Intrathecal Drug Delivery for Non-Cancer Pain

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Outline

- Patient Selection
- Polyanalgesic Consensus Conference (PACC) Guidelines 2016
- Trialing
- Evidence Non-Cancer Pain
- Drugs and Dosing
- Complications

PACC Guidelines

- PACC Guidelines IDD: Best Practices (2016)
- PACC Guidelines IDD: Trialing (2016)
- PACC Guidelines IDD: Safety & Risk Mitigation (2016)

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

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Selection Criteria: TDD Non-Cancer Pain

- Objective evidence of pain pathology
- Psychological clearance
- Inadequate pain relief and/or intolerable side effects from systemic agents and more conservative therapy
- Favorable response to screening trial?

TDD for Non-Cancer Pain

Table 5. Recommendations for Application of Intrathecal Therapy vs. Neurostimulation by the NACC Using USPSTF Criteria.

Statement	Evidence level	Recommendation grade	Consensus level
Intrathecal therapy should be considered within the same line as neurostimulation strategies to treat noncancer-related pain.	III	C	Moderate
Intrathecal therapy should be considered after neurostimulation strategies to treat noncancer-related pain if the pain is isolated and unlikely to spread.	III	I	Strong
Intrathecal therapy should be considered before neurostimulation therapy for active cancer-related pain that is mechanical and likely to spread.	III	C	Strong

- Indications
  - Axial Spine Pathology – not surgical candidate
  - Failed Back Surgery Syndrome

- Indications
  - Abdominal/Pelvic Pain (somatic/visceral)
  - Complex Regional Pain Syndrome
  - Trunk Pain
    - PHN, Post-Thoracotomy

Psychologic Screening

- Screening ≠ Clearance
- Evidence for TDD extrapolated from SCS
- Poorer outcomes associated with emotional dysfunction, somatic complaints, interpersonal problems
- Patients with a psychological profile deemed appropriate for implantable therapy have better outcomes than those deemed inappropriate (Kupers et al, 1994)
- Recommended by PACC Guidelines

Psychologic Evaluation

Psychological Indications to Proceed

- Reasonable expectations
- Understanding of the procedure
- Good social support
- Effective coping skills

Relative Psychological Contraindications

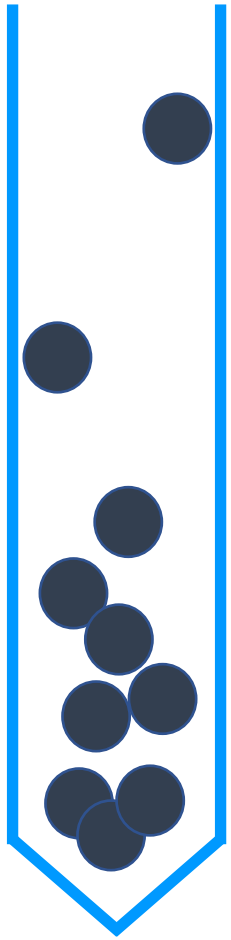
- Active psychosis
- Active suicidality/homicidality
- Uncontrolled depression/mood disorder
- Somatoform disorders
- Active substance use disorder
- Neurobehavioral or cognitive deficits

Nelson, D.V., et al., *Psychological selection criteria for implantable spinal cord stimulators*. Pain Forum, 1996. 5: p. 93-103.
Deer et al. Consensus Guidelines for the Selection and Implantation of Patients With Noncancer Pain for Intrathecal Drug Delivery. Pain Physician 2010; 13:E175-E213

Screening Trial

PACC Guidelines Recommend a Trial

- Insurance may require
- Limited evidence trialing predicts outcome



Single Injection

- Advantages
  - Low cost
  - Minimal time commitment
- Disadvantages
  - Higher placebo response?
  - Does not mimic long-term continuous infusion

Continuous Infusion

- Advantages
  - Mimics long-term infusion
- Disadvantages
  - Higher cost
  - Time/labor intensive
  - Infection risk with externalized catheters

Screening Trial: Technique

"the extracranial CSF behaves not as a river, but as a backwater bayou with multiple tributaries"
- Bert, Hayek, Yaksh

Pharmacokinetics

- Kinetics of the drug are dependent upon drug volume **and** rate infused
  - Implanted pump infusion rates range: 0.1ml - 1.5 ml/day
  - Common external infusion pumps lower limit: 0.1 ml/hour = 2.4 ml/day
- Low volume/rate delivery = target tissue effects nearest catheter/needle location
- Rapid bolus injection = greater spread
- Drug spread and diffusion into the spinal cord and out of the CSF will vary with physiochemical properties such as polarity and lipophilicity

Bert RJ, Hayek SM, Yaksh TY. Anesthesia & Analgesia. 2017; 124(5): 1403-1406

Pre-Trial Systemic Opioids

- Weaning/eliminating systemic opioids before trial
  - Recommended PACC Guidelines
  - Elimination – lower tolerance, lowered TDD starting doses, minimized dose escalation
- Retrospective Insurance Claims Study: Post-Implant
  - 43% of those on systemic opioids pre-implant are off 1 yr post-implant
  - 75% of those who don't come off had reduction in systemic opioid dose

Wilkes DM, Orillosa SJ, Hustak EC, et al. Efficacy, safety, and feasibility of the morphine microdose method in community-based clinics. Pain Med 2018;19:1782-1789.

Hatheway JA, Bansal M, Nichols-Ricker CI. Systemic opioid reduction and discontinuation following implantation of intrathecal drug-delivery systems for chronic pain: A retrospective cohort analysis. Neuromodulation 2020. 23:961-969

PACC Guidelines: IT Trial Single Bolus Doses

Drug	Trial Bolus Dose
Morphine*	0.1 - 0.5 mg#
Hydromorphone	0.025 - 0.1 mg#
Fentanyl	15 - 75 mcg#
Sufentanil	5 - 20 mcg
Ziconotide*	1 - 5 mcg
Bupivacaine	0.5 – 2.5 mg
Clonidine	5 - 20 mcg

*FDA Approved for TDD

#Dose in opioid naïve patient for outpatient bolus not to exceed 0.15 mg morphine, 0.04 mg hydromorphone, or 25 mcg fentanyl

TDD Studies Non-Cancer Pain

Study/Year	Number of Subjects	Type/Duration	Details	Efficacy
Winkelmuller et al. 1996	120	Retrospective; 6 mo to 5.7 yrs follow up	Mixed neuropathic/nociceptive pain; morphine, bupivacaine, hydromorphone	74% reported improved pain, with avg or 58% reduction
Anderson et al. 1999	30	Retrospective	PLPS; rotation from morphine to hydromorphone	37% improved pain control; decreased adverse effects
Kumar et al. 2001	25 trialed 16 implanted	Prospective, single-center, non-randomized	Non-malignant pain; morphine; follow up 13–49 months	avg reduction 57.5% at final follow up
Rainov et al. 2001	30 trialed, 26 implanted	Prospective, single-center, non-randomized	PLPS; polydrug infusion of morphine + clonidine, bupiv, or midaz; mean follow up 27 months	Average pain reduced 8/10 to 3/10, remained 3–5/10 to follow up
Deer et al. 2004	166 trialed; 136 implanted	Prospective, non-randomized, multi-center registry	Mechanical, neuropathic, mixed low back/leg pain. follow up 12 months	48% reduction in the low back; 32% for leg pain at 12 months
Rauck et al. 2006	220	Randomized, double-blind, placebo controlled	Ziconotide slow titration over three weeks; 112 ziconotide, 108 placebo	Statistical significance for ziconotide over three weeks; higher adverse effects

PACC: Drug Choices Non-Cancer Pain

Table 16. Noncancer-Related Pain With Localized Nociceptive or Neuropathic Pain.

Line 1A	Ziconotide		Morphine	
Line 1B	Fentanyl		Fentanyl + bupivacaine	
Line 2	Fentanyl + clonidine	Hydromorphone or morphine + bupivacaine	Fentanyl + bupivacaine + clonidine	Bupivacaine
Line 3	Fentanyl + ziconotide + bupivacaine	Morphine or hydromorphone + clonidine	Ziconotide + clonidine or bupivacaine or both	Bupivacaine + clonidine
Line 4	Sufentanil + bupivacaine or clonidine	Baclofen	Bupivacaine + clonidine + ziconotide	
Line 5	Sufentanil + bupivacaine + clonidine		Sufentanil + ziconotide	

Table 18. Noncancer-Related Pain With Diffuse Nociceptive or Neuropathic Pain.

Line 1A	Morphine		Ziconotide*	
Line 1B	Hydromorphone		Morphine or hydromorphone + bupivacaine	
Line 3	Hydromorphone or morphine + clonidine		Fentanyl + bupivacaine	Ziconotide + morphine or hydromorphone
Line 4	Hydromorphone or morphine + bupivacaine + clonidine	Fentanyl + ziconotide	Sufentanil + bupivacaine or clonidine	Ziconotide + clonidine or bupivacaine or both
Line 5	Fentanyl or sufentanil + bupivacaine + clonidine		Sufentanil + ziconotide	Baclofen
Line 6	Opioid + ziconotide + bupivacaine or clonidine			

*Ziconotide should be first choice in patients with >120 morphine equivalents or fast systemic dose escalation, in the absence of history of psychosis.

Starting Infusion Doses

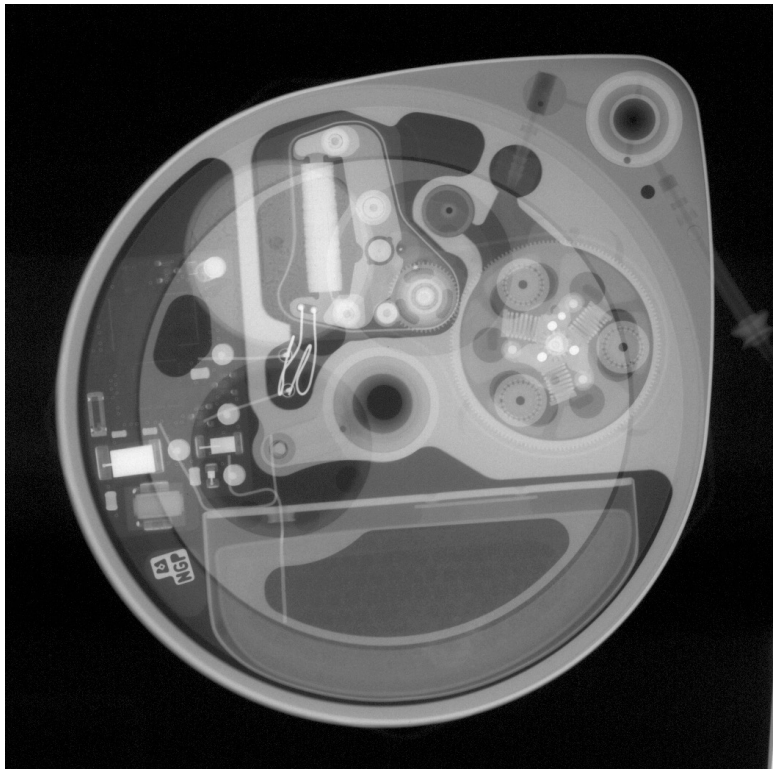
DRUG	Starting Dose/24 hrs
Morphine	0.1 - 0.5 mg/day
Hydromorphone	0.01 - 0.15 mg/day
Fentanyl	25 - 75 mcg/day
Sufentanil	10 - 20 mcg/day
Ziconotide	0.5 - 1.2 mcg/day
Bupivacaine	0.01 - 4 mg/day
Clonidine	20 - 100 mcg/day

- Starting dose for opioids should be no more than half the trial dose
- Ziconotide recommended as 1st drug in pump for non-cancer pain

PACC: Max Concentrations/Doses

DRUG	Max Concentration	Max Dose/24 hours
Morphine	20 mg/ml	15 mg
Hydromorphone	15 mg/ml	10 mg
Fentanyl	10 mg/ml	1000 mcg
Sufentanil	5 mg/ml	500 mcg
Bupivacaine	30 mg/ml	15-20 mg
Clonidine	1000 mcg/ml	600 mcg
Ziconotide	100 mcg/ml	19.2 mcg

Adverse Events



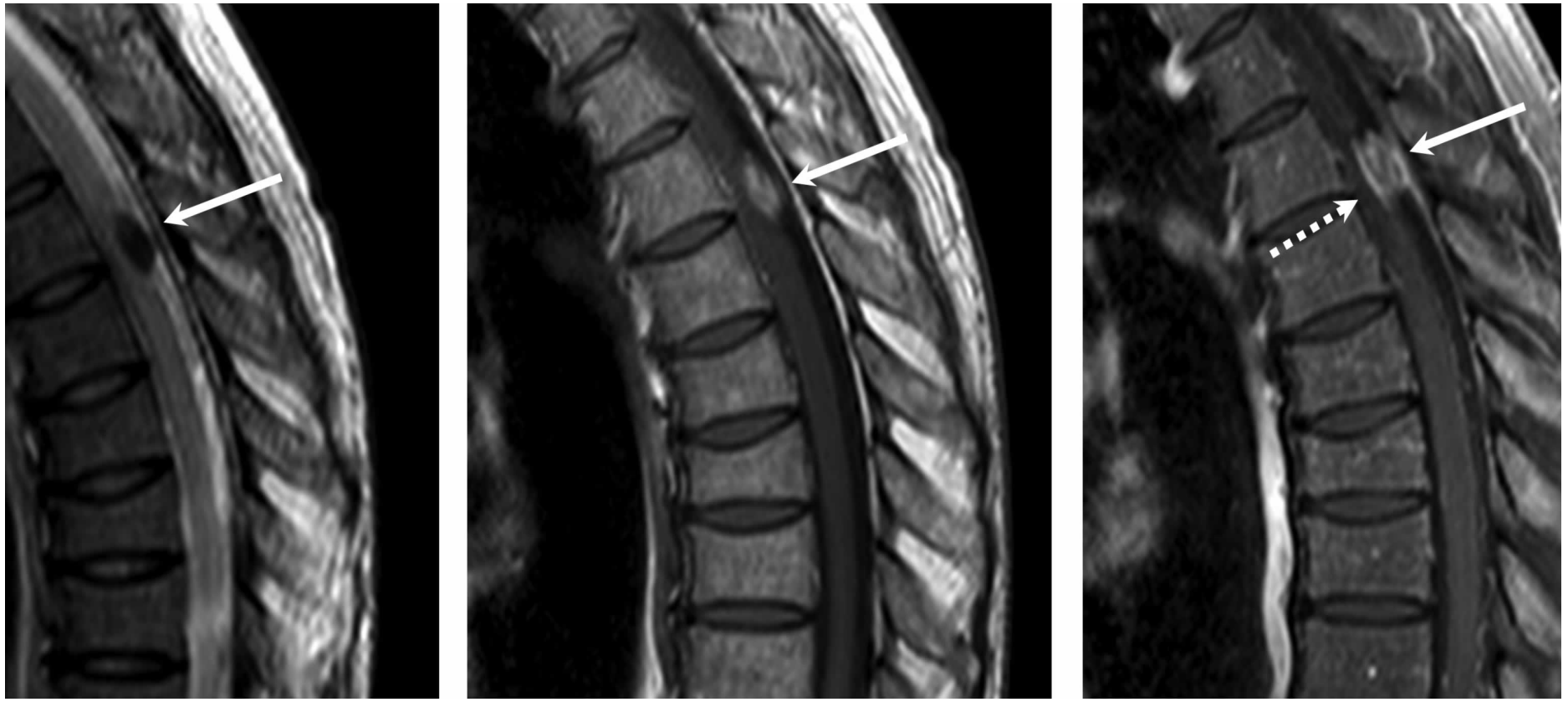
- Implant Related
  - Infection
  - Hematoma
- Device Related
  - Catheter leak, tear, kink, or dislodgement
  - Pump failure
    - **Compounded and off-label drugs (Medtronic)**
  - **Catheter Tip Granuloma**
- Refill Related – Overdose/Underdose
  - Pocket fill
  - Drug error
  - Programming error

Catheter Tip Granulomas

- Inflammatory mass
  - Lymphocytes, macrophages, plasma cells
  - Hyper-vascular fibrotic tissue
  - Inner necrotic core

- Incidence <3%
  - Likely under reported
  - Many may be present but asymptomatic
  - Onset 5 weeks – 12 years
- Association
  - Morphine, hydromorphone
  - Higher concentrations
- Baclofen
  - 2 reported cases

Catheter Tip Granuloma Diagnosis



Signs & Sx

- New neurologic findings (mass effect)
- Worsening pain/spasticity

Evaluation

- CT myelogram
- MRI with thin slices at catheter tip with/without contrast

Deer T et al. Polyanalgesic Consensus Conference—2012: Consensus on Diagnosis, Detection, and Treatment of Catheter-Tip Granulomas. Neuromodulation (2012)
Varghese T et al. Advances in Bioscience and Biotechnology; Vol. 04 No. 01 (2013)

Granuloma Treatment

- Depends on severity of symptoms
  - Stop opioid infusion
  - Switch to lipophilic opioid
  - Switch to non-opioid
  - Remove or move catheter
  - Surgical decompression or resection

Conclusion

- Patient Selection
  - Clear pain etiology
  - Psychological evaluation
- Trialing
  - Recommended/Insurance Req
  - Consider pre-trial wean
- Drugs
  - On-label 1st Line
    - Ziconotide
    - Morphine
- Granuloma Formation
  - Associated with
    - High concentrations
    - Morphine & hydromorphone