



Dr. Biro's
presentation is not
available



Slide 1





Peripheral Nerve Stimulation

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Southern Pain Society 37th Annual Meeting
New Orleans , Louisiana
September 29 - October 2, 2023





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Disclosures

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History of PNS
15 AD: Scribonius and the Torpedo Fish

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History of PNS

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1965: WALL & MELZACK GATE THEORY

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History of PNS

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Deer TR, Eldabe S, Falowski SM, Hurlston MA, Staats PS, Cassar IR, Crosby ND, Boggs JW. *Journal of Pain Research* 2021; 14: 721-736.

"Non-Nociceptive Balance"

- Sensory fiber (Aα/β)
- Motor fiber (α motor fibers)
- Pain fiber (Aδ/C fibers)

Unopposed Increased firing of pain fibers - signals amplified

PNS activates the "good" afferents, blocking the "bad" afferents and thus "balances" signals

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History of PNS

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"CNS Reconditioning"

Deer TR, Eldabe S, Falowski SM, Hurlston MA, Staats PS, Cassar IR, Crosby ND, Boggs JW. *Journal of Pain Research* 2021; 14: 721-736.

Block Afferent Pain fibers

Activate Afferent Motor/Sensory fibers

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History of PNS



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Mechanisms of Action: PNS





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Mechanisms of Action: PNS




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Mechanisms of Action: PNS



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Mechanisms of Action: PNS



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Appropriate Populations for PNS


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Appropriate Populations for PNS




- PHANTOM LIMB PAIN
- PERIPHERAL NERVE INJURIES
- COMPLEX REGIONAL PAIN SYNDROMES
- CANCER PAIN
- STROKE PAIN
- CHRONIC LOW BACK PAIN
- FIBROMYALGIA
- GUILLIAN BARRE SYNDROME






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Populations




- Severity and duration of acute postop pain is a strong predictor of development of CPS.
- 'Abnormal sprouting' of nerve fibers, neuronal hyperexcitability, and irreversible plasticity
- Peripheral and central sensitization
Woolf CJ, Mannion RJ. *The Lancet*. 1999; 353.
- Activation of NMDA receptors
Nikolajsen L et al. *Br J Anaesth*. 2001;87:107-16.






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Indicated Populations for PNS



• Occipital nerves	• Tibial Nerve
• Migraines	• Overactive bladder
• Cluster Headache	• Vagus Nerve
• Fibromyalgia	• Depression
• Hypoglossal Nerve	• Epilepsy/Seizures
• Sleep apnea	• Rheumatoid Arthritis
• Carotid Sinus Nerves	• Heart Failure
• Hypertension	• Inflammatory Bowel Disease
• Heart Failure	• Gastroparesis
	• Chron's Disease




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Indicated Populations for PNS

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- Certain surgical populations have increased incidence of acute and chronic pain

• Amputation	30-85%
• Sternotomy	28-56%
• Thoracotomy	5-67%
• Mastectomy	11-57%
• Inguinal Hernia Repair	0-63%
• Cholecystectomy	3-56%
• Knee arthroplasty	19-43%
• Craniotomy	6-23%



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Visser EJ. *Acute Pain*. 2008;9:93-103. Health.

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[illegible]

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[illegible]

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Indicated Populations for PNS



- No CI for NSAIDs, or low dose ASA
- Clopidogrel
 - D/C 7d prior to placement
 - Restart?**
- IV Heparin
 - D/C 2-4hrs prior to placing or removing catheter
 - Restart 1hr after regional technique

Horlocker et al. RAMP, 2010;35(3):64-101.


	aspirin/ASA	NSAIDs	Warfarin	DOACs	SPS
Preoperative management	Continue aspirin/ASA up to 1 week preop	Stop NSAIDs 1-2 weeks preop	Stop 5 days preop	Stop 3-5 days preop	Stop 1-2 weeks preop
Regional anesthesia	OK	OK	OK	OK	OK
Systemic anticoagulation	OK	OK	OK	OK	OK
Postoperative management	Restart aspirin/ASA 1-2 weeks postop	Restart NSAIDs 1-2 weeks postop	Restart 2-5 days postop	Restart 3-5 days postop	Restart 1-2 weeks postop

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Indicated Populations for PNS



- LMWH – (once daily dosing)
 - D/C 10-12 hrs prior to placing or removing catheter
 - Restart 4 hrs after regional technique
- LMWH – (twice daily dosing)
 - Most state to d/c catheter 2 hrs BEFORE first dose
 - BUT ACCP states BID dosing OK in pts with catheters
- Therapeutic dosing is contraindicated!



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J. Vint & J. Ramp
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Acute Pain Control in Phantom Limb Pain


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Acute Pain Control in Phantom Limb Pain


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#1 Goal: EARLY and EFFECTIVE pain control (i.e. "Pre-emptive analgesia")


- Optimal analgesia 48 hrs before and after surgery reduced incidence of phantom limb pain
Karanikolas M et al: Anesth 2011; 114: 1144-55
- Improve central inhibitory factors and reduce peripheral excitatory factors
Esther M et al. Curr Opin Anesth. 2006;19:551-555
- Alleviate peripheral, but ineffective inhibitor of central.
Woolf CJ. Pain. 2011; 152:S2-S15.





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Acute Pain Control in Phantom Limb Pain




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Traditional analgesic modality after limb amputation

- Opioids
- Perineural Local Anesthetic Infusions

And now...


- Peripheral Nerve Stimulation







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Peripheral Nerve Catheters or Stimulation?


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PNC vs PNS: Which one?


- More effective pain control?
- Longer duration of action?
- Lower risk of infection?
- Lower risk of allergic or toxic reaction?
- Lower risk of falls?
- Lower risk of masking compartment syndrome?





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Peripheral Nerve Catheters or Stimulation?




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More effective pain control?

- Literature review suggests that PNCs have clinically significant failure rates due to either primary (incorrect insertion) or secondary reasons (displacement, obstruction, disconnection).
Hauritz RW, et al. *Best Pract Res Clin Anaesthesiol.* Sep 2019;33(3):325-339
- A 2003 survey of US adults asked about postop pain showed 86% continued to experience moderate, severe, or extreme pain, despite treatment.
Apfelbaum JL. *Anesth & Analg.* 2003; 97:534-540.




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Peripheral Nerve Catheters or Stimulation?




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Longer Duration?

- Short** duration of PNB in the early postop period (1-3 days) **NOT** effective in preventing PLPS when compared to standard therapies
Madabhushi and Lakshmi et al. *J Clin Anesth.* 2007;19:226-9
- Effective postoperative pain management for **thirty** days may help reduce the incidence of chronic pain.
 - Infusion held each wk and if pain > 1 VRS (sensation), infusion restarted @ 5ml/hr. If < 1 x 48 hrs, PNC d/c'd
Borghesi B et al. *Anesth Analg.* 2010; Nov;111(5):1308-15




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Peripheral Nerve Catheters or Stimulation?




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Infection Risk

- Unfortunately, PNCs are more commonly removed after a few days due to infection risk, while postoperative pain may still be significant.
Capdevila et al. *Anesthesiology* 2009; 110:182-8
CL Jeng, A Rosenblatt. *BJA* 2010; 105:97-107
Cuvillon P et al. *Anesth Analg* 2001; 93:1045-9
- The novel percutaneous PNS device used in this study is approved for up to 60 days and carries a lower risk of infection compared to PNCs.⁴



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Peripheral Nerve Catheters or Stimulation?

Allergic and/or Toxicity Risk?

- PNCs have increased risk of seizures from inadvertent injection during placement or infusion leading to local anesthetic systemic toxicity.
Dernedde M et al. *Anesth Analg*. 2004 Feb;98(2):521-3.
- Toxic serum levels of local anesthetics seen in RCTs with continuous infusions of through nerve catheters.
Bleckner. *A&A Feb 2010; 110: 2, 630-634*



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Peripheral Nerve Catheters or Stimulation?

Insensate Limb?

- Increased risk of falls associated with lower extremity continuous nerve blocks seen after knee and hip arthroplasty
Ilfeld BM et al. *Anesth Analg* 2010; 111:1552-4
Finn DM et al. *Med Surg Nurs*. 2016; 25(1):25-30, 49
- Ineffective and/or incomplete pain control
Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: Results from a national survey suggest postoperative pain continues to be undermanaged. *Anesthesia & Analgesia* 2003; 97:534-540.

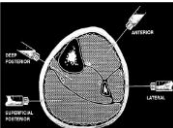
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Peripheral Nerve Catheters or Stimulation?

Insensate Limb (continued)?

- Increased risk of masking compartment syndrome (elevated pressure in confined fascial compartment, which can progress to ischemia/infarction)
- Adequate understanding of distribution and duration of PNB is key to prompt recognition and diagnosis
Walker BJ et al. *Reg Anesth Pain Med*. 2012; 37(4): 393-397.





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Winner: Peripheral Nerve Stimulation!


The now available temporary implanted Peripheral Nerve Stimulation available in the Acute to Sub-Acute period may mitigate many harmful risks



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Peripheral Nerve Stimulation for Acute Pain


- Potentially more effective pain control
- Maintain for longer duration (60 days vs 7 days)
- Decreased infection risk
- No Risk of Drug Reactions
- No toxic medication infusions
- No insensate limb
- Safer in complex patients with multiple comorbidities (ie COPD)



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Peripheral Nerve Stimulation for Acute Pain


- PNS has been reported to decrease pain and opioid requirements following total knee arthroplasty and ambulatory foot, and shoulder surgeries.⁹⁻¹¹



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Indication for Use




The Temporary Peripheral Nerve Stimulation (PNS) System is indicated for up to 60 days for:

- Symptomatic relief of chronic, intractable pain, post-surgical and post-traumatic acute pain;
- Symptomatic relief of post-traumatic pain;
- Symptomatic relief of post-operative pain.


The Temporary PNS System is not intended to be placed in the region innervated by the cranial and facial nerves.





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The Temporary PNS Device and Outcomes:
Indications




The Temporary Peripheral Nerve Stimulation (PNS) System is indicated for up to 60 days for:

- Symptomatic relief of chronic, intractable pain, post-surgical and post-traumatic acute pain;
- Symptomatic relief of post-traumatic pain;
- Symptomatic relief of post-operative pain.


The Temporary PNS System is not intended to be placed in the region innervated by the cranial and facial nerves.







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Contraindications



Use of the Temporary PNS System is contraindicated for:


- Lead placement over the heart or across the thoracic volume.
- Lead placement in the front or side of the neck.
- Lead placement on the top of the head.
- Patients who have a Deep Brain Stimulation (DBS) system.
- Patients who have an implanted active cardiac implant (e.g. pacemaker or defibrillator).
- Patients who have any other implantable neuro-stimulator whose stimulus current pathway may overlap with that of the Temporary PNS System.
- Patients who require Magnetic Resonance Imaging (MRI). The MicroLead™ and other PNS components must be removed from the body before an MRI.
- Patients who have epilepsy, if the leads are intended to be placed in the head or neck.
- Patients who have a tape or adhesive allergy.








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60-day Percutaneous PNS System


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- Temporary, 60-day treatment
- Fine-wire, open coil lead design
- Percutaneous lead placement typically under ultrasound or fluoroscopic guidance
- Single or Dual-Lead System








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60-day Percutaneous PNS System


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- Body-worn stimulator (no implanted IPG)
- Controllable by patient (via Bluetooth remote)








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60-day Percutaneous PNS

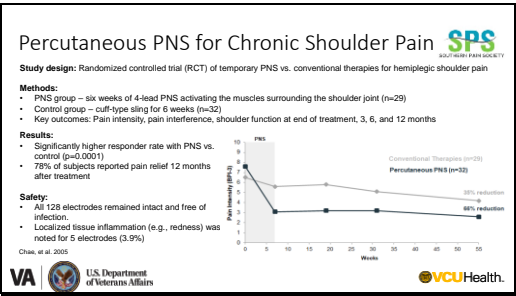

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- Lead utilizes a multi-strand coiled wire
- Lead wire diameter <0.3 mm¹
- Coiled structure enables fibrotic ingrowth

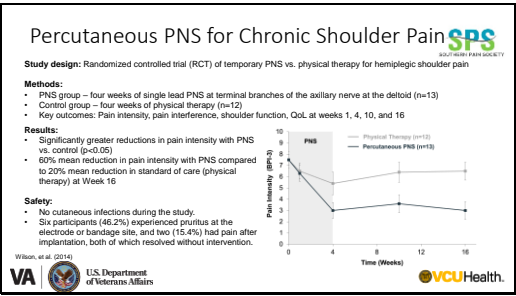




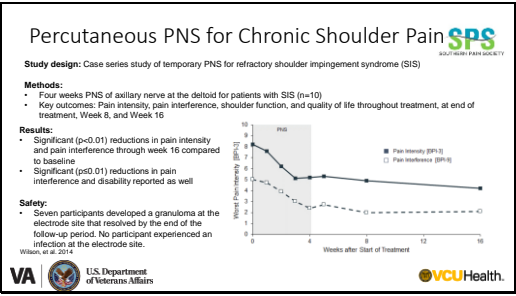
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Role of Multifidus in Axial Low Back Pain

- Multifidus atrophy is present in ~80% of LBP patients
- Reduced multifidus activity may reduce central feedback
- The absence of healthy feedback may foster centralization
- Increasing healthy proprioceptive inputs from multifidus may reverse central sensitization



Multifidus

1. Freeman et al., 2010

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Percutaneous PNS for Chronic Low Back Pain

Study design: Multicenter case series

Gilmore, et al., 2021; Gilmore et al 2023

Key Eligibility Criteria:


- Subjects with chronic axial LBP (≥ 3 mo); no radicular pain
- Stable medication usage for ≥ 1 month prior to baseline
- No prior lumbar surgery or RFA within prior 6 months

Bilateral, Percutaneous PNS Lead Implantation:

- Targeting medial branches of the dorsal ramus at the spinal level in the center of the region of back pain
- Confirmed by US visualization of multifidus activation

Percutaneous PNS Treatment:

- Stimulation for 6-12 hrs/day for up to 60 days
- Subjects continued most normal activities
- Leads removed with gentle traction
- Long-term follow-up visits, up to 12 months after the end of the 2-month PNS treatment
- Key Study Endpoints: Pain (BPI-S), Disability (ODI), Pain Interference (BPI-I), Patient Impression of Change (POIC), Analgesic Medication Usage



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
LBP Multicenter Study Participants

Participant Demographics (n=74)

Age (years)	56.3 (13.5)
Body Mass Index (BMI)	29.4 (4.6)
LBP Duration (years)	15.9 (13.9)
Sex (% Female)	53%
Baseline Opioid Usage (MME; n=20 taking opioids at baseline)	32.0 (37.1)
Previously Failed LBP Treatments:	
Non-opioid Analgesics	97%
Physical Therapy	89%
Opioid Analgesics	67%
TENS	65%
Anesthetic or Steroid Injections	57%
Epidural Injections	46%
Radiofrequency Ablation	23%

Gilmore, et al., 2021

LBP Diagnoses / Etiologies of Pain:




- Lumbar Spondylosis
- Degenerative Disc Disease
- Non-specific LBP

Percutaneous PNS Implantation:

- 81% of participants received bilateral PNS leads
- L4 & L5 were the most commonly targeted spinal levels

Spinal Level



- L2
- L3
- L4
- L5
- S1

Adverse Events (AEs):

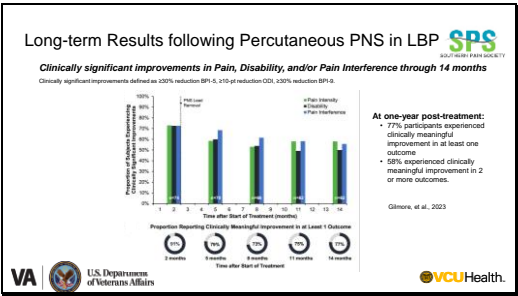
- No study-related serious or unanticipated AEs
- The most common AEs were mild skin irritation or pruritis (itching)

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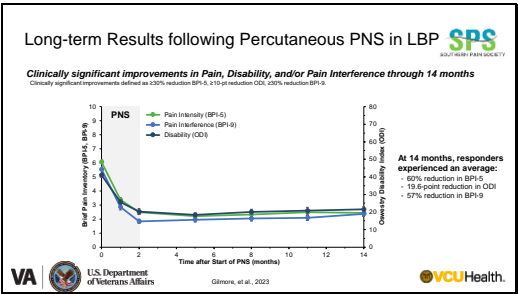
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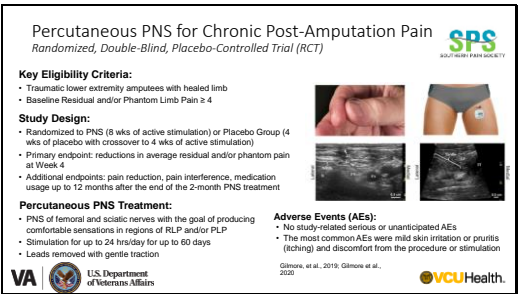
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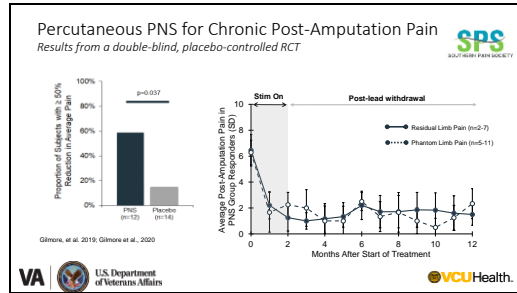
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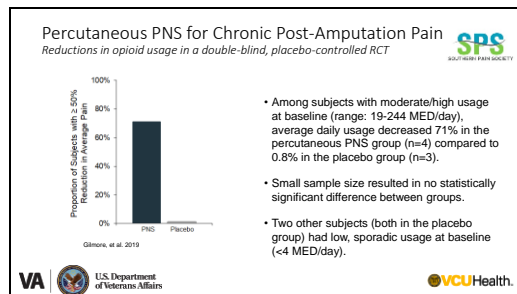
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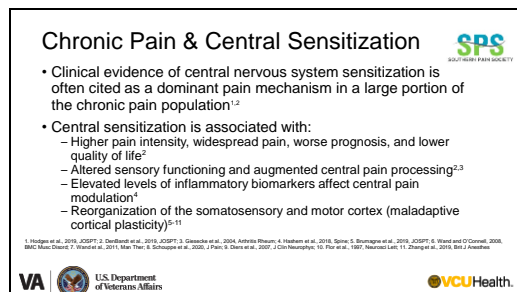
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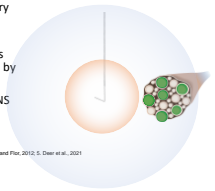
60-day PNS Proposed Mechanisms

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- Painful and non-painful signals to the brain can become unbalanced after some types of injury or disease, causing regions of the CNS to become hypersensitized to pain.¹⁻⁴
- Rebalancing the inputs to the central nervous system is proposed to help treat chronic pain by reconditioning maladaptive plastic changes.⁵
- 60-day PNS is proposed to recondition the CNS over the course of the treatment period with the goal of producing sustained relief.⁵

1. Kuper and Poo, Nat Rev, 2017; 2. Doherty, Exp Brain Res, 2020; 3. Lattimore and Wood, 2020; 4. Moolenaar and Poo, 2012; 5. Deer et al., 2021

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60-day PNS Proposed Mechanisms

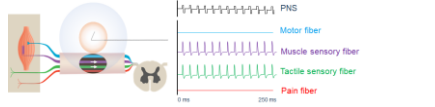
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(Deer, et al., 2021)

100 Hz stimulation is intended to activate large diameter sensory afferents **directly**, with the goal of producing comfortable stimulation-evoked sensations in the target region of pain.¹

1. Deer et al., 2021, J Pain Res

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60-day PNS Proposed Mechanisms

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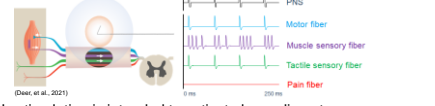
(Deer, et al., 2021)

12 Hz stimulation is intended to activate large diameter sensory afferents both **directly** and **indirectly** through **effluent fiber activation** and resulting cycling muscle tension.¹

- Efferent stimulation may use muscle as 'translator' to indirectly activate afferent fibers

1. Deer et al., 2021, J Pain Res

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60-day Percutaneous PNS: Real-World Cross-Sectional Follow-Up Survey Study

Pingree et al., 2022, Pain Management

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Goal: Summarize real-world survey data regarding the effectiveness and long-term impact of 60-day PNS treatment.

- Cross-sectional, follow-up survey distributed via email by device manufacturer to 2,028 patients who underwent treatment from 03/2018 to 12/2020.¹
- Patient-reported outcomes at end of treatment and follow-up survey included:
 - Average Pain (BPI-V)
 - Percent Pain Relief_{end} (BPI-R)
 - Patient Global Impression of Change (PGIC)
 - Changes in medication usage
- Studies suggest composite endpoints that account for multiple domains can provide a more comprehensive and sensitive assessment of patient responses.^{2,3}
- Therefore, responders were defined by substantial (≥50%)⁴ reduction in patient-reported percent pain relief and/or clinically significant (≥1)⁵ improvement in PGIC.

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Real-World Cross-Sectional Follow-Up Survey Study: End of Treatment Outcomes

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- Survey results from 252 respondents who were at least one month post lead removal
- 73% (185/252) had previously qualified as responders to PNS at the end of their 60-day treatments

Anatomical Site	Proportion of Patients with ≥50% Pain Relief and/or Clinically Significant Improvement in PGIC
All	73%
Low Back	63%
Shoulder	85%
Knee	78%
Ankle/Foot	70%
Other	73%

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Real-World Cross-Sectional Follow-Up Survey Study: Long-Term Follow-Up Outcomes

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- Among patients with clinically significant improvement at the end of treatment (EOT), a majority had sustained long-term improvements, including those who were 24+ months post-PNS

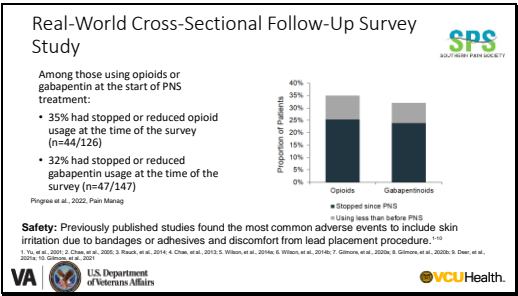
Months from Start of Treatment	Proportion of EOT Responders with Continued Improvement at Follow-Up (≥50% Pain Relief and/or Clinically Significant Improvement in PGIC)
Overall	85%
3 to 4	70%
5 to 6	60%
7 to 11	60%
12 to 17	75%
18 to 23	70%
24+	80%

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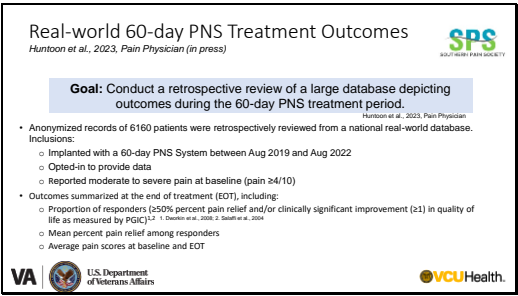
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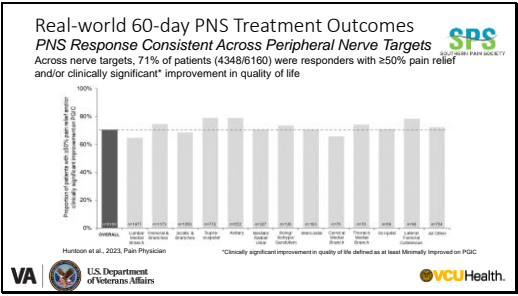
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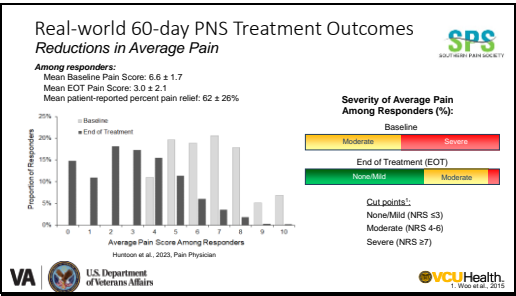
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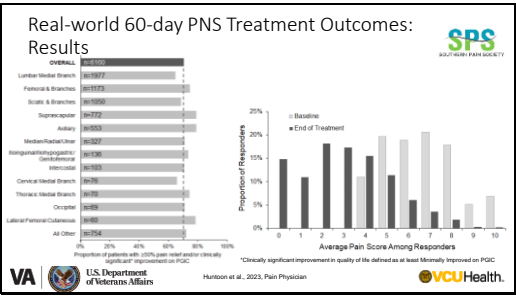
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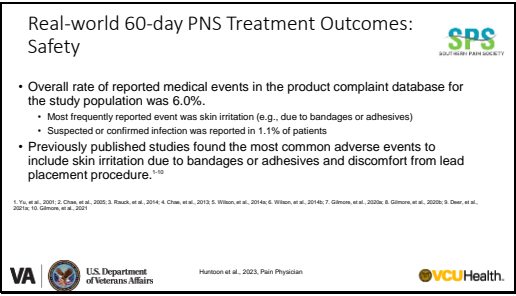
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Slide 64


RWD from 60-Day PNS of the Occipital Nerves

- Retrospective review of real-world outcomes from patients receiving a commercial 60-day PNS treatment targeting the occipital nerves.
- Anonymized records were reviewed from a national real-world database of patients who:
 - Previously underwent commercial implantation of 60-day PNS leads targeting occipital nerves
 - Opted in to provide data to the device manufacturer
 - Had baseline and end of treatment outcomes available
- Outcomes summarized at the end of treatment (EOT), including:
 - Proportion of responders (≥50% percent pain relief and/or clinically significant improvement (≥1) in quality of life as measured by PGIC^{1,2})
 - Mean percent pain relief among responders
 - Average pain scores at baseline and EOT



Sheeth et al., 2023, as presented at North American Neuromodulation Society Annual Meeting, January 12-15, 2023, Las Vegas, NV

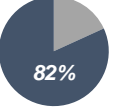
1. Dworkin et al., 2008; 2. Smith et al., 2004



Slide 65

RWD from 60-Day PNS of the Occipital Nerves

- 82%** (36/44) of patients were responders at the end of treatment.
- Responders experienced an average pain relief of **60%**
- Average pain score was reduced to none or mild in a majority of patients.



82%

■ Responders
■ Non-responders

Responders had ≥50% pain relief and/or clinically significant improvement* in quality of life



Baseline

Moderate	Severe
EOT	
None/Mild	

Cut points¹:


None/Mild (NRS ≤3)
Moderate (NRS 4-6)
Severe (NRS ≥7)

*Clinically significant improvement in quality of life defined as at least Monthly Improved on PGIC



Sheeth et al., 2023, as presented at North American Neuromodulation Society Annual Meeting, January 12-15, 2023, Las Vegas, NV

1. Worel et al., 2011


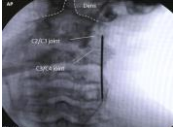


Slide 66



RWD from 60-Day PNS of the Occipital Nerves

Example Lead Placement Approaches

The occipital nerves may be targeted with various approaches under ultrasound or fluoroscopy.




Safety: Previously published studies found the most common adverse events to include skin irritation due to bandages or adhesives and discomfort from lead placement procedure.¹⁻¹⁰



Sheeth et al., 2023, as presented at North American Neuromodulation Society Annual Meeting, January 12-15, 2023, Las Vegas, NV

1. Yu, et al., 2001; 2. Chen, et al., 2005; 3. Rausch, et al., 2014; 4. Chen, et al., 2013; 5. Wilson, et al., 2014a; 6. Wilson, et al., 2014b; 7. Gilmore, et al., 2020a; 8. Gilmore, et al., 2020b; 9. Chen, et al., 2020a; 10. Gilmore, et al., 2020






Slide 67

RWD from 60-Day PNS of the Cervical Medial Branch

- Retrospective review of real-world outcomes from patients receiving a commercial 60-day PNS treatment targeting CMB nerves.
- Anonymized records were reviewed from a national real-world database of patients who:
 - Previously underwent commercial implantation of 60-day PNS leads targeting cervical medial branch nerves
 - Opted in to provide data to the device manufacturer
 - Had baseline and end of treatment outcomes available
- Outcomes summarized at the end of treatment (EOT), including:
 - Proportion of responders (≥50% percent pain relief and/or clinically significant improvement (≥1) in quality of life as measured by PGIC¹⁻²)
 - Mean percent pain relief among responders

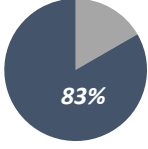
Mattie et al., 2023, as presented at North American Neuromodulation Society Annual Meeting, January 12-15, 2023, Las Vegas, NV
1. Deylon et al., 2008, 2. Saeed et al., 2014



Slide 68




RWD from 60-Day PNS of the Cervical Medial Branch

- 83% (25/30)** of patients were responders at the end of treatment.
- Responders experienced an average pain relief of **53%**



Category	Count	Percentage
Responders	25	83%
Non-responders	5	17%

Mattie et al., 2023, as presented at North American Neuromodulation Society Annual Meeting, January 12-15, 2023, Las Vegas, NV
*Clinically significant improvement in quality of life defined as at least Minimally Improved on PGIC




Slide 69

RWD from 60-Day PNS of the Cervical Medial Branch

Example Lead Placement Approach




The cervical medial branch nerves can be targeted using a fluoro-guided approach.

Example fluoroscopic image shows AP view with stimulating probe targeting medial branch over lateral lamina of C6

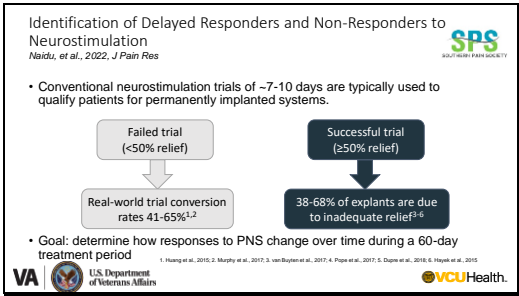


Safety: Previously published studies found the most common adverse events to include skin irritation due to bandages or adhesives and discomfort from lead placement procedure.¹⁻¹⁰

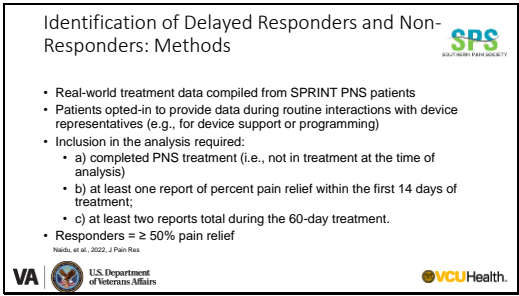
Mattie et al., 2023, as presented at North American Neuromodulation Society Annual Meeting, January 12-15, 2023, Las Vegas, NV
1. Deylon et al., 2008, 2. Saeed et al., 2014, 3. Wilson et al., 2013, 4. Wilson et al., 2014a, 5. Wilson et al., 2014b, 6. Wilson et al., 2014c, 7. Gilmore et al., 2015a, 8. Gilmore et al., 2015b, 9. Gilmore et al., 2015c, 10. Gilmore et al., 2015d



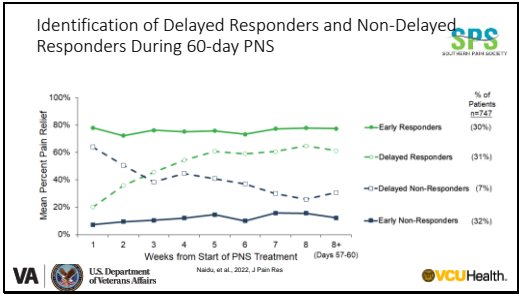
Slide 70



Slide 71



Slide 72



Slide 73

Identification of Delayed Responders and Non-Delayed Responders During 60-day PNS

SPS
SOUTHERN PAIN SOCIETY

- Previously published studies found the most common adverse events to include skin irritation due to bandages or adhesives and discomfort from lead placement procedure.¹⁻¹⁰
- 60-day treatment may help inform PNS treatment strategies to optimize patient outcomes while reducing cost and invasiveness
 - Identifying delayed responders may improve access to neurostimulation treatment
 - Identifying non-responders and delayed non-responders may prevent unnecessary permanent implantation

1. Fu, et al., 2001; 2. Chen, et al., 2003; 3. Rouch, et al., 2014; 4. Chen, et al., 2013; 5. Wilson, et al., 2014a; 6. Wilson, et al., 2014b; 7. Gilmore, et al., 2020a; 8. Gilmore, et al., 2020b; 9. Chen, et al., 2019; 10. Gilmore, et al., 2021

VA U.S. Department of Veterans Affairs Naidu, et al., 2022, J Pain Res VCUHealth.

Slide 74

Patient Preference in the Treatment Algorithm for Chronic Low Back Pain

SPS
SOUTHERN PAIN SOCIETY

Goal: Characterize patient preferences from among several interventional pain management treatment options.

- Two surveys were conducted in which chronic pain patients were given descriptions of pain treatments and asked for their preferences.
- Patients were provided with additional information about risks of each treatment and given the chance to change their treatment preference to determine patients' "final choice treatment".

SURVEY 1 (n=129)

Chronic low back pain patients completed a survey assessing preference for:

- Radiofrequency Ablation
- Temporary (60-day) Peripheral Nerve Stimulation (PNS)
- Permanent Implants: PNS or SCS/DRGS

SURVEY 2 (n=347)

Patients with chronic low back pain completed a survey assessing preference for:

- Radiofrequency Ablation
- Temporary PNS Treatment

VA U.S. Department of Veterans Affairs Shain, et al., 2022, Pain Manag VCUHealth.

Slide 75

Patient Preference in the Treatment Algorithm for Chronic Low Back Pain: Results

SPS
SOUTHERN PAIN SOCIETY

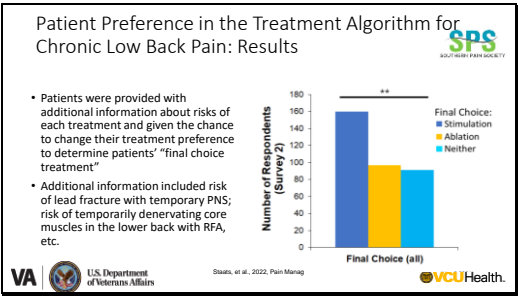
- Patients generally preferred temporary treatments (Temporary PNS, RFA) as first choice over permanent therapies
- Preference for permanent PNS increased after temporary PNS

Preferences Ranked by Survey 1 Respondents

Treatment Option	1st Choice	2nd Choice	3rd Choice	4th Choice
Temporary PNS	45	40	35	15
Radiofrequency Ablation	40	35	30	10
Permanent PNS	15	25	35	45
Permanent SCS/DRGS	10	15	20	25
Permanent PNS	10	15	20	25

VA U.S. Department of Veterans Affairs Shain, et al., 2022, Pain Manag VCUHealth.

Slide 76



Slide 77

References

SPS
SOUTHERN PAIN SOCIETY

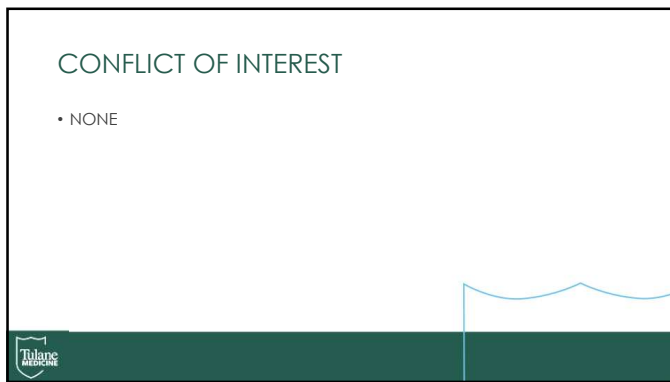
1. Brumagne, et al., 2018, *J Orthop Sport Phys*, 49(6).
2. Chai, et al., 2013, *Pain Practice*, 13(1).
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4. Daw, et al., 2021, *J Pain Res*, 14.
5. Daw, et al., 2021, *Pain Medicine*, 22(5).
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VA U.S. Department of Veterans Affairs

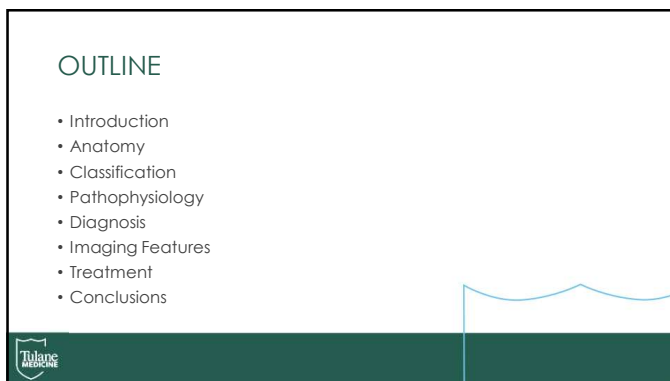
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3

TRIGEMINAL NEURALGIA - INTRODUCTION

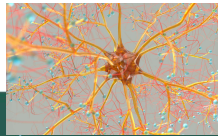
- One of the most debilitating presentations of orofacial pain
- Earliest description of TN date back to 17th century (Physicians Johannes Fehr, Elias Schmidt and philosopher John Locke)
- Nicholas Andre first linked TN to pain in nervous system in mid 1700s – described as a convulsive disorder from a nerve under distress
- Tic douloureux was used by Andre to capture the facial distortions and grimaces associated with the sharp, stabbing facial pain



4

TRIGEMINAL NEURALGIA - INTRODUCTION

- An orofacial pain syndrome characterized by unilateral, severe, shock-like paroxysmal pain within the distribution of the trigeminal nerve, precipitated by innocuous stimuli to the affected side of the face
- Associated with increased anxiety, depression and poor sleep highlighting its potential impact on mental health



IHS Cephalgia, 2018
Zakrzewska et al. Pain, 2017

5

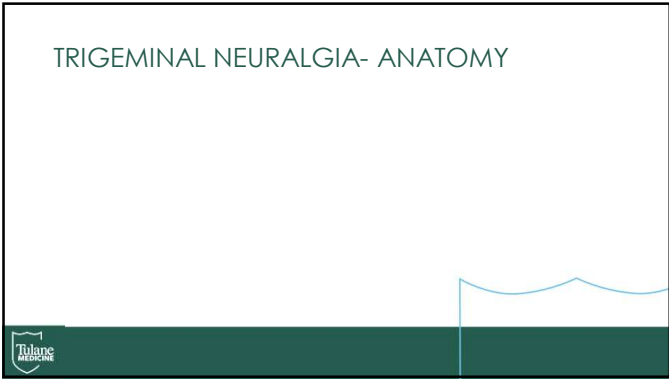
TRIGEMINAL NEURALGIA - EPIDEMIOLOGY

- Lifetime prevalence of 0.16-0.3% and an incidence of 12.6-27.0 per 100,000 person-years
- Affects females more than males (60% vs. 40%)
- Average age of onset of 53-57 years
- Studies of trigeminal neuralgia in childhood and familial clustering may suggest a possible genetic contribution (voltage-gated Na channels) but this remains to be established

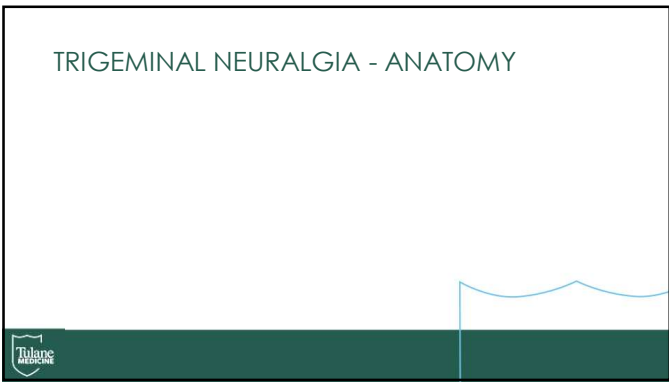


Zakrzewska et al. Pain, 2017
Bendtsen et al. Lancet Neurol, 2020

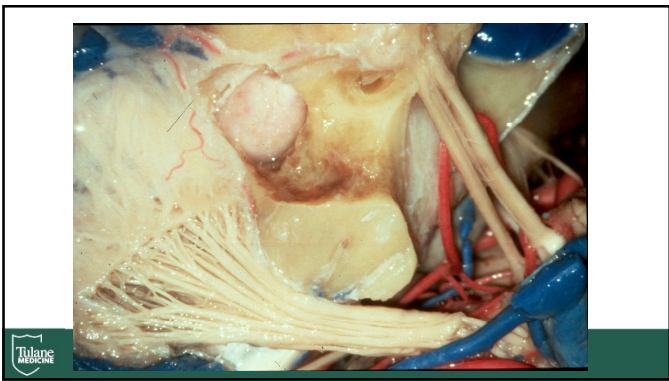
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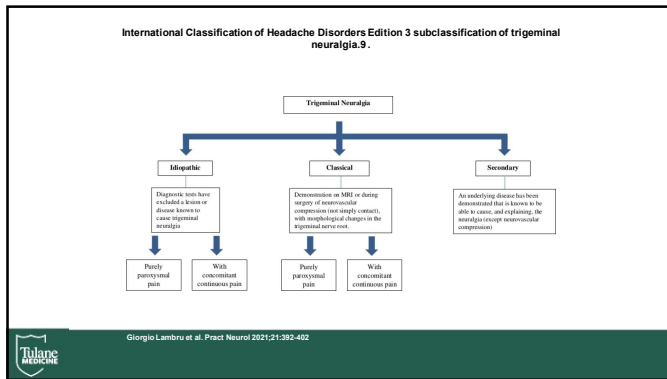


11

TRIGEMINAL NEURALGIA - CLASSIFICATION

- In 2018, the International Headache Society (IHS) and International Association for the Study of Pain (IASP) published new classifications for trigeminal neuralgia in an effort to create alignment
- Classifies trigeminal neuralgia into idiopathic, classical and secondary forms

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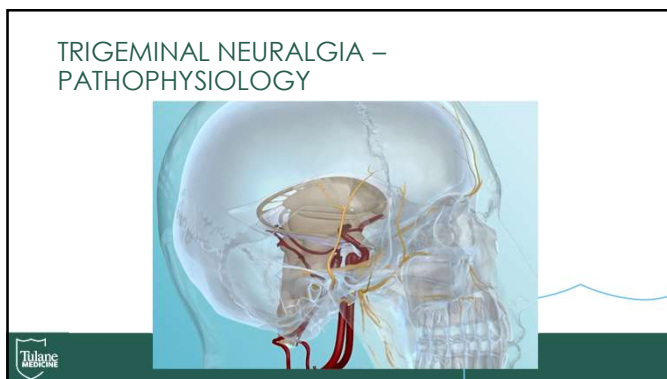
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TRIGEMINAL NEURALGIA – PATHOPHYSIOLOGY

- Symptomatology of TN is ~the same across classical, idiopathic and secondary trigeminal neuralgia
- Site of initiation is root entry zone – where transition of peripheral Schwann cell myelination to central oligodendroglia myelination occurs (may predispose to susceptibility to pressure)
- Classical TN – vascular compression at REZ

Maarbjerg et al. *Headache*, 2014
 Allam et al. *Neural Clin*, 2023
 Bendtsen et al. *Lancet Neurol*, 2020

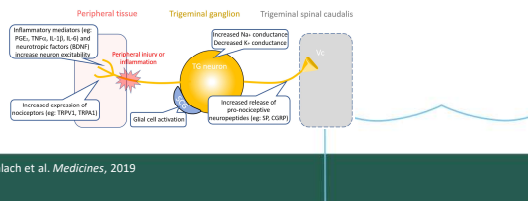
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TRIGEMINAL NEURALGIA – PATHOPHYSIOLOGY

- Idiopathic TN – neuronal voltage-gated ion channel gain-of-function mutations, neural inflammation, non-specific, non-MS lesions in brainstem

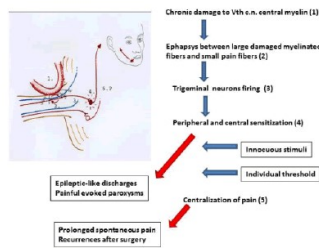


Bista and Imlach et al. *Medicines*, 2019

16

TRIGEMINAL NEURALGIA – PATHOPHYSIOLOGY

Fig. 3: Pathophysiology of Classical Trigeminal Neuralgia



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TRIGEMINAL NEURALGIA – PATHOPHYSIOLOGY

Fig. 3: Pathophysiological basis of Surgical Treatment

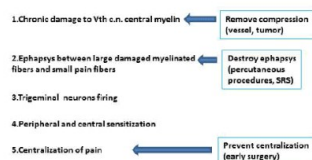


Figure 3: Pathophysiological bases of the Surgical Treatment

Maarbjerg et al.
Allam et al. A
Rendtsen et al.

18

TRIGEMINAL NEURALGIA - DIAGNOSIS

• A clinical diagnosis

Box 1 International Classification of Headache Disorders edition 3 (ICHD-3) diagnostic criteria for trigeminal neuralgia⁹

- A. Recurrent paroxysms of unilateral facial pain in the distribution of one or more divisions of the trigeminal nerve, with no radiation beyond, and fulfilling criteria B and C.
- B. Pain has all of the following characteristics:
 - A. Lasting from a fraction of a second to 2 min.
 - B. Severe intensity.
 - C. Electric shock-like shooting, stabbing or sharp in quality.
- C. Precipitated by innocuous stimuli within the affected trigeminal distribution.
- D. Not better accounted for by another ICHD-3 diagnosis.



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TRIGEMINAL NEURALGIA - DIAGNOSIS

- Made by detail history and clinical examination
- Generally physical and neurological examinations are normal in TN (and if not should prompt further investigations as raises suspicion of secondary TN)
 - Mild hypesthesia in trigeminal nerve distribution is common in TN (eg. In 29% of surgically naive patients in a Danish study)



Maarbjerg et al. *Headache*, 2014

20

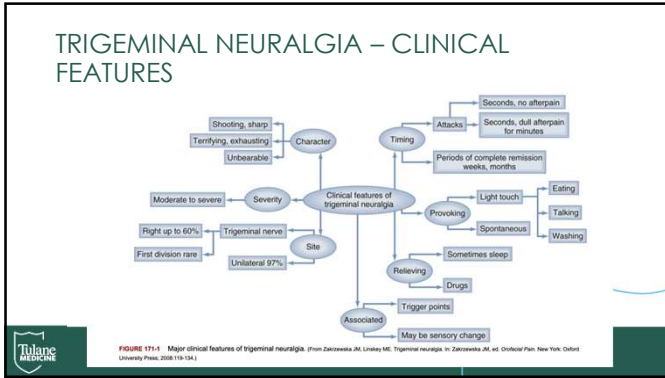
TRIGEMINAL NEURALGIA – CLINICAL FEATURES

- Short lasting pain with stabbing, sharp, shooting, electric shock-like or ice-pick like quality
- 14-50% of patients have some type of continuous pain in the same distribution of the stabbing pain
- Pain can be both extraoral and intraoral, most commonly V2 and V3 distribution (V1 pain alone is rare)
- Mild autonomic features such as lacrimation may be present
- Innocuous mechanical pain triggers – chewing, tooth brushing, face washing, talking, light touch, wind
- Pain typically a split second to 2 min



Maarbjerg et al. *Headache*, 2014
Allam et al. *Neurol Clin*, 2023
Reidson et al. *Lancet Neurol*, 2020

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TRIGEMINAL NEURALGIA – DIFFERENTIAL DIAGNOSIS

Panel 2: Primary and secondary headache and facial pain disorder as differential diagnoses to trigeminal neuralgia

The symptomatology of trigeminal neuralgia is typically characteristic with patients reporting intense stabbing, touch-evoked, unilateral facial pain in the cheek, the area of the nostrils, teeth, or jaw.

Primary headache and facial pain disorders

- Glossopharyngeal neuralgia causes episodic evoked stabbing pain located at the back of the tongue, the pharynx, or deep in the ear. Trigger factors include swallowing, coughing, and sneezing.
- Persistent idiopathic facial pain causes primarily spontaneous dull or aching constant pain that might also be touch-provoked or provoked by physiological or psychological stress.
- Short-lasting unilateral neuralgiform headache attacks with autonomic symptoms, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing, or paroxysmal hemicrania causes episodic touch-evoked and spontaneous stabbing orbital, supraorbital, or temporal pain accompanied by ipsilateral pronounced autonomic symptoms*. Unlike trigeminal neuralgia, pain can change sides and is often more prolonged with no refractory period.
- Cluster headache causes orbital, supraorbital, or temporal pain accompanied by ipsilateral pronounced autonomic symptoms* and restlessness. Duration is from 15 to 180 min. Pain can switch sides.
- Primary stabbing headache causes stabbing spontaneous pain in the scalp and is not accompanied by autonomic symptoms.

Bendtsen et al. Lancet Neurol, 2020

23

TRIGEMINAL NEURALGIA – DIFFERENTIAL DIAGNOSIS

Panel 2: Primary and secondary headache and facial pain disorder as differential diagnoses to trigeminal neuralgia

Secondary headache, facial pain disorders, and odontogenic disorders

- Painful post-traumatic trigeminal neuropathy can cause stabbing and touch-evoked pain like trigeminal neuralgia, but pain is usually constant with flare-ups and by definition preceded by trauma, and there are usually clear-cut neurological abnormalities of both gain-of-function and loss-of-function corresponding to the affected peripheral nerve.
- Painful trigeminal neuropathy attributed to acute herpes zoster causes constant burning and stabbing pain preceded by a herpetic rash in the trigeminal distribution. Tingling sensations and neurological abnormalities with both gain-of-function and loss-of-function are common.
- Cracked tooth can cause evoked shooting pain intraorally after chewing.
- Caries or pulpitis can cause evoked pain at intake of sweet, cold, or hot foods. The pain can last from 10 min up to several hours. It is not a chronic pain disorder.
- Temporomandibular disorders cause unilateral or bilateral aching pain around the ear radiating to the temple, masseter, and retromolar area. The pain can be intermittent or continuous with flare-ups. The pain starts after prolonged chewing or opening the mouth wide.

Bendtsen et al. Lancet Neurol, 2020

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TRIGEMINAL NEURALGIA – IMAGING

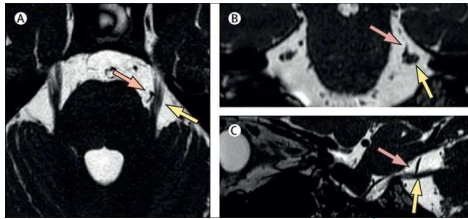
- Neuroimaging is critical for the subclassification of clinically identified TN (eg. primary versus secondary from MS or tumor)
- Three high-resolution sequences are useful: (3D) T2-weighted, MRA and 3D T1-contrasted MRI are reliable in detecting vascular contact or secondary causes
- Trigeminal nerve may have atrophy on symptomatic side
- Diffusion tensor imaging (DTI) may provide further insight
 - Fractional anisotropy (proxy measure for white matter integrity) may be altered at root entry zone



Bendtsen et al. *Eur J Neurol*, 2019
Leal et al. *Neurosurgery*, 2011
Bendtsen et al. *Lancet Neurol*, 2020

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TRIGEMINAL NEURALGIA – IMAGING



Maarbjerg et al. *Headache*, 2014
Allam et al. *Neurol Clin*, 2023
Bendtsen et al. *Lancet Neurol*, 2020

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TRIGEMINAL NEURALGIA – IMAGING

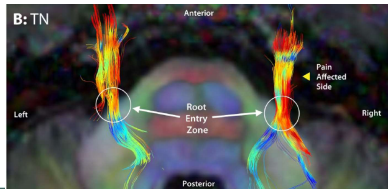


Maarbjerg et al. *Headache*, 2014
Allam et al. *Neurol Clin*, 2023
Bendtsen et al. *Lancet Neurol*, 2020

27

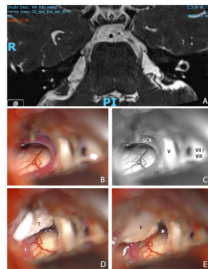
TRIGEMINAL NEURALGIA - IMAGING

- Changes in fractional anisotropy suggesting dysmyelination/demyelination at the REZ



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MR scan of the trigeminal nerve and intraoperative pictures during microvascular decompression in patient with classical trigeminal neuralgia.



Giorgio Lamiere et al. Pract Neurol 2021;21:292-402

PN

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TN- PHARMACOLOGICAL TREATMENT

- Acute treatment for severe exacerbations – very high attack frequency and can often lead to dehydration and anorexia
- Opioids are generally not effective
- Lidocaine injections into trigger areas
- Infusions of fosphenytoin and lidocaine intravenously can be effective

30

TN- PHARMACOLOGICAL TREATMENT

- Pharmacological long-term treatment
- Carbamazepine and oxcarbazepine are considered first-line agents for long-term treatment
 - If above agents are ineffective or poorly tolerated, other agents as add on or monotherapy can be tried including botulinum toxin type A



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TN- PHARMACOLOGICAL TREATMENT

Common Drugs Used for the Medical Management of Trigeminal Neuralgia (TN)

Drug	Level of Evidence	Effect	Adverse Effects	Suggested Dose	Comment
Carbamazepine (the only first-line agent)	Systematic review of four randomized controlled trials (n = 160)	NNT for pain relief is 1.9; 72% of patients had excellent or good response	Drowsiness, ataxia, nausea, constipation (minor); NNT, 3.7	100 mg twice daily; increase as necessary by 50-100 mg every 3-4 days; target range 400-1000 mg/day	Dose may need to be adjusted after 3 weeks because of enzyme induction.
Baclofen	One controlled trial compared baclofen with placebo (n = 10)	7/10 improved with baclofen; 0/10 improved with placebo (P = .05)	Drowsiness, hypotension; avoid abrupt withdrawal	10 mg three times daily; increase as necessary by 10 mg/day; target dose 50-60 mg/day	May be useful in patients with multiple sclerosis, in whom its antispasmodic effects can be harnessed.
Gabapentin	Five uncontrolled studies (n = 123)	Good to excellent pain relief in 80%; any pain relief in 55%	Drowsiness, ataxia, diarrhea (minor); NNT, 2.5	300 mg once daily; increase as necessary by 300 mg every 3 days in divided doses (five times daily); target dose 900-2400 mg/day	Widely used for TN although evidence is weak; evidence base in other types of neuropathic pains much stronger.
Lamotrigine	One randomized controlled trial with lamotrigine as add-on to carbamazepine or phenytoin (n = 14)	10/13 improved on lamotrigine; 0/14 improved on placebo; no difference from placebo	Drowsiness, dizziness, constipation, nausea; no different from placebo	25 mg twice daily; increase by 50 mg weekly; target dose 200-600 mg/day	Probably better tolerated than carbamazepine but needs slow titration; may therefore have a role in the elderly or patients with multiple sclerosis who have less severe disease.
Oxcarbazepine	Two uncontrolled studies (n = 21)	Pain relief in all 21 patients	Dizziness, fatigue, rash, and hyponatremia	300 mg twice daily; increase by 600 mg weekly; target dose 600-2400 mg/day	Evidence weak; structurally similar to carbamazepine, although probably better tolerated.
Phenytoin	Three uncontrolled studies (n = 30)	77% of patients reported some pain relief	Drowsiness, ataxia, dizziness, gum hypertrophy	300 mg/day; dose altered to achieve therapeutic plasma concentration	First drug used in the successful management of TN; little evidence but rapid dose titration and once-daily administration are advantages.

NNT, number needed to treat; ns, not statistically significant.

Modified from Zakrzewski JM, Lindsay M. Trigeminal neuralgia. In: Zakrzewski JM, ed. *Orofacial Pain*. London: Oxford University Press; 2006:119-134.

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TN- NON-PHARMACOLOGICAL TREATMENTS


- Destructive percutaneous interventions
- Peripheral trigeminal neurectomies (supraorbital, infraorbital, inferior alveolar)
- Stereotactic Radiosurgery
- Microvascular decompression



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TN- PERCUTANEOUS DESTRUCTIVE/ABLATIVE TREATMENTS

- Involves penetration of foramen ovale with a cannula and then controlled lesioning of the trigeminal ganglion or root with various means
 - Thermal – Radiofrequency thermocoagulation
 - Mechanical – Balloon compression
 - Chemical (injection of glycerol)
- Suitable for patients who are at high risk for microvascular decompression or patient preference
- Recurrence is common, may be repeated

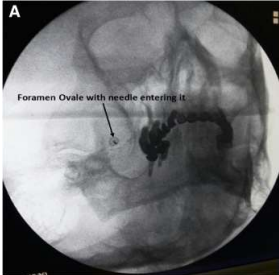


34



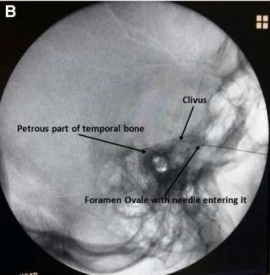
35

A




Foramen Ovale with needle entering it

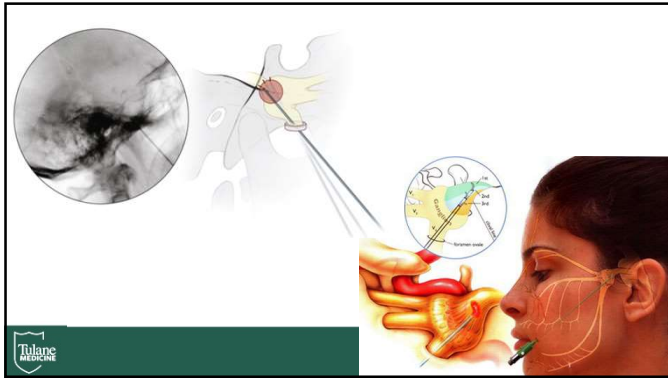
B



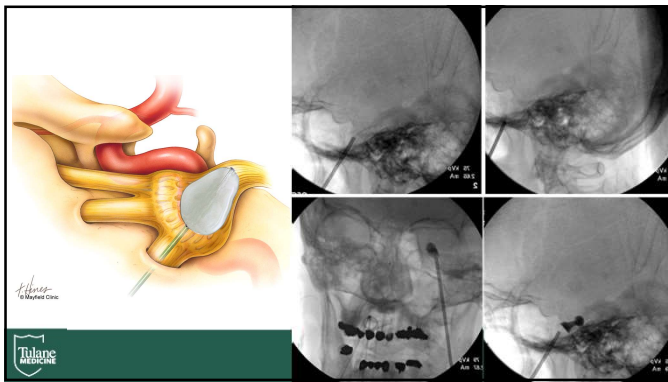
Clivus
Petrus part of temporal bone
Foramen Ovale with needle entering it



36



37



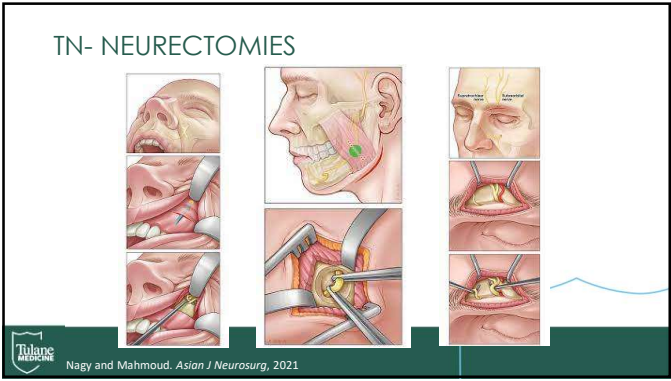
38

TN- NEURECTOMIES

- Peripheral neurectomy is a simple, low-risk procedure that involves surgical avulsion of the postganglionic part of the trigeminal nerve divisions
- Mean pain free interval of ~ 29 months
- 2, 3, 4 and 5 year pain-free survival was 92.9%, 79.6%, 59.7% and 29.8%, respectively
- Supraorbital, infraorbital, inferior alveolar neurectomies
- Not performed commonly in contemporary practice but may be suitable for refractory patients at high surgical risk

Nagy and Mahmoud. *Asian J Neurosurg*, 2021

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40

TN- RADIOSURGERY

- The only non-invasive but destructive technique
- Focused beam of radiation is delivered to the trigeminal root entry zone
- Typical maximum dose of 70-85 Gy
- Pooled analysis after radiosurgery (n=4533) with follow-up of 4-11 years, 26-82% of patients were pain-free

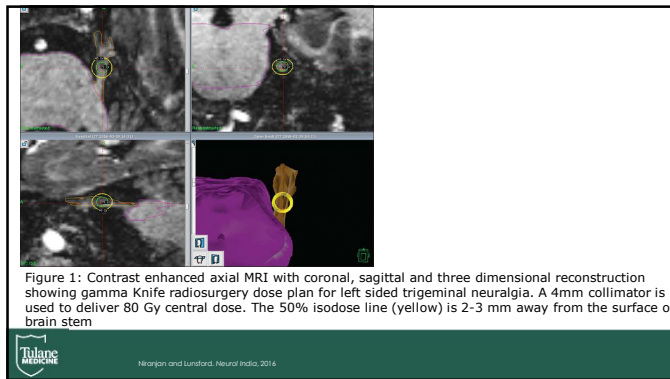
Tulane MEDICINE
Bendtsen et al. Eur J Neurol, 2019

41

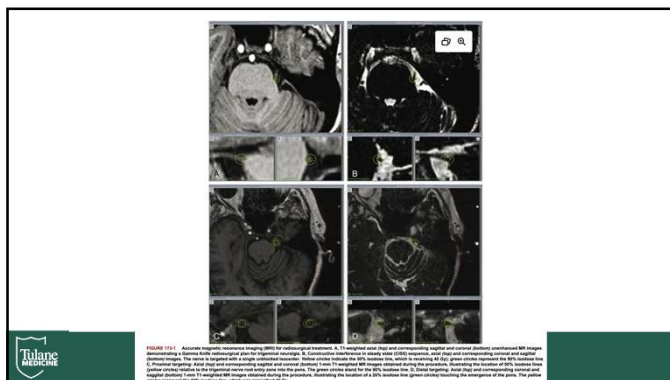
TN- RADIOSURGERY

Series	No. Patients	Median Follow-up (yr)	Mean age (Median Age)	Device	Mean Dose (Range Gy)	Time to Pain Response (Days)	Pain Score (0-10)	Good Facial Pain Outcome (%)	Treatment Failure	Recurrence	Repeat Stereotactic Radiosurgery (%)	Facial Numbness (%)
McNair et al (2007) ¹⁷	49	23 (5-55)	68	CRS	60 (50-80)	375	21	61	39	23	NA	26
Bendtsen et al (2009) ¹⁸	28	14 (5-51)	74	LINAC	80	30	74	75	14	46	NA	18
Sheth et al (2009) ¹⁹	136	17 (6-52)	68	CRS	60 (50-80)	24 (1-181)	54	90 (vs 70-75)	10	24	NA	51
Regin et al (2009) ²⁰	100	19 (2-60)	68	CRS	60 (50-80)	10 (0-179)	42	83	17	34	18	9
Forsgren et al (2007) ²¹	106	12 (3-61)	72	CRS	60 (50-75-80)	28	46	90	10	8	NA	4
Longstaff et al (2007) ²²	160	12 (1-60)	63	CRS	60 (50-80)	43	43	90	10	18	NA	0
Perrenoud et al (2007) ²³	12	23 (11-46)	71	LINAC	50-50	30 (14-180)	59	70	30	29	NA	47
Villaverde et al (2008) ²⁴	95	40 (12-90)	70	Cyberknife	75 (50-86.4)	14 (2.3-100)	37	67	33	31	18	30
Adler et al (2009) ²⁵	65	14.7 ²⁶	79 ²⁶	Cyberknife	73.5	28	96	96	4	9	9	15
Chhabria et al (2009) ²⁷	112	49 ²⁸	64 ²⁸	CRS	75 (75-80)	14 (0-94)	33	63	19	56	27	8
Chen et al (2010) ²⁹	14	23	67 ³⁰	LINAC	60 all	28	NA	91	9	25	11	11
Bendtsen et al (2010) ³¹	303	24 (4-156)	72 ³²	CRS	60 (50-80)	30 (1-305)	43	90 (vs 75-75)	11	43	18	11
Vermeir et al (2010) ³³	365	28 (4-83)	65	CRS	60 all	20 (1-150)	46	75 (vs 60-75)	10	NA	NA	6.5 for first CRS, 26 for 2nd CRS
Sauk et al (2012) ³⁴	179	26.4 ³⁵ (9-120)	74 ³⁶	LINAC	60 (50-80)	60	28	79	21	19	6.3	50
Marshall et al (2012) ³⁷	448	21 (3-86)	67 ³⁸	CRS	60 (50-80)	NA	NA	96	14	40	NA	25
Young et al (2013) ³⁹	250	49 ⁴⁰	70.6 ⁴¹	CRS	60 all	51	11.6	89.3	6	14.3	NA	15

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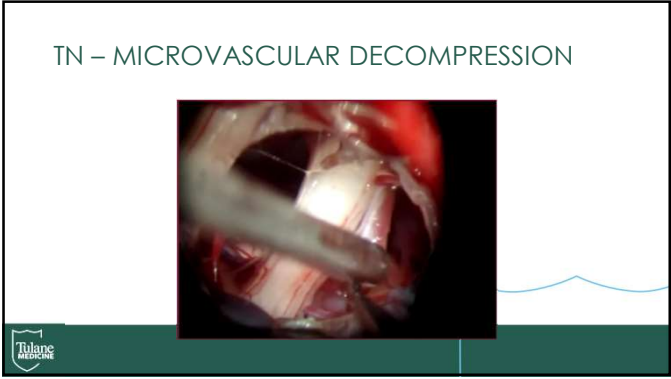


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TN- MICROVASCULAR DECOMPRESSION

- First-choice surgery in patients with classical TN
- Pooled analysis of 5149 patients – high efficacy – 62-89% of patients were pain free at follow-up (3-11 years)
- Severe complications are rare - death (0.3%), edema/hemorrhage/stroke (0.6%), anesthesia dolorosa (0.02%)
- Less severe complications – cranial nerve palsy (4%), hearing loss (1.8%), facial hypesthesia (3%) were more common

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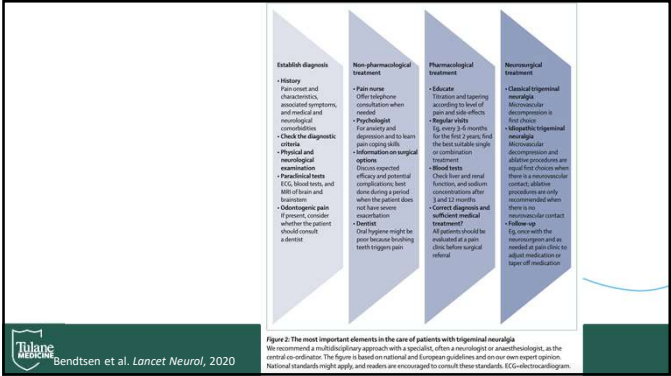
46

Patients outcomes %min-max (mean)	MVD	RFT	GR	PBC	SRS
Initial pain relief ^a	80-98 (92)	81-99 (94)	42-98 (75)	82-100 (96)	75-92 (80) ^a
Long-term pain relief ^b	62-89 (77)	20-93 (60)	18-59 (38)	54-91 (67)	46-65 (50)
Facial hypoesthesia ^c	2-15	5-98 (40)	1-29	20-35	10-42
Facial dysesthesia ^c	0-1	1-12	0.7-12	1.5-5	0-4
Anesthesia dolorosa ^c	0	0-2	0-3	0	0
Corneal sensory loss ^c	0	1-20	0-5	rare	rare
Masticatory weakness ^c	0	3-29	0-4	0-10	rare
Diplopia ^c	0-1	0-1	0-0.2	0-1	rare
Hypoacusia ^c	0.8-5	0	0	0	rare
Major neurological deficits ^c	0-1	0	0	0	0
Mortality	0-1	>1/1000	0	>2/1000	0

MVD: Microvascular decompression. RFT: Radiofrequency thermocoagulation. GR: Glycerol rhizolysis. PBC: Percutaneous microcompression. SRS: Stereotactic radiosurgery.
^aPain relief within 1 year from the procedure. ^bMean values of long-term pain relief are calculated at least at 5 years from the procedures. ^cDefinitive neurological deficits.

Table 2: Patients outcomes after different surgical procedures for TN.

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CONCLUSIONS

- TN is a devastating orofacial pain syndrome
- TN can be categorized into primary (classical and idiopathic) and secondary forms
- Imaging helps to categorize TN
- Medical therapy should be initiated first
- MVD is the first-line surgical treatment, especially in patients with classical TN
- Many other treatment options exist including percutaneous interventions, stereotactic radiosurgery and neurectomies
- Treatment in the setting of a multidisciplinary team is highly effective



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Slide 1

Non-Operative Intraarticular Pain Treatment.

Southern Pain Society Annual Meeting
October 1st, 2023
R. Amadeus Mason, MD, CAQSM, RMSK, FAAP
Assistant Professor of Orthopaedics and Family Medicine
Emory University School of Medicine
Emory Sports Medicine Center

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Disclosures

I, R. Amadeus Mason MD, nor any immediate family members, have no relevant financial or nonfinancial relationship(s) within the products or services described, reviewed, evaluated or compared in this presentation.

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Slide 3

Objectives

- **Define the problem**
 - Understand the different causes of joint pain
 - Discuss the Etiology, and Pathophysiology
 - Review Prevalence and Classification systems
 - Outline Symptoms, Evaluation & Diagnosis
- **Discuss Treatment options**
 - Rationale for use
 - What's in the literature
 - General considerations
 - What we do at Emory

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Slide 4

Etiology, and Pathophysiology

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Slide 5

Etiology, and Pathophysiology

- More than 100 types of joint disease
- Two main Categories
 - inflammatory
 - RA, PsA, Gouty, Juvenile
 - non inflammatory
 - OA

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Etiology, and Pathophysiology
Inflammatory Arthritis

- Autoimmune Disease
 - The immune system attacks healthy cells in the body by mistake,
 - causes inflammation (painful swelling) in the affected parts of the body.
 - the lining of the joint becomes inflamed, causing damage to joint tissue.

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Etiology, and Pathophysiology
Inflammatory Arthritis

- **Mainly attacks the joints, usually many joints at once.**
 - commonly affects joints in the hands, wrists, and knees.
- **Associated with tissue damage**
 - can cause long-lasting or chronic pain
 - unsteadiness, and deformity
- **Affects other tissues throughout the body**
 - causes problems in organs such as the lungs, heart, and eyes.

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Etiology, and Pathophysiology
Inflammatory Arthritis

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Etiology, and Pathophysiology
non-Inflammatory Arthritis

- **This a degenerative disease**
 - “wear and tear” arthritis.
- **Osteoarthritis (OA) is the most common form of arthritis.**
- **It most frequently occurs in the hands, hips, and knees.**
 - one joint or a pair of joints at the same time

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Etiology, and Pathophysiology
non-Inflammatory Arthritis

- **With OA, the cartilage within a joint begin to break down.**
 - and eventually spreads to the bones
- **Changes usually develop slowly and get worse over time.**
- **Causes pain, stiffness, and swelling**
 - can result in significant disability.

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Etiology, and Pathophysiology
non-Inflammatory Arthritis

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Slide 12

Symptoms and Evaluation

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Symptoms/risk factors

- **Pain or aching.**
 - worse with weight bearing
 - worse at night
- **Stiffness.**
- **Decreased range of motion.**
- **Swelling (+/-).**

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Symptoms/Risk factors

- **Joint injury or overuse**
 - repetitive stress on a joint.
- **Age**
 - the risk of developing OA increases with age.
- **Gender**
 - women are more likely than men,
 - especially after age 50.

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Symptoms/Risk factors

- **Obesity**
 - Extra weight puts more stress on joints,
 - Especially weight-bearing joints like the knees.
- **Genetics**
 - People who have family members with OA are more likely to develop OA.
 - People who have hand OA are more likely to develop knee OA.
- **Race**
 - some Asian populations have **lower** risk for OA.

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Evaluation/diagnosis

- **OA is diagnosed**
 - physical examination
 - review of symptoms,
 - X-rays,
 - Bilateral standing AP, lateral, merchant view
 - NO MRI is needed !!!!
 - lab tests
 - Especially if inflammatory arthritis is suspected

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Evaluation/diagnosis

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Classification systems

- **Over 50 different classification systems**
- **2 most commonly used**
 - Kellgren and Lawrence
 - WOMAC

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Classification systems

- **Kellgren and Lawrence**
 - radiographic assessment
- **WOMAC**
 - Western Ontario and McMaster Universities Osteoarthritis Index
 - functional assessment

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K/L Classification systems

- **Grade 0-1**
 - no radiographic features of OA present
 - doubtful joint space narrowing (JSN) and possible osteophytic lipping
- **Grade 2**
 - definite osteophytes and possible JSN
- **Grade 3**
 - multiple osteophytes,
 - definite JSN,
 - sclerosis,
 - possible bony deformity

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K/L Classification systems

- **Grade 4**
 - large osteophytes,
 - marked JSN,
 - severe sclerosis
 - definite bony deformity

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K/L Classification systems

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WOMAC Classification systems

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Prevalence

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Prevalence

- **54.4 million adults in the U.S. (22.7 % of all adults) had doctor-diagnosed arthritis**
 - 3.7 million (43.5 % of those with arthritis) had arthritis-attributable activity limitation.

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Prevalence

- **More than ¼ adults with arthritis had severe joint pain (27 %).**
- **Among adults with arthritis, the highest prevalence of adults with severe joint pain was among persons 45 to 64 years old (31 %)**

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Prevalence

- **Almost one-third (30.6 %) of all adults who are obese also have arthritis.**
 - about half (49 %) of adults with arthritis and who are obese have activity limitations.

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Prevalence

- OA has a significant negative impact on co-morbidities.
 - and visa versa
- Physical activity can reduce OA pain and improve physical function by as much as about 40 %.

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Prevalence

- In 2013, total medical costs and earnings losses due to arthritis
 - \$304 billion !!!!!
 - (about 1 percent of the U.S. GDP)
 - earnings losses were \$164 billion
 - (for adults with arthritis between ages 18 and 65).
 - the average adult with arthritis earned **\$4,040** less than an adult without the disease

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Knee OAEpidemic

- 18 million Americans
 - Currently living with symptomatic knee OA.
- 4.1 million Americans
 - Difficulty with ambulation - having failed conservative treatment,
 - Candidates for knee arthroplasty or high tibial osteotomy (HTO).
- 500,000 Americans
 - Knee arthroplasties and HTOs are performed annually in the United States.
- 3.6 million Americans
 - "stuck" in a treatment gap
 - Unwilling or not a candidate to undergo arthroplasty/ HTO
 - Remain in "gap" for an average of 20 years.

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London Ho, M.D., et al. (2014) The economic consequences of the treatment gap in knee osteoarthritis management. Medical Economics, 91(10): 100-105.

Slide 31

Knee OA Treatment Gap

- Particularly important in the younger population
 - Potential risk of revision surgery
 - 38.3% of OA patients are under 55
 - 10.5% of patients are under 35

This highlights the necessity for the development of safe, effective, minimally invasive, treatments that provide favorable efficacy and safety profiles.

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BMJ Open

Knee arthroscopy versus conservative management in patients with degenerative knee disease: a systematic review

Conclusions Over the long term, patients who undergo knee arthroscopy versus those who receive conservative management strategies do not have important benefits in pain or function.

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EVIDENCE AND RESEARCH STUDIES: SURGERY

Clinical Trials update
September 27, 2016

Surgery No Benefit to Patients With Meniscal Tears

Arthroscopic surgery is no effective at improving knee function or at slowing joint space narrowing for middle-aged patients with degenerative meniscal tears, according to a trial that compared the 2 commonest knee Arthroscopic surgery to arthroscopic surgery for meniscal tears, or to no surgery at all. The trial found that patients who had arthroscopic surgery had no better knee function or joint space narrowing than those who had no surgery at all. The trial also found that patients who had arthroscopic surgery had a higher risk of complications than those who had no surgery at all.

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Treatment Options

- **Physical activity**
 - low-impact aerobic exercises,
 - neuromuscular control
- **Weight loss**
 - every 5lbs of body weight lost = 25lbs of knees
- **Physical therapy?**
 - muscle strengthening exercises
 - Neuromuscular education

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Treatment Options

- **Medications**
 - NSAIDs vs Tylenol
- **Supportive devices**
 - such as crutches or canes.
 - bracing
- **Injectables**
 - steroids
 - Biologics
 - HA
 - PRP
 - Stem cells

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Steroids

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The Effect of Intra-articular Corticosteroids on Articular Cartilage


- Methylprednisolone, dexamethasone, hydrocortisone, betamethasone, prednisolone, and triamcinolone were reported to display dose-dependent deleterious effects on cartilage morphology, histology, and viability in both in vitro and in vivo models.
 - Effects of local administration of hydrocortisone on cartilage degradation in vivo; A. D. SEDGWICK, Y.M. SIN, A. R. MOORE, J. C. W. EDWARDS, AND D. A. WILLOUGHBY
Annals of the Rheumatic Diseases, 1984, 43, 418-420
 - The Effect of Intra-articular Corticosteroids on Articular Cartilage A Systematic Review; Chloe Werncke,* BS, Hillary J. Braun,* BS, and Jason L. Dugas,*† MD The Orthopaedic Journal of Sports Medicine, 3(5), 232597115581163



Slide 38

Anesthetic agents are also a concern...


- In Vivo Effects of Single Intra-Articular Injection of 0.5% Bupivacaine on Articular Cartilage. Chu CR, et al. JBJS Mar 2010; 92: 5990608
- Lidocaine Potentiates the Chondrotoxicity of Methylprednisolone Seshadri et al Arthroscopy, April 2009;25:4: 337-347



Slide 39

Biologics

HA visco-supplementation



Slide 40

Knee OA treatments ranked according to effect sizes for pain relief at 3 months (relative to oral placebo)	
Treatment	Effect size (95% credible interval)
IA hyaluronic acid	0.63 (0.39 to 0.88)
IA corticosteroids	0.61 (0.32 to 0.89)
Diclofenac	0.52 (0.34 to 0.69)
Ibuprofen	0.44 (0.25 to 0.63)
Naproxen	0.38 (0.27 to 0.49)
Celecoxib	0.33 (0.25 to 0.42)
IA placebo	0.29 (0.04 to 0.54)
Acetaminophen	0.18 (0.04 to 0.33)

Baxauer RB, Schmid CH, Kent DM, Vachon EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a network meta-analysis of randomised clinical trials. *BMC Med*. 2015;13(21):46-54.

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Althman et al. *BMC Musculoskeletal Disorders* (2015) 15:321
DOI 10.1186/s12915-015-0775-z

BMC
Musculoskeletal Disorders

RESEARCH ARTICLE **Open Access**

The mechanism of action for hyaluronic acid treatment in the osteoarthritic knee: a systematic review

RD Althman^{1*}, A. Manjoor², A. Fierlinger³, F. Niaz³ and M. Nicholls⁴
Althman RD, Manjoor A, Fierlinger A, Niaz F, Nicholls M. The mechanism of action for hyaluronic acid treatment in the osteoarthritic knee: a systematic review. *BMC Musculoskeletal Disorders*. 2015;15:321. doi: 10.1186/s12915-015-0775-z.

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- **Mechanical effects of HA in the joint**
 - Lubricant
 - Shock absorption
- **Analgesic effects of HA in the joint**
 - Binds to mechanosensitive, pain-transducing ion channels
 - Reduces the action of sensitized joint nociceptor terminals
- **Biosynthetic effects of HA in the joint**
 - Enhances proteoglycan and glycosaminoglycan synthesis by chondrocytes
 - Promotes intrinsic (endogenous) synthesis of HA by joint tissues
- **Chondroprotective effects of HA in the joint**
 - Reduces chondrocyte apoptosis and increases cellular proliferation
 - Reduces production of matrix metalloproteinases (MMPs) and aggrecanases (ADAMTSs)
- **Anti-inflammatory effects of HA in the joint**
 - Suppresses expression of pro-inflammatory cytokines such as IL-1 β , TNF-alpha, IL-8, and IL-6

Althman RD, Manjoor A, Fierlinger A, Niaz F, Nicholls M. The mechanism of action for hyaluronic acid treatment in the osteoarthritic knee: a systematic review. *BMC Musculoskeletal Disorders*. 2015;15:321. doi: 10.1186/s12915-015-0775-z.

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HA treatment options

1-injection course of therapy

3-injection course of therapy

5-injection course of therapy

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Summary of indications for use

HA is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacological therapy or simple analgesics, e.g. acetaminophen.

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Summary of indications for use

Do not inject HA in patients

- knee joint infections,
- skin diseases,
- other infections in the area of the injection site.
- with known hypersensitivity or allergy to sodium hyaluronate preparations.
- Risks can include transient pain or swelling at the injection site.

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 Arthritis

McGrath et al., J Arthritis 2015, 3:1
http://jia.amepub.org/10.4236/jia.2015.31001

Review Article Open Access

A Comparison of Intra-Articular Hyaluronic Acid Competitors in the Treatment of Mild to Moderate Knee Osteoarthritis

AF McGrath^{1*}, AM McGrath², ZM Jessop MA², Surya Gandham², G Datta¹, Sebastian Dawson-Bowling¹ and SR Cannon¹

¹Royal National Orthopaedic Hospital, Stanmore, UK
²Tandem Quinary, London, UK
³Royal Free Hospital, London, UK

*These authors contributed equally and share combined first authorship

McGrath A, McGrath AM, Jessop ZM, et al. A comparison of intra-articular hyaluronic acid competitors in the treatment of mild to moderate knee osteoarthritis. J Arthritis. 2015;3(1):1-10. doi:10.4236/jia.2015.31001

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Rheumatol 2008; 48:327-331
DOI 10.1007/s00393-008-0063-2
Published online: June 23, 2008
© Springer Medizin Verlag 2008

D. Kroczer¹, G. Matziolis¹, J. Talscher¹, J. Funk¹, S. Tehtz¹, F. Buttgenell², C. Perka¹

¹Center for Musculoskeletal Surgery, Charité University Hospital, Berlin
²Clinic for Internal Medicine Specializing in Rheumatology and Clinical Immunology, Charité University Hospital, Berlin

Reduction of arthritis associated knee pain through a single intra-articular injection of synthetic hyaluronic acid

Kroczer D, Matziolis G, Talscher J, et al. Reduction of arthritis associated knee pain through a single intra-articular injection of synthetic hyaluronic acid. Z Rheumatol. 2008;68(4):327-331.

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Orthobiologics

- The use of **biological substances** to help **MSK tissue** heal more quickly.
- **Biological substances**
 - Naturally occurring in the body
 - Normally associated with healing
- **MSK tissue**
 - Muscle
 - Tendon
 - Ligament
 - Bone

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Platelet Rich Plasma



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Platelet Rich Plasma (PRP)


- **Autologous blood**
- **Concentrated above baseline**
- **Usually 4-5 times baseline (1.5 – 4.5 x 10⁵ uL)**
 - **PeRP** – platelet enriched plasma,
 - **PRC** – platelet rich concentrate
 - **APG** – autologous platelet gel
 - **ACP** – autologous conditioned plasma
 - **A2M** - α -2-Macroglobin
- **Use variable speed centrifuge**



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Platelet Rich Plasma (PRP)

- **Characterization**
- **Leukocyte rich vs Leukocyte poor** Dragoo, et al AJSM (2012)
 - Decreased pain
 - Decreased inflammation
 - No increase infection
- **Low RBC**
 - Intra-articular administration Braun, et al AJSM (2014)



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Platelet Rich Plasma (PRP)

- **Classification system** Mishra, et al CPB(2012)
 - 4 types
 - Based on
 - WBC's
 - Platelet activation
 - Platelet Concentration

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Types of Injectable MSC's for Cartilage/ OA

- **Autologous**
 - Bone Marrow
 - BMA (bone marrow aspirate)
 - BMC (bone marrow concentrate)
 - Culture/ expanded
 - Adipose Derived Stem Cells
 - Lipo-aspirate
 - SVF (stromal vascular fraction)
 - Culture/ expanded
- **Allogenic**
 - Placental Derived Cells
 - Umbilical Cord Blood/ Tissue

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Sources of Birth Tissue
Injectables

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Rational for Use

- **Acute vs Chronic**
 - Chronic usually more problematic
 - Over use
 - Repeated Micro-traumatic events
 - Disruption of the internal structure
 - Degeneration of the cell and matrix
 - Mismatch of injury and healing response
 - Augmented delivery of appropriate substance
 - PRP/BT – growth factors
 - MSC – Stem cells

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Osteoarthritis

- **PRP** Spaková, et al. AJPM&R (2012,2014)
 - RCT, 120 patients
 - Out performed HA
- **PRP vs Stem cell**
 - PRP following HA series
 - Single injection “series”
 - Bone Marrow vs Adipose

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A multi-center analysis of adverse events among two thousand, three hundred and seventy two adult patients undergoing adult autologous stem cell therapy for orthopaedic conditions

Christopher J. Catano^{1,2}, Hasan M. Sayegh³, Michael B. Freeman^{1,2}, Jay Smith⁴, William D. Marmor⁵, Rastislav Babos⁶

- A total of **3012 procedures** were performed on 2372 patients with follow-up period of 2.2 years.
- 325 adverse events were reported.
 - majority were pain post-procedure** (n=93, 3.9% of the study population) and pain due to progressive degenerative joint disease (n= 90, 3.8 % of the study population).
- Seven cases reported neoplasms, **a lower rate than in the general population**.
- Our findings are **consistent with prior investigations** demonstrating a **favorable safety profile for the percutaneous use of BMC** and MSC injections for the treatment of orthopaedic conditions

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MSC Literature Review

PMB 2019 Feb;11(2):177-191. doi: 10.1016/j.pmrj.2018.06.019. Epub 2019 Jan 16.

Bone Marrow-Derived and Adipose-Derived Mesenchymal Stem Cell Therapy in Primary Knee Osteoarthritis:
A Narrative Review.

Jayaram P, IkReema U, Rothenberg JB, Malanga GA.

- 14 studies
- 3 RCTs
- Bone Marrow: 6 studies
- Adipose Tissue: 8 studies
- Culture Expanded: 7 studies

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Summary

- Results : all 14 studies
 - No major adverse events
 - Improved pain and function
 - Only 1 study with “negative” results

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Take Home Points

- Intraarticular treatments should be used in combination
- Steroids really should be for acute flairs
- HA DOES works better than placebo
- Orthobiologic can be used stand alone or in combination.

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Be Aware of all the options available NOT just the one's that you know to perform

- Avoid treatments that are **KNOWN** to be harmful.
- Be aware of the **evidence** of the treatments offered.
- Be aware of your **patient's preferences** !
- Keep up with **scientific literature** on the evolving area of Orthobiologics (PRP, stem cell, etc) and how they may apply to various orthopedic conditions

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