# Neuropathic Pain Rapid Fire: Diagnostic, Testing, and Treatment Pearls

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# Disclosures

- I have no conflicts of interest.

- This presentation contains off-label or investigational use of drugs or products

# Learning Objectives

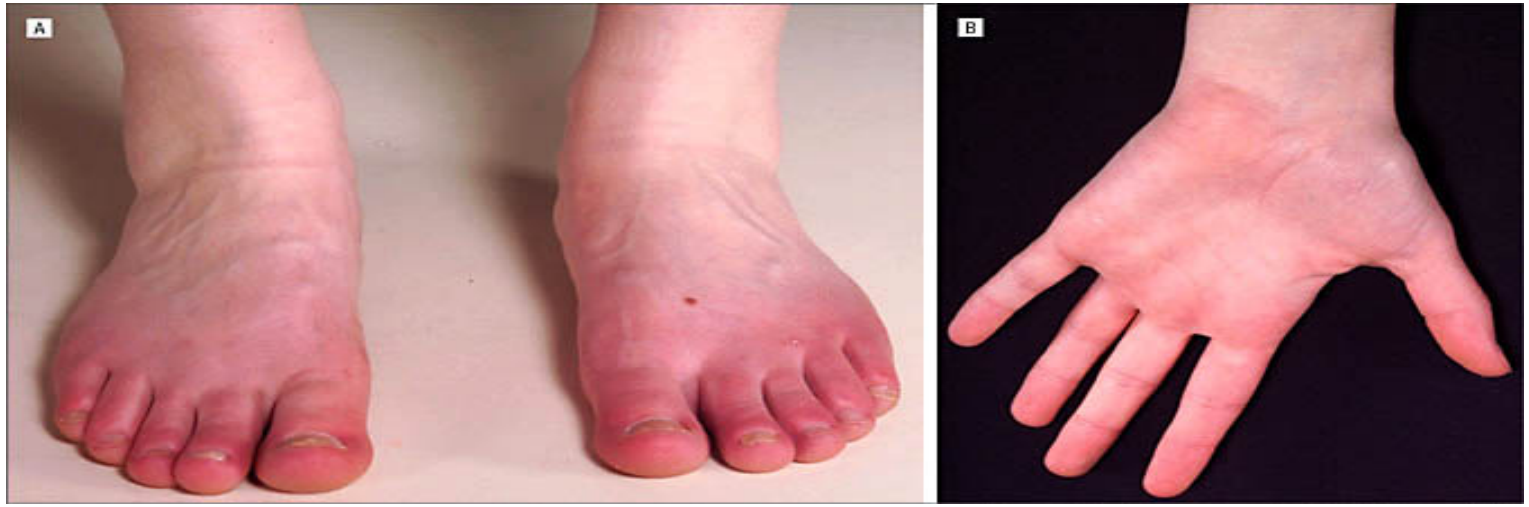
- Understand the natural history of erythromelalgia and recent updates on treatments options.
- Understand critical elements to diagnosing central neuropathic pain.
- Understand how to differentiate trigeminal neuralgia from trigeminal neuropathy and persistent idiopathic facial pain and the treatment implications.
- Understand the risk profile and durability of interventions for trigeminal neuralgia.

- References listed  in presentation

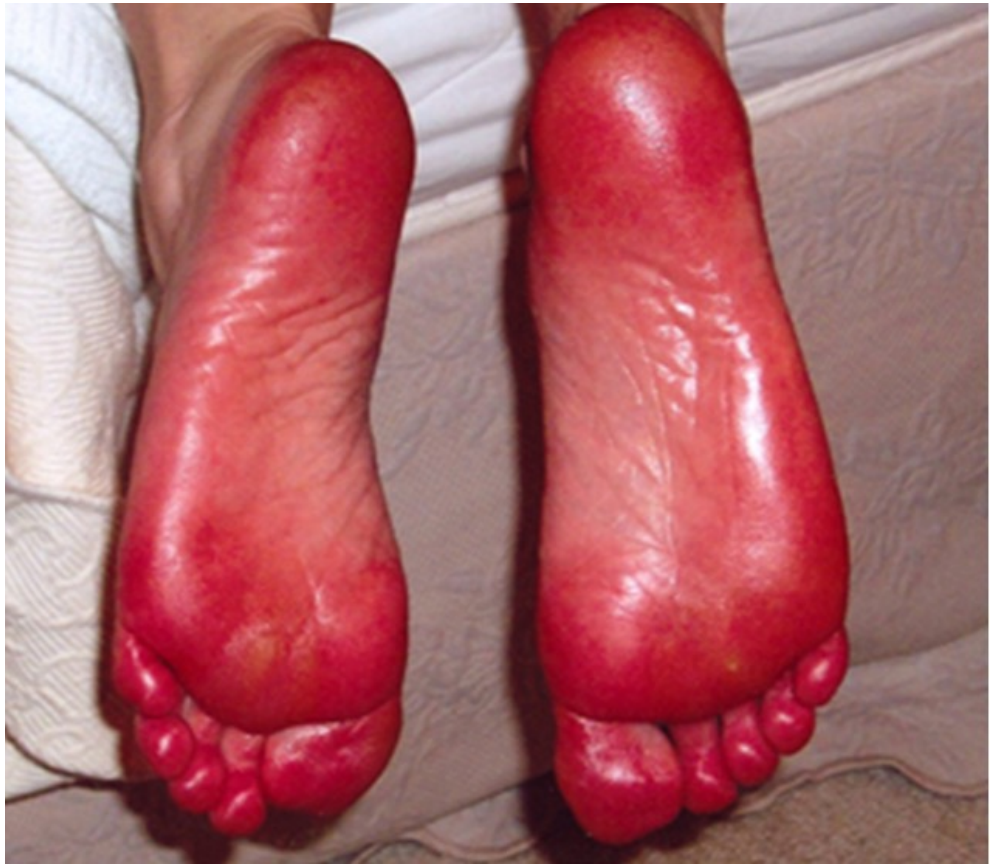
# Case

- 44 year-old,  smoker
- Symmetric burning pain in her feet x several months
- Intermittent  - several times weekly and lasting several hours
  - Severe ‘14/10’ pain – incapacitating
  - Feet become hot to touch and turn bright red
  - Relief placing her feet in ice water
- Between episodes her feet feel normal.
- No sensory loss, weakness, or orthostatism

# Erythromelalgia




Arch Derm 2006: 142: 283-



# Questions

- Which of the following is most correct regarding erythromelalgia?
  A. Survival estimates show a decreased life expectancy.
  B. This is an autosomal recessive inherited pain disorder.
  C. Cooling therapy is an effective, benign treatment.
  D. Progression of symptom distribution (i.e. to higher in the legs or to arms) is common.

- New evidence for treatments of erythromelalgia?

# Erythromelalgia

- Rare → Incidence: 1.3 per 100,000*
- Otherwise unexplained triad of symptoms:
  - Redness
  - Increased temperature
  - Pain
- Disorder intermittent (97%)→ signs may not be present at evaluation
- Usually in extremities
  - 88% feet, 25% hands, 14% legs, ears and face described
- Avg age 55 +/- 19 yrs (but range 5-91)+
  - F:M 3:1
  - Mayo series ^3 of 168 pts < 11 y.o.
  - Pediatric series similar characteristics #
- Exacerbate symptoms
  - Heat 50%
  - Exercise 25%
    - 50% limited in gait from (but low need for gait aide)
- Relieve symptoms
  - Cooling extremity (H20, ice) 70%
    - 22% complications from
- Exam – abnormal 2/3
  - 50% erythematous
  - 10% acrocyanosis
  - 6% ulcers
  - 5% reticular cutaneous pattern

# J AM ACAD DERMATOL 2011 (66): 416-
* J Eur Acad Dermatol Venereol. 2009

+ Arch Dermatol. 2000; 136: 330
Clin Exper Rheum 2017; 35: 80-84
^Mayo Clin Proc. 2004; 79(3):298

# Primary vs. Secondary EM

- Primary EM* - SCN9A gene mutation
  - AD
  - Voltage gated sodium channel
    - DRG (neuropathic pain)
    - Sympathetic ganglion (vasomotor sx)

- Secondary EM
  - Smoking 50%
  - Myeloproliferative disorders 9% (other studies 25%)
    - Polycythemia rubra vera
    - Essential thrombocytopenia
    - Chronic granulocytic leukemia

*Brain 2016: 139; 1052–1065
*Arch Dermatol 2008; 144: 1578-

# Erythromelalgia Mechanistically

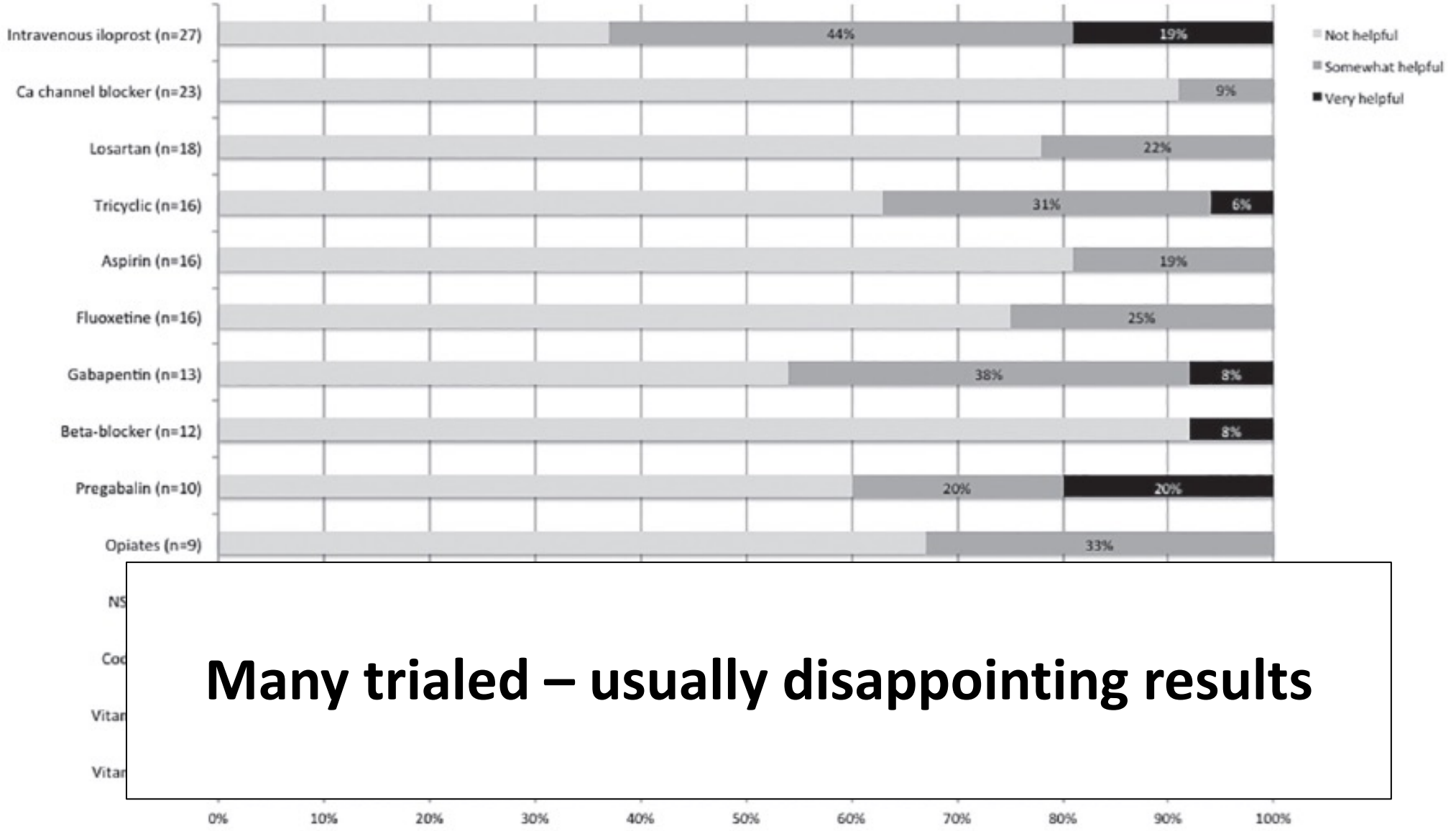
- **Vasculopathy**
  - Temp increase
  - Laser flow increase
  - Paradoxically decreased transcutaneous oximetry measurement (TcPO2)

- **Neuropathy**
  - EMG abnl 20%
  - Epidermal nerve fiber density
    - Usually nl (90%)
    - Fxn isn't nl
  - Sudomotor fxn impaired
    - TST 88% abnl
    - QSART 69% abnl

# Natural History

- Many remain static or improve (58%)
  - Resolution uncommon (10%)
- Avg. 1.4 attacks per week
- Symptoms usually stay where start
  - LE only at onset – 14% spread to hands
  - UE only at onset – none to legs
  - 1 limb only (rare) at onset – rare to other limb
- Review 168 pts - Ulcers 13%, infection 16%, no limb loss
- Kaplan Meier survival curves - decrease in expected survival
  - Several suicides

Mayo Clin Proc. 2004; 79(3):298




# Many trialed – usually disappointing results

Clin Exper Rheum 2017; **35**: 80-84

# Neuromodulation

- Case report of successful Rx with DRG stimulation for EM most severely affecting plantar aspect bilateral feet
- Postulate mechanistically advantageous given sodium channel effects at DRG
- Literature review of neuromodulation for EM

**Table 1. Literature Review of Neuromodulation for Chronic Pain from Erythromelalgia**

| Author, year | Study design | Demographics | Pain site | Programming information | Lead information | Results |
|---|---|---|---|---|---|---|
| Graziotti, 1993[4] | Case report | 69-year-old woman with secondary erythromelalgia related to history of multiple deep venous thromboses | Bilateral feet | Paresthesia-based<br>Amplitude: 8 V<br>Frequency: 80 Hz<br>Pulse width: 400 μs<br>Set to cycling mode (1 minute on, 1 minute off) | Single T9 to T10 4-contact lead | Immediate 75% decrease in pain with sustained relief out to 18 months |
| Patel, 2015[5] | Case report | 15-year-old girl with primary erythromelalgia | Bilateral feet | Paresthesia-based<br>Amplitude: 2 V<br>Frequency: 10 Hz<br>Pulse width: 300 μs | Two T12 to L1 eight-contact leads | Satisfactory pain relief at 24 months with combination of SCS and oral mexiletine |
| Matzke, 2016[6] | Case report | 80-year-old woman with secondary erythromelalgia related to diabetes mellitus type II | Bilateral distal lower extremities | Paresthesia-based<br>Amplitude: 4.7 V<br>Frequency: 50 Hz<br>Pulse width: 330 μs | Two T11 eight-contact leads | At 4 months, NRS scores were 0 to 1/10 and opioid use was decreased<br>At 18 months post-implant, NRS scores were 2 to 4/10 and pain medication use was less than 2 times per month |
| Eckman, 2017[7] | Case report | 20-year-old man with primary erythromelalgia | Bilateral distal upper and lower extremities | Paresthesia-based<br>No other details were provided | Implantation: Four total leads and two generators; two 8-contact cervical leads (trial—top of C3) and two 8-contact thoracic leads (trial—top of T8) | At 6 months, he had 100% pain relief in his upper and lower extremities, and discontinued all pain medications |

Pain Practice 2021; 21(6): 698–702

# IV Corticosteroids

**Erythromelalgia: Identification of a corticosteroid-responsive subset**

Gabriel L. Pagani-Estévez, MD,[a] Paola Sandroni, MD, PhD,[a] Mark D. Davis, MD,[b] and James C. Watson, MD[a,c]

**J AM ACAD DERMATOL 2017; 76 (3): 506-**

## 55% respond to corticosteroids – predictors:

- Subacute onset of EM
  - 87% respond to steroids
- Identifiable stressor trigger to EM development
  - 67% of those w/ a complete resolution of sx with steroid administration
- Shorter duration of symptoms  til steroid trial

## Higher dose steroids more effective (76% of those Rx w/ high dose responded)

- 1000mg IV Methylprednisolone daily or > 40 mg po prednisone daily
- At least 5 consecutive days

Pediatrics. 2013;131:e1091-e1100.

# Chemical Lumbar Sympathectomy

- n=13
  - 5 w/ SCN9A gene mutation (i.e. primary EM)
- Mean follow-up 6.2 +/- 3.8 years

- **Complete (90-100%) response at 1 week post CLS**
  - 9/13 (69%)
  - 3/5 (60%) with SCN9A mutation

- **Relapse**
  - 1/6 secondary EM (i.e. no SCN9A mutation) relapsed
  - 3/3 primary EM
    - 2 partial return of symptoms
      - still 60-89% improved from baseline
    - 1 full relapse 2 years later
  - 3 repeated CLS – 1/3 successful but duration of benefit only 2 months

J Vasc Surg 2018;68:1897-905

# Erythromelalgia Take Home Points

- Episodic, bilateral red, painful limbs & cooling efforts characteristic

- Exclude myelodysplastic syndrome ($2^{ndary}$ EM)
- Consider SCN9A mutation

- Consider corticosteroid trial if
  - Subacute onset
  - Identified trigger stressor
  - Shorter duration of symptoms (regardless of onset acuity)

- Chemical Lumbar Sympathectomy?

- Neuromodulation - DRG stim preferentially?

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# Case

- 68 M
- Right cerebral infarct 9 months prior
  - Affecting left face and upper limb
- Presents with left upper limb pain

# Question

**Which of the following clinical features should be demonstrable in the symptomatic limb affected by central pain?**

A. Reduced pinprick sensation
B. Weakness
C. Hyperreflexia
D. Spasticity

# Definitions

- IASP neuropathic pain
  - pain originating from a lesion or disease of the somatosensory nervous system
- Most is peripheral
- Central neuropathic pain
  - Pain directly from dysfunction of CNS somatosensory pathways
    - Where pain generator is this dysfunction
  - Results from any type of lesion of CNS – post-stroke, MS, SCI most common

Pain 2019; 160: 53–59

# What central pain is not

- Central Sensitization
  - Chronic nociceptive afferent input
    - → reversible ('plastic') changes of central nociceptive pathways
      - 'upregulation' or 'wind-up'
  - Result:
    - Allodynia
      - Non-painful peripheral stimuli interpreted as painful
    - Hyperalgesia
      - Painful peripheral stimuli (e.g. pinprick) interpreted as overly painful

- Can occur with, but does not define, central neuropathic pain

# What central pain is not

- Spasticity
  - Increased tone in the neurologically affected limb
    - Velocity dependent
  - Complaints – tightness, stiffness, or discomfort
  - Poorly controlled spasticity must be excluded
    - Exam can define severity of spasticity

# Obligate sensory dysfunction

- To classify as central pain syndrome
  - Pain must occur in body region clinically affected by CNS insult
- Pain need NOT involve entirety of affected region
- **Spinothalamic tract dysfunction obligate to development central neuropathic pain**
  - Examine pinprick, temperature in affected segment
    - If normal, unlikely central neuropathic pain
  - Best predictor of developing CNP after SCI*
    - Decreased pain adaption at level of injury

J Pain 2020; 21(3–4): 262–280
Mayo Clin Proc 2016; 91(3):372-385
*Pain 2020; 161: 545–556

# Pain in Neurologically Impaired Patients

- Pain common
  - Usually NOT central neuropathic pain
- Musculoskeletal pain 2º immobility
  - CVA w/ arm paresis → 30-40% MS shoulder pain
  - Gait disorders → knee, hip, LBP
  - SCI pts wheelchair bound → LBP, UE overuse syndromes (75%)
- Central pain cohorts
  - Usually have comorbid musculoskeletal and visceral pain

Mayo Clin Proc 2016; 91(3):372-385

# International Spinal Cord Injury Pain (ISCIP) Classification

- **Nociceptive Pain**
  - ***Musculoskeletal pain***
    - Joint pain, axial spine pain, overuse syndromes; muscle spasms
  - ***Visceral pain***
    - From complications of neurogenic bowel and bladder
  - ***Other nociceptive pain***
    - e.g. headache or skin ulcer

- **Neuropathic Pain**
  - ***At-level neuropathic pain***
    - Neuropathic pain within the dermatomes at the level of the SCI
    - e.g. from nerve root or dorsal horn injury from the SCI
  - ***Below-level neuropathic pain***
    - **A central pain type**
  - ***Other neuropathic pain***
    - Neuropathic pain unrelated to the SCI
      - Compressive mononeuropathies
      - Painful diabetic neuropathy

- **Other or Unknown Pain Type**
  - Fibromyalgia
  - Interstitial cystitis

# Pain in Neurologically Impaired Patients

- Distinguishing musculoskeletal from neuropathic pain may NOT be straightforward
  - Impaired sensory discrimination
    - Pain descriptors vague
    - Localization / pain triggers poorly defined
  - Paraplegia / quadriparesis
    - Office examination / positioning challenging
  - Unique considerations
    - Referred visceral pain

Mayo Clin Proc 2016; 91(3):372-385

# Temporal Onset

- Highly variable – at onset to years later

| | At Time of Stroke | Within 1 Month | 1-3 Months | 4-6 Months | 6-12 Months | >1 year |
|---|---|---|---|---|---|---|
| **CPSP - all stroke types** | ---- | 62% | 19% | | 19% | ---- |
| **CPSP – thalamic strokes** | 18% | 38% | 15% | 12% | 6% | 11% |
| **CPSP – lateral medullary infarcts** | 14% | 29% | 43% | 7% | 7% | ---- |

## MS

- Presenting feature in 5.5-10%
- When pain part of original MS presentation, chronic / central pain more likely future

## SCI

- Longest average latency
- At–level pain
  - Mean time 1.2 years post-SCI
  - 50% w/in 3 months of SCI
  - Up to 5 years
- Below–level pain
  - > 50% develop 2+ years post-SCI

Mayo Clin Proc 2016; 91(3):372-385

# Central Pain – Take Home Points

- Musculoskeletal pain and spasticity are more common than central neuropathic pain in neurologically impaired patients
  - Central neuropathic pain more severe / limiting than other pain types

- Pain descriptors are limited in sensitivity and specificity for discriminating:
  - Neuropathic from other pain types
  - Peripheral from central neuropathic pain types

# Central Pain – Take Home Points

- Central neuropathic pain onset variable – may occur ***months to years*** after the CNS insult

- Spinothalamic tract dysfunction obligate to development central neuropathic pain
  - If normal, unlikely central  neuropathic pain

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# Case

- 70 M
- HTN, HLD,
- 3 months
  - Right V3 paroxysms of stabbing pain (seconds) 15 x / day
    - Shaving, touching face, chewing precipitates
- Decreased oral intake – losing weight

- No illness, exposure, trauma prior to onset
- No other neurologic complaints – no ocular symptoms
- No constitutional symptoms, jaw claudication, myalgias
- No prior HA history

# Question

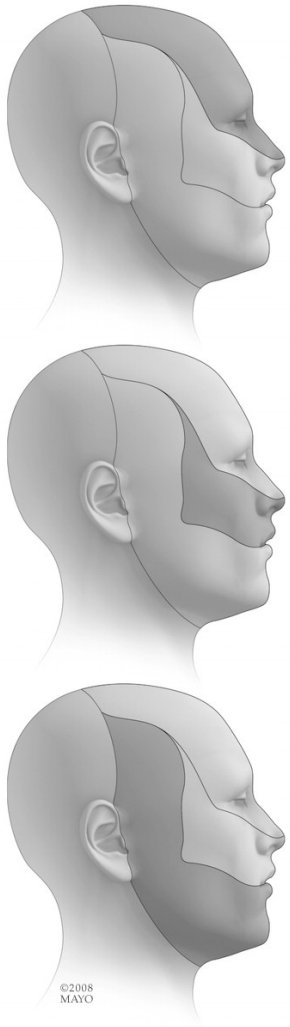
- Which Therapy Offers the Most Durable Response?
  A. Carbamazepine
  B. Gasserian  ganglion balloon compression
  C. Gamma knife stereotactic radiosurgery
  D. Microvascular decompression

# Trigeminal Neuralgia

- Classical TN (Tic douloureux)
  - At least three attacks of *unilateral* facial pain
  - Occur 1+ *divisions of the trigeminal nerve*- no radiation beyond
  - Pain character 3 of:
    1. recurring in paroxysmal attacks lasting from a fraction of a second to 2 min
    2. severe intensity
    3. electric shock-like, shooting, stabbing or sharp in quality
    4. precipitated by innocuous stimuli to the affected side of the face
  - No clinically evident neurological deficit
  - Not better accounted for by another ICHD-3 diagnosis

https://ichd-3.org/

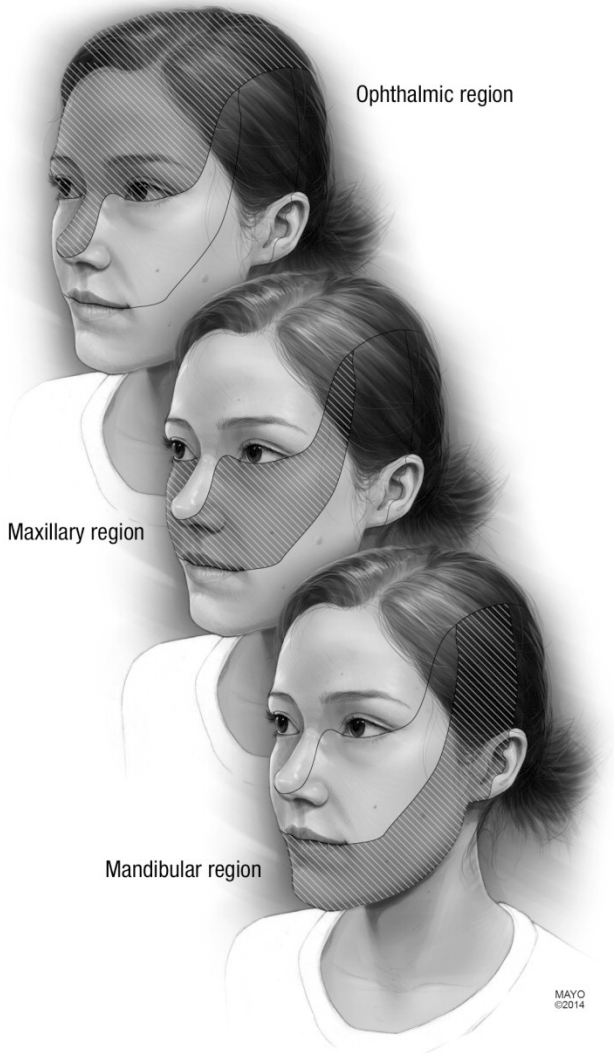
# Classical TN




Affected regions of the face

| | |
|---|---|
| **Bilateral** | **3%** |
| **Right** | **56%** |
| **Left** | **41%** |

| | |
|---|---|
| **V1** | **4%** |
| **V2** | **17%** |
| **V3** | **19%** |
| **V1+2** | **10%** |
| **V2+3** | **33%** |
| **V1+2+3** | **13%** |




Regions of face affected by branches of Trigeminal nerve

Maarbjerg S. Headache 2014;54:1574-1582

# Classical Trigeminal Neuralgia

Purely Paroxysmal

- No persistent pan between attacks
- Typically responsive pharmacologic and other treatments

With concomitant persistent facial pain in affected area

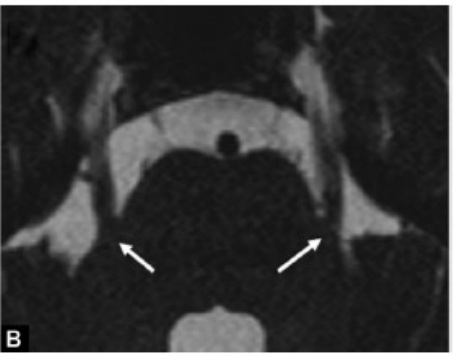
- 'Atypical TN'
- 'Type 2 TN'

- Function of central sensitization

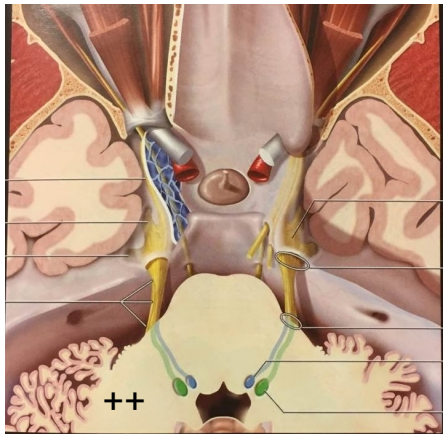
Less likely:

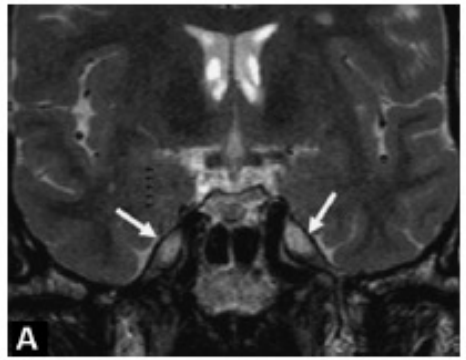
- Vascular compression
- Precipitated by innocuous stimuli
- Responsive to conservative or surgical intervention

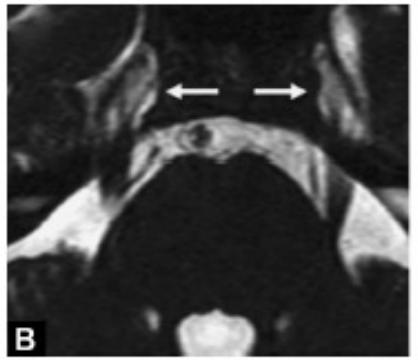
# Classical TN Anatomy / Pathogenesis




*Axial T2. CN V emerging from pons. Arrows – root entry zones.



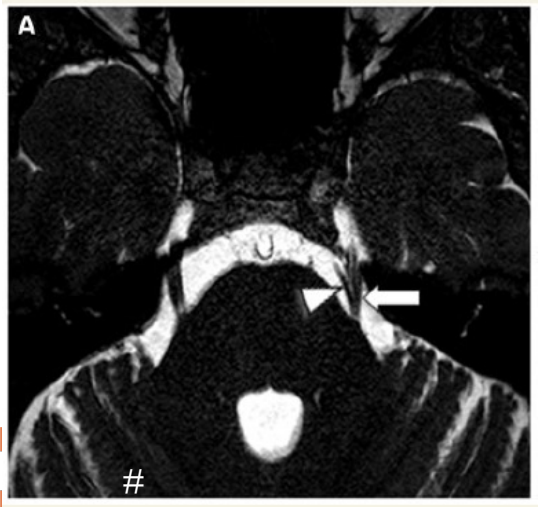



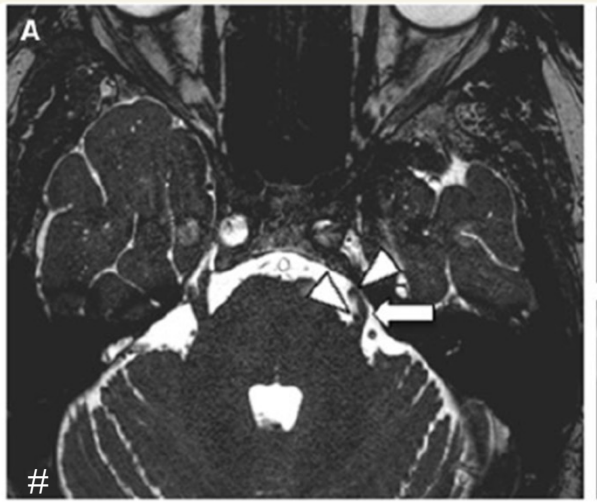



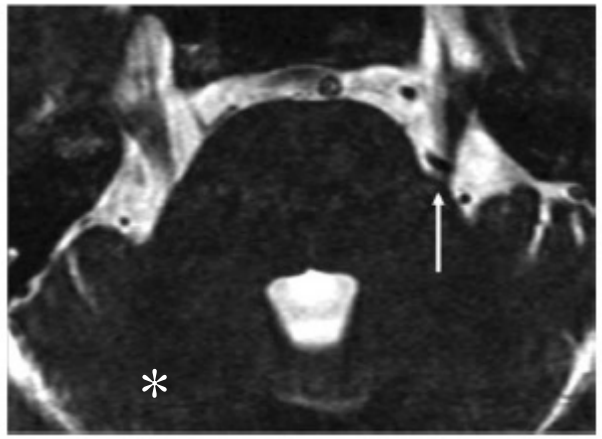

*Meckel's cave (trigeminal fossa) - arrows

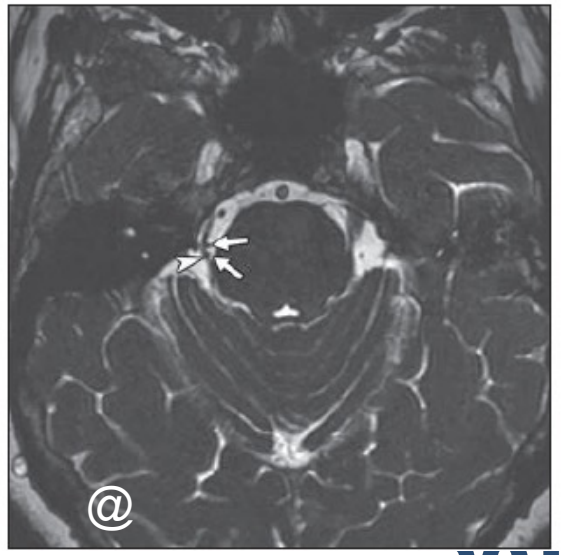
Axial T2

Coronal T2



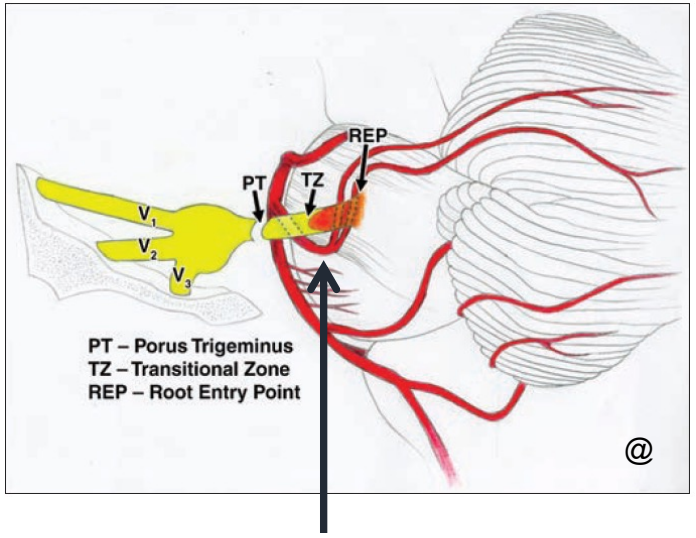



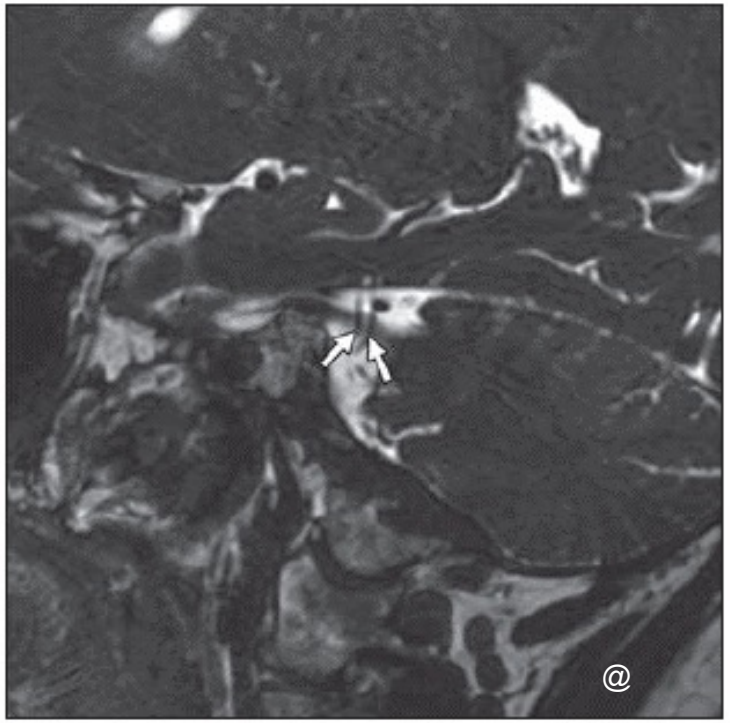




* Leclercq D. Diagnostic and Interventional Imaging (2013) 94, 993—1001
++ Harnsberger HR, et al. . Diagnostic and Surgic Imaging Anatomy – Brain, Head & Neck, Spine. 1st edition. A
# Maarbjerg S. Brain 2015: 138; 311–319
@ Hughes MA. *AJR* 2016; 206:595–600

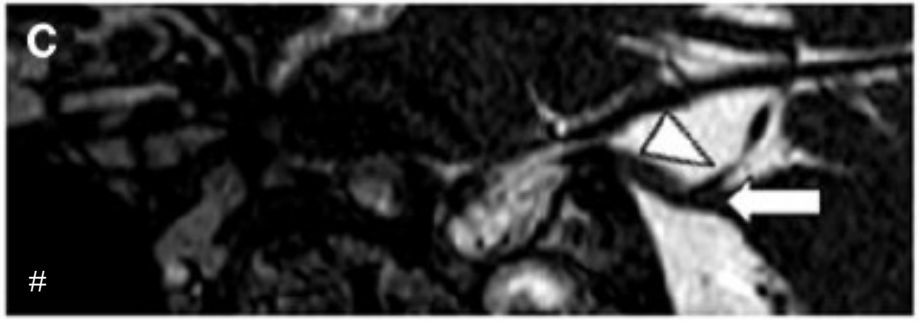
# Classical TN – Anatomy / Pathogenesis

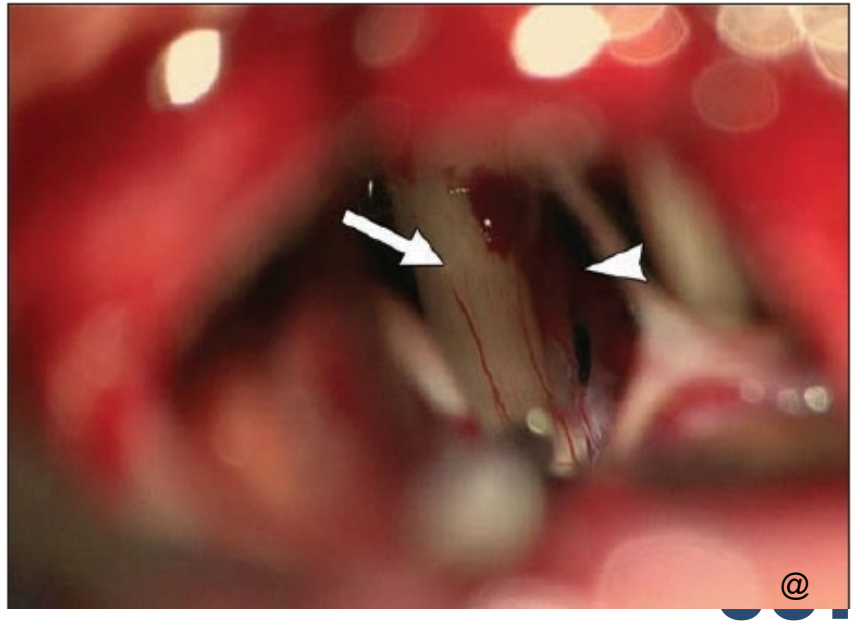



Superior Cerebellar Artery




Sagital T2
Arrows – superior cerebellar artery




@ Hughes MA. *AJR* 2016; 206:595–600
# Maarbjerg S. Brain 2015: 138; 311–319

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# Classical TN

- Key --- NO neurologic deficit

- If trigeminal sensory impairment or trigeminal motor impairment (mastication) = **trigeminal neuropathy**

# TN in MS – 2% develop

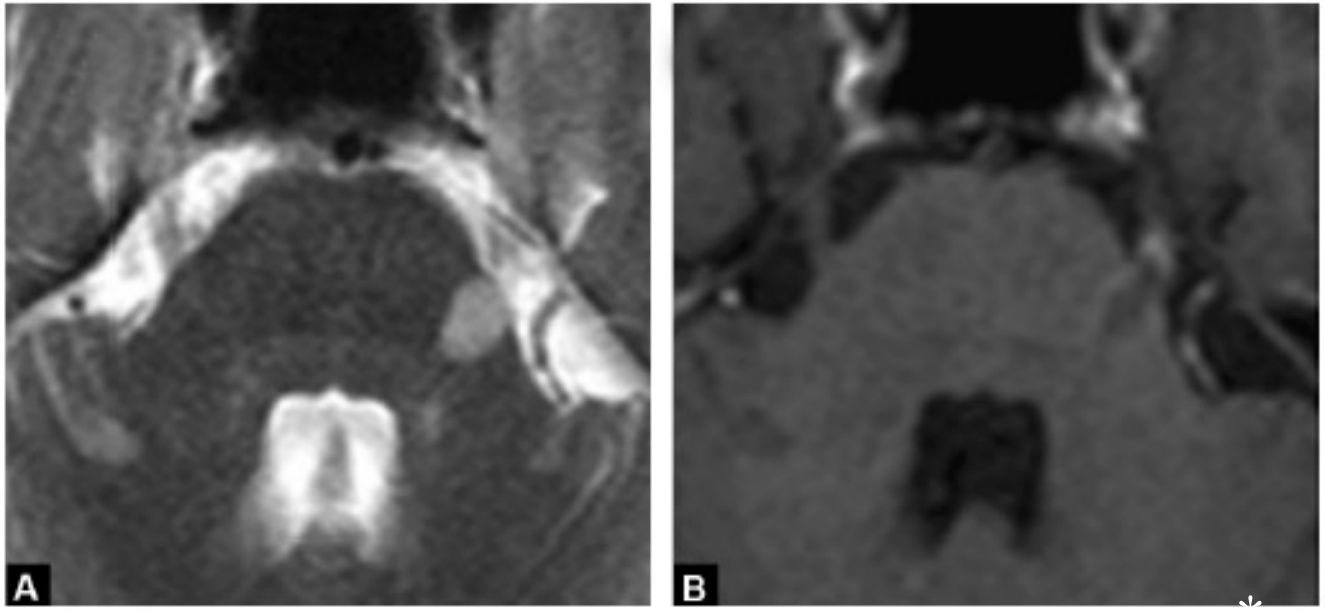



Figure 12. Multiple sclerosis lesion responsible for left CN V neuralgia of the essential type in T2 axial (A) and T1 after injection (B). Interestingly, enhancement of the first millimetres of the root of CN V is observed (central myelin zone ahead of REZ).

Rx: High dose IV methylprednisolone 1000mg daily x 5

* Leclercq D. Diagnostic and Interventional Imaging (2013) 94, 993—1001
Hooge JP. Neurology 1995; 45(7): 1294-6
Solaro C. Neurology 2004; 63(5): 919-21.

# Painful post-traumatic trigeminal neuropathy

- **'Anesthesia dolorosa'**

- Unilateral facial and/or oral pain
- Signs of trigeminal nerve dysfunction
- Usually pain within 3-6 months of trauma

- Most commonly from rhizotomy or thermocoagulation done to treat trigeminal neuralgia
  - After glycerol rhizotomy 0-1.6%
  - After radiofrequency rhizotomy 0.8 to 2%
  - After percutaneous controlled thermocoagulation 3%
- "More difficult to treat than TN"

# Persistent Idiopathic Facial Pain (PIFP)

- 'Atypical Facial Pain'
- Facial / oral pain
- > 2 hours/day x > 3 months
- Pain
  - Poorly defined localization (not nerve territory)
  - Non-specific descriptors (nagging, aching, dull)
    - Not neuralgiform or neuropathic
- Normal neurologic exam
- No dental cause
- Other chronic pain and psychiatric comorbidities common

Traditional interventions for TN do not help PIFP and may cause harm

# TN First Line Treatment

| | Carbamazepine (FDA approved) | Oxcarbazepine |
|---|---|---|
| BID dosing? | Long acting formulations | Yes |
| Dosing increments | 200mg | 150-300mg |
| **Median effective dosage** | **600mg/d** | **1200mg/d** |
| Max dosing | 1200mg/d | 2400mg/d |
| **Response Rate** | **98%** | **94%** |
| Withdraw Rate | 27% | 18% |
| **Black Box Warning** | **Yes – monitor CBC, LFTs** | **No** |
| Risk of hyponatremia | Yes | Yes |
| May affect oral contraceptive | Yes | Yes |
| | | |
| **Asian descent – screen for HLA-B*1502 allele – presence = risk SJS or TEN** | | |

Stefano GD. Journal of Headache and Pain 2014, 15:34

# 2nd Line Agents

- Lamotrigine
  - 6 week titration, risk of Steven's Johnson Syndrome
  - Goal dosing 200-400mg/d (split BID)
- Baclofen
  - As monotherapy, more commonly as adjuvant to first line agents
  - 5mg TID, max 20mg TID
- Topiramate
  - 100mg/d
  - Studied in classical TN, TN w/ MS, post-injury pain
- GBP
  - Mean effective dosage 900mg/d
- PGB
  - Mean effective dosage 270mg/d
- No good data comparing 2nd line agents
  - Consider comorbidities and rational polypharmacy

Reddy GD. Neurol Clin 32 (2014) 539–552

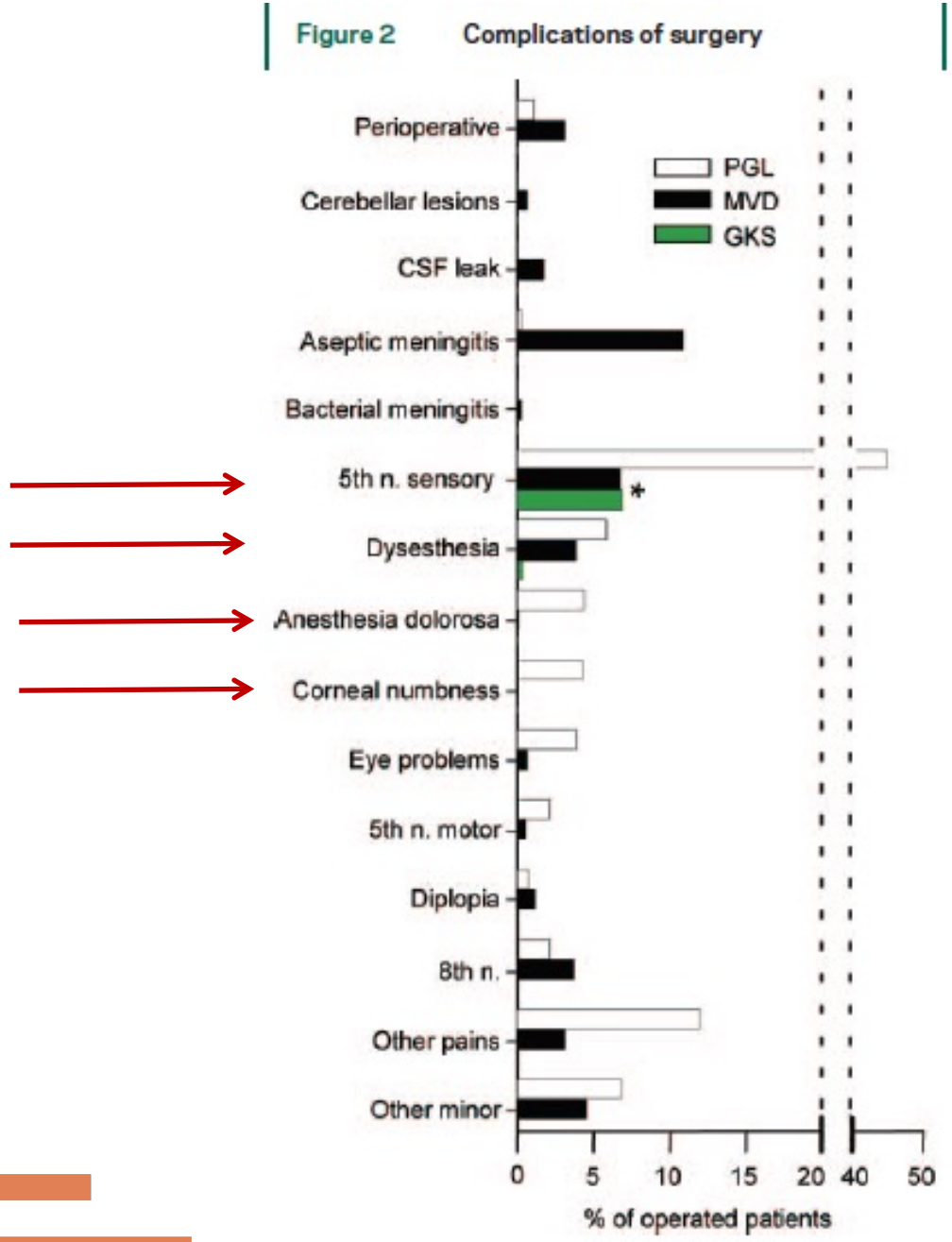
# Interventional Treatments

- **Microvascular decompression**[+]
  - 91% cure (med-free) at 1 year
  - 74% at 15 years - most durable intervention for TN

- **Internal neurolysis** when no vascular compression identified intraoperatively[@]
  - Pain free 85% immediately, 58% at 1 year, 47% at 5 years
  - Pain improved 96% immediately, 77% 1 year, 72% 5 years
  - 96% hypoesthesia
    - 4% anesthesia dolorosa

- **Gamma knife stereotactic radiosurgery***
  - 88% initial response (mean by 4 weeks, but may take up to 6 mos to note)
  - Less effective the longer the TN diagnosis has been
    - Median pain free interval 68 mos if done w/in 1 mo of diagnosis, 10 mos benefit if done > 3 years after diagnosis
  - 12% sensory loss (No anesthesia dolorosa)

+J Neurosurg 107:1144–1153, 2007
*Neurology® 2015;85:2159–2165
@J Neurosurg 122:1048–1057, 2015




**PGL** -percutaneous Gasserian lesions (includes radiofrequency thermocoagulation, glycerol rhizotomy, balloon compression);

**MVD –** microvascular decompression

**GKS –** gamma knife stereotactic radiosurgery

*Neurology*® 2008;71:1183–1190

Thank you

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