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Patient Identification Strategies for Neuromodulators

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Disclosure

- Nothing to disclose

Learning Objectives

- Describe patient selection criteria for implantable pain therapies.
- Compare systemic and intrathecal drug delivery.
- Differentiate FDA-approved intrathecal analgesics.

WHAT TO DO WITH PATIENTS WITH SEVERE CHRONIC PAIN?

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Neuromodulation Defined

The International Neuromodulation Society defines therapeutic neuromodulation as “the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body.” In appropriate patients, this growing class of therapies, in common use since the 1980s, can help restore function or relieve symptoms that have a neurological basis.

https://www.neuromodulation.com/neuromodulation-defined- accessed 8/21/20

Why Neuromodulation?

- Testable
- Completely reversible
- Non-destructive
- No limitation to future therapy

Neuromodulation Approaches to Mention

- SCS
- DRG
- PNS
- HF-10
- Intraspinal analgesics

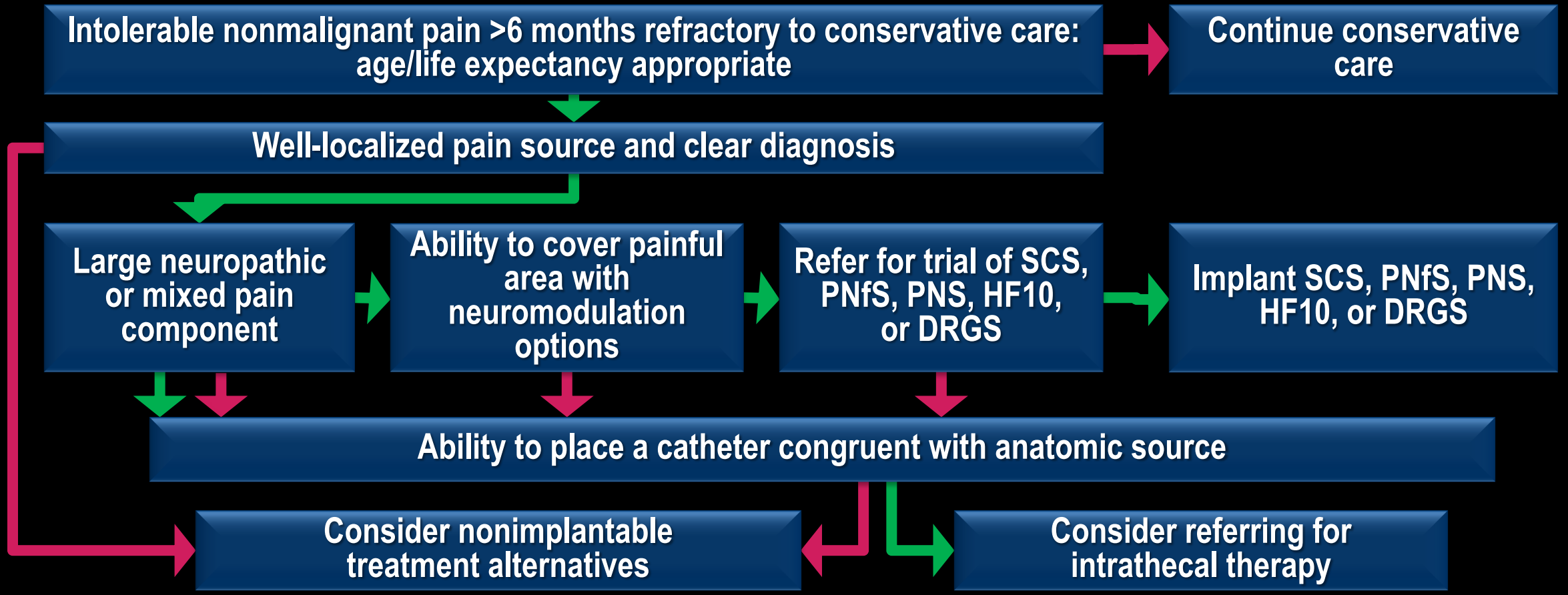
Are These Patients Good Candidates?

- 53 year old male with post laminectomy pain syndrome with persistent right lower extremity pain
- 43 year old female with small fiber neuropathy associated with celiac disease
- 36 year male with fibromyalgia and pain everywhere on 200mg of morphine daily
- 40 year old female with CRPS that has ”spread” to her entire body
- 40 year old female with CRPS that affects right lower extremity
- 32 year old male with traumatic brachial plexopathy

Principles of Screening

- Identify and accurately select patients who will achieve long-term success following implantation of a SCS or ITDD system
- Goals should be discussed and defined by both the physician and patient BEFORE the trial
- Goals are not uniform across patients – they need to be defined on a case-by-case basis
- Trial should approximate as closely as possible the conditions of long-term therapy
- SCS represents a SINGLE element in overall long-term pain management for a given patient

Intrathecal Therapy for Chronic Noncancer Pain
Placement in Interventional Pain Algorithms



DRGS, dorsal root ganglion stimulation; HF10, high frequency stimulation; PNfS, peripheral nerve field stimulation; PNS, peripheral nerve stimulation; SCS, spinal cord stimulation.
Green arrows indicate affirmation or positive response; red arrows signify negative response.
Adapted from Deer TR, et al. *Neuromodulation*. 2017;20(2):96-132.

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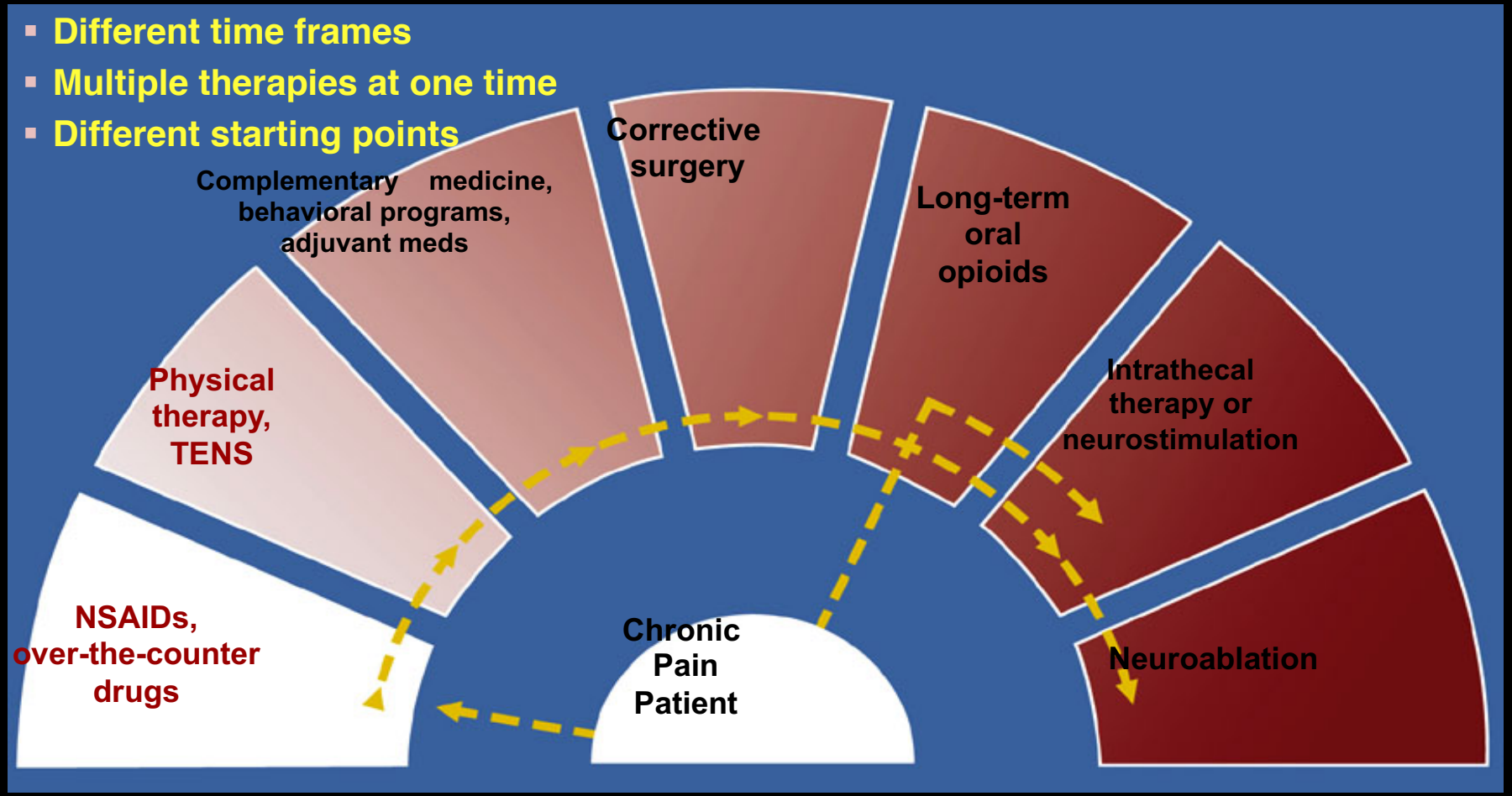
Pain Management: A More Flexible Approach*



Patient Referral

Finding the Right Partner in Interventional Pain Management

Oral Medication Prescriber

Comprehensive Interventional Pain Management

Interventional Spine Injector

Physical Therapist

Surgeon

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Patient Selection
Pretrial Workup

- **Medical history**
  - Review diagnosis, comorbidities, previous treatments, and outcomes
  - Social issues (eg, home environment, insurance)
- **Physical examination**
  - Spinal and anatomic factors
  - Device-related limitations
- **Patient education**
  - Informed consent
  - Potential benefits and risks
  - Caregiver education
  - Compliance requirements
  - Identification of realistic functional goals

Deer TR, et al. *Neuromodulation*. 2012;15(4):420-435; Deer TR, et al. *Pain Physician*. 2010;13:E175-E213; Prager J, et al. *Neuromodulation*. 2014;17(4):354-372.

Patient Selection Criteria for Implantable Pain Therapies: SCS and IT Drug Delivery

- Failure of more conservative therapies
- Further surgical intervention is not indicated
- Absence of serious untreated drug habituation
- Psychological evaluation and clearance for implantation has been obtained
- No contraindications to implantation exist.
  - sepsis, coagulopathy, etc.
- Successful screening trial

Patient Selection
Elements of Psychological Evaluations

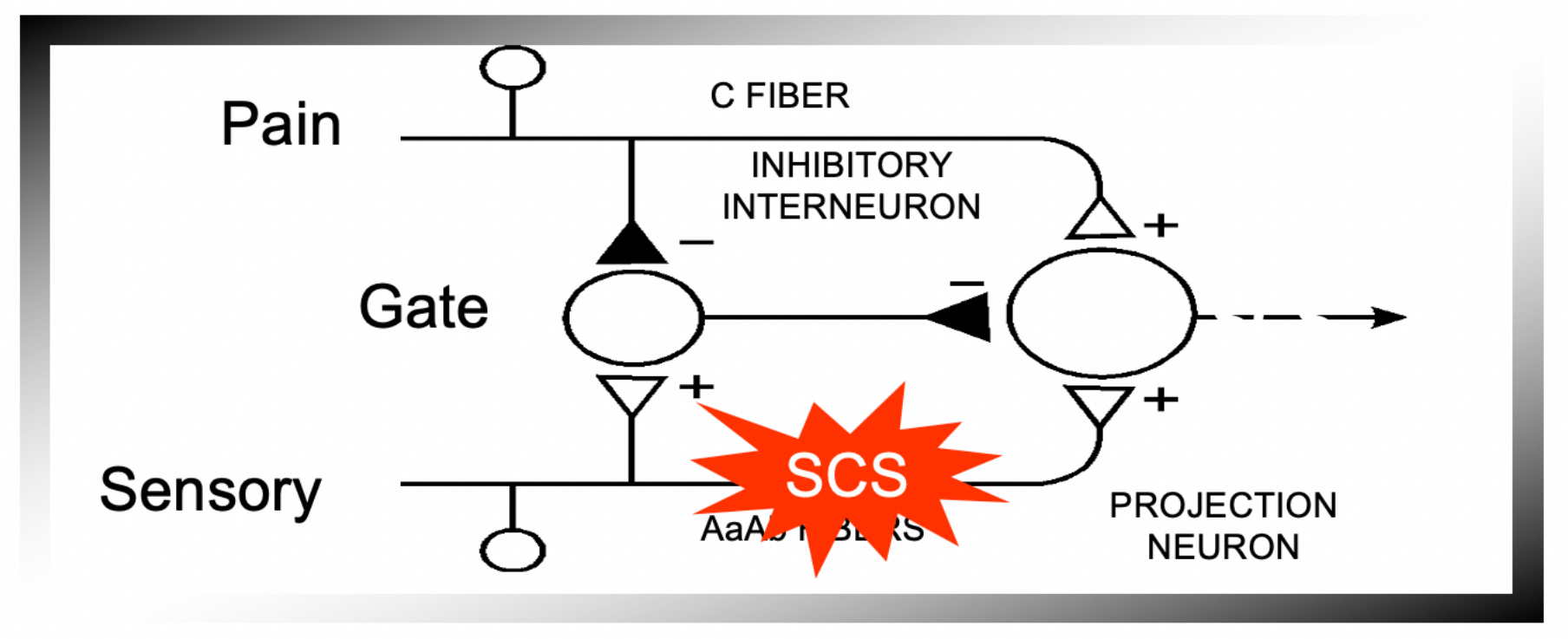
- Informed consent and rationale for psychological evaluation
- Current concept of pain and beliefs about treatment
- Current psychological consequences of pain
- Current emotional status
  - Depression, anxiety
  - Sleep, appetite
  - Suicidal ideation
  - Irritability, anger, guilt
- Review of mental health–related therapies
- Observation of pain behaviors
- Psychosocial and developmental history
- Clinical evaluation of psychological and cognitive functioning
- Standardized psychological testing
  - eg, MBMD, MMPI-2

MBMD, Millon Behavioral Medicine Diagnostic; MMPI-2, Minnesota Multiphasic Personality Inventory-2.

Prager J, et al. *Neuromodulation*. 2014;17(4):354-372.

Gate Theory and SCS

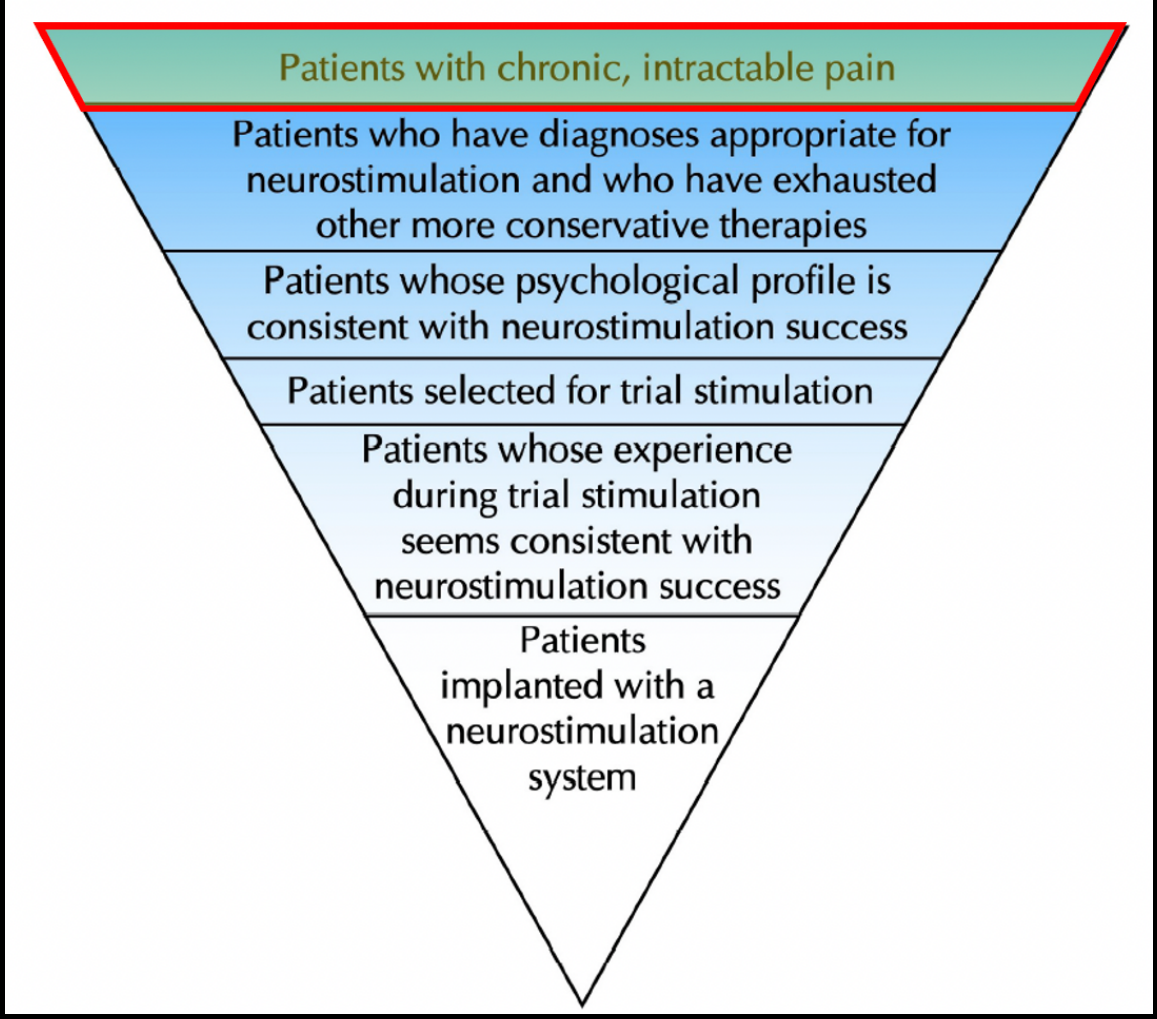
- SCS Implanted Near Dorsal Column Stimulates the Pain-inhibiting Nerve Fibers Masking Painful Sensation With a Tingling Sensation (Parathesia)



SCS: Mechanisms of Action

- Releases certain neurotransmitters that cause **vasodilation**- helpful for angina, PVD and CRPS
- Increases levels of **GABA**… in patients with allodynia (CRPS), GABA levels are decreased in the CSF
- **Blocks sympathetic outflow**. For some CRPS patients, abnormal activity of the SNS is responsible for a lot of their symptoms, and SCS can help significantly with temperature and skin color changes as well as with pain.

Screening Paradigm for SCS



Clinical Factors

- Indication
  - Neuropathic pain
  - Static
- Disease Etiology
  - Disease likely to progress not a good candidate
- Pain Distribution
  - Multi site and broad pain patterns often require more leads and electrodes
  - Back pain will likely require current fractionalization
- Patient Factors
  - Anatomy
  - Physiology
  - Selection

Diagnoses

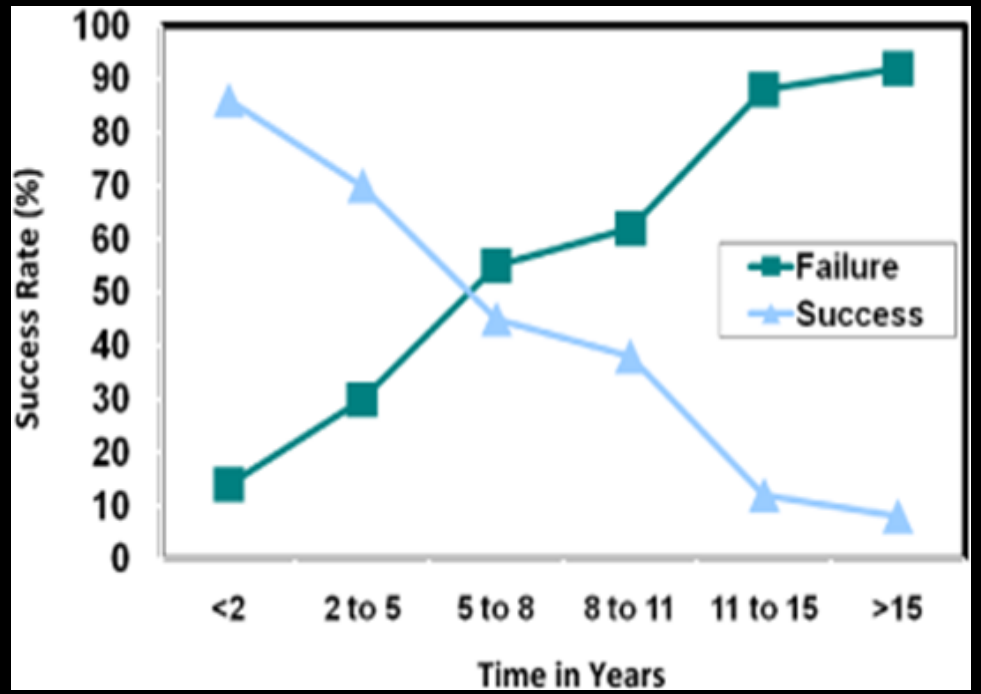
- In our patient population, we use SCS for **FBSS** (low back or neck), **CRPS**, chronic pain s/p crush injury, and phantom limb pain.
- However, this doesn't mean that any patient who carries one of these diagnoses is a good candidate…

Neuropathic vs Nociceptive Pain

- Patients with **neuropathic** pain respond better to SCS. Peripheral neuropathy has published success rates of nearly 75%, whereas FBSS (which is both neuropathic + nociceptive) has published success rates closer to 60%.
- **Nociceptive** pain is more responsive to anti-inflammatories and opioid medication, whereas neuropathic pain typically is not.

Duration of Symptoms

- Inverse relationship b/n the chronicity of the pain and the outcomes of SCS
- For FBSS, patients who received their SCS within 2 years of symptoms onset had a success rate of 85%. Those with pain >15 years only had a 9% success rate.[1]
- CRPS- considered before central sensitization has set in/ as soon as other treatments have failed.[2]



1.Kumar et al 2013. Impact of Wait Times on Spinal Cord Stimulation Therapy Outcomes. Pain Practice 2013

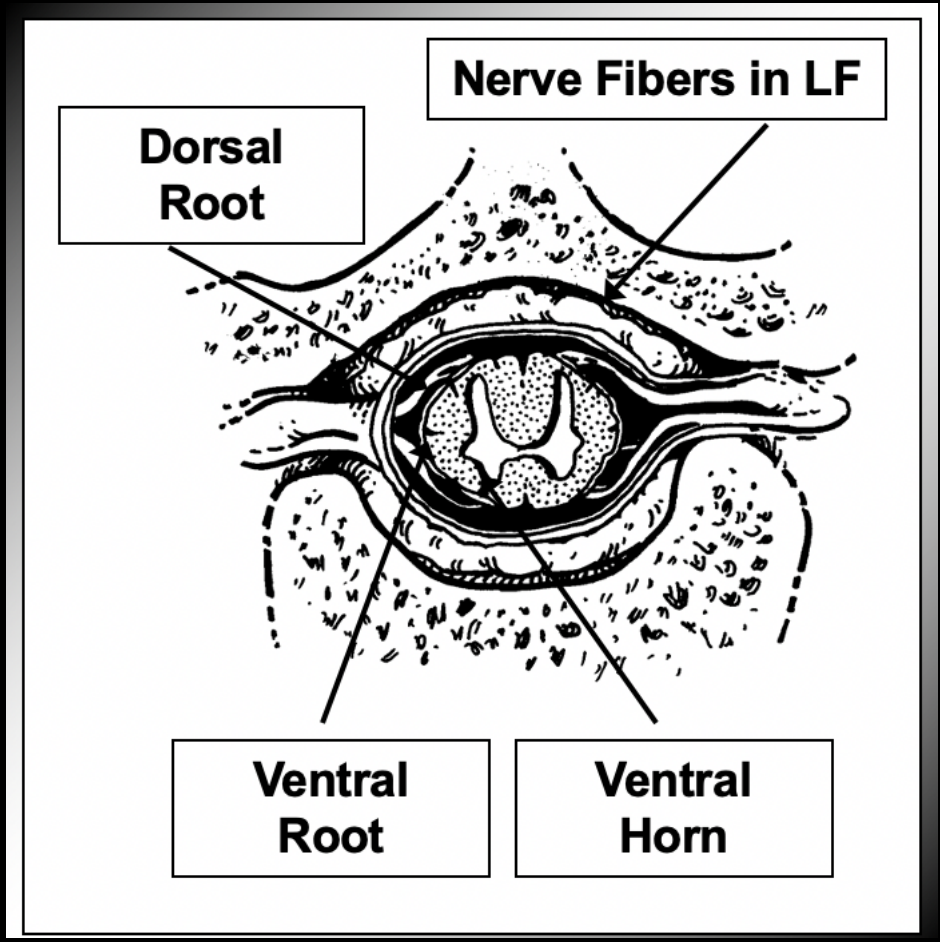
2.Kumar et al 2011. Neurosurgery 69;566-78.

Stimulation Paradigms

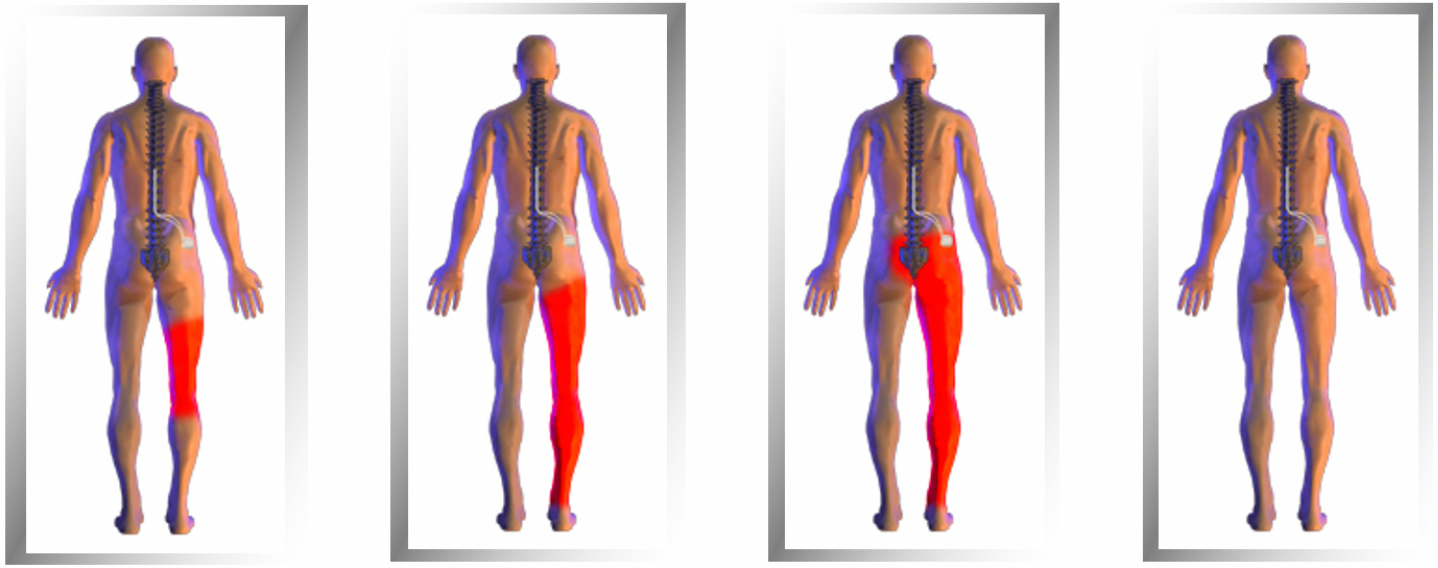
- Paresthesia-based (P-SCS)
- Paresthesia-free (PF-SCS)
- Burst (B-SCS)
- High Frequency (HF-SCS)
- Evoked Compound Action Potential (ECAP-SCS)
- Dorsal Root Ganglion (DRG-S)

Potential Painful Stimulation

- Dorsal Roots
  - SCS of specific dorsal roots may result in paresthesia in 1 or 2 corresponding dermatomes
  - May produce painful stimulation
- Ventral Roots and Horn
  - SCS of ventral roots or horn will likely produce painful motor stimulation
- Stimulation of Nerve Fibers in Dorsal Ligamentum Flavum may Produce Painful Stimulation



Programs Can Be Activity or Pain-Based



Program 1 | Program 2 | Program 3 | Program 4

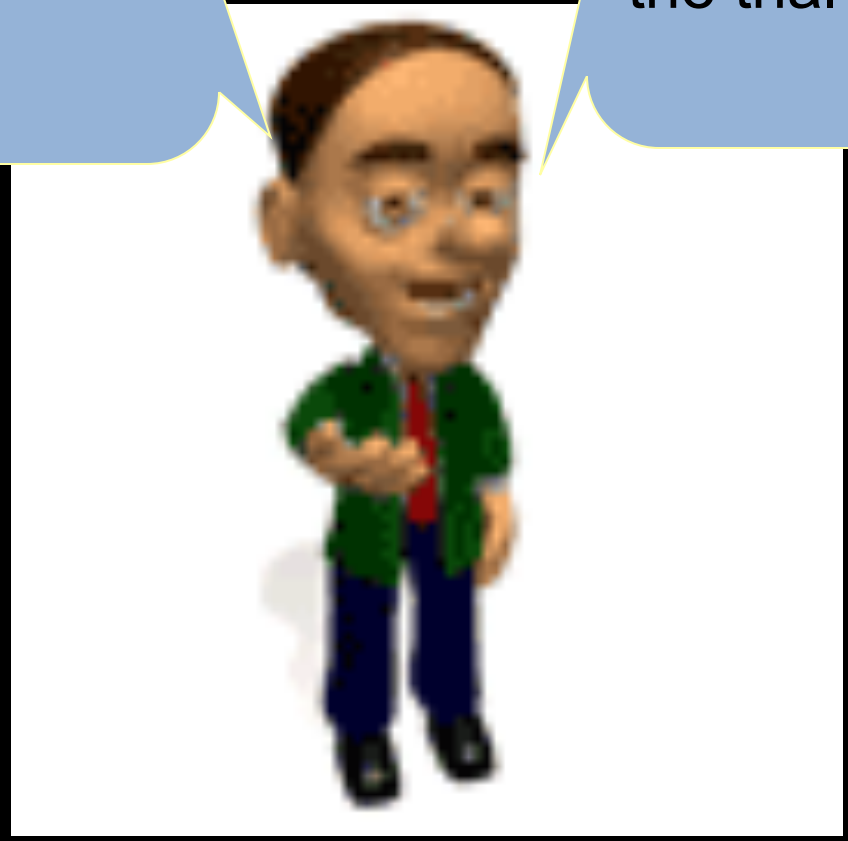
EXAMPLE

Essential Information from Trial

- Is there adequate paresthesia overlap of the pain?
- Can coverage be obtained with multiple contacts?
- Did coverage of different pain areas require different electrode combinations?
- Stimulation parameters to achieve the ideal results?
- Were there any adverse effects of stimulation?
  - Painful stimulation, root/trunk stimulation
- What degree of analgesia was achieved?
- Were the goals of the trial as determined by the patient and physician met?

SCS – The Biggest Lies Ever Told

"This device is going to relieve all of your pain"



"Don't worry, the permanent stimulator will work better than the trial"

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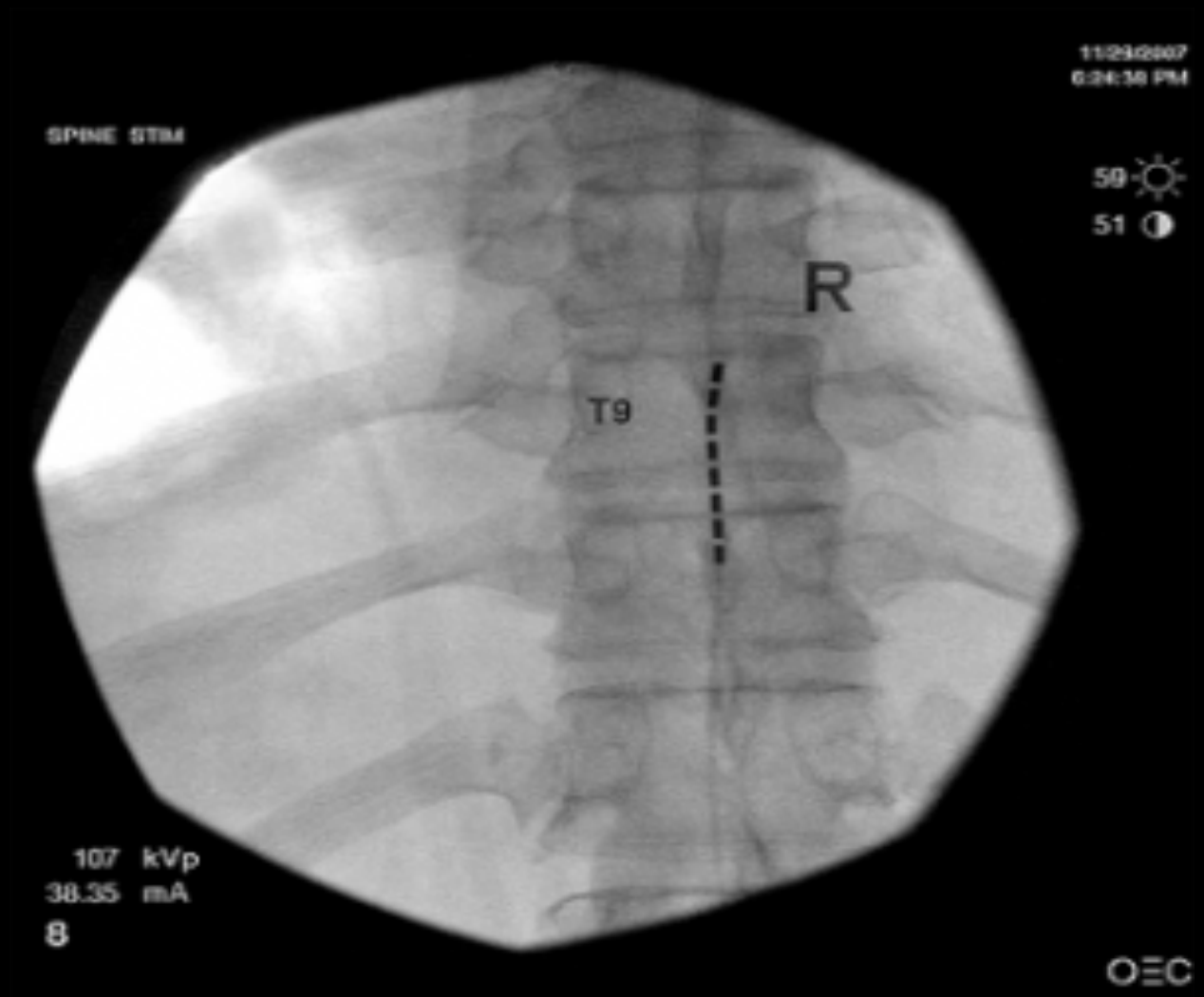
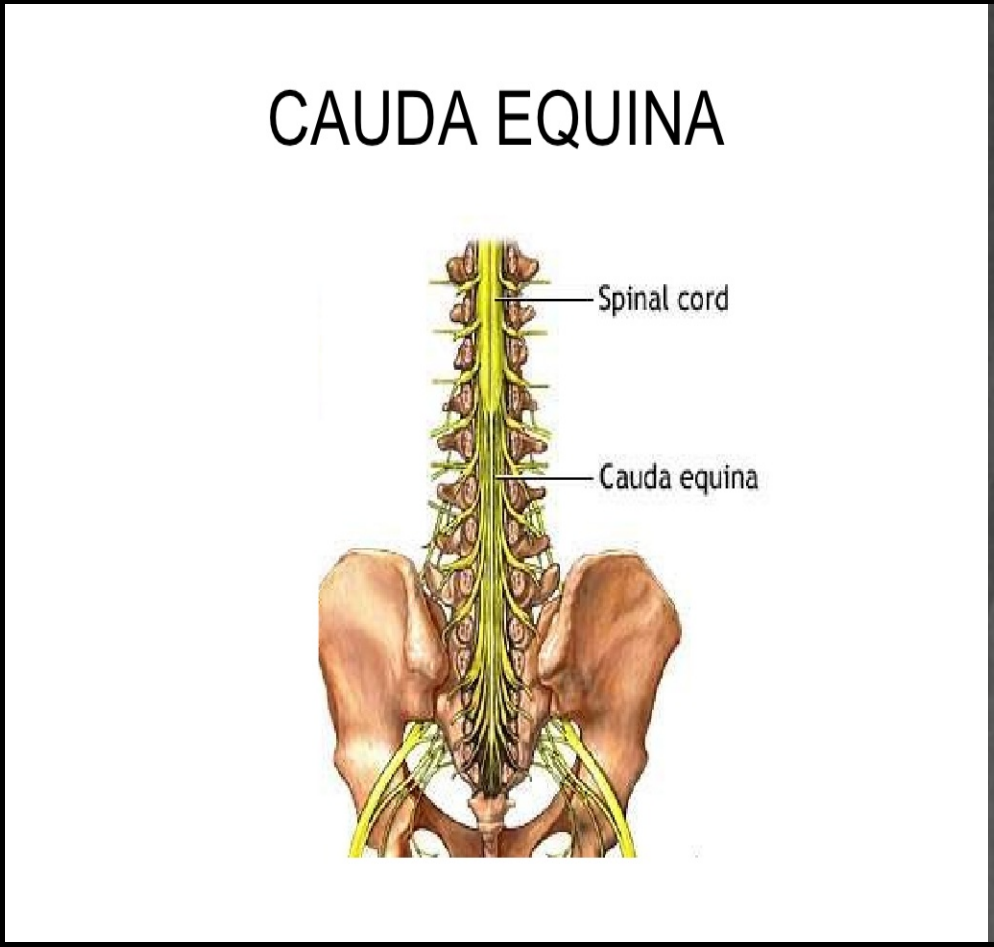
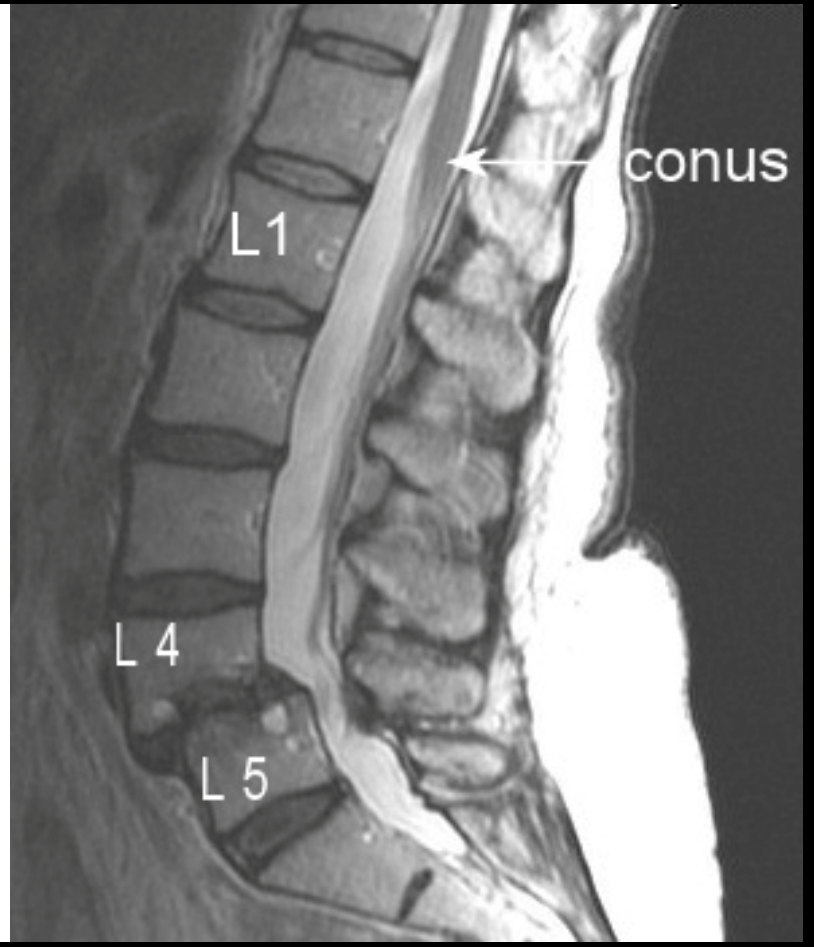
SCS Trial



Trial Lead Placement





SCS Trial… Realistic Expectations

SCS Trial

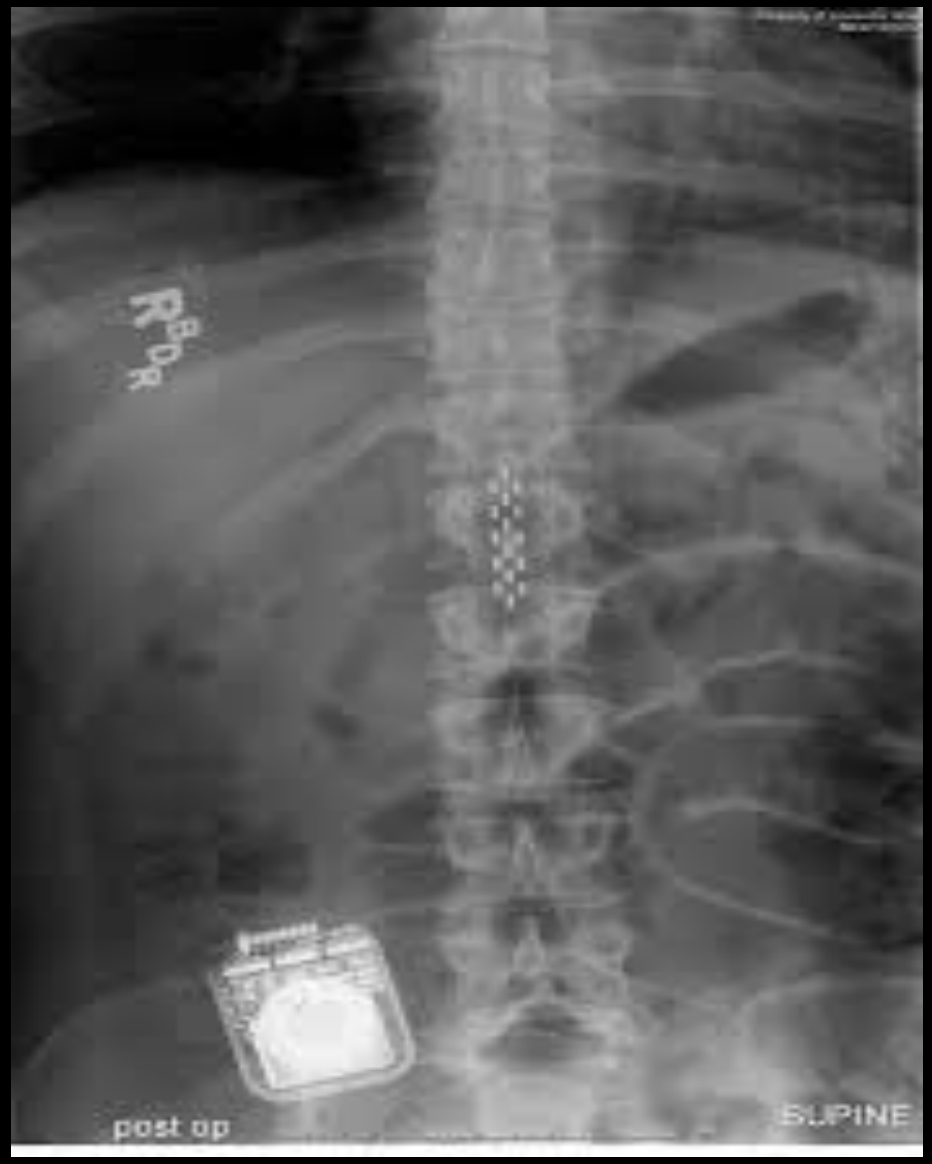
- The trial process is not ideal
- **Positionality:** the leads are in the epidural space and float around a bit. With change in position, there is a change in coverage.
- Type of sensation?
- Patients must be able to understand that the purpose of the trial is 'does this help with your pain/function'
- Trial duration – infection risk? No shower?!
- Generally speaking, the trial success rate is 70%, however in the WC population this number is lower.

Trial Follow Up

- 1) **Pain relief:** what percentage? Did the stimulator cover the whole painful area? Reprogramming…
- 2) **Function:** hard because of the positionality, but look for sitting/standing tolerance, walking. Not going to be able to assess things like bending/lifting during the trial.
- 3) **Medication usage**: did they need less medication? Short trial period, plus procedural pain, may be hard to assess

SCS Implant

- 2 ways to implant- surgical and percutaneous
- One of the variables in how patients respond during a trial is the amount of space- (CSF)- between the electrode and the cord.
- Paddle lead eliminates this, and gives a greater area of coverage. Also, because the lead is fixed, there is less chance of breakage.


post op
SUPINE

Outcomes: FBSS- Pain

Only 2 Randomized Controlled Trials, both industry sponsored!

1. North et al 2005: 45 FBSS pts- compared SCS to re-operation; at 3 year follow up SCS had a more favorable outcome than re-op, nearly obviated the need for re-op, and sig less meds. **67% of the re-op patients then crossed over to SCS
2. Kumar et al 2007: 100 FBSS patients randomized to CMM vs SCS with 2 year f/u. 48% of SCS vs 9% of CMM had 50% improvement in pain. Also with better function and QOL
3. Overall for FBSS, **50-60%** of patients get >=50% better

Turner JA et al. Spinal Cord Stimulation for Patients with Failed Back Surgery Syndrome or Complex Regional Pain Syndrome: A Systematic Review of Effectiveness and Complications. Pain 2004;108:137-47.

Outcomes: FBSS- Function/Med Intake

- No RCT has looked specifically at function
- 3 case series did show improvements in function
- Functional outcome is also a function of timing- Study looked at long term outcomes of SCS; noted that function was most improved in patients who were implanted <1 year after onset of symptoms[1]
- North study- SCS group used significantly less opioids than the re-operation group- 45%[2]

[1]Kumar K et al. Spinal Cord Stimulation is Effective in Management of Complex Regional Pain Syndrome 1: Fact or Fiction. Neurosurgery 2011;69(3):566-78.

[2]North RB et al. Spinal Cord Stimulation versus Repeated Lumbosacral Spine Surgery for Chronic Pain: A Randomized Controlled Trial. Neurosurgery 2005;56:98-107.

What About WC?

- Study compared **ONLY WC** patients with FBSS who had a SCS, were treated in a pain clinic, or had no specialized treatment.
- Trial success rate was **53%.**
- Overall, this study showed no benefit to SCS, either in terms of long term pain relief, function, or return to work status.

Turner JA et al. Spinal Cord Stimulation for Failed Back Surgery Syndrome: Outcomes in a Workers' Compensation Setting. Pain 2010;148:14-25/

Outcomes: FBSS-RTW

- Several studies have looked at FBSS patients' return to work after SCS: in one, 8/23 resumed work[2], in a second 4/32 resumed[3], in a third 15% of the 60 patients who received a SCS returned, vs 0/44 who did not get implanted[4].
- In the outcome paper specifically looking at SCS for FBSS in WC, fewer than 10% of patients in any group were working at 12 months

2. Dario A et al. Treatment of failed back surgery syndrome. Neuromodulation 2001;4:105-110
3. Ohnmeiss DD et al. Prospective outcome evaluation of spinal cord stimulation in patients with intractable leg pain. Spine 1996;21:1344-51.
4. Kumar K et al. Treatment of chronic pain iwht spinal cord stimulation versus alternative therapies: cost-effectiveness analysis. Neurosurgery 2002;51:106-16.

Outcomes: CRPS

- One Randomized Controlled Trial!
- 24/36 patients got SCS + PT, 18 only PT
- SCS group had reduced pain (-3.6/10 compared to +0.2), overall 39% of the SCS group were ‘much improved’, and all 24 had improved HR QOL at 6 months
- No improvement in functional status in either group
- At 1 year follow up, results the same. At 5 year follow up, results became less impressive, but 20 of the SCS patients still had improved global perceived effect and pain relief.
- **95% of the patients who had SCS would opt for it again

Kemler et al. Spinal Cord Stimulation in Patients With Chronic Reflex Sympathetic Dystrophy. NEJM 2000;353:618-24.

Outcomes: CRPS

- Prospective study followed 84 consecutive patients with CRPS who underwent SCS implantation[1]
- SCS was determined to be an effective long-term treatment (12 years) for 63% of patients
- Average decrease in pain 25-30% from baseline, but 59% rated their pain as much or very much improved.
- No data on function or medication intake
- Meta-analysis performed in 2006 showed **67%** of CRPS patients got at least 50% better following SCS, with sig improved QOL and functional mobility[2]

Geurts JW et al. Spinal Cord Stimulation for CRPS 1; A Propsepctive Cohort Study with Long-Term Follow up. Neuromodulation 2013;16(6):523-9.
Journal of Pain and Symptoms Management 2006;31(4):S13-19.

Outcomes: CRPS/RTW

- Several studies have looked at CRPS patients' return to work after SCS: in one study, 41% of 24 patients returned,[1] in another 5/25 returned[2], and one study had a 70% RTW rate[3]

1. Calvillo O et al. Neuroagumentation in the treatment of CRPS of the upper extremity. Acta Orthop Belg 1998;64:57-63.
2. Kumar K et al. Spinal cord stimulation is effective in management of complex regional pain syndrome I: fact or fiction. Neurosurgery 2011;69:566-78.
3. Harke H et al. Spinal cord stimulation in sympathetically maintained complex regional pain syndrome type I with severe disability. Eur J Pain 2005;9:363-73.

What About Depression?

- Severe depression is seen as a contra-indication to SCS.
- However, unlike physical functioning, the level of depression has been shown to markedly improve following SCS implantation.[1-31]
- Pre-implantation depression scores have not been shown to affect long term outcomes.

Pain Physician 2013;16(3):265-75.

How to Improve Outcomes?

- Smart patient selection
- Psychological factors/eval
- **TIMING-** Much better response at <2 years for FBSS
- For CRPS, before dystrophic changes are present. Best results seen within a year of symptom onset.[1]
- For CRPS, SCS should be considered as soon as alternative therapies have failed; even within the first 3 months.[2]

1. Kumar et al. Neurosurgery 2011;69;566-78.
2. Poree et al. Neuromodulation 2013;16(2):125-41

Do the Results Wane Over Time?

- Results vary. Some studies show that the effect decreases 25-50% over 2 years, others only see a slight decrease in efficacy over time. This may be due to progression of disease, or electrode dislocation/ breakage.
- In 2011 an outcome analysis of patients with paddle electrodes was published- in patients with CRPS, more than 50% of patients still had greater than 50% pain relief at 4.4 years, and 77.8% of them would choose to get implanted again.

- www.neuromodulation.org

Overview Of Systemic vs Intrathecal Therapy

Systemic drug delivery	Intrathecal drug delivery
• Drug distributed via bloodstream	• Implantable pump sends drug via catheter to intrathecal CSF
• Drug interacts with receptors throughout the body	• Drug targeted to spinal receptors
• Oral dosing produces peaks and troughs in plasma levels	• Steady-state around-the-clock dosing can be achieved
• Relatively high daily dosages – High systemic side effect risk and drug-elimination load	• Relatively low daily dosages – Reduced systemic side effects and low drug-elimination load
• Concerns about adherence, abuse, and diversion	• Potential for better adherence and less diversion

CSF, cerebrospinal fluid.

Bagnall D. *Phys Med Rehabil Clin N Am*. 2010;21(4):851-858; Deer TR, et al. *Pain Physician*. 2010;13(3):E175-E213; Hayek SM, et al. *Pain Physician*. 2011;14(3):219-248; Onofrio BM, et al. *Mayo Clin Proc*. 1981;56(8)516-520; Prager J, et al. *Neuromodulation*. 2014;17(4):354-372.

New PACC Recommendations

The Polyanalgesic Consensus Conference (PACC): Recommendations on Intrathecal Drug Infusion Systems Best Practices and Guidelines

The Polyanalgesic Consensus Conference (PACC): Recommendations for Intrathecal Drug Delivery: Guidance for Improving Safety and Mitigating Risks

The Polyanalgesic Consensus Conference (PACC): Recommendations for Trialing of Intrathecal Drug Delivery Infusion Therapy

PACC, Polyanalgesic Consensus Conference.

Deer TR, et al. Neuromodulation. 2017;20(2):96-132; Deer TR, et al. Neuromodulation. 2017;20(2):133-154; Deer TR, et al. Neuromodulation. 2017;20(2):155-176

Patient Selection for Intrathecal Therapy: Disease State Indications

- FDA approvals for intrathecal morphine and ziconotide
  - Management of severe chronic pain (no specific diagnoses)
- Potential clinical scenarios
  - Axial pain
    - Failed back surgery syndrome
    - Vertebral compression fractures
    - Refractory facet arthropathy, spondylosis, nonoperative spondylolisthesis
  - Extremity pain
    - Radiculopathy following failed back surgery
    - Radiculopathy that cannot be addressed with surgery
  - Visceral pelvic or abdominal pain
  - Complex regional pain syndrome
  - Postsurgical or traumatic nerve damage
  - Peripheral neuropathies
  - Cancer pain
  - End-of-life pain

FDA, US Food and Drug Administration.

Deer TR, et al. *Neuromodulation*. 2012;15(4):420-435; Deer TR, et al. *Pain Physician*. 2010;13(3):E175-E213; Deer TR, Pope JE. *Expert Rev Clin Pharmacol*. 2015;8(5)507-510; Prager J, et al. *Neuromodulation*. 2014;17(4):354-372.

Patient Selection: PACC Recommendations

Statement	Evidence Level	Recommendation Grade	Consensus level
Localized pain can be adequately covered with intrathecal therapy	II	B	Strong
Diffuse pain can be adequately treated with intrathecal therapy	III	C	Moderate
Global pain can be adequately treated with intrathecal therapy	III	D	Moderate
Intrathecal therapy should not be used as salvage therapy for failing systemic opioids[a]	II	B	Moderate

[a]Sustained success more likely when patients are weaned off opioids before trialing; different titration schedules have been recommended.
Deer TR, et al. *Neuromodulation*. 2017;20(2):96-132.

Patient Selection:
Important Patient Characteristics

- Well-managed comorbidities
  - Intrathecal opioids require increased vigilance for patients with comorbidities that negatively affect cardiopulmonary function
- Sufficiently fit for surgery
- Autonomous with a good understanding of intrathecal therapy and other treatment options
  - Can be addressed with strong social structure
- Appropriate psychological status
- Ability to comply with requirements of care, including office visits for refills

Deer TR, Pope JE. *Expert Rev Clin Pharmacol*. 2015;8(5)507-510; Deer TR, et al. *Neuromodulation*. 2017;20(2):96-132; Prager J, et al. *Neuromodulation*. 2014;17(4):354-372.

Patient Selection:
Potential Complicating Issues in Intrathecal Therapy

- Consider comorbidities that increase risks (no absolute contraindications)
  - Sleep apnea
  - Obesity or metabolic syndrome
  - Diabetes
    - Poor wound healing and increased surgical-site infections
  - Coagulopathies and anticoagulant therapy
  - Chronic lung disease
  - Reduced cardiac function
  - Immunocompromised status
  - Substance abuse issues

Deer TR, et al. *Neuromodulation*. 2017;20(2):96-132; Deer TR, et al. *Pain Physician*. 2010;13(3):E175-E213; Prager J, et al. *Neuromodulation*. 2014;17(4):354-372.

Drug Selection:
Intrathecal Options for Pain Management

Drug	Recommended Starting Dosage	Maximum Concentration	Maximum Dose/Day
Morphine	0.1–0.5 mg/day	20 mg/mL	15 mg
Hydromorphone	0.01–0.15 mg/day	15 mg/mL	10 mg
Ziconotide	0.5–2.4 µg/day	100 µg/mL	19.2 µg
Fentanyl	25–75 µg/day	10 mg/mL	1000 µg
Bupivacaine	0.01–4 mg/day	30 mg/mL	15–20 mg[a]
Clonidine	20–100 µg/day	1000 µg/mL	600 µg
Sufentanil	10–20 µg/day	5 mg/mL	500 µg

[a]May be exceeded in end-of-life care and complicated cases as determined by medical necessity.

Deer TR, et al. *Neuromodulation*. 2017;20(2):96-132.

Intrathecal Drug Selection: 2016 Guideline Recommendations For Nociceptive/Neuropathic Noncancer Pain

Line	Recommended Regimens	
1A	• Ziconotide	• Morphine
1B	• Fentanyl	• Fentanyl + Bupivacaine
2	• Fentanyl + Clonidine • Hydromorphone or Morphine + Bupivacaine	• Fentanyl + Bupivacaine + Clonidine • Bupivacaine
3	• Fentanyl + Ziconotide + Clonidine • Morphine or Hydromorphone + Clonidine • Ziconotide + Clonidine or Bupivacaine or Both • Bupivacaine + Clonidine	
4	• Sufentanil + Bupivacaine or Clonidine • Baclofen • Bupivacaine + Clonidine + Ziconotide	
5	• Sufentanil + Bupivacaine + Clonidine • Sufentanil + Ziconotide	

Line	Recommended Regimens	
1A	• Morphine	• Ziconotide
1B	• Hydromorphone	• Morphine or Hydromorphone + Bupivacaine
2	• Hydromorphone or Morphine + Clonidine	• Fentanyl + Bupivacaine • Ziconotide + Morphine or Hydromorphone
3	• Hydromorphone or Morphine + Bupivacaine + Clonidine • Fentanyl + Ziconotide	• Sufentanil + Bupivacaine or Clonidine • Ziconotide + Clonidine or Bupivacaine or Both
4	• Fentanyl or Sufentanil + Bupivacaine + Clonidine	• Sufentanil + Ziconotide • Baclofen
5	• Opioid + Ziconotide + Bupivacaine or Clonidine	

Deer TR, et al. *Neuromodulation*. 2017;20(2):96-132.

Intrathecal Drug Selection
2016 Guideline Recommendations for
Nociceptive/Neuropathic Cancer-Related Pain

Localized Pain

Line	Recommended Regimens	
1A	• Ziconotide	• Morphine
1B	• Fentanyl • Morphine or Fentanyl + Bupivacaine	
2	• Hydromorphone • Hydromorphone or Fentanyl or Morphine + Clonidine	• Hydromorphone + Bupivacaine • Morphine or Hydromorphone or Fentanyl + Ziconotide
3	• Hydromorphone or Morphine or Fentanyl + Bupivacaine + Clonidine • Ziconotide + Bupivacaine • Ziconotide + Clonidine	• Hydromorphone or Morphine or Fentanyl + Bupivacaine + Ziconotide • Sufentanil
4	• Sufentanil + Ziconotide • Sufentanil + Bupivacaine • Baclofen • Sufentanil + Clonidine	• Bupivacaine + Clonidine + Ziconotide • Bupivacaine + Clonidine
5	• Sufentanil + Bupivacaine + Clonidine	
6	• Opioid + Bupivacaine + Clonidine + Adjuvants	

Diffuse Pain

Line	Recommended Regimens	
1A	• Ziconotide	• Morphine
1B	• Hydromorphone • Morphine or Hydromorphone + Bupivacaine	
2	• Hydromorphone or Morphine + Clonidine • Morphine or Hydromorphone + Ziconotide	
3	• Hydromorphone or Morphine or Fentanyl + Bupivacaine + Clonidine • Ziconotide + Bupivacaine • Ziconotide + Clonidine	• Hydromorphone or Morphine or Fentanyl + Bupivacaine + Ziconotide • Sufentanil
4	• Sufentanil + Ziconotide • Baclofen • Sufentanil + Bupivacaine • Sufentanil + Clonidine	• Bupivacaine + Clonidine + Ziconotide • Bupivacaine + Clonidine
5	• Sufentanil + Bupivacaine + Clonidine • Sufentanil + Bupivacaine + Ziconotide • Sufentanil + Clonidine + Ziconotide	
6	• Opioid + Bupivacaine + Clonidine + Adjuvants	

Deer TR, et al. *Neuromodulation*. 2017;20(2):96-132.

FDA-APPROVED INTRATHECAL ANALGESICS

Morphine

- μ-Opioid receptor agonist
- Most serious AE is respiratory depression
  - Risk increased with other agents that depress the CNS (eg, benzodiazepines)

Ziconotide

- N-type Ca^{2+} channel blocker
- Most serious AEs are neurocognitive
  - eg, confusion, dizziness, hallucinations
  - Urinary retention also can lead to treatment discontinuation

AE, adverse event; CNS, central nervous system.

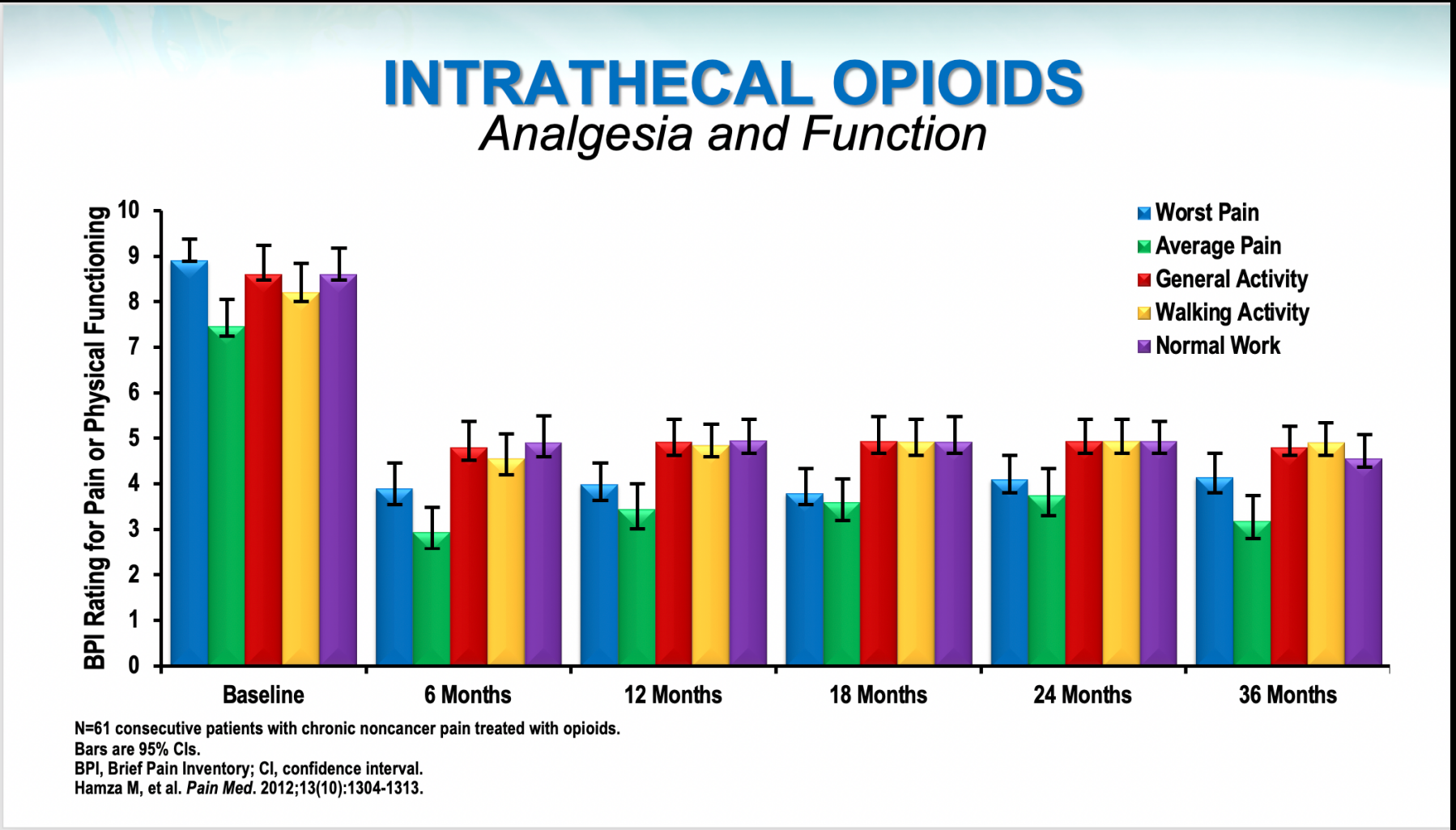
Coffey RJ, et al. *Anesthesiology*. 2009;111(4):881-891; Deer TR, et al. *Neuromodulation*. 2012;15(5):436-466; Prager JT, et al. *Neuromodulation*. 2014;17(4):354-372;
Webster LR, et al. *J Pain Symptom Manage*. 2009;37(3):363-372.

INTRATHECAL MORPHINE
Overview

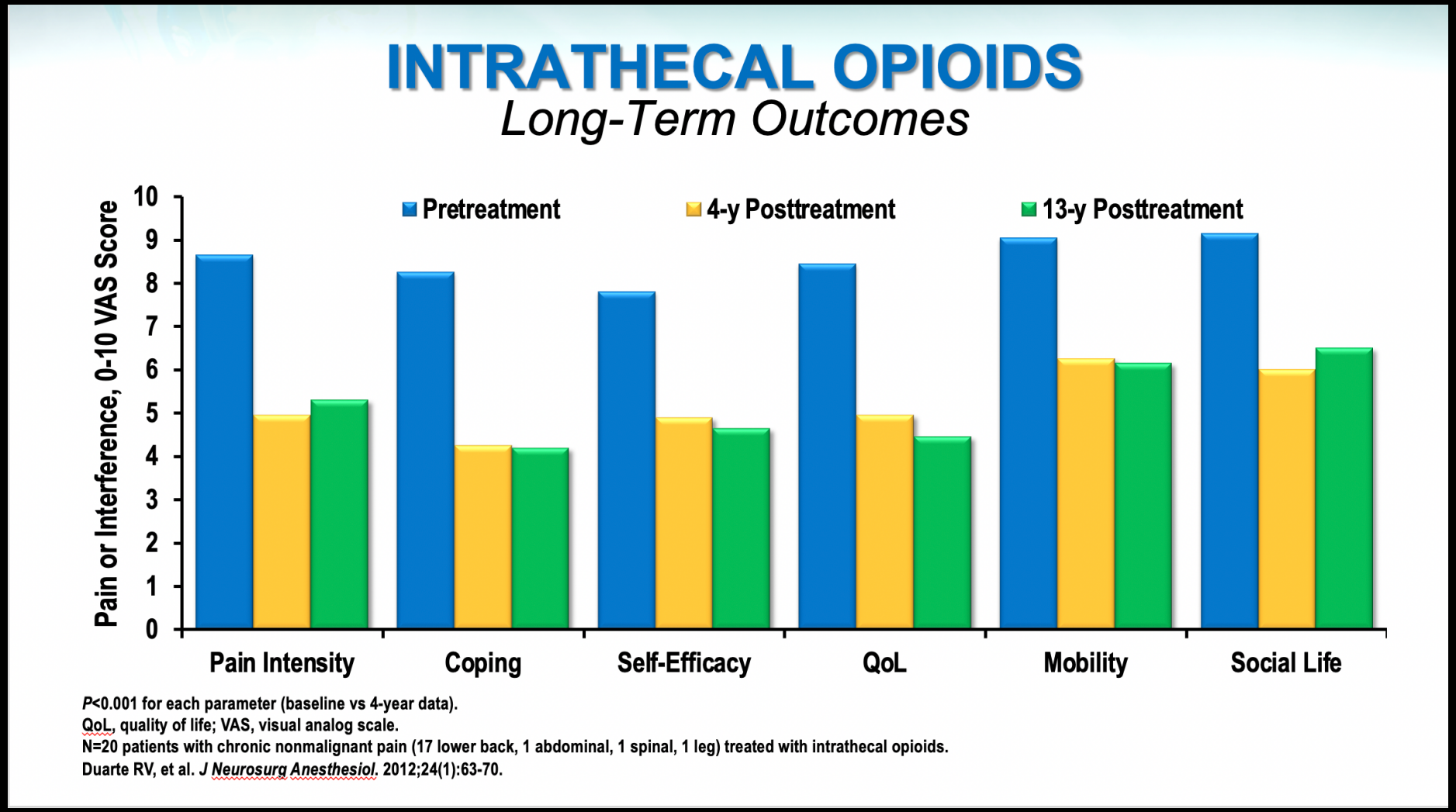
- Recommended starting dose
  - 0.1 to 0.5 mg/day
- Recommended maximum dose
  - 15 mg/day (concentration, 20 mg/mL)
- Monitoring for granuloma formation is essential
- Consider endocrine evaluation before initiation and periodically during therapy
  - Treatment-related hypogonadism may reduce libido, mood, and bone density (with increased fracture risk)
  - Consider estrogen/testosterone replacement, if needed
- AEs may include respiratory depression, fluid retention, urinary retention, sedation, pruritus, and endocrine and immunologic issues

Deer TR, et al. *Neuromodulation*. 2017;20(2):96-132; Prager JT, et al. *Neuromodulation*. 2014;17(4):354-372; Webster LR, et al. *J Pain Symptom Manage*. 2009;37(3):363-372.

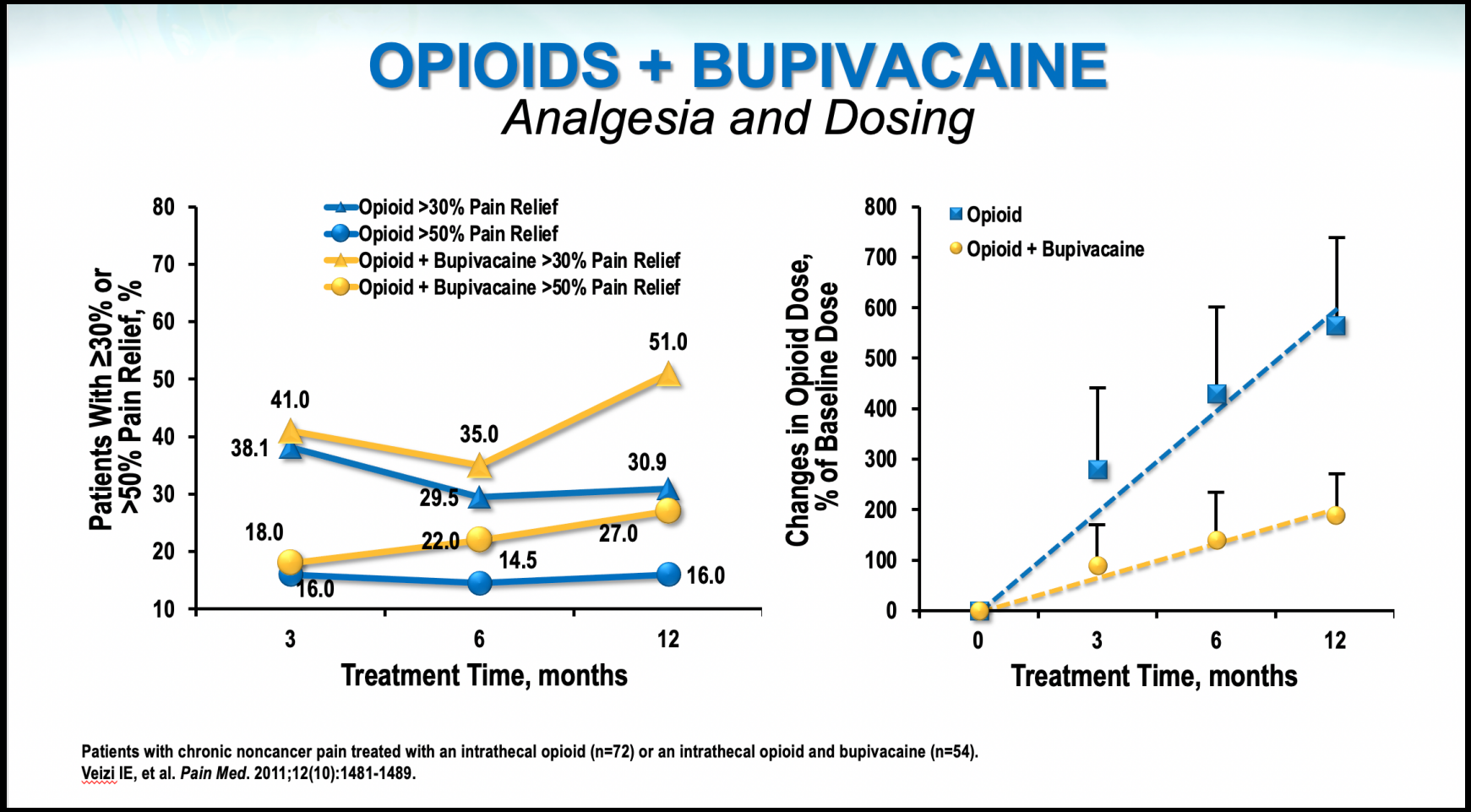
Intrathecal Opioids
Analgesia and Function



Intrathecal Opioids
Long-Term Outcomes



Opioids + Bupivacane
Analgesia and Dosing



Patients with chronic noncancer pain treated with an intrathecal opioid (n=72) or an intrathecal opioid and bupivacaine (n=54).
Veizi IE, et al. *Pain Med.* 2011;12(10):1481-1489.

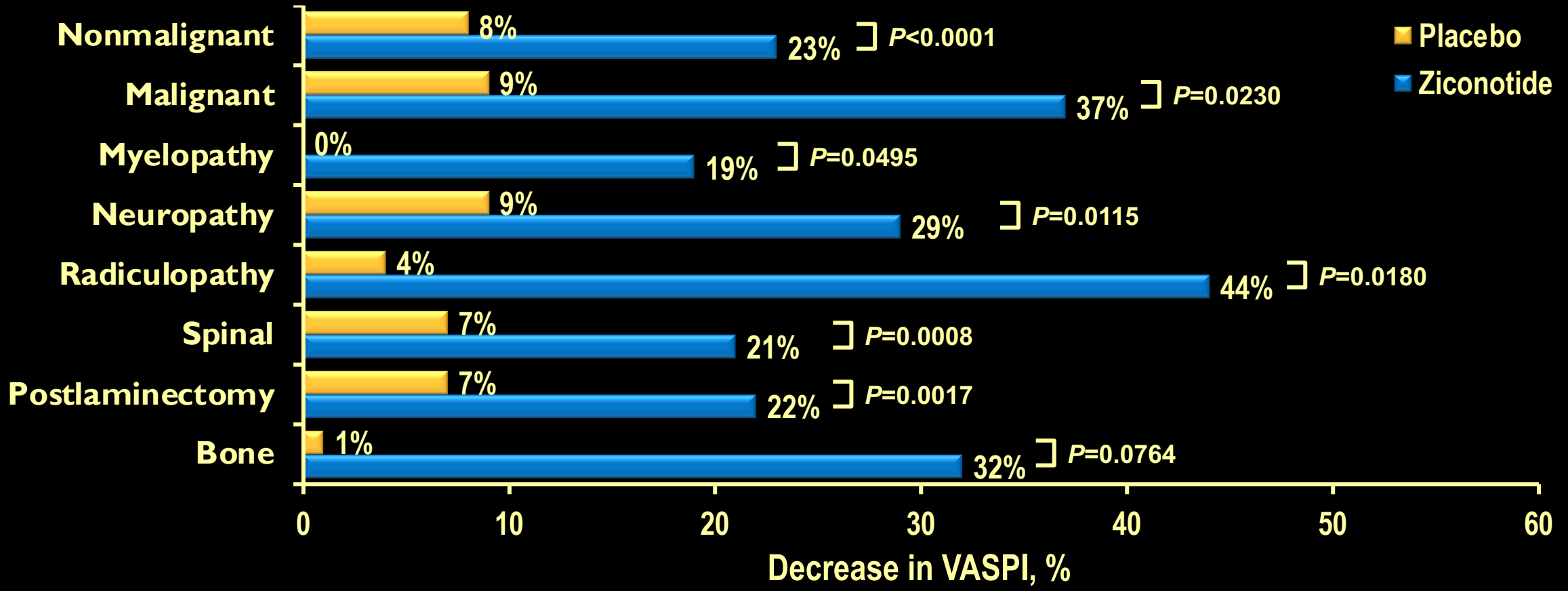
Intrathecal Ziconotide

- For use in the SynchroMed II Infusion System and CADD-Micro Ambulatory Infusion Pumps
- Recommended starting dose: 0.5 to 2.4 µg/day
- Recommended maximum dose: 19.2 µg/day
- AEs include sedation, somnolence, nausea, headache, and lightheadedness
- Not associated with granuloma formation or overdose
- New PACC recommendations: unless contraindicated, intrathecal ziconotide should be considered as an alternative to opioids, and in certain circumstances, should be considered first-line therapy

Deer TR, et al. *Neuromodulation*. 2017;20(2):96-132; Deer TR, et al. *Neuromodulation*. 2017;20(2):133-154; Dupoiron D, et al. *Pain Physician*. 2012;15(5):395-403; Prager J, et al. *Neuromodulation*. 2014;17(4):354-372; Webster LR, et al. *J Pain Symptom Manage*. 2009;37(3):363-372.

INTRATHECAL ZICONOTIDE

Evidence of Efficacy

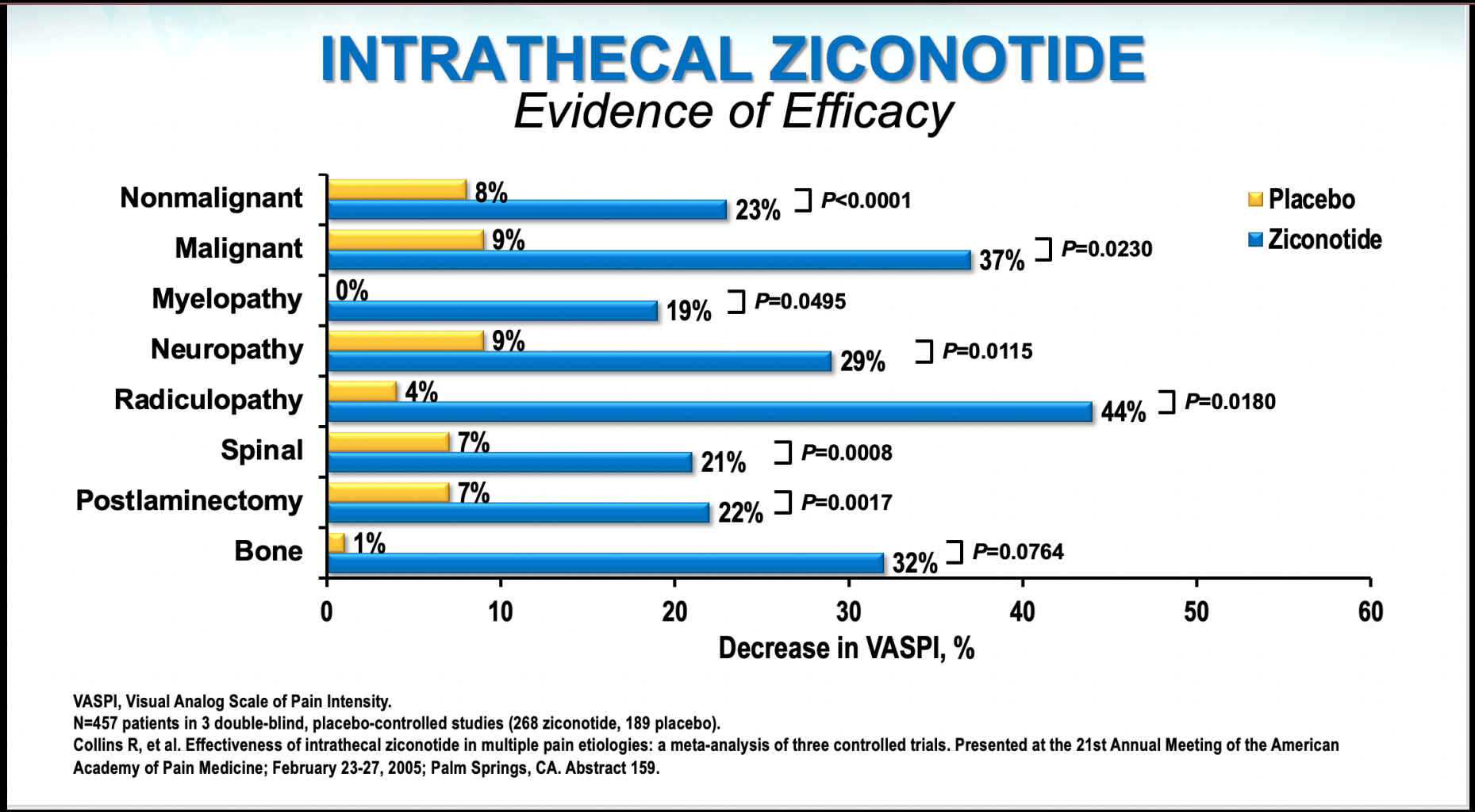


VASPI, Visual Analog Scale of Pain Intensity.

N=457 patients in 3 double-blind, placebo-controlled studies (268 ziconotide, 189 placebo).

Collins R, et al. Effectiveness of intrathecal ziconotide in multiple pain etiologies: a meta-analysis of three controlled trials. Presented at the 21st Annual Meeting of the American Academy of Pain Medicine; February 23-27, 2005; Palm Springs, CA. Abstract 159.

Intrathecal Ziconotide
Evidence of Efficacy



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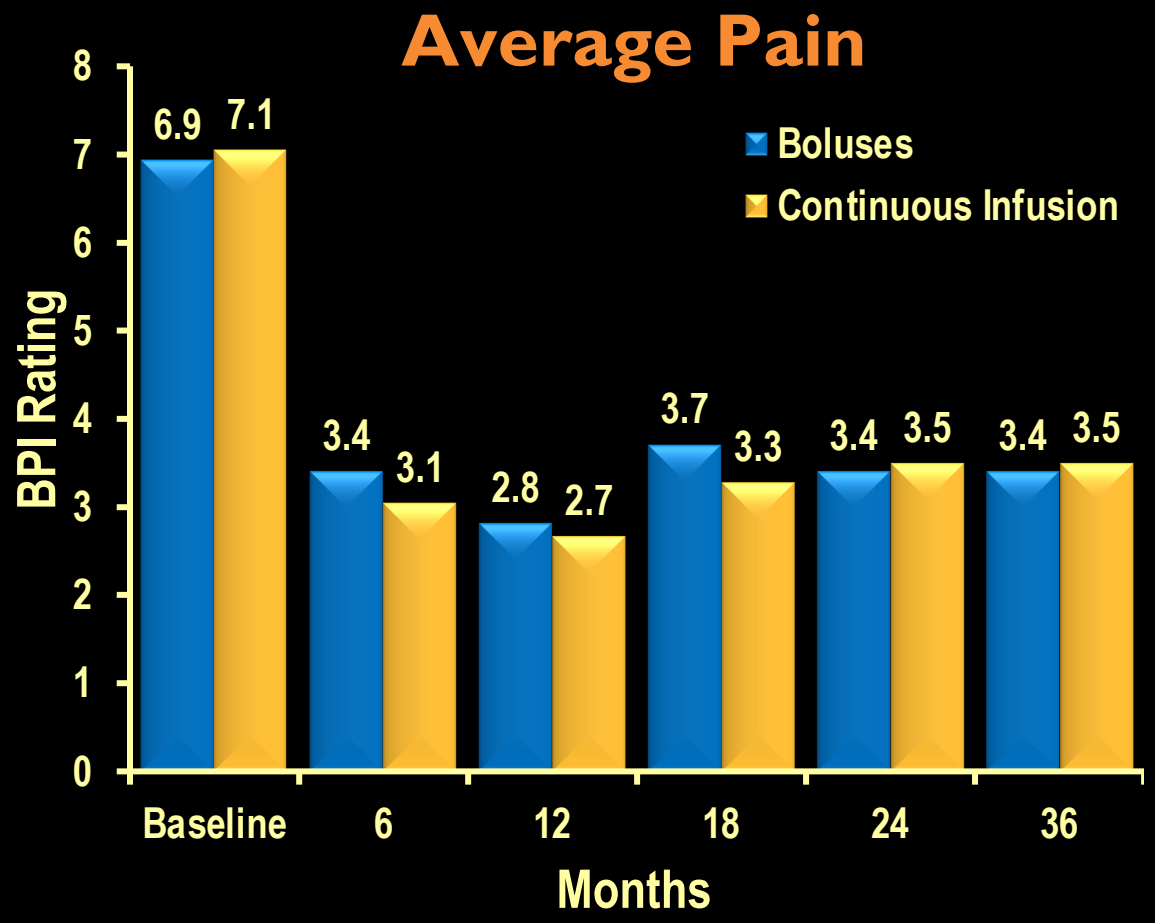
Intrathecal Trials
Overview

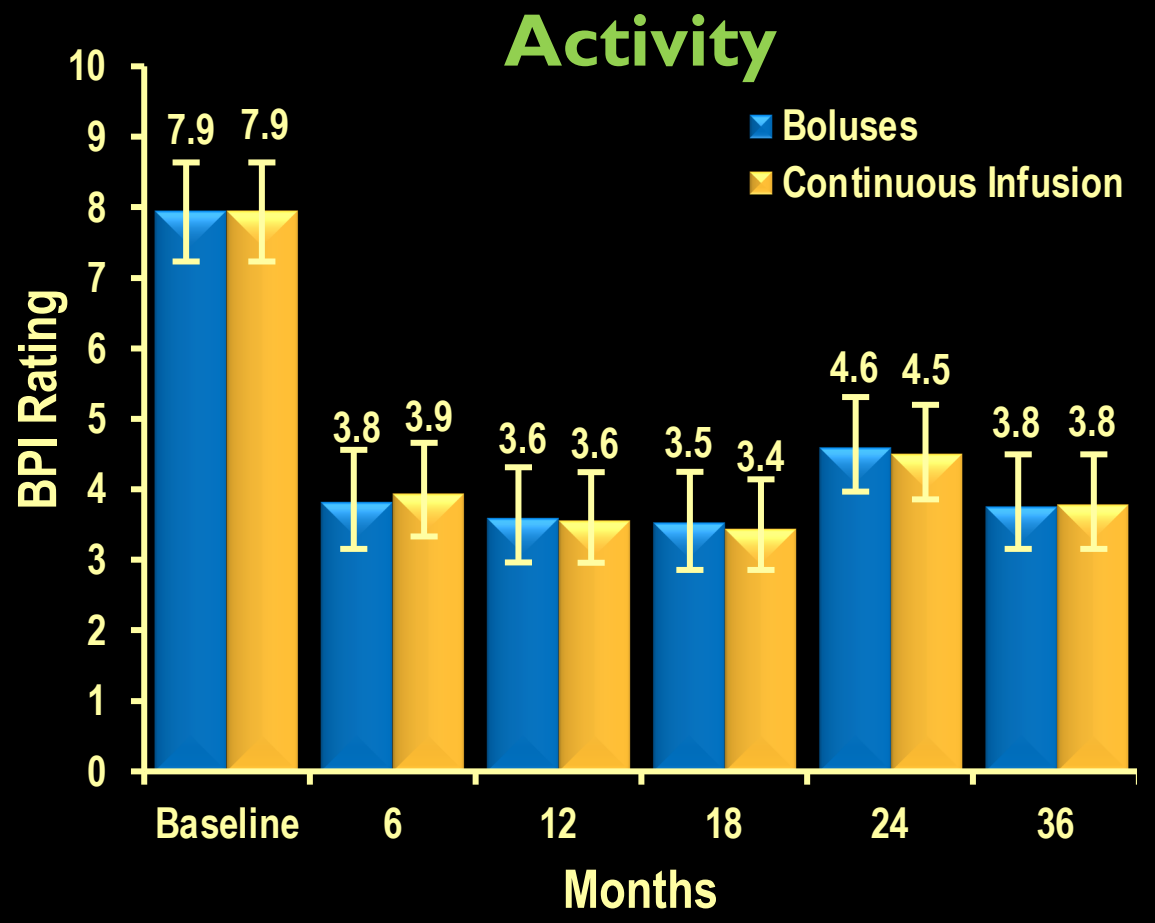
- Purpose of intrathecal trials
  - Evaluate potential pain relief
  - Gauge patient's level of commitment to treatment
- Specific methods vary
  - Single injection
  - Continuous infusion
  - Intermittent boluses
- No evidence that trial results predict outcomes
  - No particular trialing method has been associated with better prediction of long-term benefits
- Trialing doses should be conservative

Deer TR, et al. *Pain Physician*. 2010;13(3):E175-E213; Deer TR, et al. *Neuromodulation*. 2017;20(2):133-154; Prager J, et al. *Neuromodulation*. 2014;17(4):354-372.

INTRATHECAL TRIALS

Intermittent Boluses vs Continuous Infusion

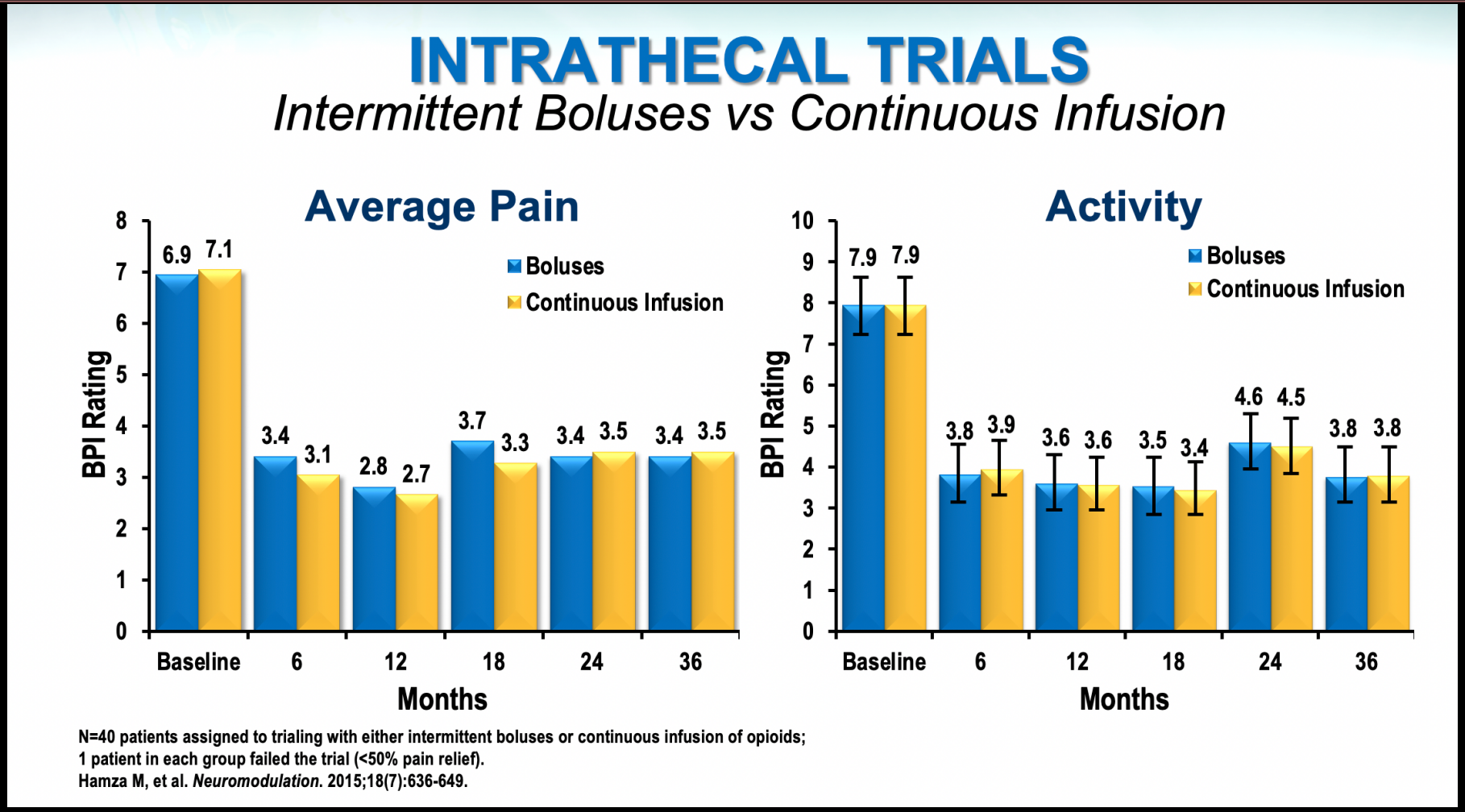




N=40 patients assigned to trialing with either intermittent boluses or continuous infusion of opioids; 1 patient in each group failed the trial (<50% pain relief).

Hamza M, et al. *Neuromodulation*. 2015;18(7):636-649.

Intrathecal Trials
Intermittent Boluses vs Continuous Infusion



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Intrathecal Therapy
Potential Complications

- Pump failure
- Hemorrhage leading to spinal hematoma
- Wound infection
- CSF leakage
- Catheter-related complications
  - Dislodgement or migration from intrathecal space
  - Fracture or breakage
  - Kink or occlusion
  - Puncture or cut
- Granulomas
  - Inflammatory masses at the catheter tip

Chou T, et al. *Pain Physician*. 2013;16(2):E107-E111; Deer TR, et al. *Neuromodulation*. 2017;20(2):96-132.

SCS Complications

- Hardware complication- most common with SCS. Less with paddle leads, and also less of an issue with new technology. With new leads/programming, revision rates for this complication dropped to 4% from 15%
- Pain at surgical site
- Lead migration
- Thoracic radiculopathy- 2% ? Pre-op MRI
- Infection
- Serious neurologic sequelae (ie hematoma)- very rare

Conclusions

- Multiple approaches to neuromodulation are currently available and in use
- Identifying best approach for indivual patients remains challenging
- Steps can be taken to optimize patient selection

Thank You!