other peripheral neuropathies
- spinal cord injury NP
- central post-stroke pain
- radiculopathy
- failed back surgery syndrome (FBSS)
- complex regional pain syndrome (CRPS)
- **trigeminal neuralgia and neuropathy**

Evidence is summarized and presented for

- neural blockade,
- spinal cord stimulation (SCS),
- intrathecal medication,
- and neurosurgical interventions

evidence, including degree of efficacy and safety, are: (1) epidural injections for herpes zoster; (2) steroid injections for radiculopathy; (3) SCS for FBSS; and (4) SCS for CRPS type 1. Based on the available data, we recommend not to use sympathetic blocks for PHN nor RF lesions for radiculopathy

Alternative analgesic therapies

- Homeopathic
  - Arnica reduces bruising and swelling
- Hypnotherapy
  - self hypnosis
  - induced hypnosis
- Counselling
  - Chronic pain patients may need counselling to improve their coping strateg
- CBT
- Sleep
- Biofeedback
  - training in changing function to reduce pain
- Tens shown to reduce the discomfort of ID blocks
- Pet therapy
- Mirror therapy

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CLINICAL REVIEW

Sleep disorders and chronic craniofacial pain: Characteristics and management possibilities

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SUMMARY

Chronic craniofacial pain involves the head, face and oral cavity and is associated with significant morbidity and high levels of health care utilization. A bidirectional relationship is suggested in the literature for poor sleep and pain, and craniofacial pain and sleep are reciprocally related. We review this relationship and discuss management options.

Part I reviews the relationship between pain and sleep disorders in the context of four diagnostic categories of chronic craniofacial pain: 1) primary headaches: migraines, tension-type headache (TTH), trigeminal autonomic cephalalgias (TACs) and hypnic headache, 2) secondary headaches: sleep apnea headache, 3) temporomandibular joint disorders (TMD) and 4) painful cranial neuropathies: trigeminal neuralgia, post-herpetic trigeminal neuropathy, painful post-traumatic trigeminal neuropathy (PTTN) and burning mouth syndrome (BMS). Part II discusses the management of patients with chronic craniofacial pain and sleep disorders addressing the factors that modulate the pain experience as well as sleep disorders and including both non-pharmacological and pharmacological modalities.

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