Review of BTX-A in Neuropathic Pain Syndromes -

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Disclaimer

- Allergan
- Pfizer
- Purdue
- AstraZeneca
- Janssen Ortho
- Merck
- Valeant
- Lilly
- Sanofi

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WPMC

- Neurology
- Nursing
- Dentistry
- Anaesthesia
- Psychiatry
- Gynecology
- Family Medicine/Behavioural
- Sex Therapy
- Access through Rehab and Wellbeing to Physio, Chiropractic, Massage, Podiatry, Acupuncture and Tai Chi, Laser, Shockwave
- Function and Pain

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ADDOP: The Five Pillars of Pain Management

- **A**ssess risk assessment / symptom assessment
- **D**efine the problem and treat it
- **D**iagnose the kind of pain and treat it: NeP Nociceptive
- **O**ther issues: mood, anxiety, sleep, addiction, sexual, catastrophization
- **P**ersonal management / self management

Programs of Care

- Pain and Addiction
- Individuals with Complex Pain Issues
- Craniofacial Pain and Headache
- Neuropathic Pain
- Pelvic and Genital Pain
- Musculoskeletal Pain

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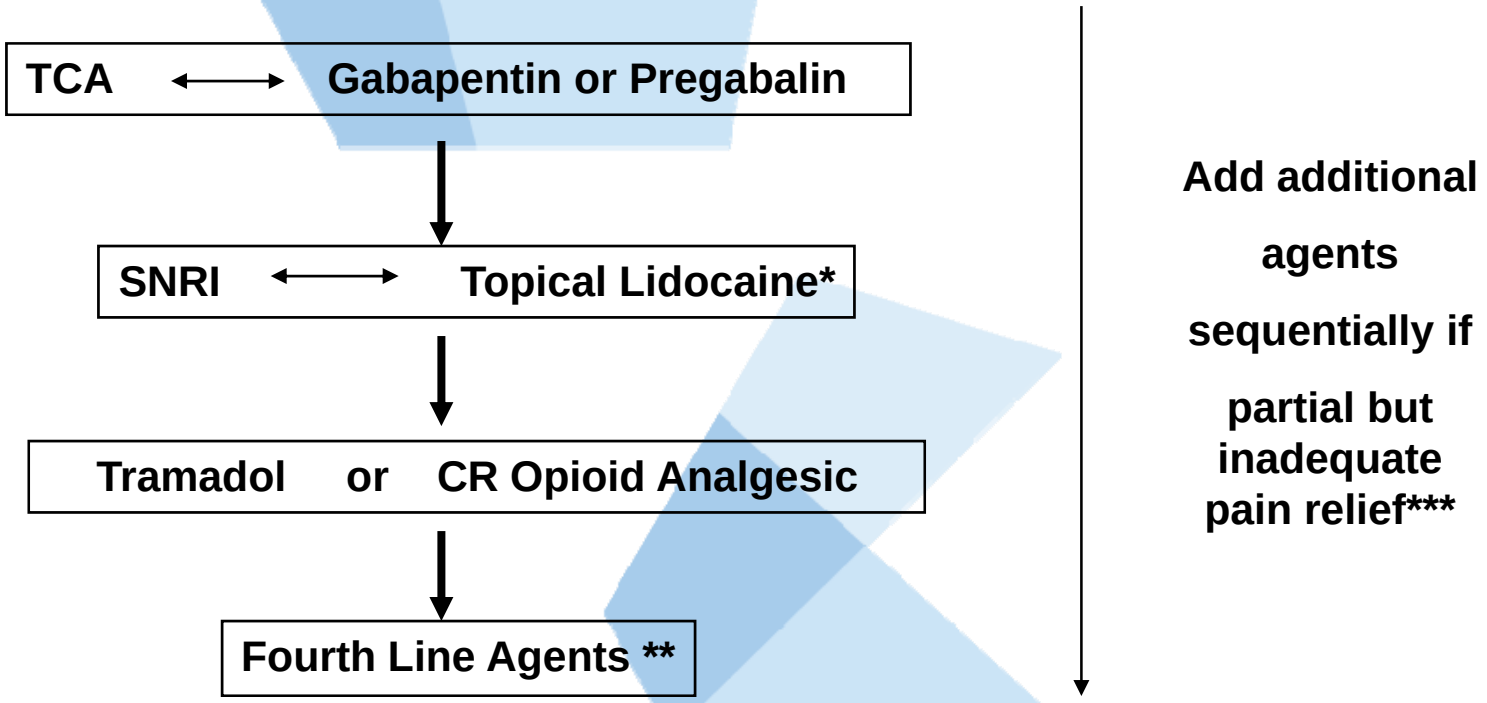
What is Neuropathic pain?

- IASP (original): pain initiated or caused by a primary lesion or dysfunction in the nervous system
- “Pain arising as direct consequence of a lesion or disease affecting the somatosensory system” Expert panel

We Manage Neuropathic Pain

- Numbness, allodynia, hyperalgesia
- Seen in TN, PHN, Diabetic neuropathy, Post traumatic
- Central
- Phantom limb
- Normally with various medications

STEPWISE PHARMACOLOGIC MANAGEMENT OF NEUROPATHIC PAIN



* 5% gel or cream – useful for focal neuropathy such as postherpetic neuralgia..

** eg Cannabinoids, methadone, lamotrigine, topiramate, valproic acid

*** Do not add SNRI to TCA

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Trigeminal Nerve Pain Conditions

A Trigeminal Neuralgia

Other syndromes

B Secondary Trigeminal Neuralgia or Central Neuropathic Pain including MS

...Trigeminal Neuropathic Pain

C Atypical Facial Pain

D Post-herpetic Neuralgia

A Trigeminal Neuralgia

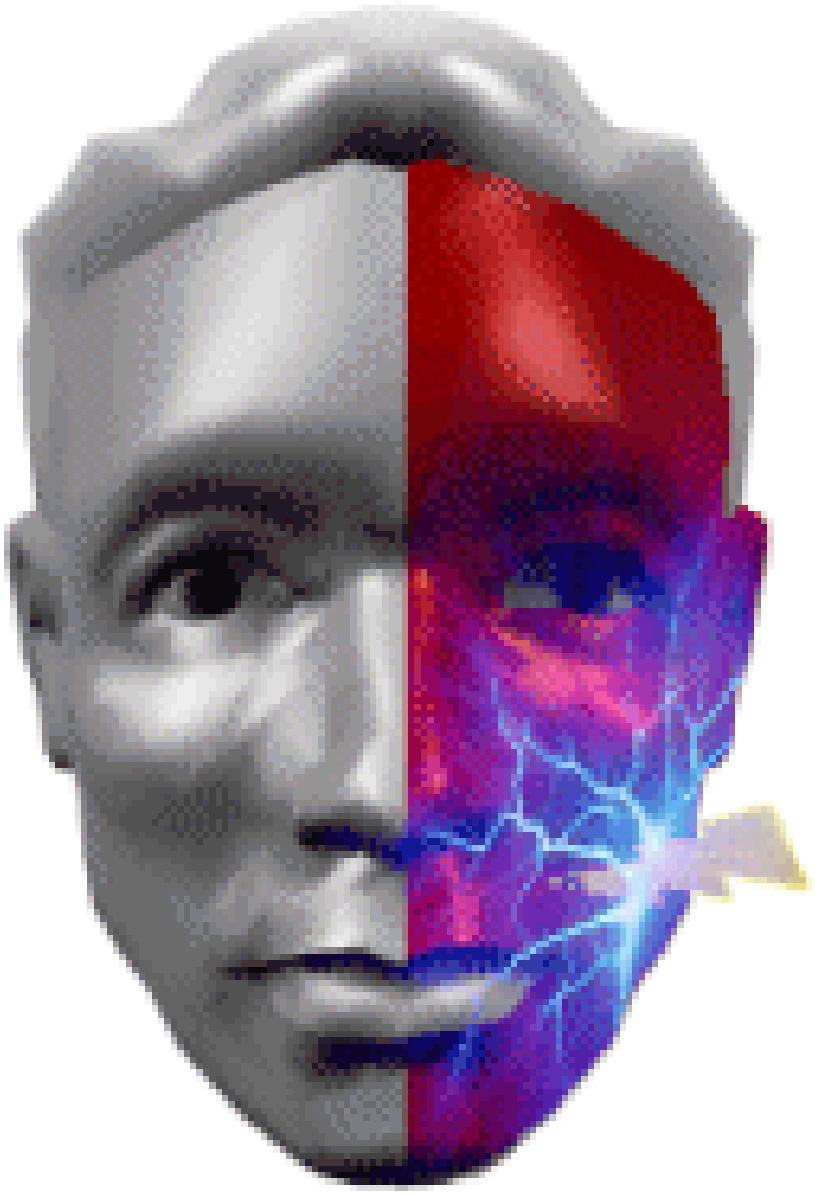
- Seen more commonly after the age of 50
- If before age of 50, think ‘secondary’ TN
- However some patients are younger
- Often seen with dental presentation

Symptoms

- Stabbing, jabbing pain
- Wince in pain
- Trigger zone
- In all 3 divisions of the trigeminal nerve but V2 most common
- ?R>L; rarely simultaneously bilateral
- May have dental presentation

Pathophysiology

- Vascular compression of trigeminal root leading to neuropathic changes
- Sometimes seems to come after unsuccessful endodontic procedure



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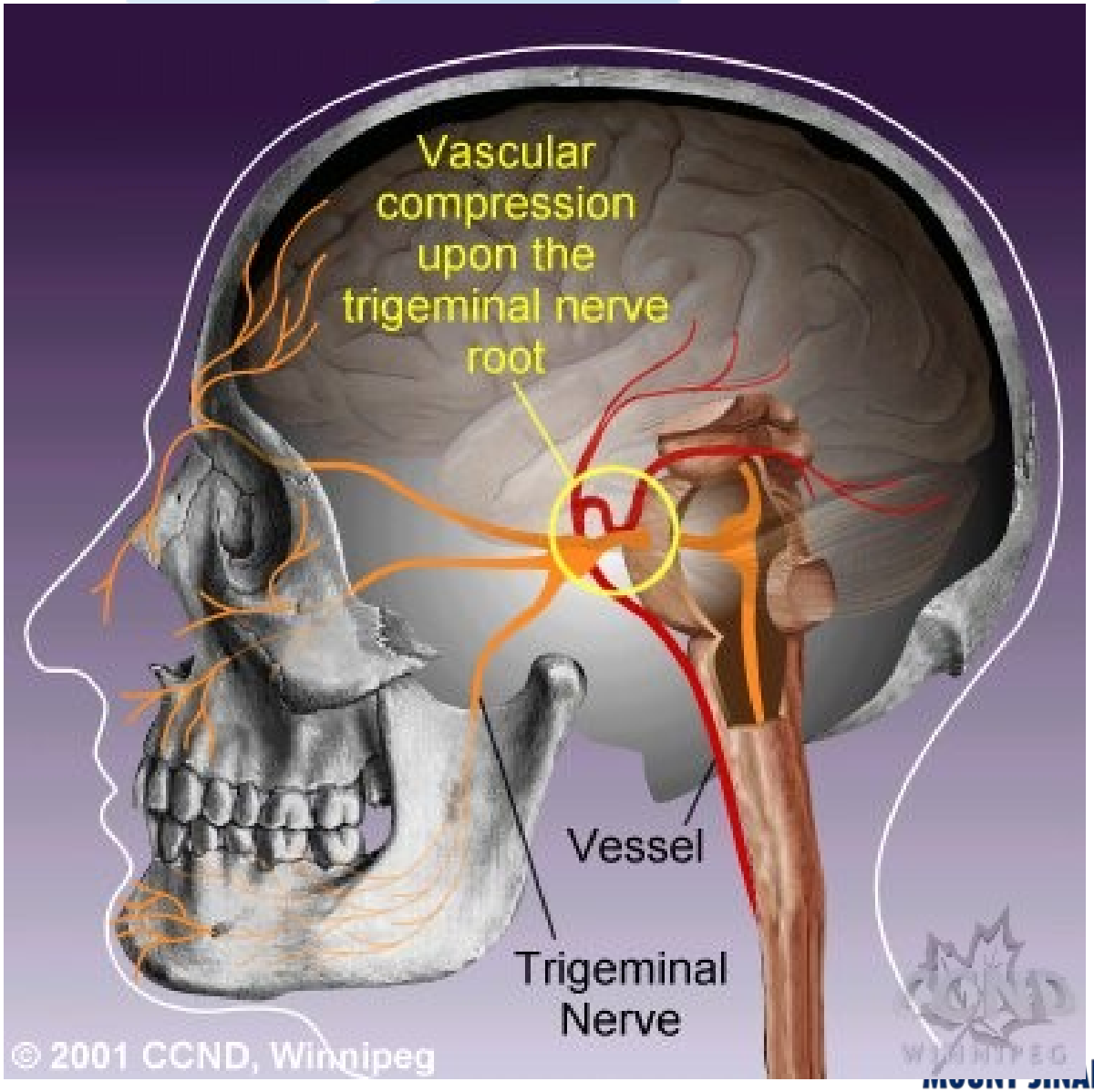

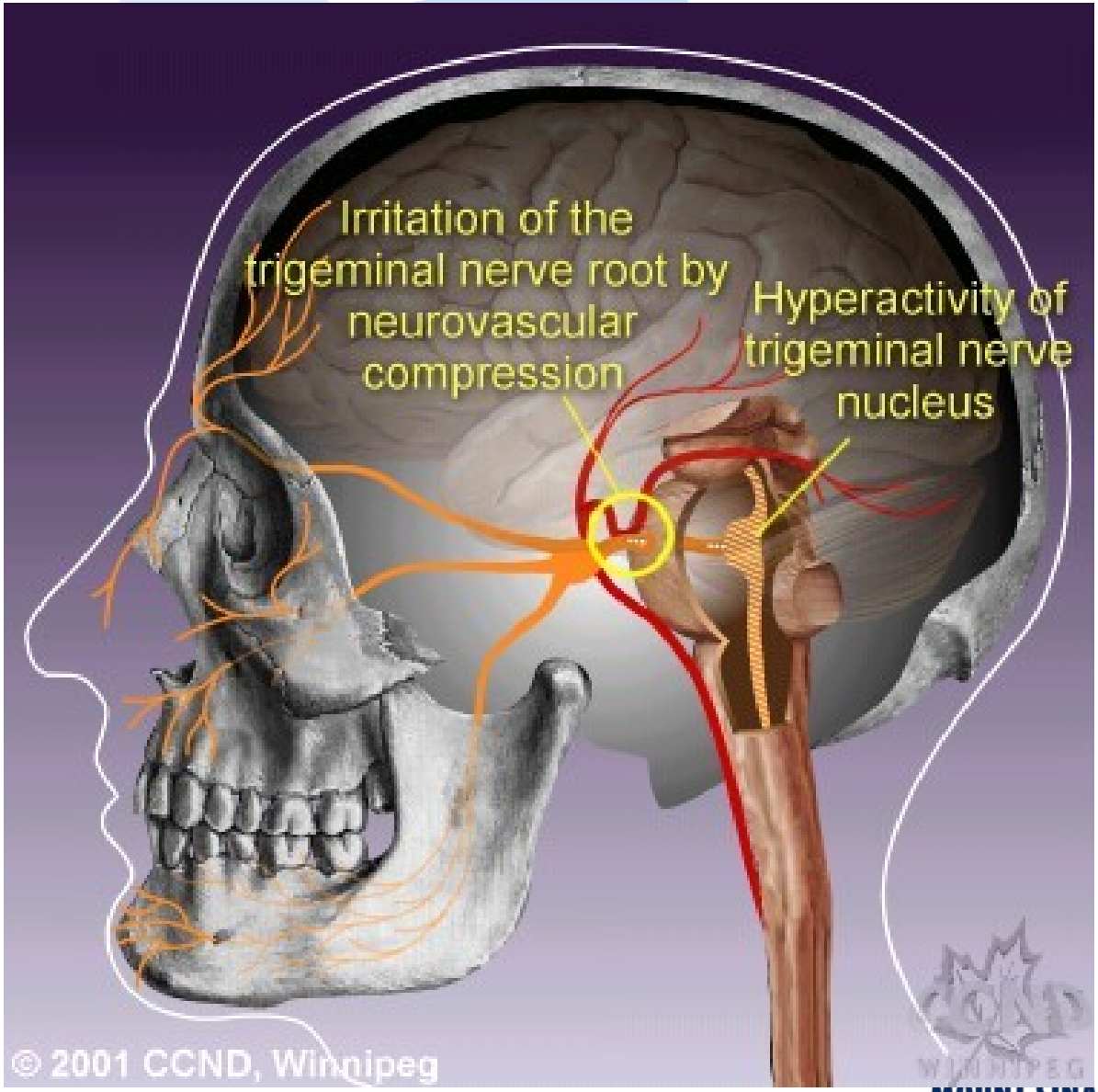

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Huan-Jie Wu et al (Cephalgia 2012)

- Botulinum toxin type A for the treatment of trigeminal neuralgia: results from a randomized, double, placebo-controlled trial

Trial

- 42 patients with TN randomized into 2 groups for injection into painful area
- A 75u/1.5ml of intradermal and/or submucosal BTX-A
- B 1.5 ml of saline
- Primary endpoint pain severity (VAS) and pain attack frequency per day
- Secondary Patient Global Assessment of Change scale (50% reduction at 12 weeks were responders

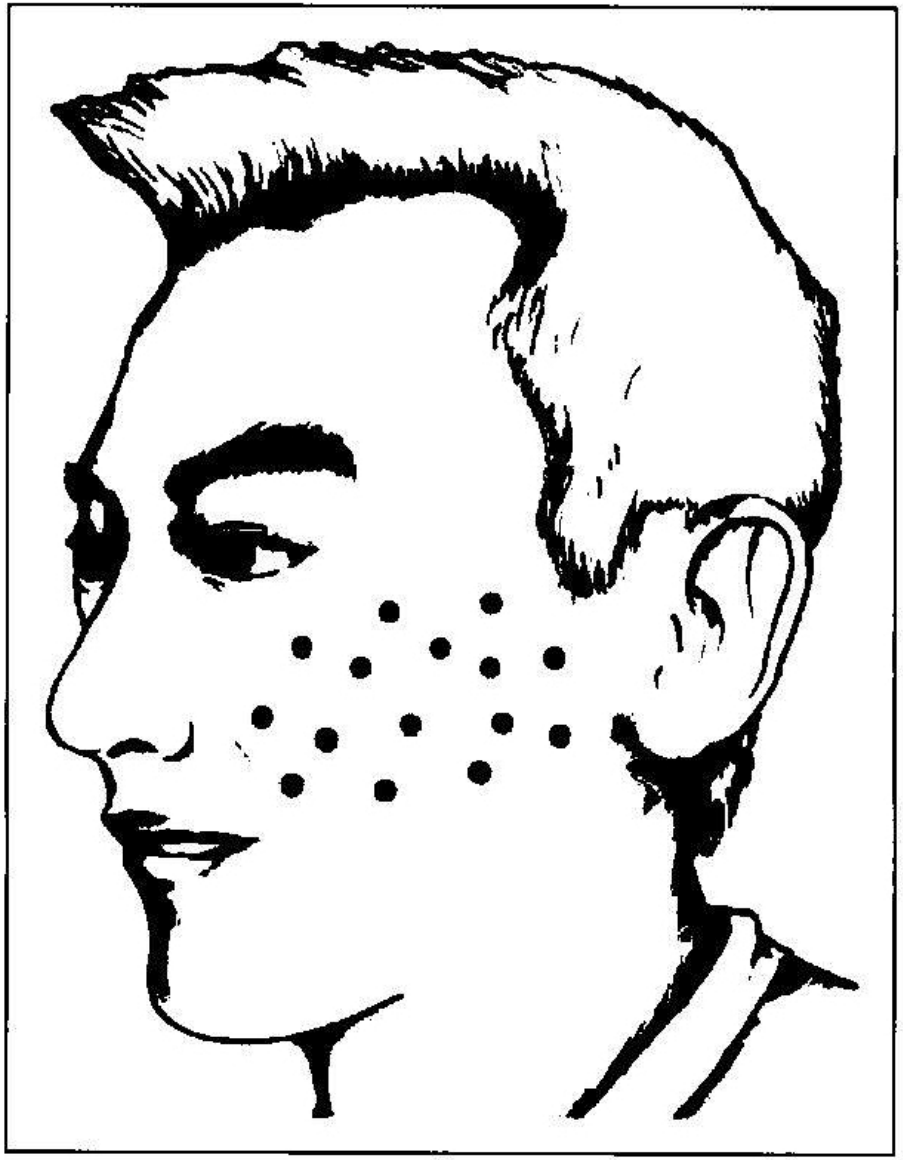

Figure 1. Schematic showing injection sites for BTX-A or pla cebo. The shading shows the distribution of pain and the filled circles represent BTX-A or placebo injection sites.

Results

- 40 patients completed the study
- BTX-A significantly reduced pain intensity at week 2 and pain attack frequency at week 1
- Efficacy improved during the course of the study…more BTX-A patients reported improvement by the end of the study
- BTX-A 68.18%
- Placebo 15%

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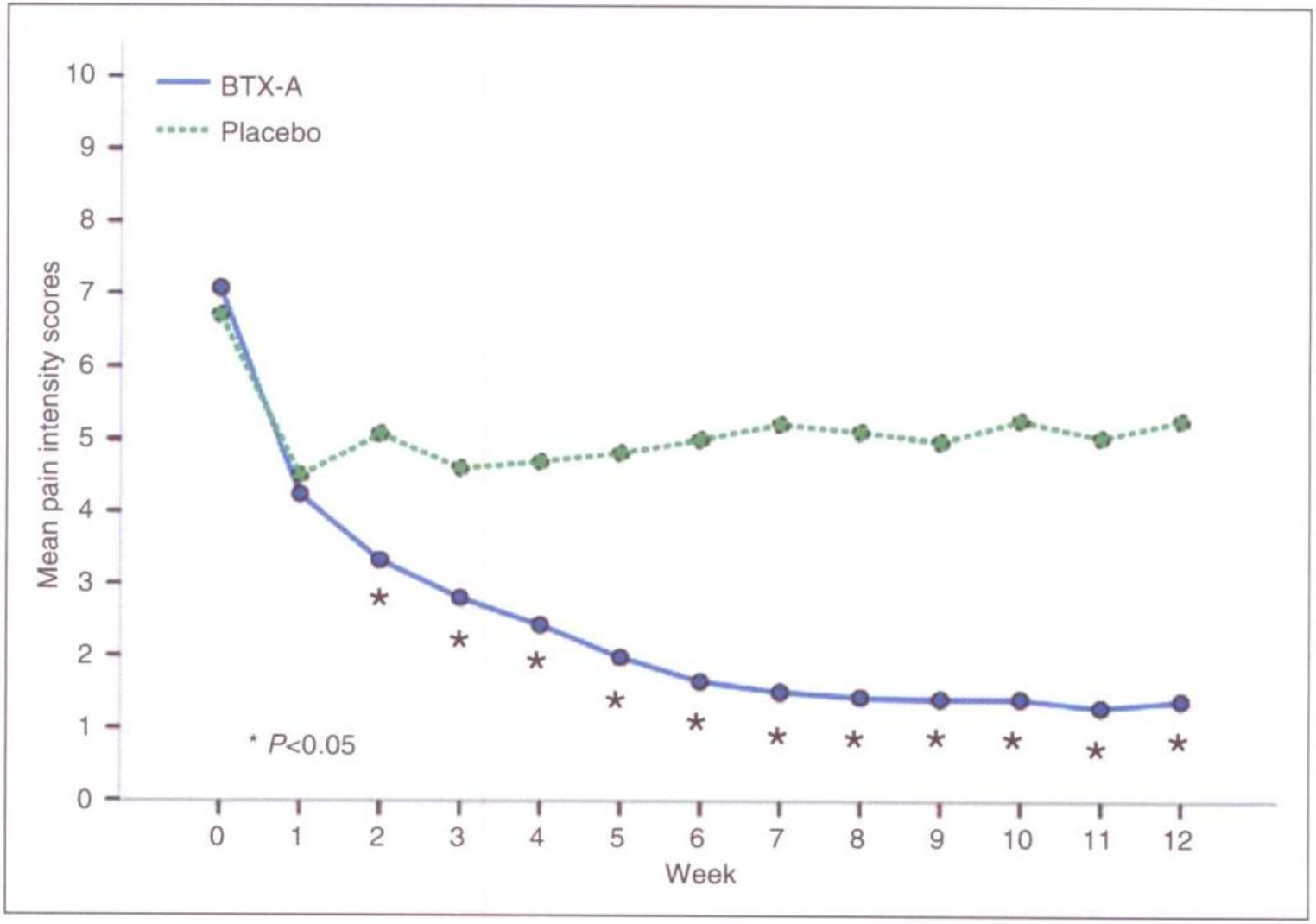


Weekly mean scores as measured by VAS.

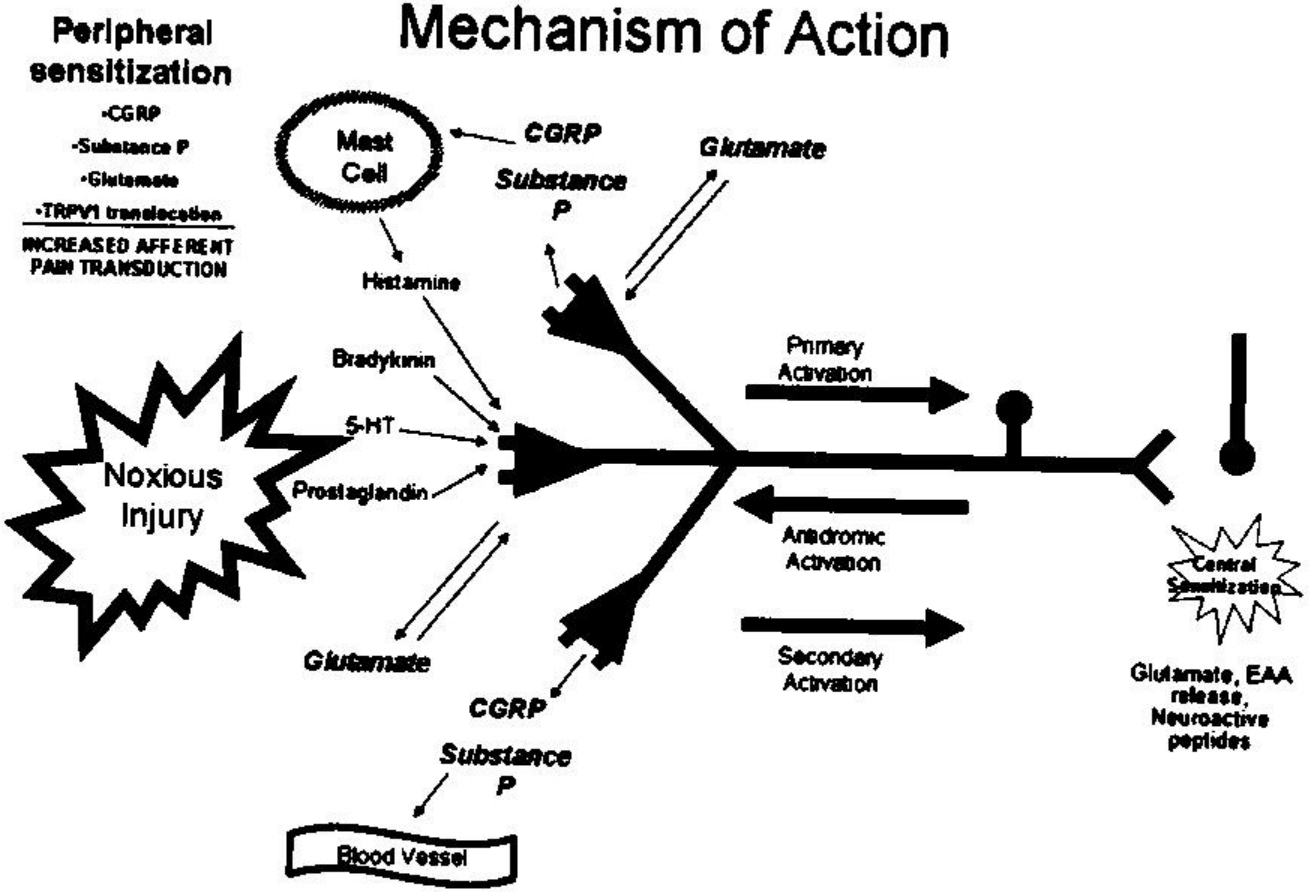
Was it really blinded?

- 7 has transient facial asymmetry gone by week 7
- 3 had edema (including 1 placebo)

Possible Mechanisms

- Inhibit peripheral sensitization of nociceptive fibres thereby reducing central sensitization thru inhibiting release of glutamate and substance P (Aoki 2003)
- Inhibits depolarization-induced release of substance P and CGRP from terminals in the scalp (Cutrer et al 2010)

Mechanism of Action



1 *The postulated mechanisms of action of botulinum neurotoxin (BoNT) in the treatment of neuropathic pain include decrease in peripheral calcitonin gene-related peptide (CGRP), substance P, glutamate, and transient receptor potential cation channel subfamily V member 1 (TRPV1) receptor translocation.*

Other studies

- Bohluli et al (2011) treated 15 patients with refractory TN with 50-100 units at each trigger zone
- All experience relief
- Similar results by Turk et al (2005) and Zuniga et al (2008)
- Lack of control group
- Ngeow et al (2010) Allam et al 2008 case reports

In my patients

- Facial weakness can be seen
- None will keep doing it even with improved pain
- That led to mixing it with lidocaine 0.5%

SUNCT: Short-lasting, Unilateral, Neuralgiform headache attacks with Conjunctival injection and Tearing

- A rare form of headache that is most common in men after age 50.
- The disorder is marked by bursts of moderate to severe burning, stabbing, or throbbing pain, usually on one side of the head and around the eye or temple.
- Attacks typically occur in daytime hours and last from 5 seconds to 4 minutes per episode.
- Patients generally have five to six attacks per hour.

Cephalalgia. 2012 Aug;32(11):869-72.

Sustained response to botulinum toxin in SUNCT **syndrome.**

Zabalza RJ.

- **INTRODUCTION:** Short-lasting, unilateral, neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) is a rare condition grouped in the category of trigeminal autonomic cephalalgia. The syndrome is characterized by very frequent, unilateral attacks of pain in the ocular and periocular region accompanied by ipsilateral conjunctival injection and lacrimation.
- **PATIENTS AND METHODS:** We present the case of a patient diagnosed with SUNCT refractory to pharmacological treatment; duration of the SUNCT was 20 years. OnabotulinumtoxinA was infiltrated at four points around the orbit.
- **RESULTS:** The pain showed a dramatic response to onabotulinumtoxinA infiltration. Efficacy has been maintained for 18 months with 3-monthly infiltrations, with no adverse effects.

Trigeminal autonomic cephalgia BTX-A

- Most have daily headaches, including chronic migraine, trigeminal autonomic cephalalgias, or other primary headaches.
- BTX-A mentioned in Headache. 2012
- **Advanced interventions for headache.**
- Tepper SJ
- No well controlled studies

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Jabbari and Machado (Pain Medicine 2011)

- Treatment of Refractory Pain with Botulinum Toxins –An Evidence-Based Review
- Level A evidence for trigeminal neuralgia
- Level B evidence (AAN) for PHN and Post-traumatic Neuralgia
- Level C allodynia in diabetic neuropathy

Post-herpetic neuralgia

- Persisting pain and other symptoms after acute shingles
- Xiao et al 2010: Subcutaneous injection of botulinum toxin a is beneficial in post-herpetic neuralgia (Pain Med)
- 60 patients in 3 groups: BTX A, Lidocaine, saline BoNT superior to others and required less opioids

Post-traumatic neuralgia

- NeP after nerve injury
- Ranoux et al (2008)
- Double blind placebo controlled study on 29 patients with refractory NeP (25 with PTN and 4 with PHN
- BTX –A 20-190 units were injected intradermally into the affected area
- Improved pain intensity, neuropathic symptoms, allodynic brush sensitivity, reduced numbers of pain paroxysms and improve QOL

Frey's Syndrome

- Neurologic disorder after parotid surgery or other pre-auricular surgery whereby injury to parasympathetic fibres regenerated at attach to subcut glands and vessels
- 20-65.9% (Lima-ortiz et al 2004)
- Sweating, flushing and warmth on one side of face in auriculotemporal and/or greater auricular nerve because of a gustatory stimulus

Cantarella et al 2010
Treatment of Frey's syndrome with Botulinum Type B

- 7 patients rxd with BTX B intracutaneous
- @ 1 month 6/7 reported resolved gustatory sweating and flushing. Last 1 was improved
- 6-9 months up to 12 months
- BTX A cleaves SNAP-25 transport ptn
- BTX B cleaves VAMP transport ptn

(Neurology) Yuan et al 2009
Botulinum Toxin for Diabetic Neuropathic Pain

- Randomized double – blind crossover trial of intradermal BTX-A
- C level evidence
- BTX A may modulate afferent sensory fibre firing
- 18 patients

- Significant reduction in VAS
- 1 0.83 +/- 1.11
- 4 2.22 +/- 2.24
- 8 2.33 +/- 2.56
- 12 2.53 +/- 2.48
- All compared to control ($p<0.05$)
- At 4 weeks improved sleep
- Crossover a possible issue. Also small numbers

Jin et al 2008
Treatment of Phantom Limb Pain with BTX-A

- 3 patients
- Up to 500 units
- Clinical global improvement with decrease pain intensity and pain meds
- Improve stump and phantom pain
- Other reports positive

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Francisco et al 2012

- Do Botulinum Toxins Have a Role in the Management of Neuropathic Pain?

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- Animal data strongly suggests potential benefits in painful neuropathic states
- BoNT is probably effective in treating post herpetic neuralgia, probably or possibly treating post-operative or post-traumatic neuropathic pain, and probably treating painful diabetic neuropathy

- BoNT is injected usually through intradermal or subcutaneous injection

Mechanisms for BoNT in NeP

- Inhibiting glutamate release in peripheral tissues
- Decreasing CRGP release in peripheral tissues
- Decreasing transient receptor potential cation channel subfamily V member 1 trafficking to peripheral neuron cell membrane
- Decreasing release of substance P in peripheral tissue

Pain Med. 2010 Sep;11(9):1415-8.

Botulinum toxin A (Botox**) for treatment of proximal myofascial** pain **in** complex regional pain **syndrome: two cases.**

Safarpour D, Jabbari B.

- **OBJECTIVES:**
- To describe development of myofascial pain syndrome (MFPS) with trigger points in the proximal muscles of the patients with complex regional pain syndrome (CRPS1) and improvement of distal symptoms of CRPS 1 after successful treatment of proximal MFPS.
- **SETTING AND DESIGN:**
- In our practice, we frequently encounter patients in whom a proximal myofascial pain syndrome develops ipsilateral to the distal limb of CRPS1 patients. We describe two such patients in detail with their treatment.
- **RESULTS:**
- In both patients treatment with BoNT-A improved the proximal pain of MFPS and the distal symptoms of CRPS1.
- **CONCLUSION:**
- Proximal MFPS develops ipsilateral to the distal painful limb in patients with CRPS1. Administration of BoNT-A into the affected proximal muscles may alleviate both MFPS and the distal allodynia, discoloration and, tissue swelling of CRPS.

Efficacy of high doses of botulinum toxin A for treating provoked vestibulodynia
F. Pelletier et al (2011) BJD

- Objective To evaluate the efficacy of botulinum toxin A in the treatment of provoked vestibulodynia.
- Methods Patients aged between 18 and 60 years presenting with provoked vestibulodynia (according to the 2003 International Society for the Study of Vulvar Disease classification) received 50 U of botulinum toxin A bilaterally in the bulbospongiosus muscle under electromyographic monitoring. Pain was evaluated by a visual analogue scale (VAS), quality of life was evaluated by the Dermatology Life Quality Index and sexual function by the Female Sexual Function Index.
- Results: Twenty patients received the injections. Sixteen patients presented with a muscular hyperactivity on electromyography. After 3 months, 80% of the patients improved in terms of pain.

- Quality of life and sexual function improved significantly during the first 6 months (P < 0Æ0001). After 3 months, 13 patients (out of 18 for whom intercourse was not possible before the injections; 72%) were able to have sexual intercourse.
- Conclusion Botulinum toxin A seems to be an effective and safe treatment for provoked vestibulodynia; 100 U botulinum toxin A significantly reduced pain 3 and
- 6 months after injections without side-effects. The treatment also improved quality of life and sexual function of patients.
- Botulinum toxin A appears to be a promising option for managing sexual pain disorder.

Conclusions

- BoNT (mainly BTX-A) is being used in neuropathic pain conditions
- Evidence is increasing for effectiveness in certain conditions
- Intradermal or subcutaneous injection can be quite painful
- Toxin may act in a number of mechanisms