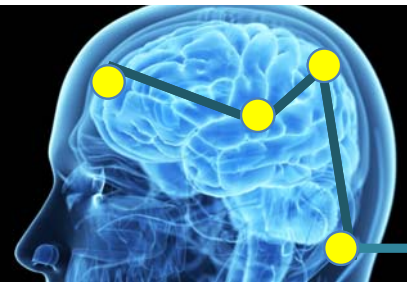


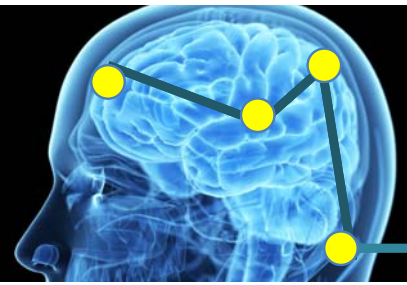
Neuropathic pain and Neuromodulation

Neurologist and Interventional Pain Physician at Spartanburg Regional Health System

Presenter

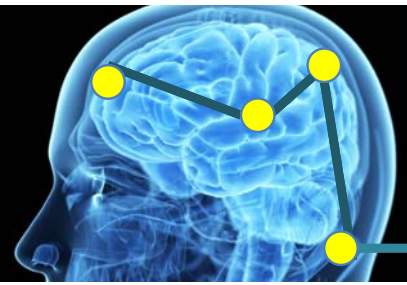
Dr. Ketan Jhunjhunwala

MD Ph.D



Topics to discuss

1. *What is Neuropathic pain (NP)?*
2. *Types of Neuropathic pain*
3. *Medical treatment of Neuropathic pain*
4. *Neuromodulation*

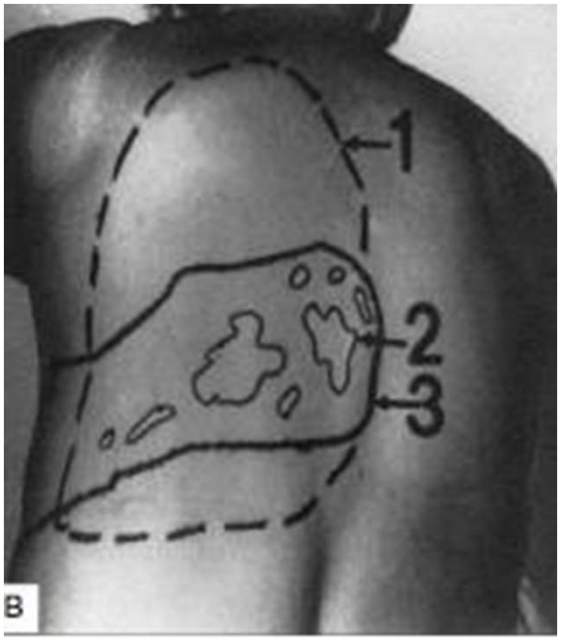


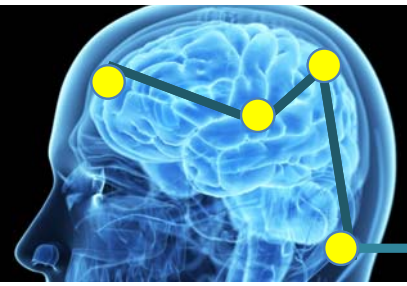
CASE 1

- 55 yr. , Female
- Presented with pain in back of chest for 5 yrs
- No h/o HZ, DM, Trauma, Loss of weight
- Quality - burning
- Intensity 5 - 6 / 10
- Tried NSAIDs multiple times

CASE 2

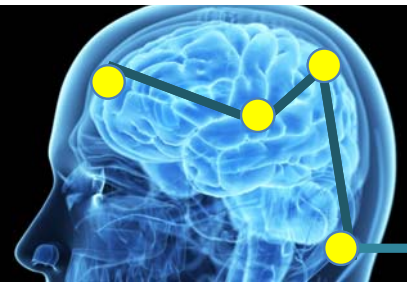
- 75 yrs, Female
- Feels Depressed due to Pain in chest
- Severe lancinating pain with increased sensitivity
- H/O very painful rash in the same distribution 5 months back
- Rash subsided but pain didnt





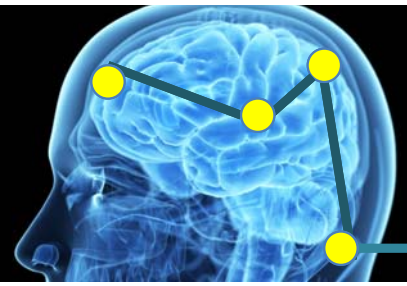
CASE 3

- 35 yr., female patient with severe headache.
- Diagnosed as a case of migraine
- Wincing in pain , c/o jolts of pain while combing her hair
- On Migraine prophylaxis



CASE 4

- 45 yr. Old Male on a hot summer day with a wool shawl draped around his shoulder and right arm
- % Pain in the right hand following closed reduction of wrist fracture
- Right arm was cold and sometimes sweaty
- Severe pain on cutting nail
- Visited three physician who referred her to a psychiatrist with the diagnosis of Conversion disorder



What is Neuropathic pain (NP)?

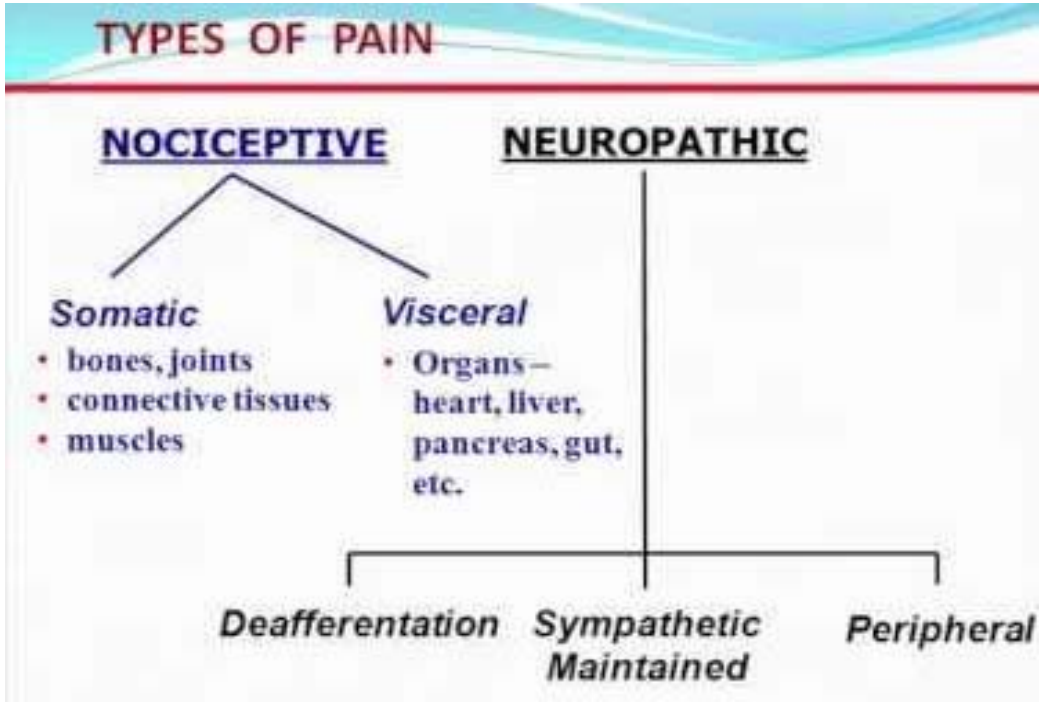
Nociceptive

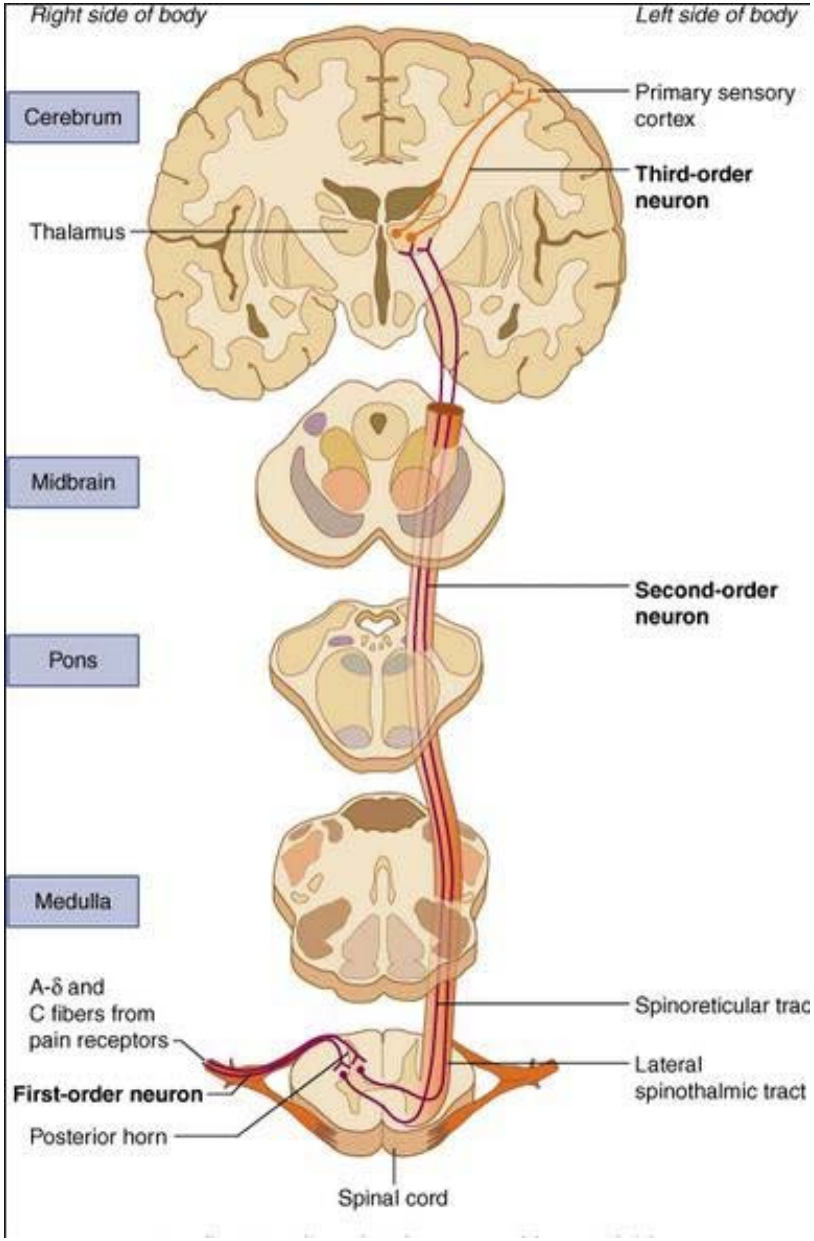
Neuropathic

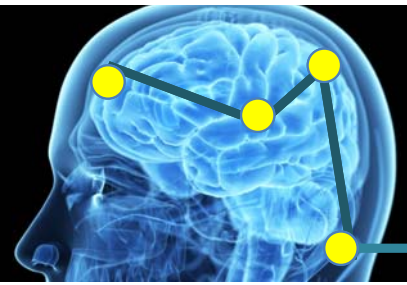
Dysfunctional

CHRONIC
V.S.
ACUTE

What is Neuropathic pain (NP)?







What is Neuropathic pain (NP)?

Neuropathic pain is a medical term used to describe the pain that develops when the nervous system is damaged or not working properly due to disease or injury.

It is different from nociceptive pain because it does not develop in response to any specific circumstance or outside stimulus.

Chronic low back pain (CLBP) is a very common complaint, but in 90 percent of cases, doctors are not able to identify a physical cause. Often, some of the discomfort people have from CLBP is neuropathic pain.

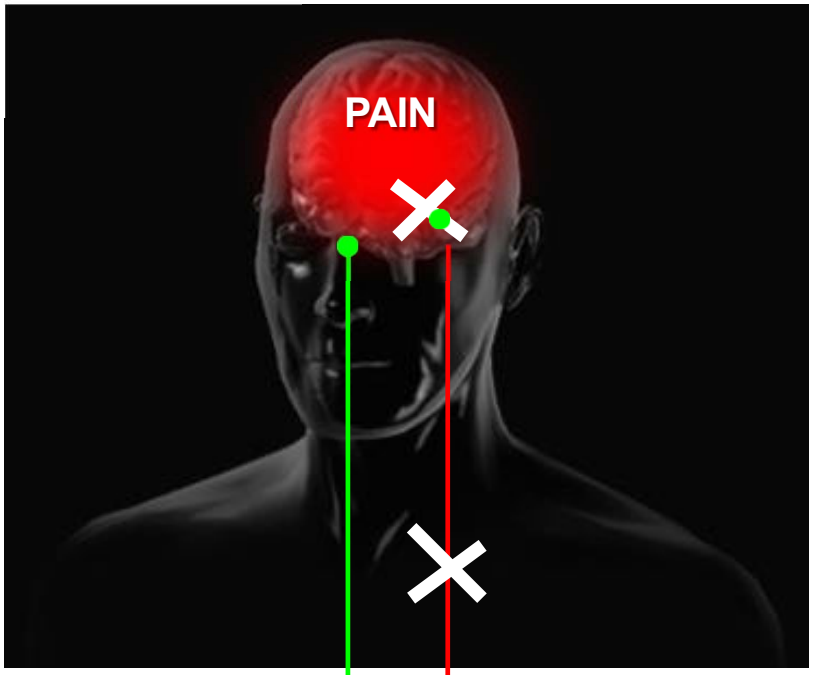
Many different conditions and diseases cause neuropathic pain, including:

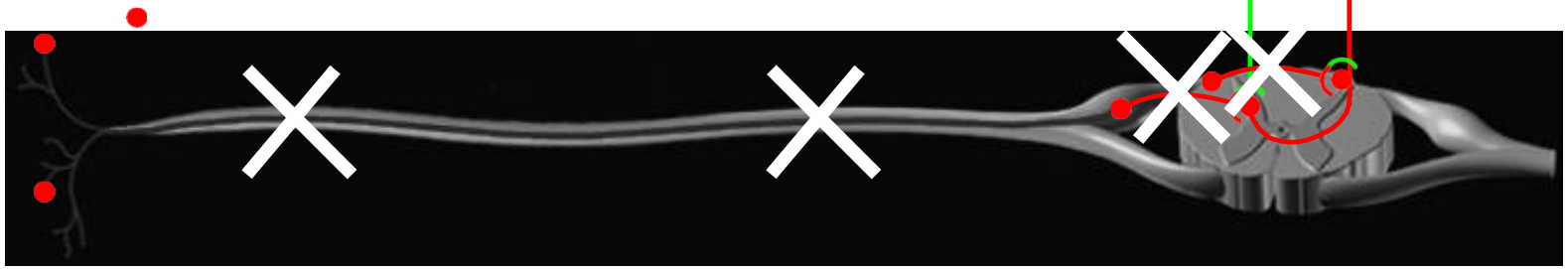
- diabetes
- multiple sclerosis
- stroke
- cancer
- cytomegalovirus
- amputation

What is Neuropathic pain (NP)?

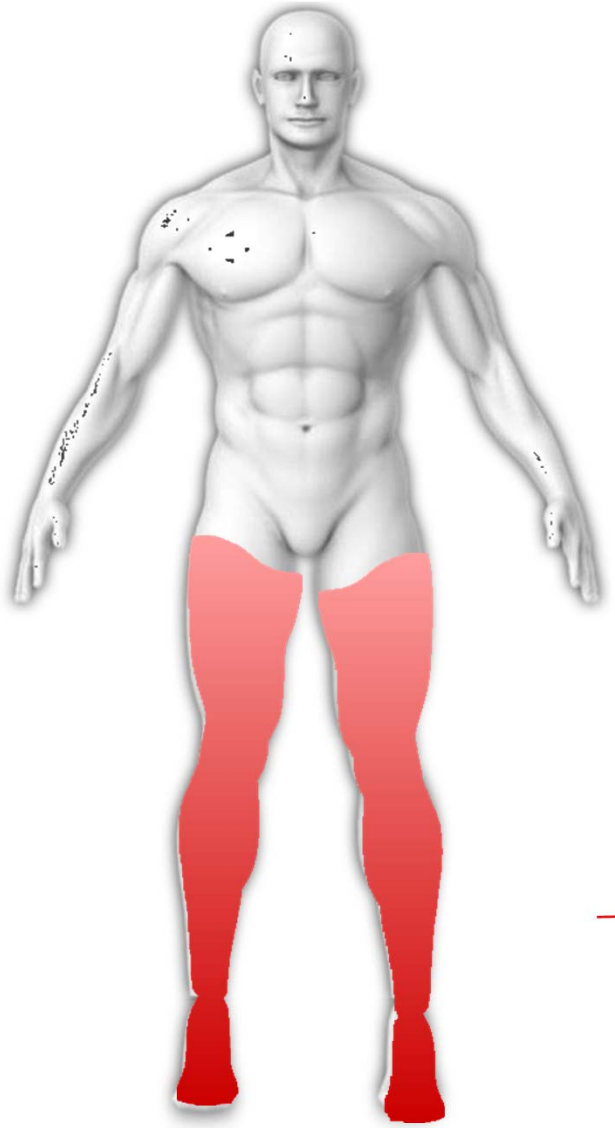
Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system

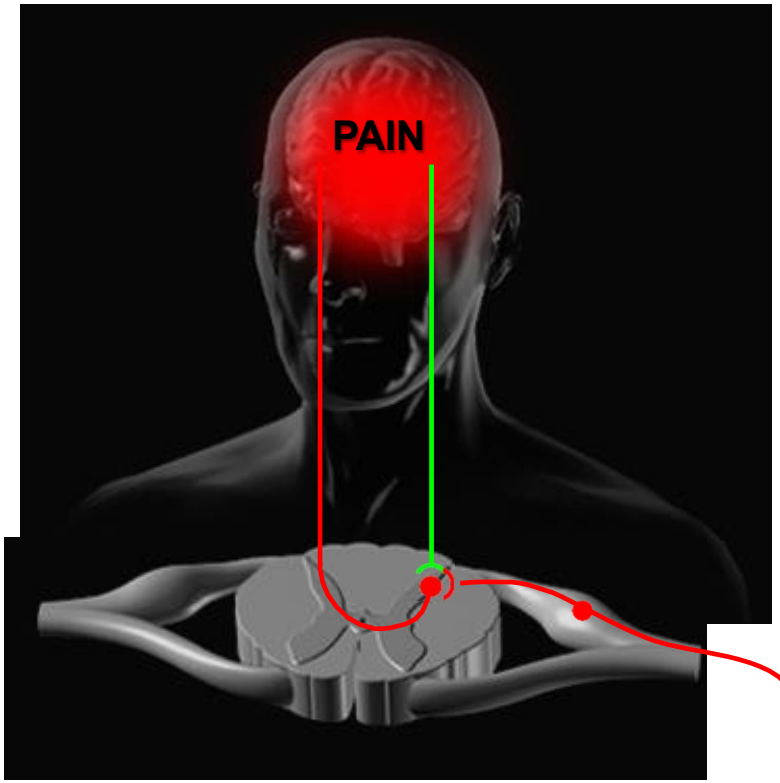
- Diabetic polyneuropathy
- Postherpetic neuralgia
- Spinal injury
- Poststroke central pain



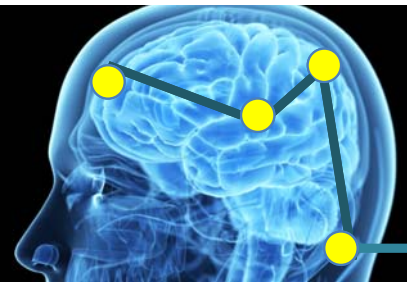


What is Neuropathic pain (NP)?





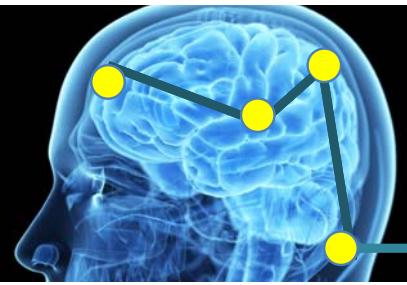
Pain is arising as a direct consequence of a lesion of peripheral sensory nerves



Types of Neuropathic pain (NP)

- **Direct nerve root injury: radiculopathy**
  - Battered root syndrome
  - Perineural fibrosis
  - Intrafascicular fibrosis
  - Adhesive arachnoiditis
- **Peripheral deafferentation**
  - Phantom limb pain
  - Sympathetic-mediated pain syndrome
  - Herpetic neuralgia
  - Diabetic polyneuropathy
- **Central deafferentation-thalamic stroke**

Cole AJ. In Low Back Pain Handbook, 2nd ed. 2003; pg 361-374



Pharmacologic management of Neuropathic pain (NP)

Firstline Medications

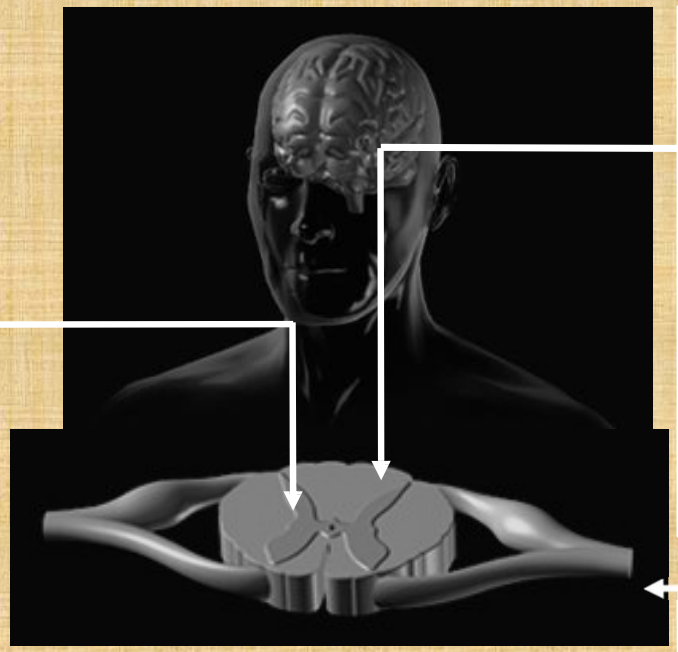
Drug Class	Drug	Recommendations	Cautions
Gabapentinoids	Gabapentin	Slow titration up to 600 mg PO TID. Max daily dose = 3600 mg.	Reduce dose for renal impairment
	Pregabalin	Start at 150 mg PO BID or TID. Max daily dose = 600 mg.	
Serotonin and norepinephrine reuptake inhibitors	Duloxetine	Start at 30 mg PO daily. Max daily dose = 60 mg.	Renal or liver disease
	Venlafaxine	Start at 37.5 mg PO daily. Max daily dose = 225 mg.	
Tricyclic antidepressants	Nortriptyline	Start at 10–25 mg PO QHS. Max daily dose = 150 mg.	Autonomic neuropathy, urinary retention, glaucoma
	Amitriptyline	Start at 10–25 mg PO QHS. Max daily dose = 150 mg.	Taking SNRI, SSRI, MAOI, and/or tramadol
Topicals (focal neuropathic pain)	5% lidocaine	Available in cream or patch. Apply to site of pain 12 hours on, 12 hours off. Max of three patches at one time.	
	8% capsaicin	Apply for 60 minutes under supervision of a physician.	Avoid in diabetic peripheral neuropathy
Combination therapy	Gabapentinoid + TCA	Only use if single agent provides inadequate relief and no adverse effects.	Avoid in elderly
	Gabapentinoid + SNRI	Titrate as indicated for single agent. Aim for lower doses of both.	
Weak μ-opioid agonists and serotonin and norepinephrine reuptake inhibitors	Tramadol	Start at 50 mg IR PO BID-QID prn. Max daily dose = 400 mg.	Seizure disorder Taking SNRI, SSRI, TCA, and/or MAOI Reduce dose for renal impairment

The mechanisms of neuropathic pain are the therapeutic targets for medications

Central Sensitization

Ca^{2+}

- Pregabalin
- Gabapentin



Disinhibition, Pain Facilitation

- TCAs
- SNRI

NA, 5HT

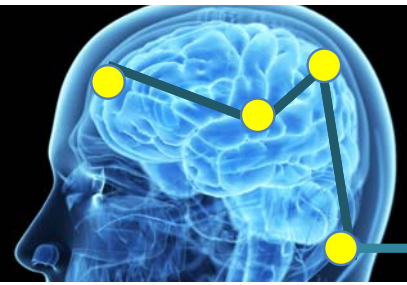
Peripheral Sensitization

- Carbamazepine
- Lamotrigine
- Lidocaine

Na^{+}

- Capsaicin

TRPV



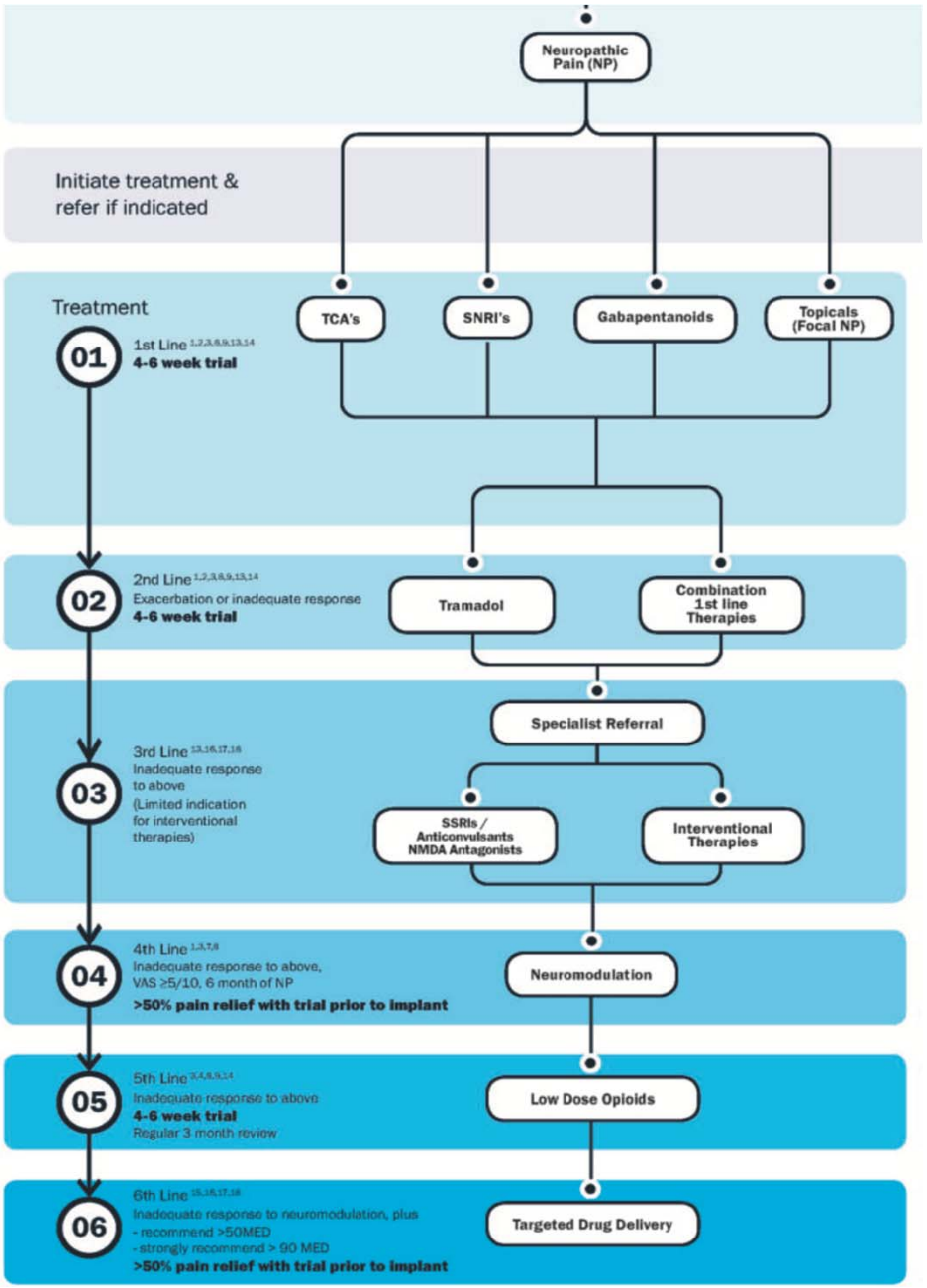
Pharmacologic management of Neuropathic pain (NP)

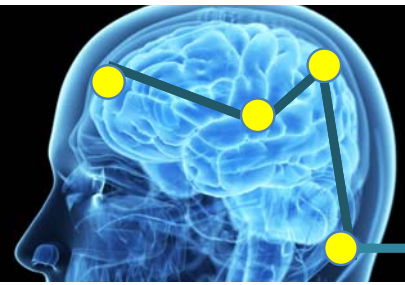
Table 1 Selected guideline recommendations for drugs used for pain in diabetic neuropathy

Drug	NNT	AAN	NICE	EFNS	NeuPSIG IASP	Mechanism of action
GABA analogues				Fist line	Fist line	
Pregabalin	5.0	First line	First line			Bind to voltage-gated calcium channels and reduces the synaptic release of several neurotransmitters
Gabapentin	6.0		First line			
TCAs				First line		
Amitriptyline	1.3	Second line	First line			Inhibit reuptake of noradrenaline and serotonin
Imipramine	2.2	Second line			First line	
Desipramine	2.6				First line	
SNRIs		Second line		First line	First line	
Duloxetine	5.0		First line			Inhibit reuptake of noradrenaline and serotonin augmenting descending inhibitory pathways
Venlafaxine	3.1					
Opioids		Second line		Second line	Second line	
Strong opioids	4.1			Second line		
Tramadol	4.4		Second line	Second line		Partial μ-receptor Agonists weak opioid and inhibits noradrenaline and serotonin reuptake
Topical						
Capsaicin (0.075% cream)	6.6			Second line		By depleting substance P at vanilloid nerve
Lidocaine 5% patch	4.0		Second line	Second line		Local anaesthetic

AAN, American Academy of Neurology; EFNS, European Federation of Neurological Societies; IENFD, intraepidermal nerve fibre density; NeuPSIG IASP, Neuropathic Pain Special Interest Group of the International Association for the Study of Pain; NICE, National Institute for Health and Care Excellence; NNT, Number Needed to Treat for at least 50% pain relief. Adapted Ref. [11].

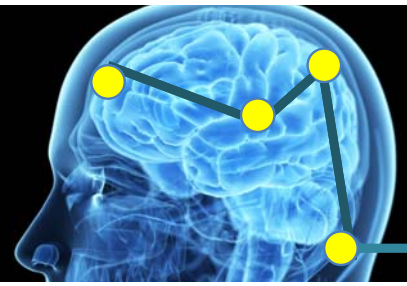
Management of Neuropathic pain (NP)





Neuromodulation

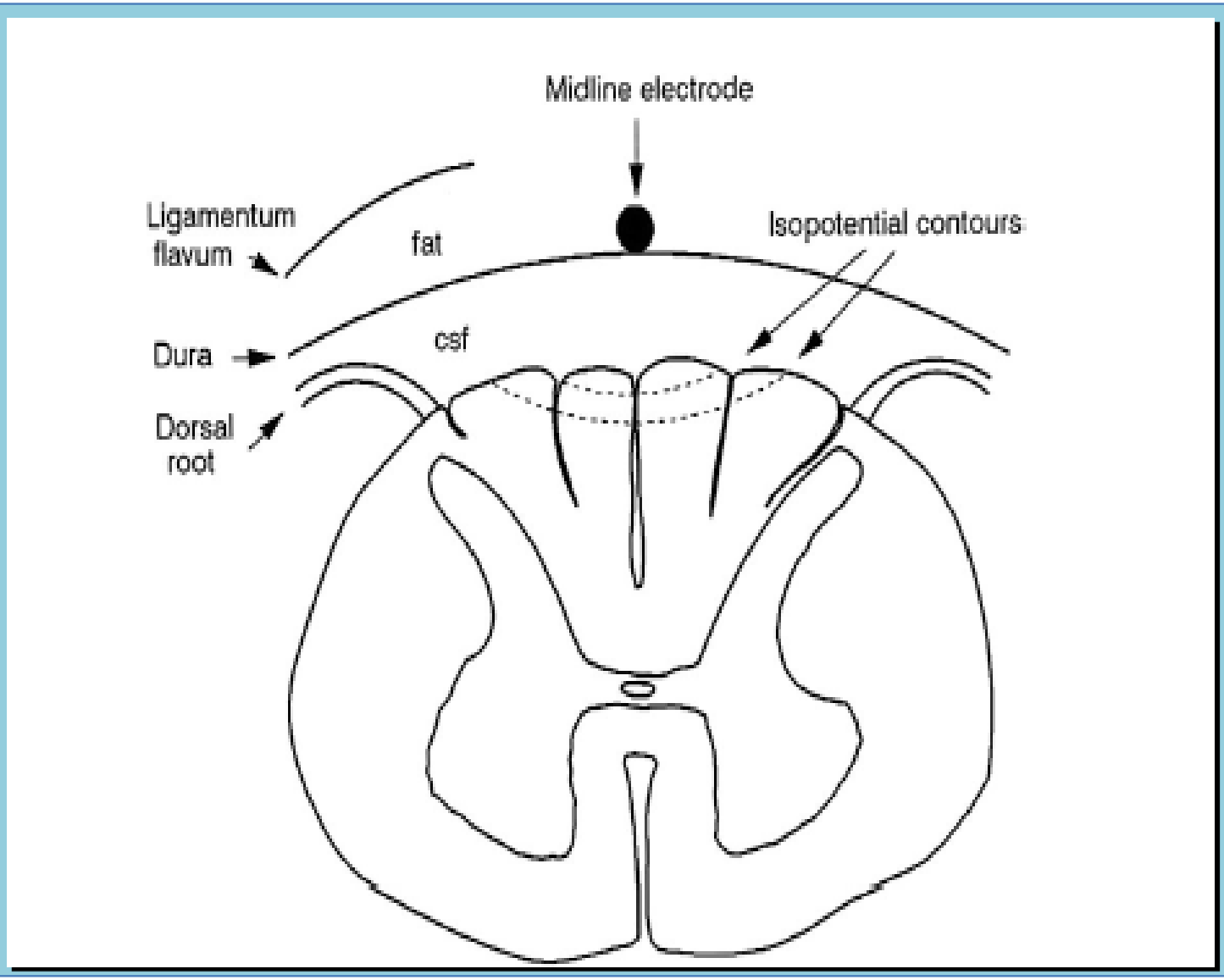
- **ELECTRICAL = NEUROSTIMULATION**
- **CHEMICAL: INTRATHECAL DRUG DELIVERY**
  - **OPIOIDS**
  - **NON-OPIOIDS**



Spinal Cord Stimulation

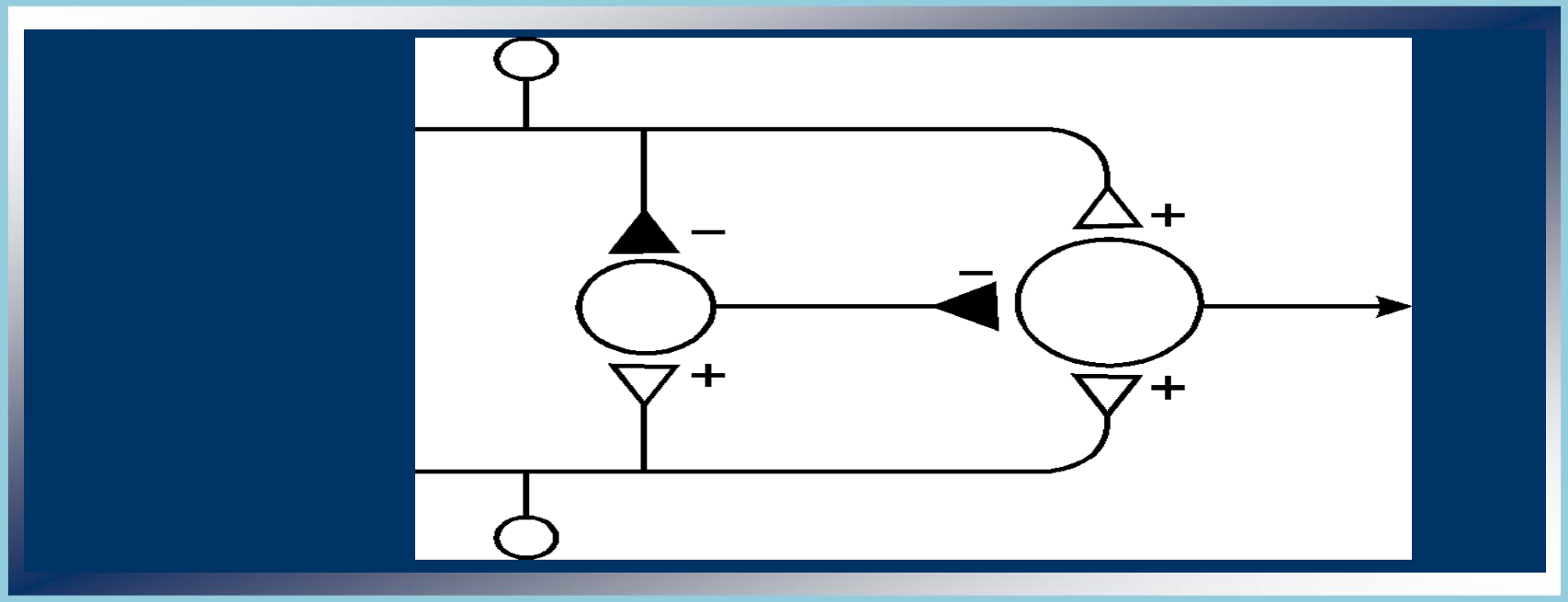
- **What is Neurostimulation?**
  - **A technique that alleviates pain by sending electrical impulses via implanted leads to the spinal cord**
    - **The impulses activate pain-inhibiting neuronal circuits in the dorsal horn and induce a tingling sensation (paresthesiae) that masks the sensations of pain**
- **What is the goal of Neurostimulation?**
  - **To obtain more than 80% coverage of the painful areas with paresthesiae, so that at least a 50% reduction in pain can be maintained at one year follow-up**

Spinal Cord Stimulation

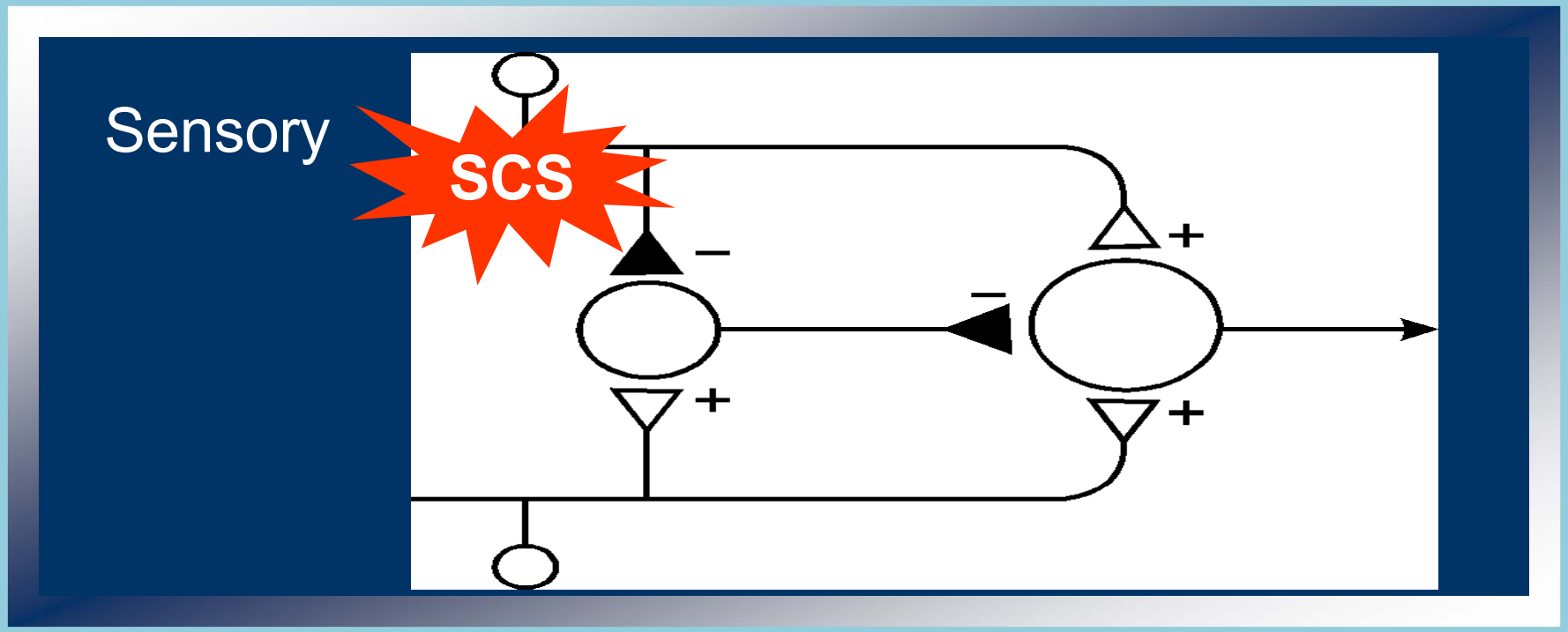


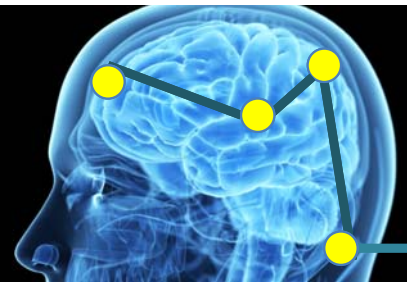
Spinal Cord Stimulation

- When sensory impulses are greater than pain impulses
- "Gate" in the spinal cord closes preventing the pain signal from reaching the brain



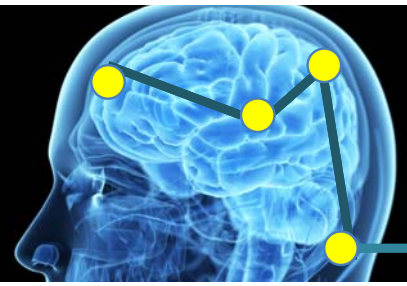
Spinal Cord Stimulation





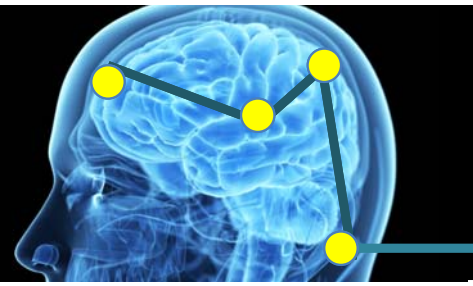
Indications for Spinal Cord Stimulation

- **Back Pain**
  - **Failed Back Syndrome**
- **CRPS 1 & 2**
- **Diabetic Neuropathic pain**
- **Radiculopathy – non-operative**
- **Peripheral vascular disease**
- **Post Herpetic Neuralgia**
- **Ischemic Heart Disease**
- **Arachnoiditis**



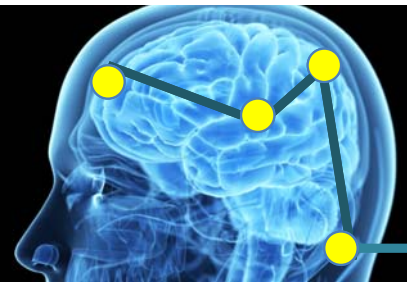
Pain Indications for Stimulation

- Intractable neuropathic pain
- Any body region: Head-to-Toe
- Properly screened patient



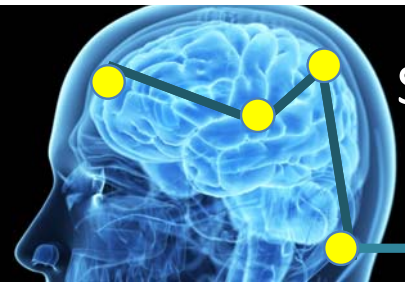
Neurostimulation: Reduction in Pain

Reference	# of Patients	Mean Follow up	Results
North ***Pain, 1993***	**171**	**7 years**	**52% with > 50% relief**
Turner ***Neurosurgery, 1995***	**39 study meta analysis**	**16 months**	**59% with > 50% relief**
De la Porte ***Pain, 1993***	**64**	**4 years**	**55% good to excellent relief**
Segal ***Neurol Research, 1991***	**24**	**19 months**	**78% good to very good effect**
Kumar ***Surg Neurol, 1991***	**111**	**5.6 years**	**59% good to excellent results**
Burchiel ***Spine, 1996***	**70 Multi-center**	**1 year**	**55% with > 50% relief**



Reduction in Analgesic Consumption

Reference	# of Patients	Mean Follow-up	Results
Ohnmeiss *Spine*, 1996	40	2 years	66% decreased eliminated narcotics
North *Neurosurgery*, 1995	171	7 years	58% reduced/eliminated analgesics
De La Porte *Pain*, 1993	64	4 years	90% reduced medication
Kumar *Surg Neurol*, 1991	111	5.6 years	59% satisfactory relief
Racz *Spine,* 1989	26	1.8 years	81% reduced/eliminated narcotics
Segal	24	19 months	59% satisfactory relief



Spinal Stimulation (SCS) vs Conventional Medical Management (CMM) for Neuropathic Pain…in Patients with Failed Back surgery Syndrome

- **RCT-100 patients w FBSS (neuropathic radicular pain)**
- **SCS+CMM vs CMM**
- **48% of SCS and 4% of CMM achieved primary outcome of ≥ 50% pain relief**
- **SCS group also had**

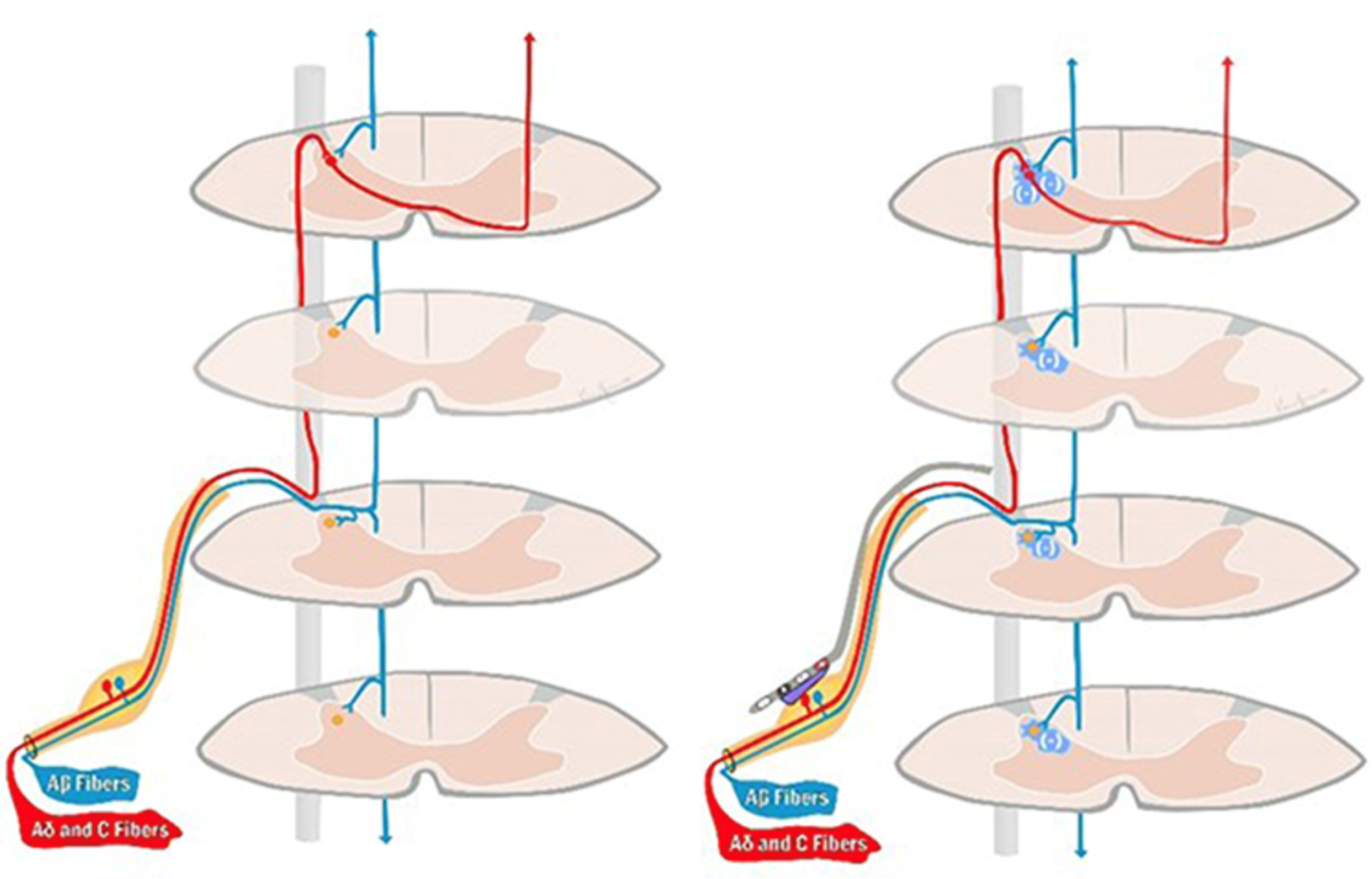
  -improved Q.O.L.

  -improved functional measures

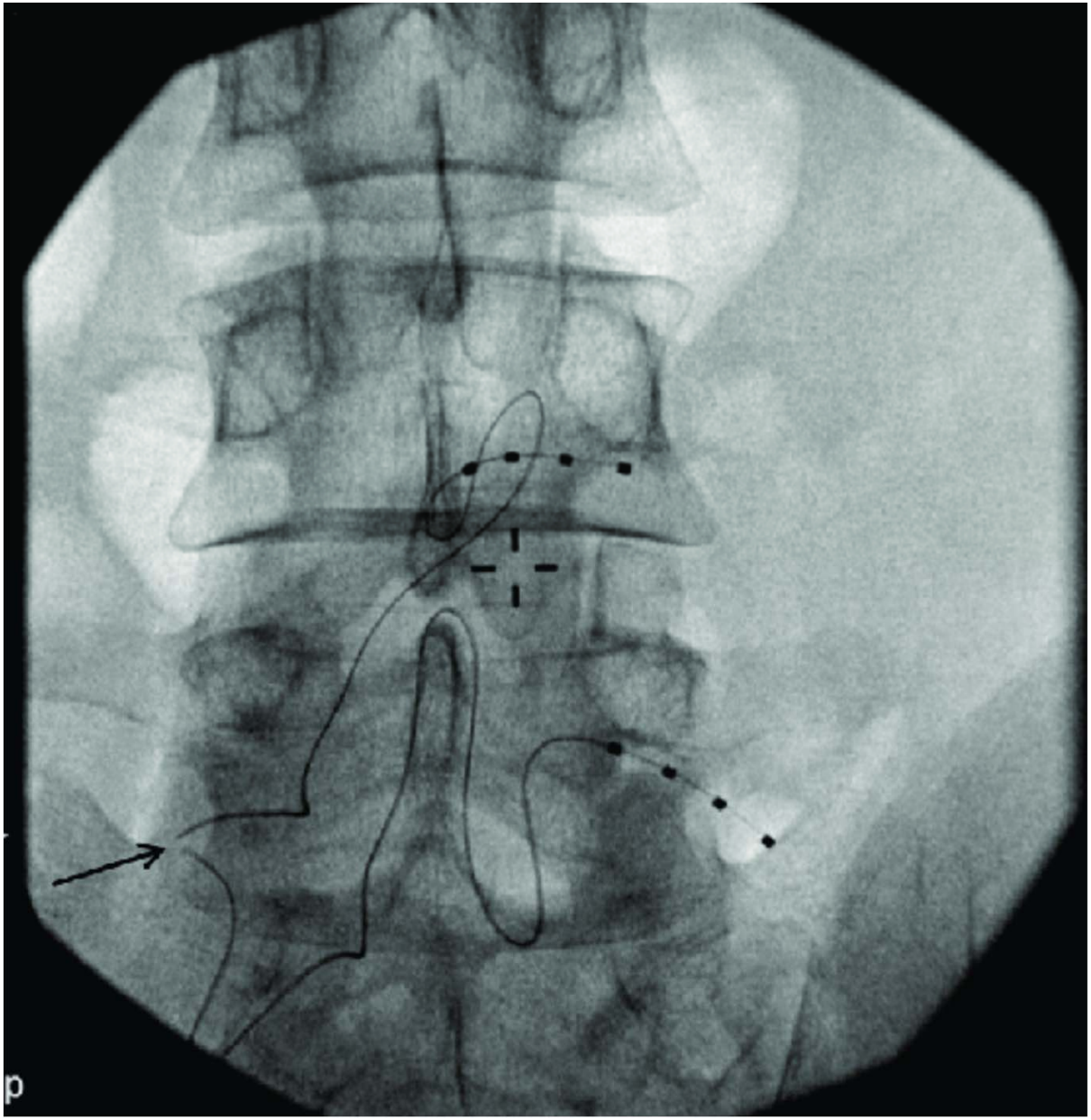
  -greater treatment satisfaction

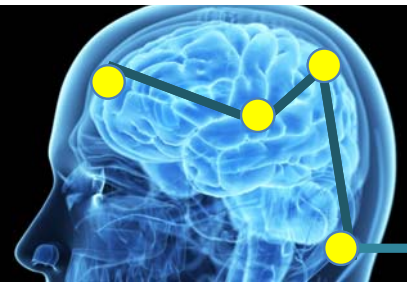
Kumar K. et al. Pain 2007;132:179-188

Dorsal Root Ganglion Stimulation



Dorsal Root Ganglion Stimulation



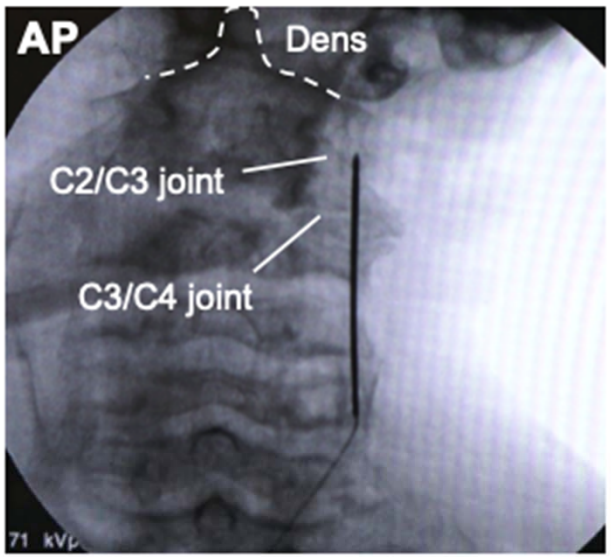


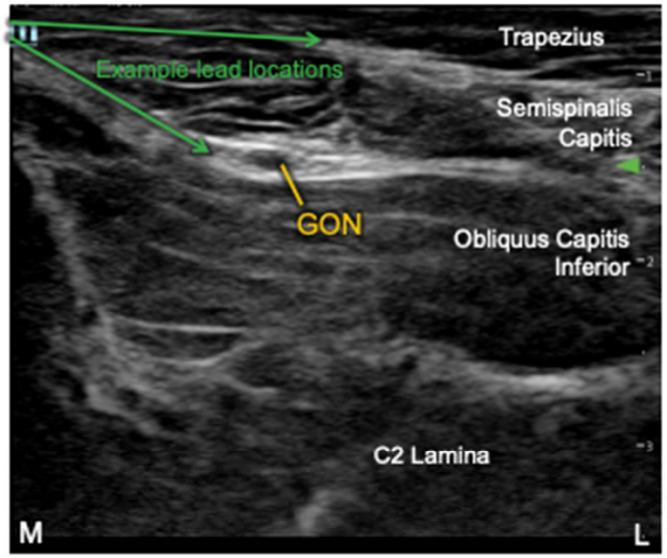
Dorsal Root Ganglion Stimulation

Indication	Grade	Level of Certainty	Evidence
CRPS I and II	A	High	I
Post-Hernia Repair	B	Moderate	II-2
Post-Joint Surgery	C	Low	III
FBSS	C	Low	III
Post-Amputation	I	Low	III
Nonsurgical Low Back Pain	C	Low	III
Peripheral Neuropathy	C	Low	III
Pelvic Pain	C	Low	III
Post-Herpetic Neuralgia	I	Low	III

Peripheral Nerve Stimulators

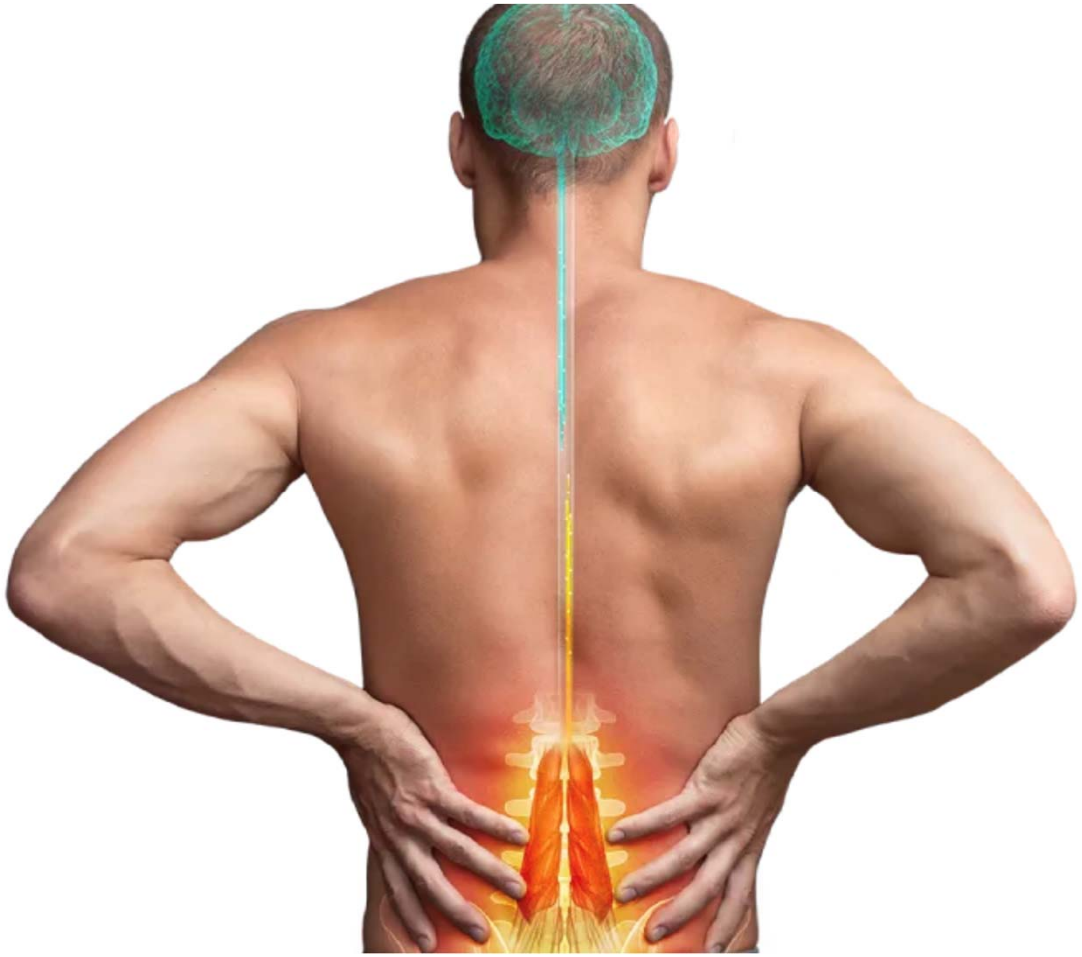
Peripheral Nerve Stimulators



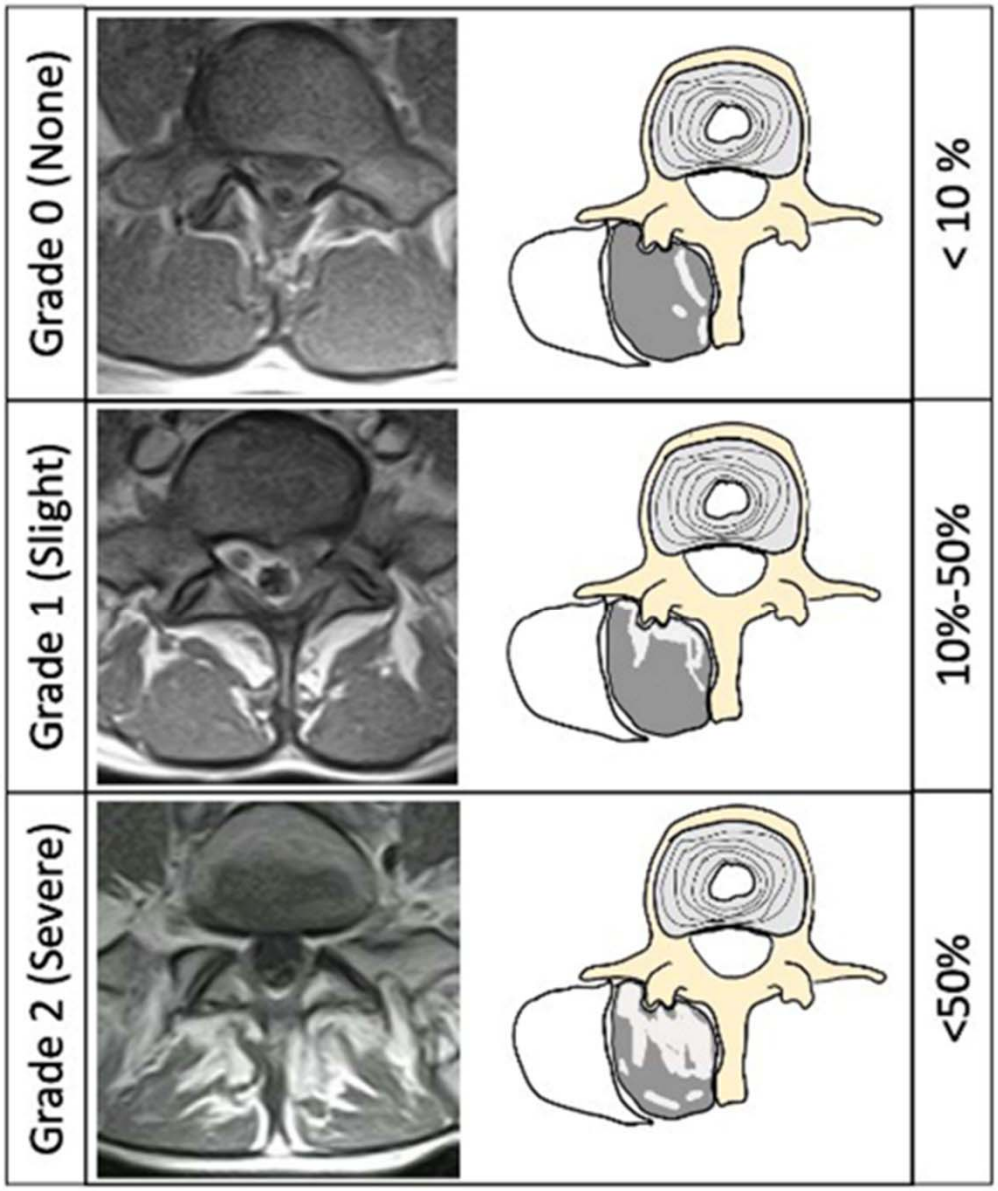


- The occipital nerves can be targeted with various approaches under ultrasound or fluoroscopy. Images show different example approaches to the greater and/or third occipital nerves at the level of C2.
- While safety was not directly analyzed here, published studies indicate the most common events are skin irritation due to adhesive bandages, pain or discomfort due to stimulation, and pain due to the lead placement procedure.

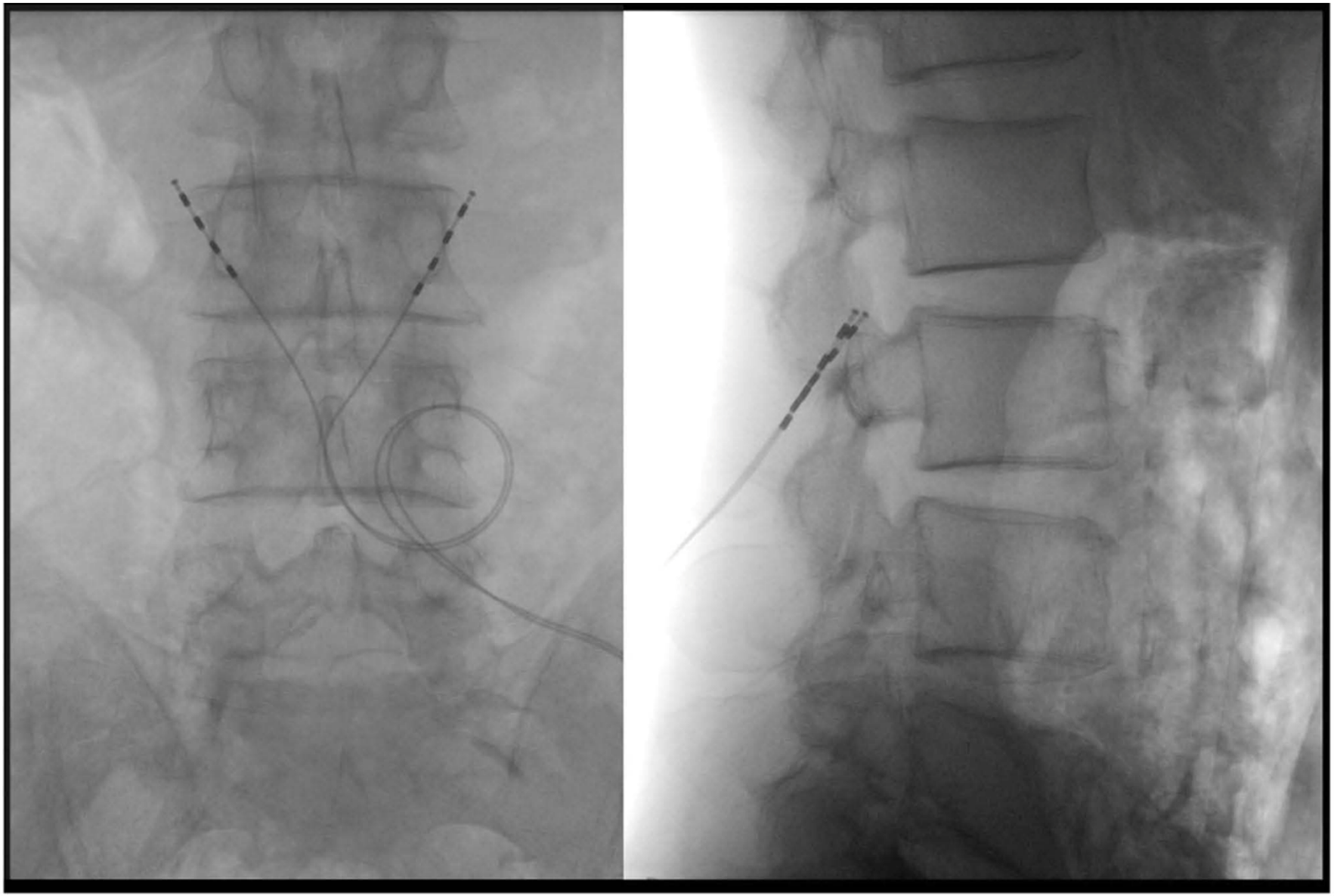
Restorative Neuromodulation



Restorative Neuromodulation



Restorative Neuromodulation



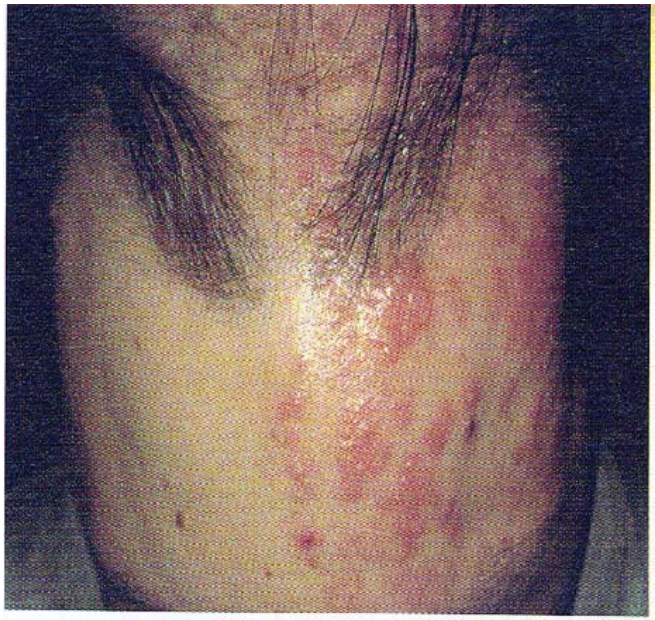
Motor Cortex Stimulation-Indications and Outcomes

- **Indications**

-Post-stroke pain (thalamic pain)

-anesthesia dolorosa (surgery, trauma)

-postherpetic neuralgia



- **Results**

-No large scale series and/or RCTs

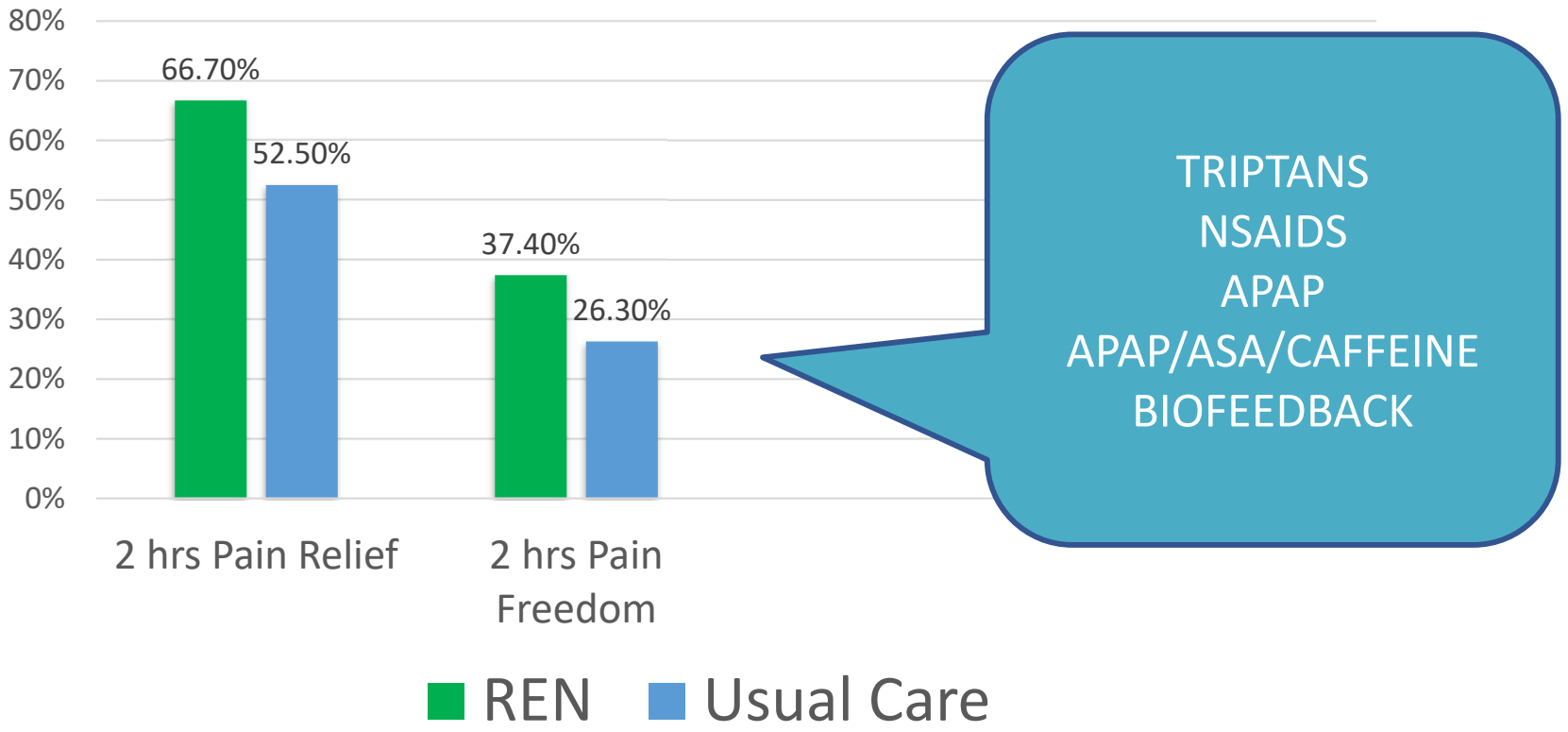
-multiple clinical series since 1993: 40-75% of patients with > 50% pain relief

-Largest series;29/38(76%) of patients improved

Neurosurgical Focus 2006;21:1-4

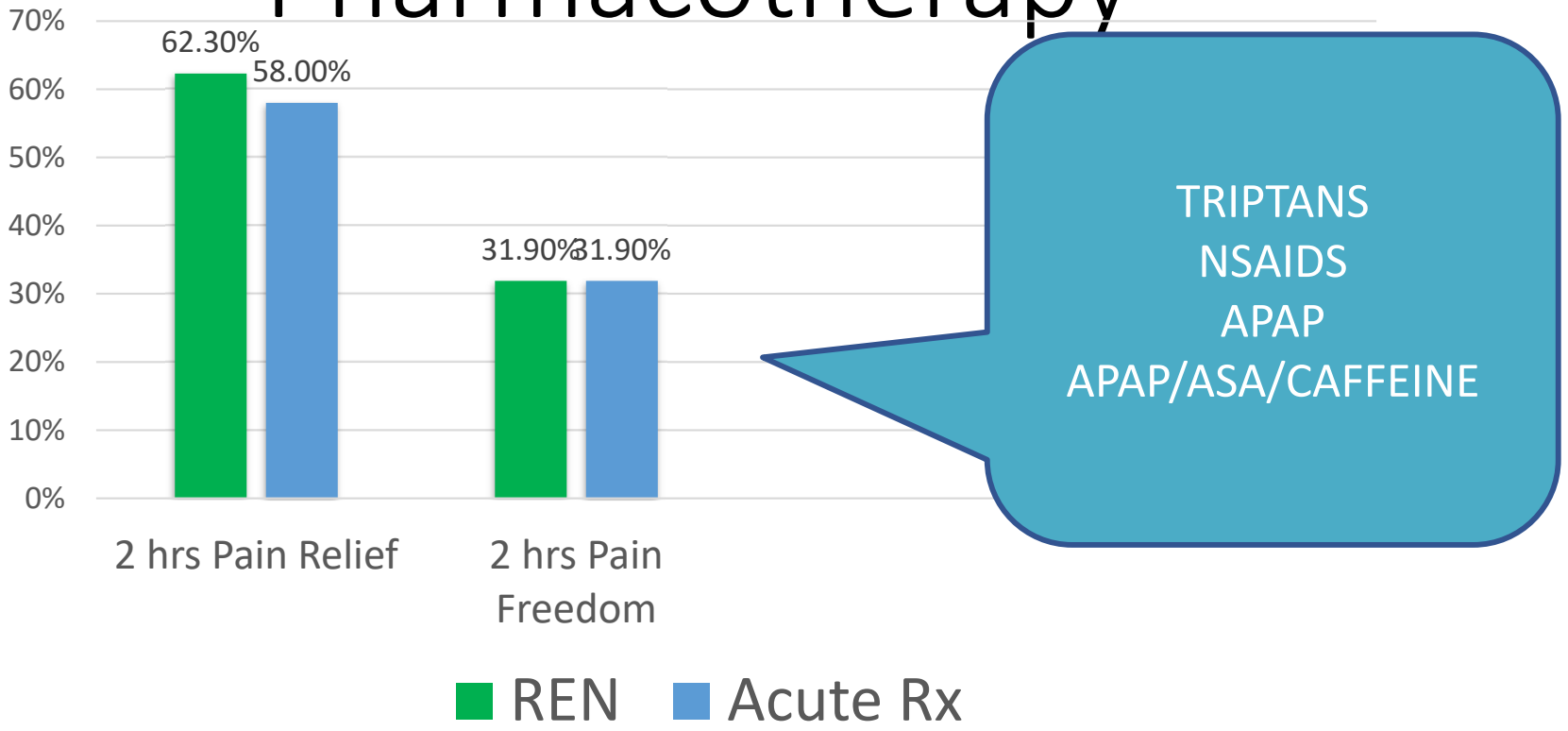
Nerivio (Remote Electrical Neuromodulation)

Nerivio VS Usual Care



Rapoport AM, Bonner JH, Lin T, Harris D, Gruper Y, Ironi A, Cowan RP. Remote electrical neuromodulation (REN) in the acute treatment of migraine: a comparison with usual care and acute migraine medications. J Headache Pain. 2019 Jul 22;20(1):83

Nerivio VS Acute Pharmacotherapy



Rapoport AM, Bonner JH, Lin T, Harris D, Gruper Y, Ironi A, Cowan RP. Remote electrical neuromodulation (REN) in the acute treatment of migraine: a comparison with usual care and acute migraine medications. J Headache Pain. 2019 Jul 22;20(1):83

Nerivio

- FOR ACUTE TREATMENT OF EPISODIC
- AND CHRONIC MIGRAINE

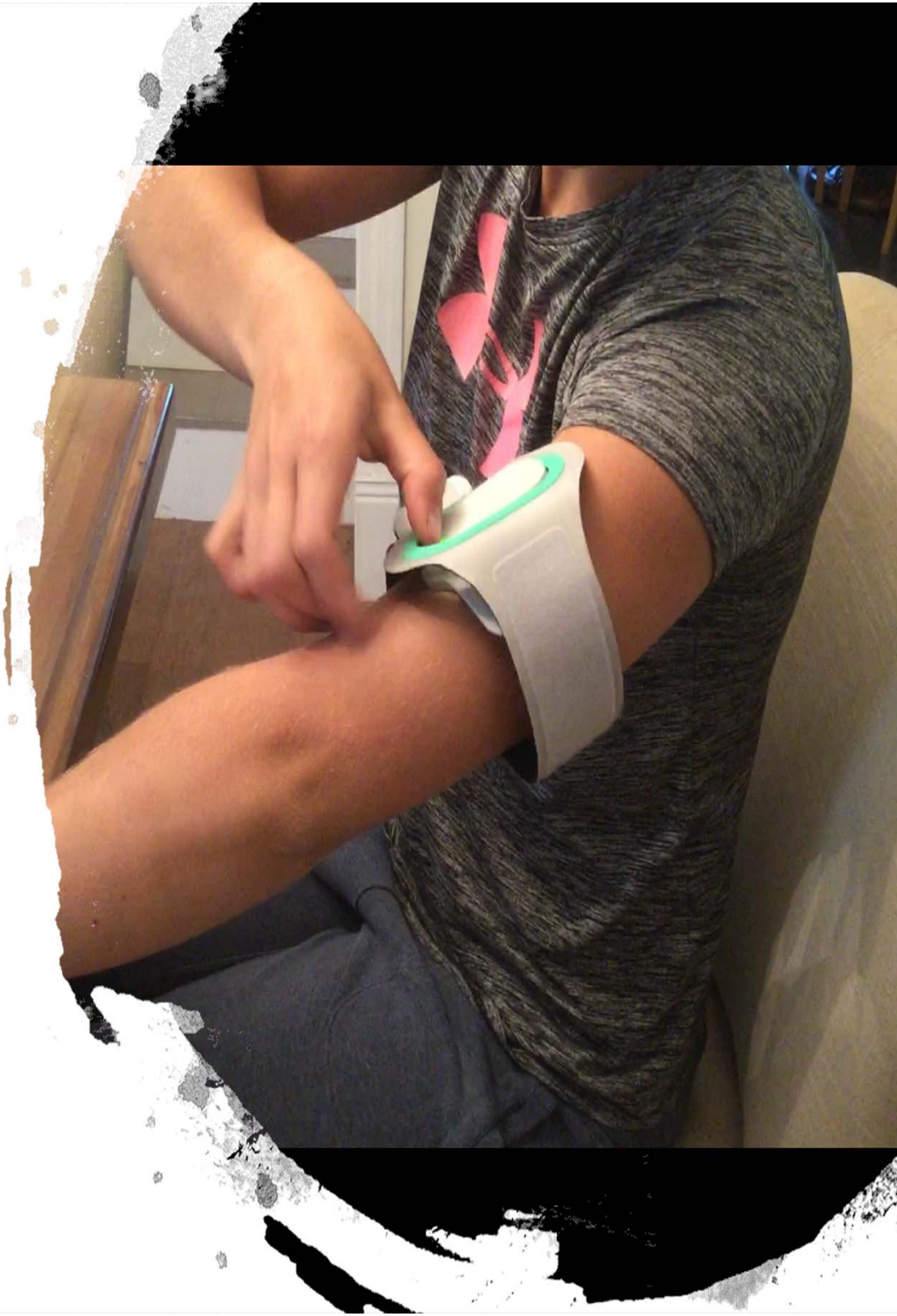
- FOR ADULTS AND ADOLESCENTS

- 1 DEVICE = 12 TREATMENTS

- START STIMULATION WITHIN 1 HR

- DURATION – 45 MINUTES

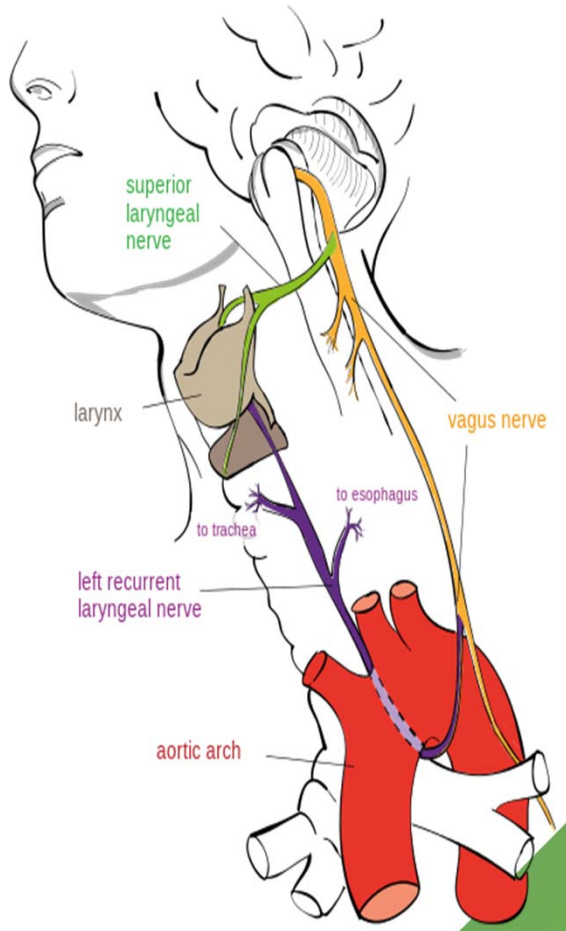
- PERCEPTIBLE BUT NOT PAINFUL STIMULATION



GammaCore – Noninvasive vagus nerve stimulator

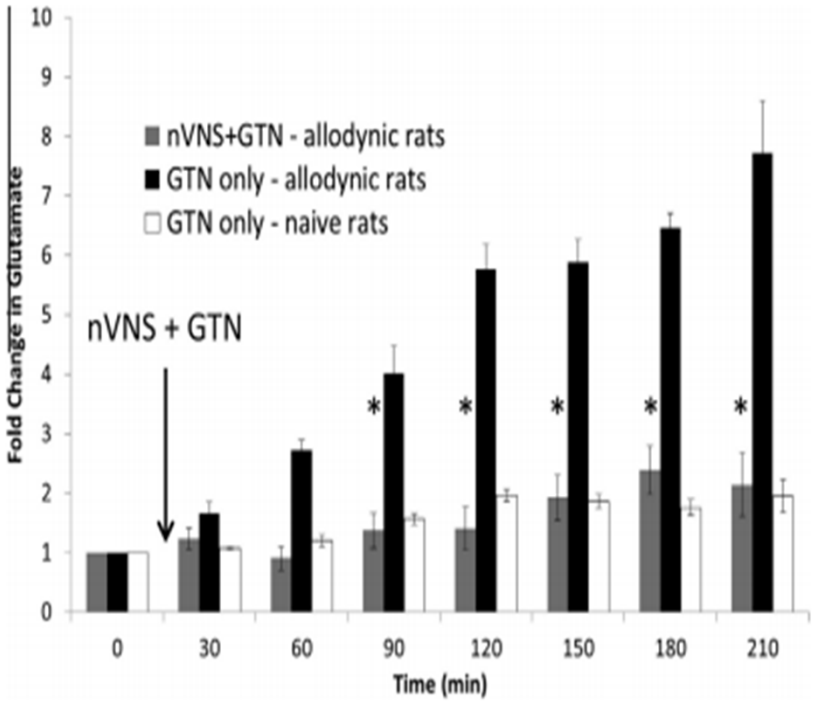
Vagus Nerve Stimulation

- 1997 – iVNS for refractory epilepsy
- 2005 – iVNS for treatment-resistant depression
- 2017 – nVNS for acute treatment of cluster HA
- 2018 – nVNS for acute treatment of migraine
- 2019 – nVNS for cluster prevention
- 2020 – nVNS for migraine prevention



GammaCore: MOA

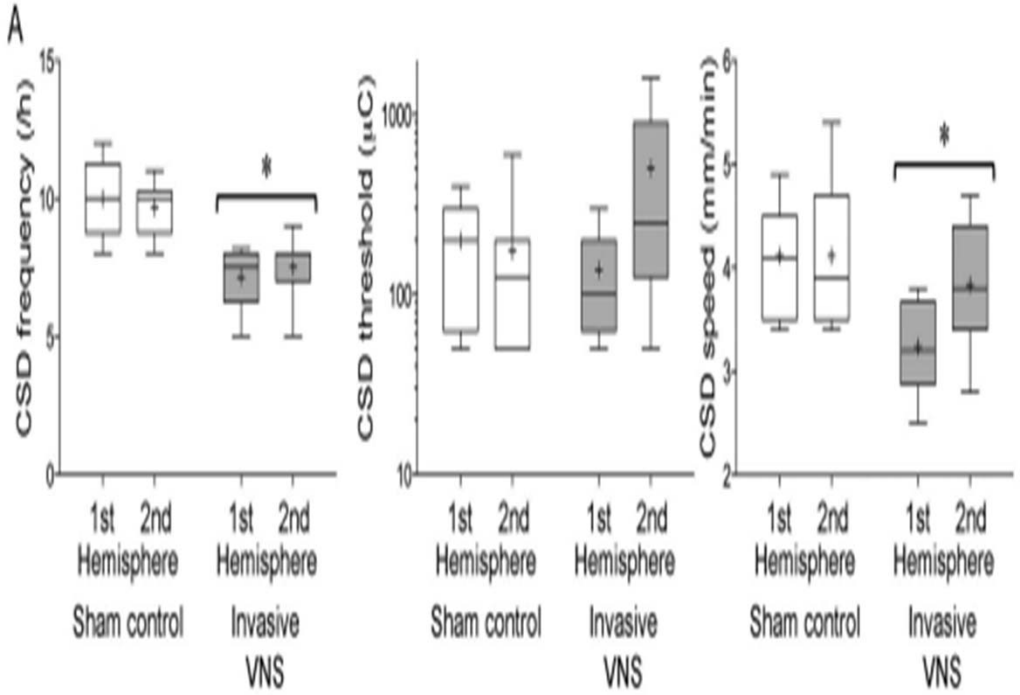
Reduces Glutamate in TNC



Oshinsky ML, Murphy AL, Hekierski H Jr, Cooper M, Simon BJ. Noninvasive vagus nerve stimulation as treatment for trigeminal allodynia. Pain. 2014 May;155(5):1037-1042.

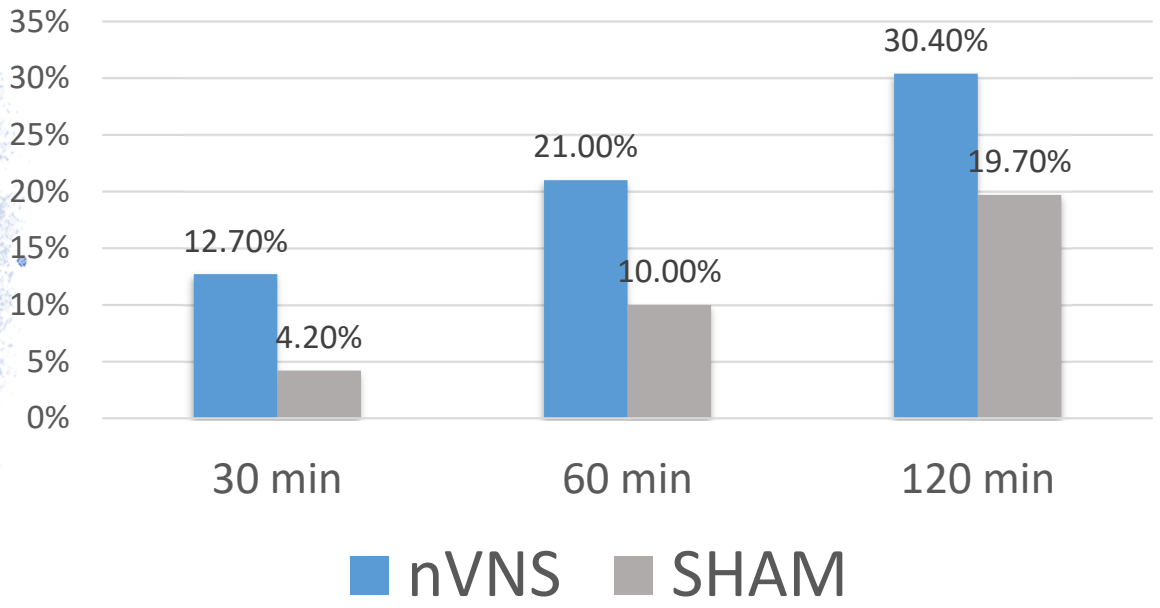
GammaCore: MOA

CSD supression

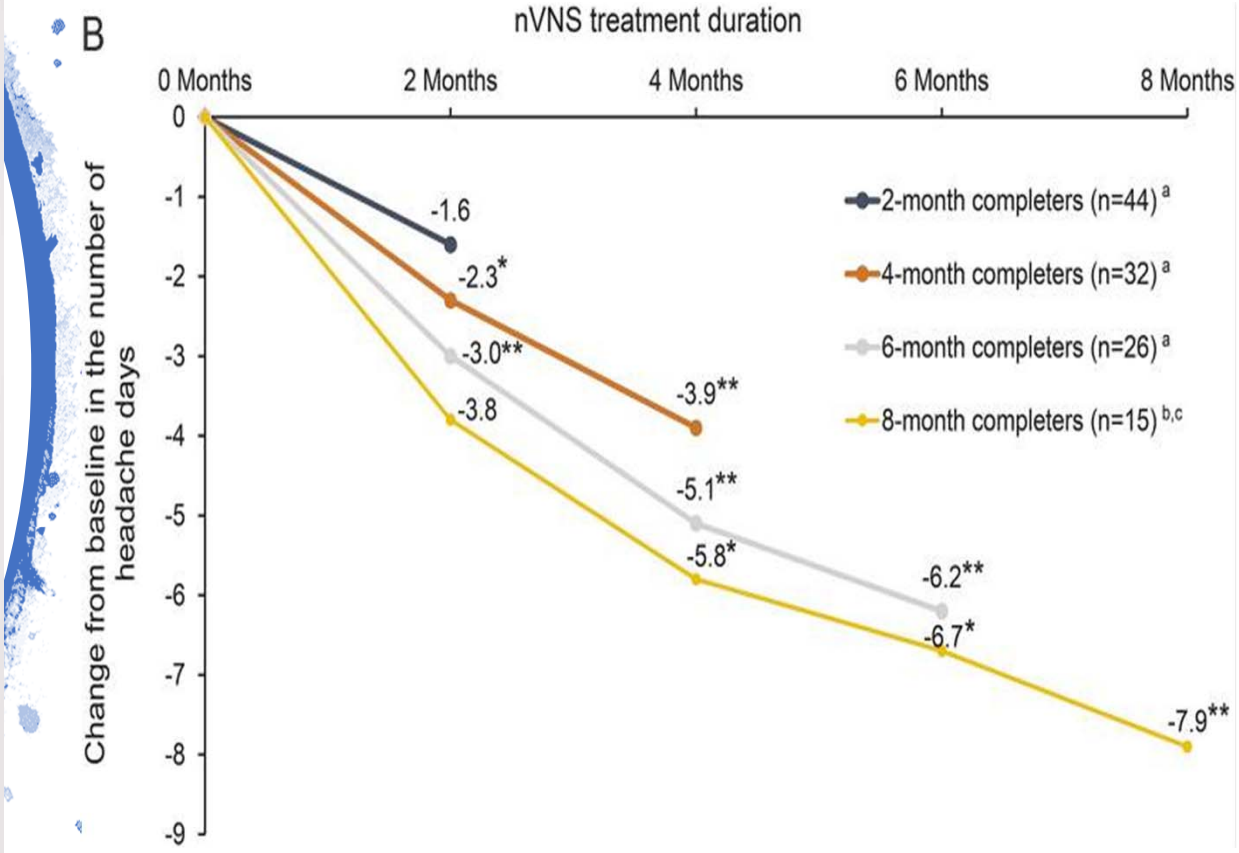


Chen SP, Ay I, Lopes de Morais A, Qin T, Zheng Y, Sadeghian H, Oka F, Simon B, Eikermann-Haerter K, Ayata C. Vagus nerve stimulation inhibits cortical spreading depression. Pain. 2016 Apr;157(4):797-805.

Pain Freedom for First Migraine Treatment

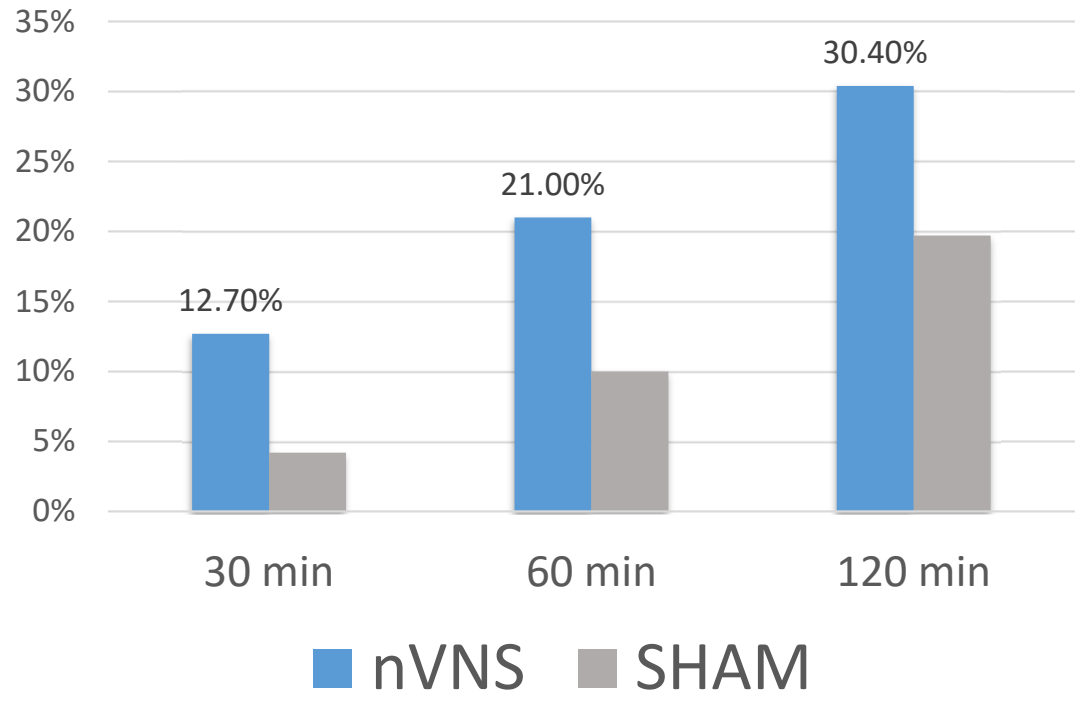


Change in Number of Headache Days



Silberstein SD, Calhoun AH, Lipton RB, Grosberg BM, Cady RK, Dorlas S, Simmons KA, Mullin C, Liebler EJ, Goadsby PJ, Saper JR; EVENT Study Group. Chronic migraine headache prevention with noninvasive vagus nerve stimulation: The EVENT study. Neurology. 2016 Aug 2;87(5):529-38

50% Response Rate



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GammaCore: Side Effects

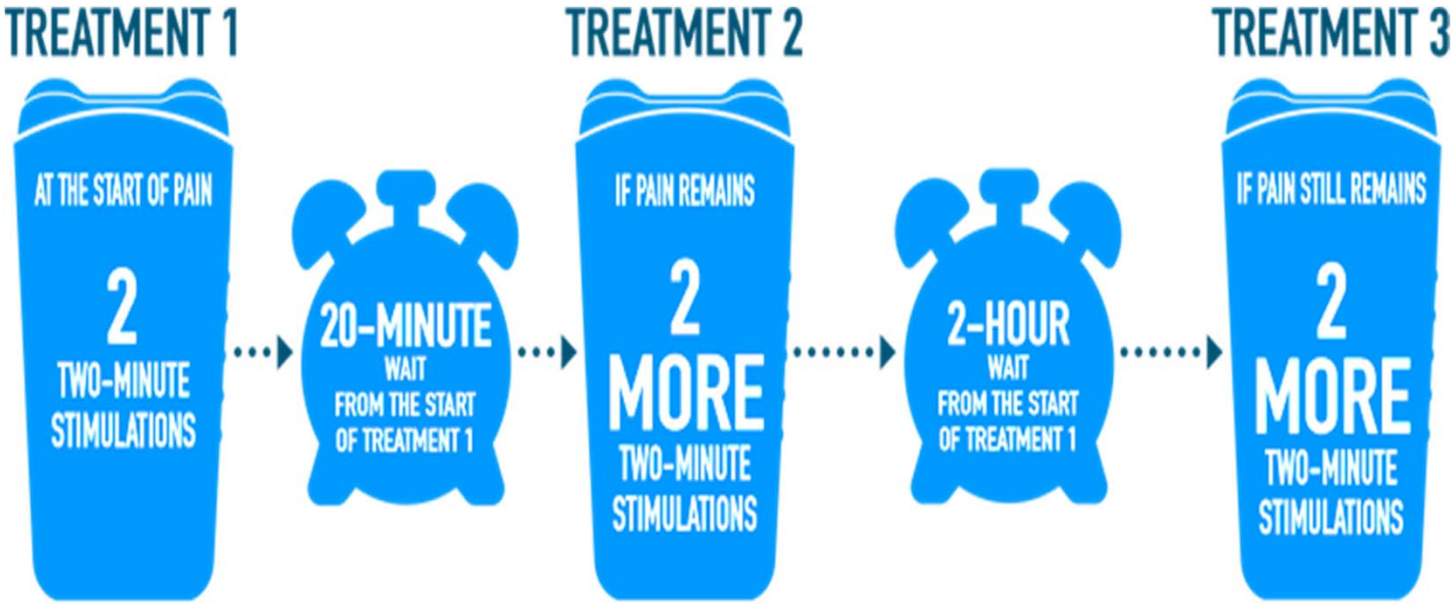
SIDE EFFECT	nVNS	SHAM
FACIAL PAIN NUMBNESS	10%	3%
UPPER RESP TRACT INFECTION	10%	21%
GASTROINTESTINAL SYMPTOMS	10%	14%
EYE TWITCH	7%	3%
TREATMENT SITE SKIN REACTION	3%	3%

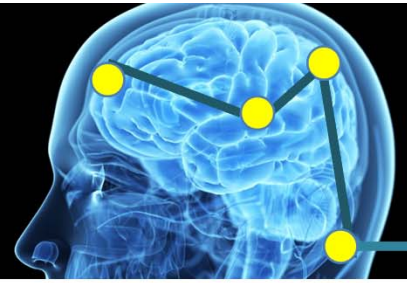
Silberstein SD, Calhoun AH, Lipton RB, Grosberg BM, Cady RK, Dorlas S, Simmons KA, Mullin C, Liebler EJ, Goadsby PJ, Saper JR; EVENT Study Group. Chronic migraine headache prevention with noninvasive vagus nerve stimulation: The EVENT study. Neurology. 2016 Aug 2;87(5):529-38

Gamma Core for Migraine Treatment

Prophylactic

Acute

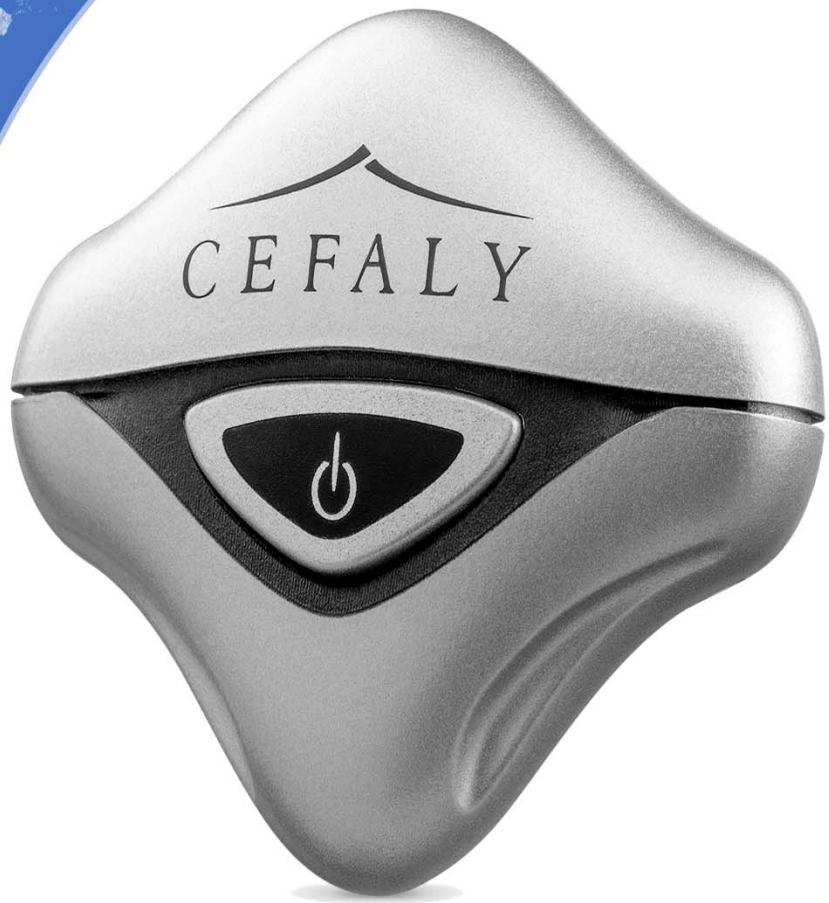




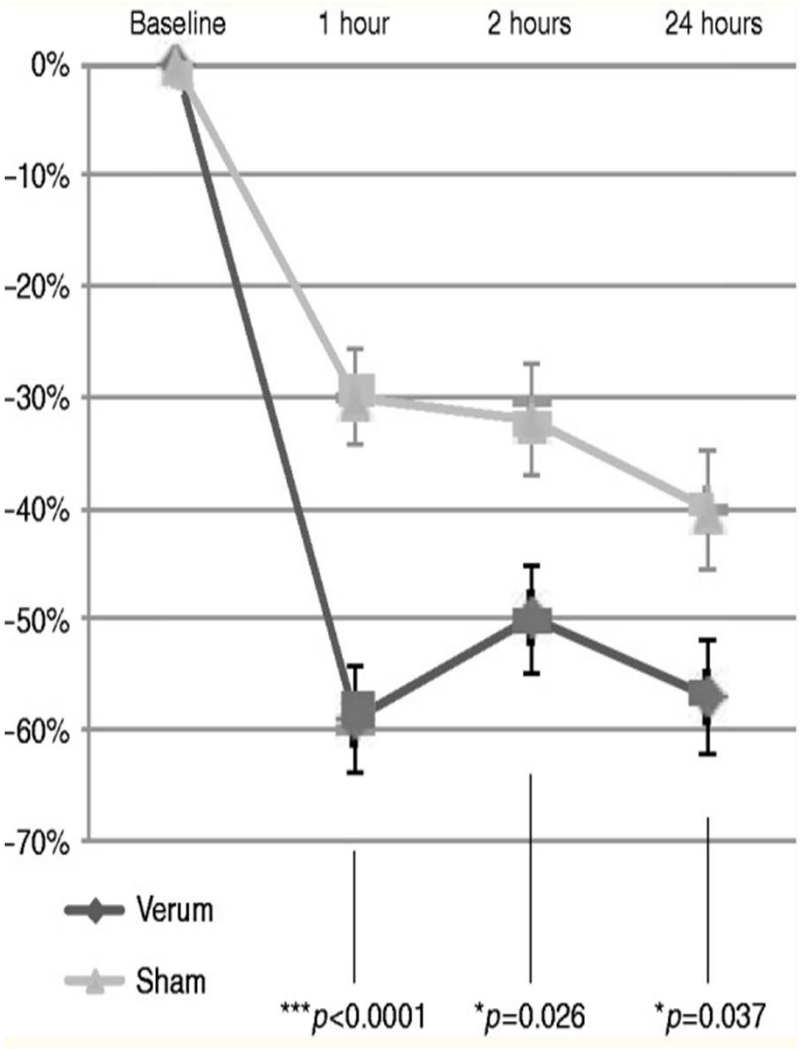
Cefaly
(Transcutaneous
Supraorbital
Nerve Stimulator)

Cefaly MOA

- Not fully understood
- Possibly segmental “gate control” mechanism
- No effect on cerebral metabolism after single treatment
- With chronic use there is an increase in metabolism
- in areas that were depleted before treatment



Relative Change in VAS over time

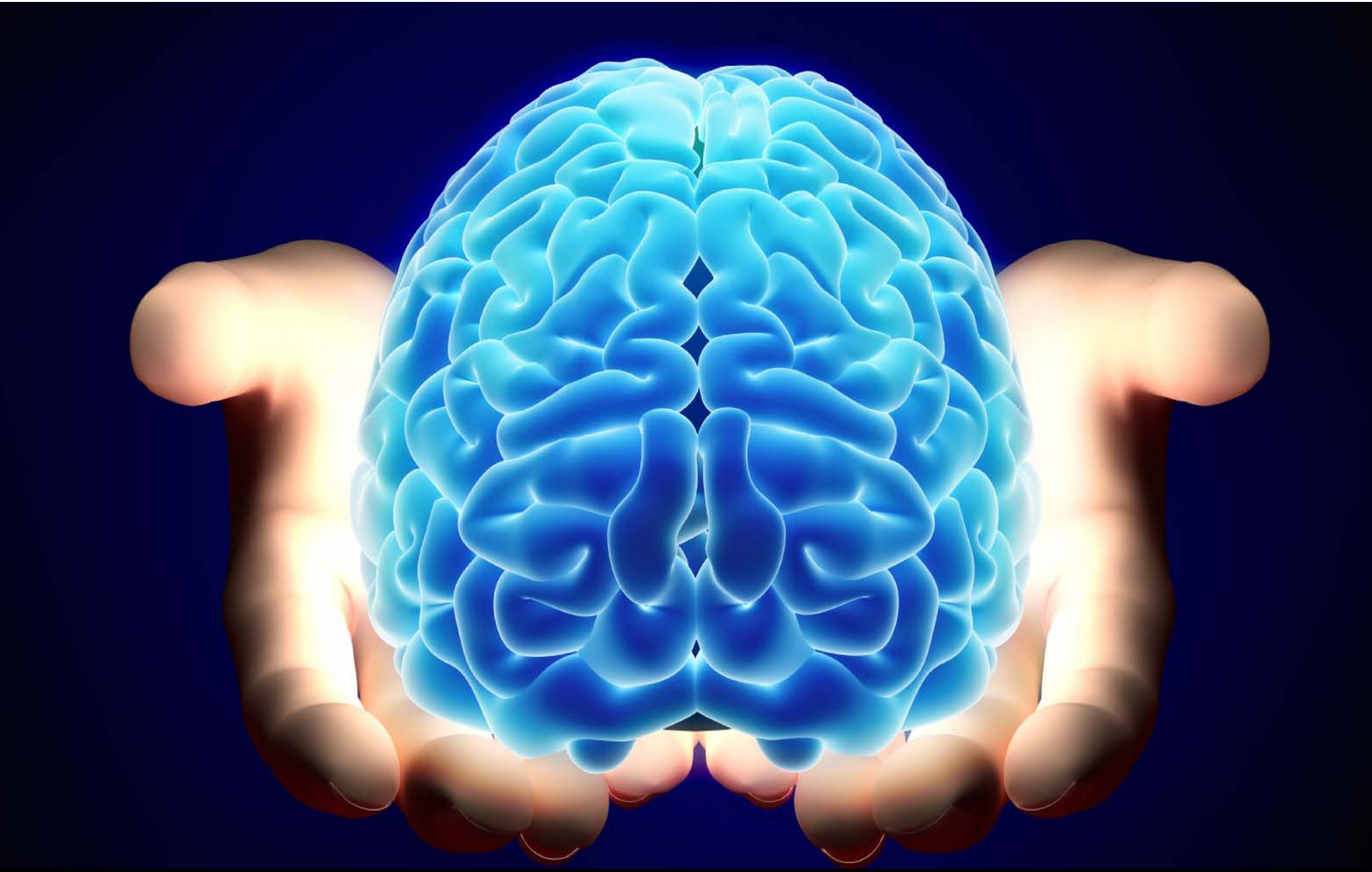


Chou DE, Shnayderman Yugrakh M, Winegarner D, Rowe V, Kuruvilla D, Schoenen J. Acute migraine therapy with external trigeminal neurostimulation (ACME): A randomized controlled trial. Cephalalgia. 2019 Jan;39(1):3-14

Cefaly: Side Effects

SIDE EFFECT	CEFALY
INTOLERANCE	2-5%
MILD SEDATION	5%
ALLERGIC CONTACT DERMATITIS	5%
NAUSEA	<2%
TINNITUS	<2%

QUESTIONS?



THANK YOU