Non-CME Webinar Series
designed with the trainee in mind
first Tuesday of the month

ASRA PAIN MEDICINE
THE ASSOCIATION OF PAIN PROGRAM DIRECTORS
ADVANCING EDUCATION IN MULTIDISCIPLINARY PAIN MEDICINE

Intrathecal Pump for Cancer Pain: Implant Considerations

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DISCLOSURE

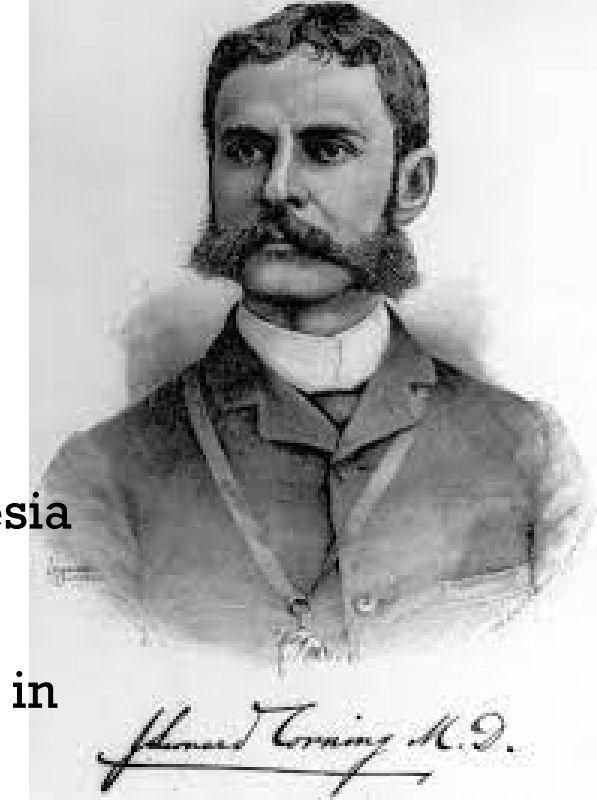
- Salary support as a KL2 scholar from 2018 to 2020 (mentored career development award) at Georgia Clinical and Translational Science Alliance, supported in part by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award number UL1TR002378 and KL2TR002381
- Scientific Advisory Board, Releviate LLC – 2020 to 2021

OBJECTIVES

- Intrathecal drug delivery for cancer pain indications
- Implant considerations
  - Types of pumps available
  - Trial vs no trial
  - Factors to consider for tip catheter placement
  - Intrathecal meds

Good morning I was in the bathroom and didn't hear my phone. I know I have to work on this. I would like to share with you guys that Dr.Singh put the perfect numbers in my pain pump and saved my life. I feel like I woke up from a deep sleep and I'm so alert and so ready to live and battle this with every force I have left in me. So thank you so much Dr.Singh you don't understand how much clearer I can think and how aware I am of everything around me. Last week I recieved my treatment and bone infusion. However I am suffering very bad nausea, vomiting and loose stools and still unable to keep food or interested in food. Is their anyway I can get prescription for nausea and nutrition shakes? I'm holding on to my phone so your welcome to call me again. God bless and thank you all.

INTRATHECAL DELIVERY: ORIGIN



- 1885- James Leonard Corning administered intrathecal cocaine spinal anesthesia
- 1971- Opioid receptor discovery
- 1976- Yaksh and Rudy- animal studies demonstrating intrathecal opioids result in selective analgesia with fewer side effects
- 1977- Wang, Nauss, and Thomas- First human study demonstrating pain relief with intrathecal morphine
- 1990s- Reports of intrathecal baclofen use
- 2000s- Ziconatide-

Rizvi *Neuromodulation* 2015
neuromodulation.com-brief history of neuromodulation

INTRATHECAL PUMP: ORIGIN

- 1935- Grafton Love- idea of continuous catheter access
- 1940- William Leonard- clinical continuous spinal anesthesia with procaine (n=200)
  - Control syringe attached to a malleable needle
- 1944- Edward Tuohy- 15 gauge directional spinal needle- nylon ureteric catheter intrathecal facilitating fractional administration of spinal anesthetics
- 1969- First totally implantable drug administration system developed at Univ of Minnesota
- 1982- First human clinical implant of an intrathecal programmable pump
- 1988- Medtronic Inc. received FDA approval for the first battery-powered and programmable pump for cancer-related pain
  - 1991 for chronic pain

Rizvi *Neuromodulation* 2015
neuromodulation.com-brief history of neuromodulation

WHY INTRATHECAL PUMP/"TARGETED DRUG DELIVERY"?

Systemic Analgesia

- Distributes drug via blood stream
- High serum levels of drug
- Brain receives high proportion of drug
  - Sedation, mental fog
- High dose of drug required
- Increase in systemic side effects

Spinal Analgesia

- Intrathecal drug distribution
- Low serum levels of drug
- Most drug binds to **TARGET** (spinal cord pain receptors)
- Low dose of drug is effective
- Reduced systemic effect on brain and gut

NCCN GUIDELINES: REGIONAL (NEURAXIAL) INFUSIONS

- **Epidural**:
  - easy to place, requires large volumes and externalized catheter;
  - for infusions of opioids, local anesthetics, and clonidine;
  - use beyond several days to a few weeks is limited by concerns for catheter displacement and infection
- **Intrathecal**:
  - easy to internalize to implanted pump;
  - for infusions of opioids, local anesthetics, clonidine, and ziconatide;
  - implanted infusion pumps may be costly;
  - refills require technical expertise

ANESTHESIOLOGY
The Journal of the American Society of Anesthesiologists, Inc.

From: Molecular Mechanisms of Opioid Receptor-dependent Signaling and Behavior

Anesthes. 2011;115(6):1363-1381. doi:10.1097/ALN.0b013e318238bba6

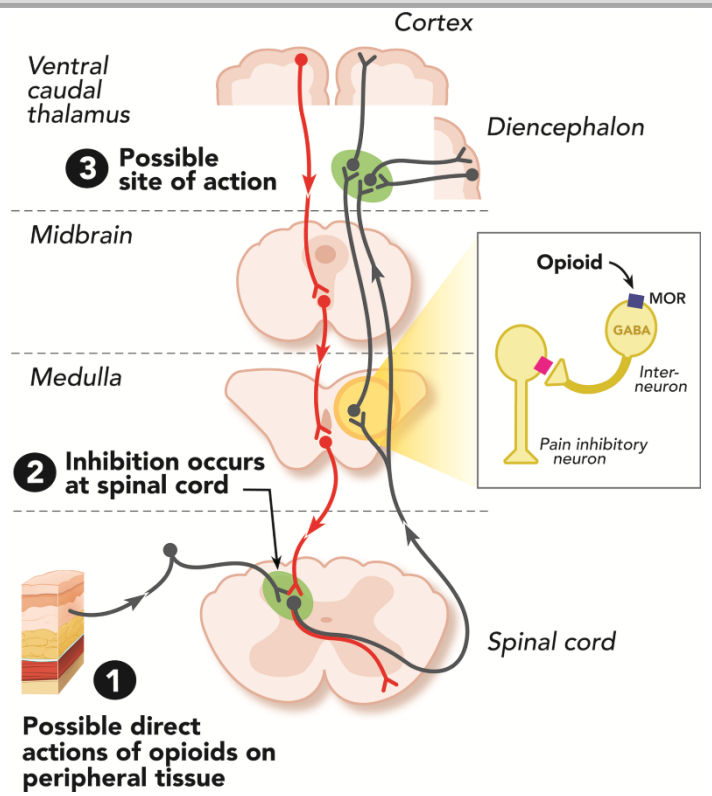


Figure Legend:

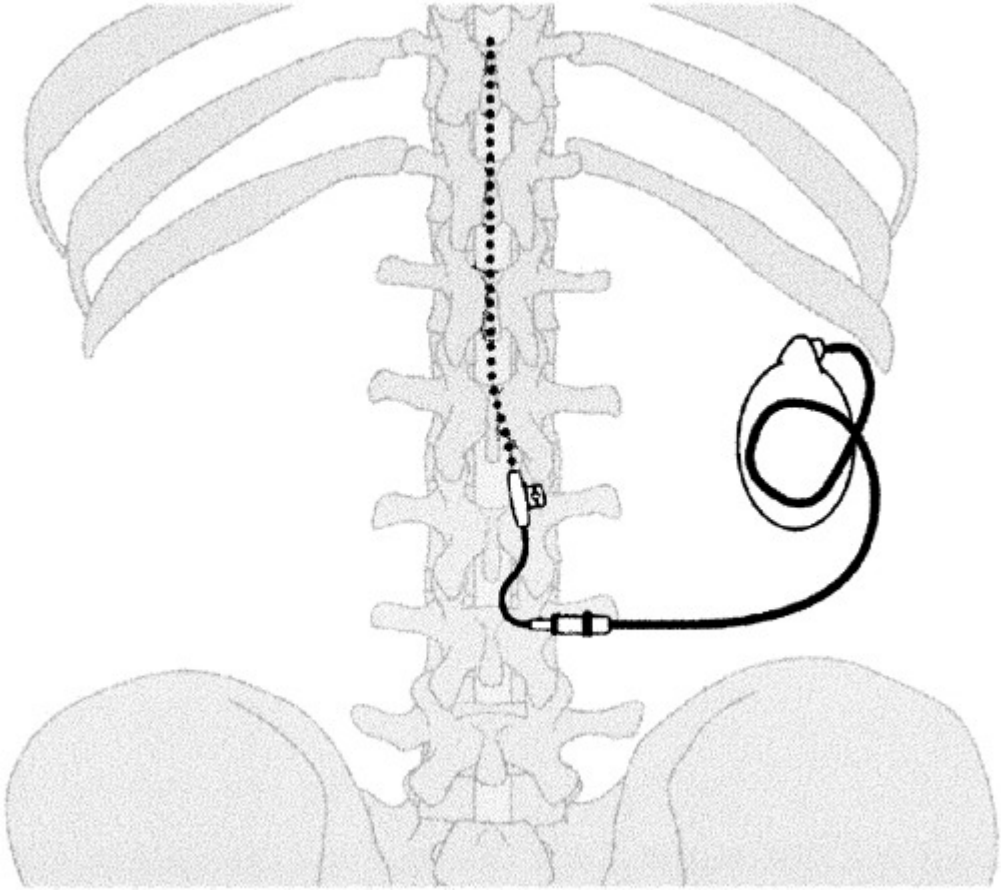
Fig. 1. Sites of action of opioid analgesics. The gray pathway shows the sites of action on the pain transmission pathway from periphery to central nervous system. The red pathway shows the actions on pain-modulating neurons in the midbrain and medulla. GABA = γ-aminobutyric acid; MOR = μ opioid receptor.

INTRATHECAL DRUG DELIVERY FOR CANCER PAIN: WHEN TO CONSIDER

- Pain due to advanced cancer, with a minimum life expectancy of > 3 months.
- Refractory to conventional pain management because of intractable drug adverse effects or unsatisfactory analgesia.
- Visual analog scale (VAS) ≥ 5, despite 200 mg/day of oral morphine equivalent.
- Consider patients on lower doses if opioid side effects are refractory to conservative treatment and severe enough to prevent upward titration.

- Smith. *J Clin Oncol 2002*
- *Stearns. J Support Oncol*. 2005
- Smith. *J Pall Med.* 2005
- Brogan. *Curr Pain Head Rep.* 2006

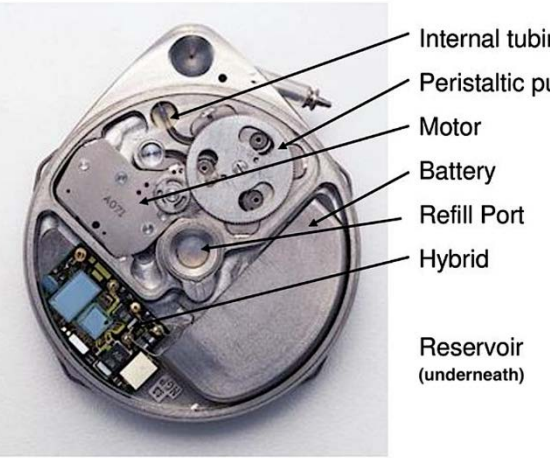
Implantable drug delivery systems (IDDS) after failure of comprehensive medical management (CMM) can palliate symptoms in the most refractory cancer pain patients. *Journal of Palliative Medicine. Volume 8, Number 4, 2005.* S. Narang, S. Srinivasan, N. Nguyen, D. Palombi, E.L. Ross



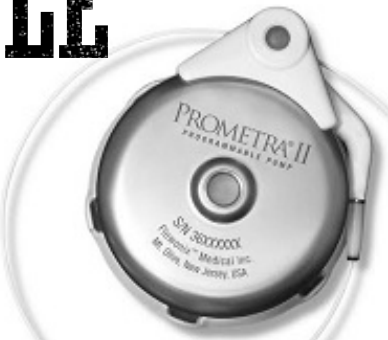
TYPES OF INTRATHECAL PUMPS AVAILABLE

Synchromed II (Medtronic)

- MRI conditional 3T
- Peristaltic rotor
- 4-7 years battery life



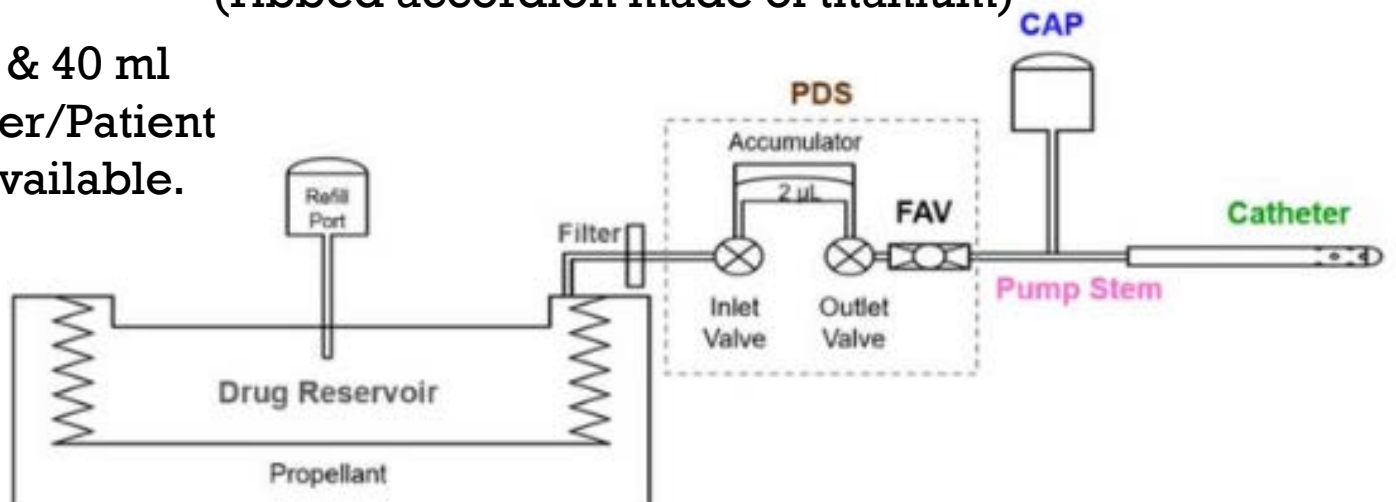
Prometra II (Flowonix)



- MRI conditional 1.5T
- Valve gated bellow- microdosing capabilities
- 10+ year battery life
- Refill septum- 3mm raised ridge, 61% wider opening
- Natural aspiration- avoid pocket fills
  - 22 pounds of pressure with gas (R21) in reservoir (ribbed accordion made of titanium)

SIMILARITIES

- Two sizes available- 20 & 40 ml
- Patient Therapy Manager/Patient Controlled Analgesia available.



mypainweb.org/intrathecal-pump/
Flowonix.com
Medtronic.com

IT PUMP AND MAGNET

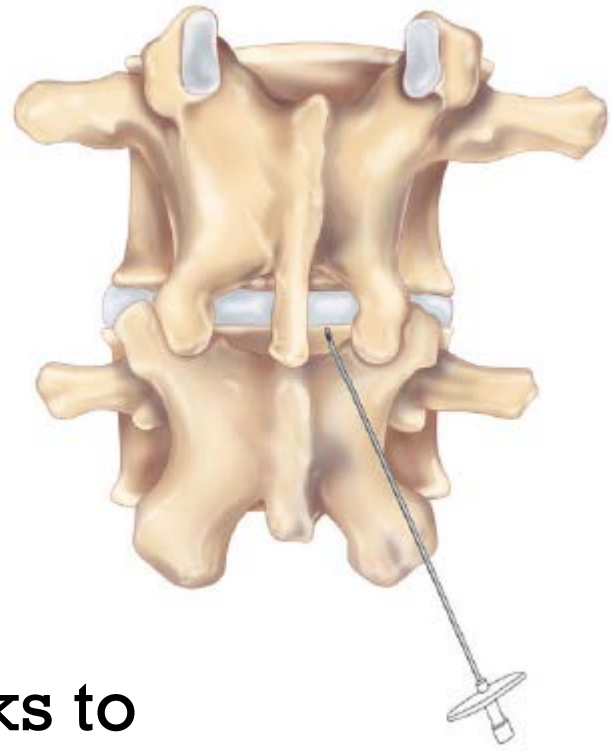
- Medtronic
  - IT pump is fully MRI compatible
  - Magnet stops the IT pump
    - Can use magnet to stop the IT pump in cases of suspected overdose- helpful suggestion for ED when called for possible IT pump related overdose
    - Pump may dysfunction if stopped for more than 24 hours
  - May use PTM to check if pump is functioning after an MRI
- Flowonix
  - Recommendation is to empty the contents of the pump prior to MRI
  - Flow valve gate in Prometra II should technically avoid pump dumps under MRI
  - Nurse coverage available to empty the pump and refill after MRI

WORK-UP

- Clear diagnosis
- Physical exam
- Psychological evaluation may be optional, however, imperative to have psychological help as end-of-life distress can compound pain experience and suffering
- Imaging- review safety on spine imaging

TRIAL

- Performed to
  - elucidate goals for pain relief and functional improvement
  - test for potential adverse reactions to intrathecal medications
- Trial options
  - No trial
  - Intrathecal or epidural
    - Single shot
    - Catheter
      - Continuous
      - Bolus



- No gold standard
- Usually low yield as it may take longer than 1-2 weeks to demonstrate efficacy

- Deer. *Neuromodulation* 2007

Disadvantages of Intrathecal Trialing	Advantages of Intrathecal Trialing
• Delays definitive therapy in a population with limited life expectancy • Many cancer patients are on anticoagulation; trialing requires an additional discontinuation of anticoagulation therapy and increased risk of thromboembolic events. • Additional risk of trial • Additional cost • Inpatient trials are laborious	• Payor authorization • Assessment of efficacy in the reluctant patient • Assess for tolerability

Mansoor *Journal of Pain Research* 2021

RECOMMENDED DOSES FOR INTRATHECAL BOLUS TRIALING

Drug	Recommended dose*
Morphine	0.1–0.5 mg
Hydromorphone	0.025–0.1 mg
Ziconotide	1–5 mcg
Fentanyl	15–75 mcg
Bupivacaine	0.5–2.5 mg
Clonidine	5–20 mcg
Sufentanil	5–20 mcg

*Starting doses of medication in the opioid-naive patient for outpatient bolus delivery do not exceed 0.15 mg morphine, 0.04 mg hydromorphone, or 25 mcg fentanyl.

- Deer. *Neuromodulation* 2017

INTRATHECAL PHARMACOKINETIC CONSIDERATION

- Target of action IT opioids is lamina II(substantia gelatinosa)
- IT opioids needs to diffuse through pia arachnoid and white matter
- Lipid solubility and molecular weight play important role
- Hydrophilic agents
  - longer half lives
  - Small vol of distribution- more rostral spread
- Lipophilic agents
  - faster clearance into vascular system
  - Limited spread- precise delivery

IT PUMP MEDS AND CATHETER TIP: FACTORS TO CONSIDER

- CSF kinetics—pulsatile dispersion of drug
  - Drug spread within CSF is limited and not homogenous
  - CSF sloshes back and forth in the spinal intrathecal space in a complex fashion with the cardiac cycle→ affected by HR, CSF stroke volume
  - Variable Drug to CSF Mixing parameter (Kmix)→ Cervical>low thoracic
    - Local anatomy at drug injection site→ some sites in a channel of rapid movement vs some in quiet
  - Heterogeneous CSF spinal pulsation
    - Heterogeneous spinal compliance based on epidural veins and fat
- Lipid solubility
  - Lipid soluble opioids
    - Are rapidly cleared into plasma and eliminated from CSF
    - Sequestered into epidural fat
    - Have slow cephalic spread
- Spine Anatomy

Jose *Korean J Pain* 2013
Flack *Pain Medicine* 2010
Pahlavian *Plos One* 2014
Eisenach *Anesthesiology* 2003
Henry Fuegeas *Mag Reson Imaging* 2000
Bernards *Anesthesiology* 2006

CATHETER TIP LOCATION

Pain location	Vertebral body catheter tip location
Brachial plexus	C3-5
Arm	C3-5
Breast	T1-2
Upper chest wall	T3-4
Visceral abdomen	T5-6
Lower chest wall	T6-7
Abdominal wall	T6-7
Pelvis	T9-12
Leg	T10
Sacral	Vertebral body level corresponding to conus

Chen *Neuromodulation* 2020

IMPLANT PLANNING

- Infection risk –low WBC, ongoing chemotherapy
- Bleeding risk- low platelet count, coagulation status (esp., in the presence of liver mets), taking anticoagulants
- Body habitus
  - Implant depth greater than 2.5 cm below skin
  - Insufficient body size
  - Location of pump- presence of ostomy, prior abdominal surgeries
  - Back incision/ Catheter entry site- spinal anomalies, presence of tumor near spine
- Identify your neurosurgery friend

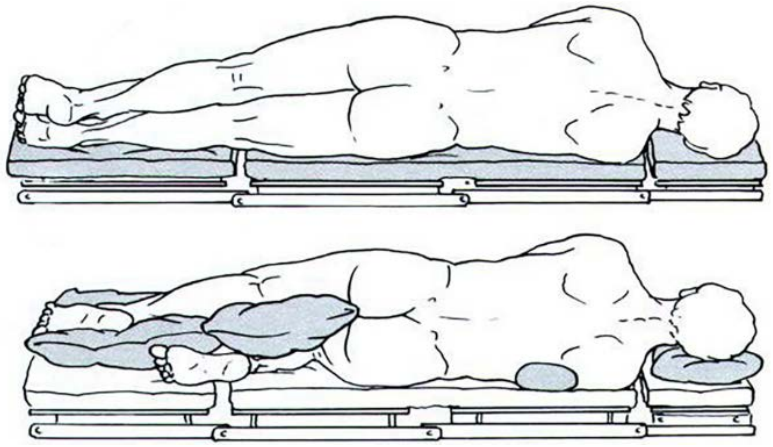
GA VS LOCAL FOR IMPLANT

- Local
  - Lower risk of spinal cord damage as pt is awake and therefore a vital monitor
- General Anesthesia
  - IT pump candidates are typically opioid tolerant- may not tolerate- lateral decubitus position- insertion of catheter, placing a pump, tunneling the catheter.
  - Challenging to gain airway control in lateral decubitus position if lost under deep sedation
  - Excessive movement under local can lead to neurologic injury or predispose to infection

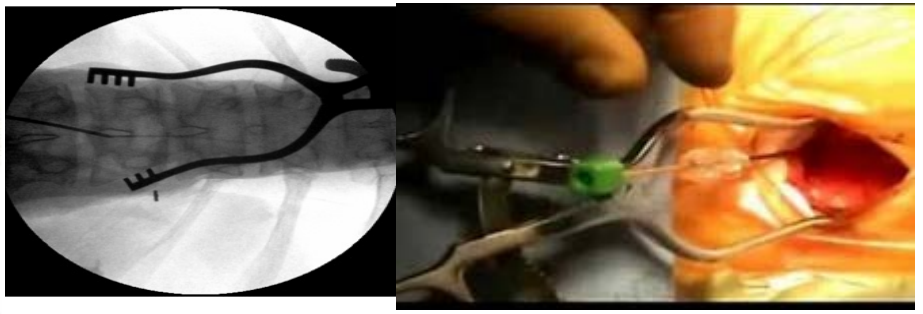
- Staats. *Pain Medicine* 2008

Implant overview

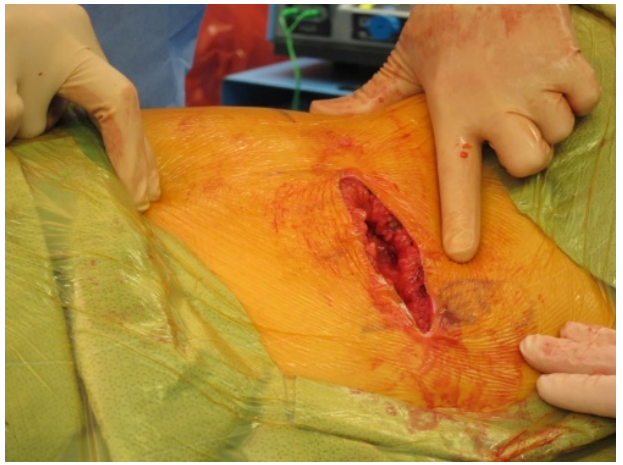
1. Positioning



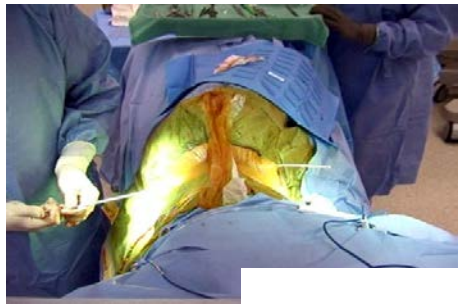
2. Intrathecal catheter placement



3. Pump pocket preparation

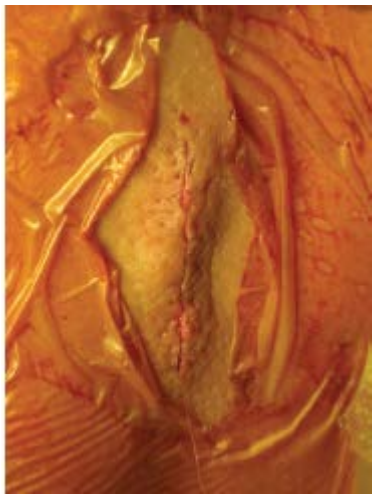


4. Tunnel catheter



5. Connect pump and catheter

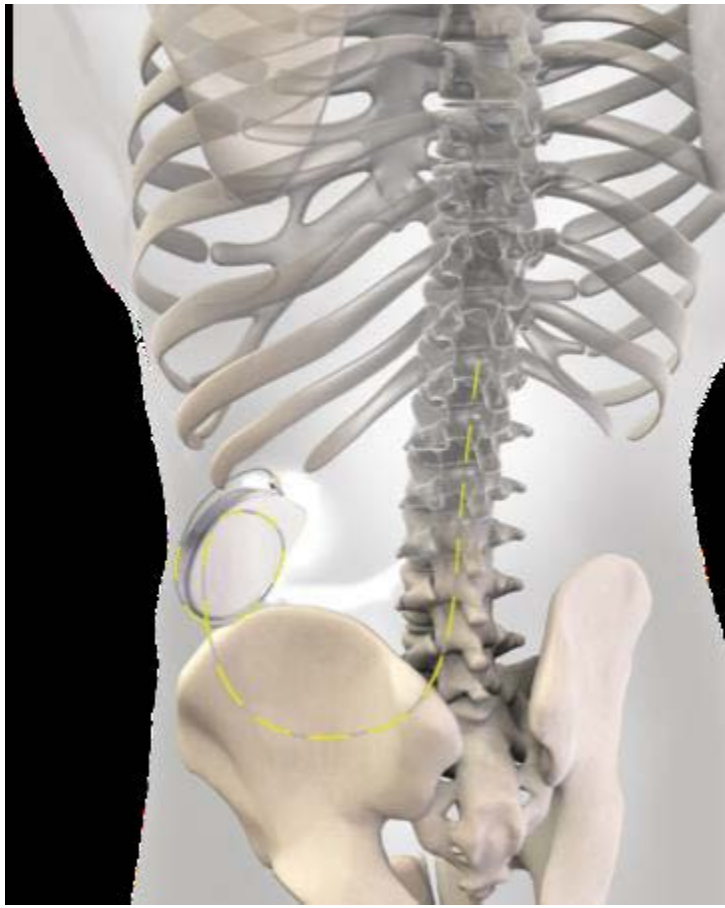
6. Close the incisions



- StormAnesthesia.com
- Narang *Surgical Pain Management 2017*

TARGETED DRUG DELIVERY REQUIRES SAME STRATEGIES AS SYSTEMIC DELIVERY

- If trial done- start at no greater than 50% of the trial rate
- Early titration to achieve analgesia/therapy goals
- Careful consideration of dose increases
- Monitor for side effects, efficacy



Deer *Neuromodulation* 2017
Knight *Croat Med J* 2007

IT MEDS REGULATIONS – USP 797

- Compounding pharmacies preparing medications for intrathecal use should follow United States Pharmacopeia (USP) 797 standards
  - A set of enforceable sterile compounding standards
  - Standards on procurement, storage, handling and compounding
  - Standards on design of the cleanroom where compounding takes place, equipment uses, operational protocols and personnel training
- Regular inspection for USP 797 compliance is performed by State Boards of Pharmacy

Usp.org

IT PUMP MEDS

- FDA approved
  - Only morphine, ziconotide and baclofen
- Opioids are the mainstay
  - Reducing neurotransmitter release in the substantia gelatinosa in the dorsal horn
- Local anesthetics - bupivacaine
  - Voltage gated sodium channel blockade→ inhibit action potential in the dorsal horn
- Clonidine, an α2 agonist
  - Activation of postsynaptic α2 repectors in substantia gelatinosa
- Ziconotide
  - N-type voltage sensitive calcium channel blockade in the superficial lamina of dorsal horn
  - Blocks neurotransmitter release in primary nociceptive afferent fibers
- Polyanalgesia/combination therapy
  - Synergistic modulation of multiple nociceptive mechanisms
  - Attenuate development of tolerance associated with an equipotent monodrug regimen
    - May help stabilize opioid dosing and reduce the need for constant opioid dose escalation

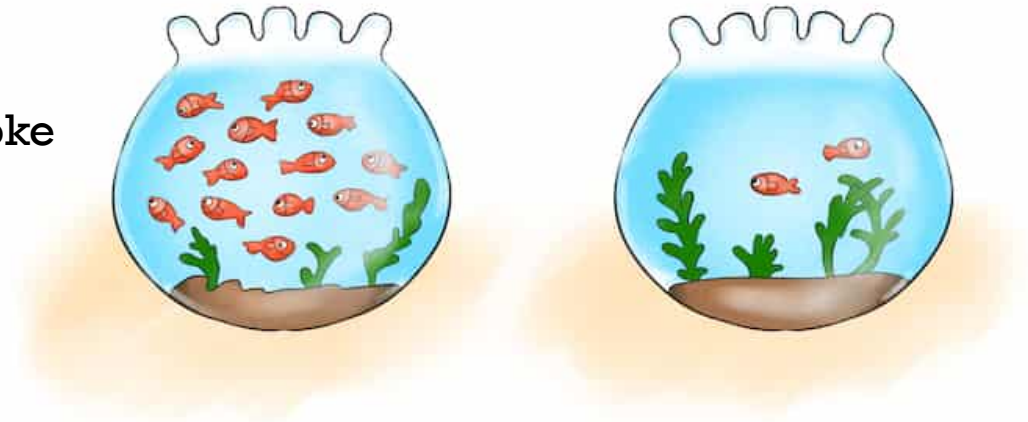
Manchikanti *Pain Physician 2009*
Strichartz *Local Anesthesthetics: Miller* 1994
Eisenach *Pain* 1995
Olivera *Ann Rev Biochem* 1994
Miljanich *Curr Med Chem* 2004
Rizvi *Neuromodulation* 2015
Kumar *Pain Medicine* 2013

IT MEDS-POSSIBLE SIDE EFFECTS

- Opioids
  - Nausea, vomiting, itching, respiratory depression, constipation, hormonal imbalance, sedation, hyperalgesia, tolerance
  - Peripheral edema
- Bupivacaine
  - Urinary retention, hypotension, numbness, motor weakness
- Clonidine
  - Hypotension
- Ziconotide
  - Hallucinations, GI upset

IT MEDS: WITHDRAWAL VS OVERDOSE

- Opioids
  - Overdose- sedation, respiratory depression
  - Withdrawal- lack of pain relief, sweating, rhinorrhea, diarrhea, tachycardia, hypertension, etc.
- Bupivacaine
  - Overdose- numbness, weakness
  - Withdrawal- lack of pain relief, ?burning sensation
- Clonidine
  - Overdose- sedation, hypotension
  - Withdrawal- lack of pain relief, rebound hypertension, stroke
- Ziconotide
  - Overdose- hallucinations, psychosis
  - Withdrawal- lack of pain relief
- Baclofen
  - Overdose- sedation, weakness
  - Withdrawal- pruritus, sedation, respiratory depression, decrease consciousness, hyperthermia, DIC, renal failure, multiorgan failure, death



POLY-ANALGESIC CONSENSUS CONFERENCE (PACC) RECOMMENDATION FOR IT MEDICATION

Table 12. Cancer or Other Terminal Condition-Related Pain With Localized Nociceptive or Neuropathic Pain.

Line 1A	Ziconotide			Morphine		
Line 1B	Fentanyl			Morphine or fentanyl + bupivacaine		
Line 2	Hydromorphone	Hydromorphone + bupivacaine		Hydromorphone or fentanyl or morphine + clonidine	Morphine or hydromorphone or fentanyl + ziconotide	
Line 3	Hydromorphone or morphine or fentanyl + bupivacaine + clonidine	Ziconotide + bupivacaine		Ziconotide + clonidine	Hydromorphone or morphine or fentanyl + bupivacaine + ziconotide	Sufentanil
Line 4	Sufentanil + ziconotide	Sufentanil + bupivacaine	Baclofen	Sufentanil + clonidine	Bupivacaine + clonidine + ziconotide	Bupivacaine + clonidine
Line 5	Sufentanil + bupivacaine + clonidine					
Line 6	Opioid* + bupivacaine + clonidine + adjuvants†					

*Opioid (all known intrathecal opioids).
†Adjuvants include midazolam, ketamine, octreotide.

- Deer. *Neuromodulation* 2017

POLYANALGESIC CONSENSUS CONFERENCE RECOMMENDATION FOR IT MEDICATION

Table 20. Recommended Starting Dosage Ranges of Intrathecal Medications for Long-Term Therapy Delivery.

Drug	Recommendation of starting dose*
Morphine	0.1–0.5 mg/day
Hydromorphone	0.01–0.15 mg/day
Ziconotide	0.5–1.2 mcg/day (to 2.4 mcg/day per product labeling)
Fentanyl	25–75 mcg/day
Bupivacaine	0.01–4 mg/day
Clonidine	20–100 mcg/day
Sufentanil	10–20 mcg/day

*Starting doses of continuous intrathecal delivery should be half of the trial dose for opioid-based medications.

- Deer. *Neuromodulation* 2017

RECOMMENDED MAX CONC AND MAX DAILY DOSE

Drug	Maximum concentration	Maximum dose per day
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

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

- Deer. *Neuromodulation* 2017

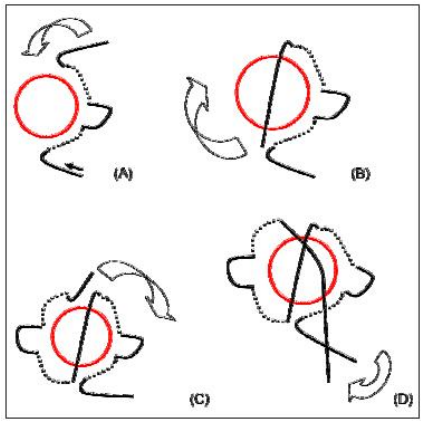
INTRATHECAL OPIOID CONVERSION

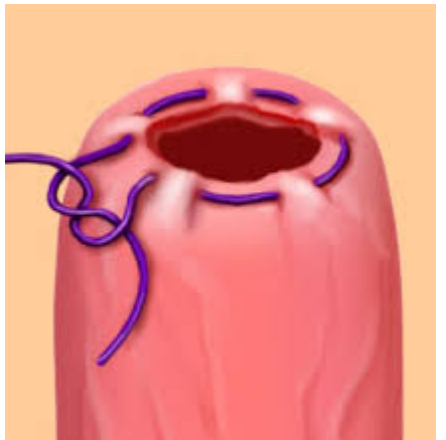
- No definitive evidence of a true conversion factor
- Caution when converting from a more lipophilic drug to a less lipophilic drug- increased risk of respiratory depression
- Slow titration is key→ add new drug at low dose while slowly decreasing the old drug

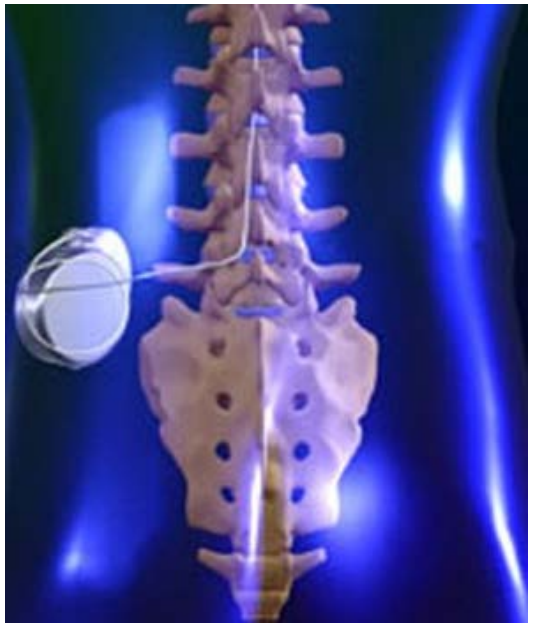
- Deer. *Neuromodulation* 2007

MITIGATING RISKS DURING IMPLANT

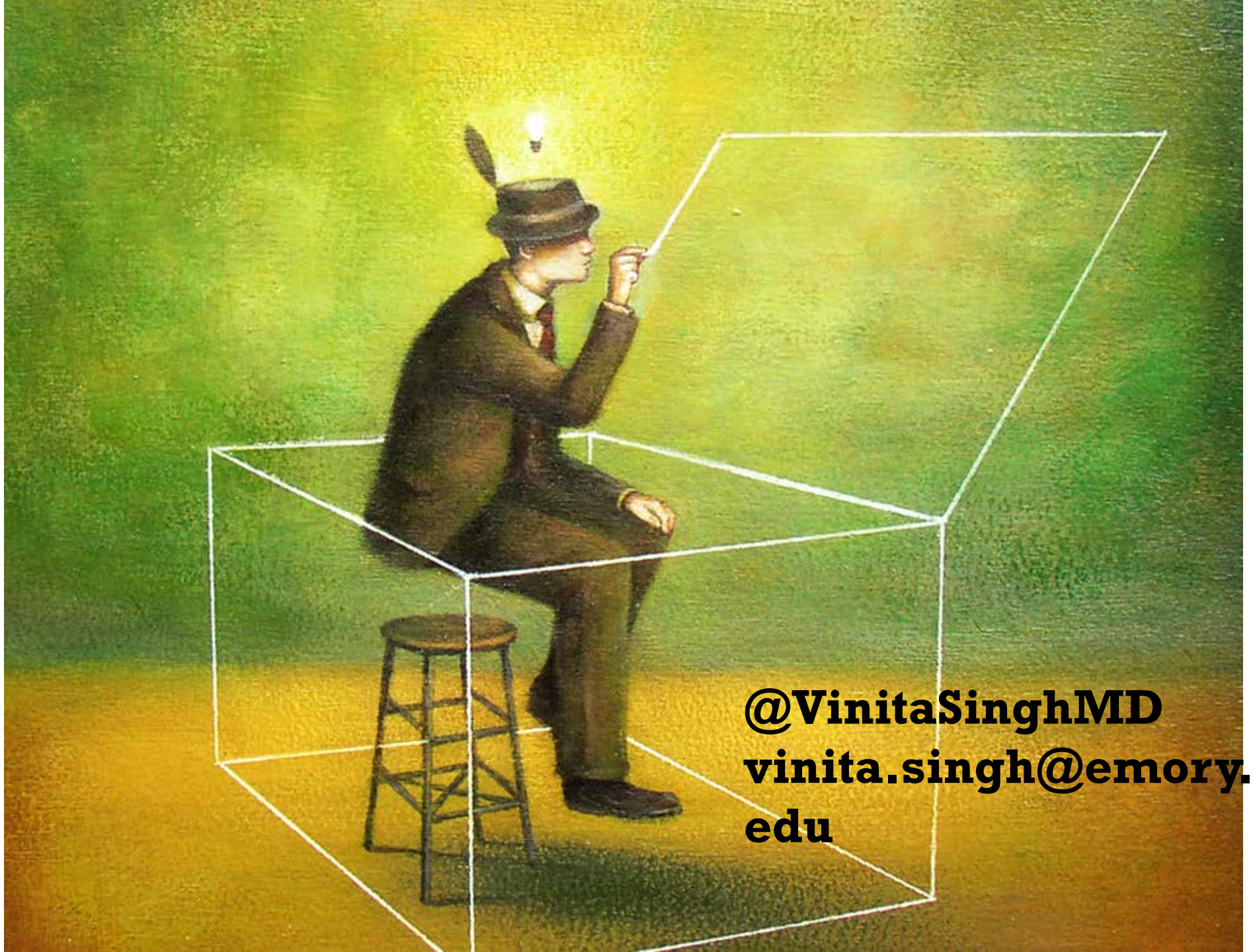
- Avoiding spinal cord/nerve injury
  - Use fluoroscopic guidance
  - Needle entry site below conus medullaris whenever possible
- Avoiding catheter fracture, kinks
  - Use gentle angle in a paramedian approach
  - Avoid catheter entry through interspinous ligament
- Avoiding CSF leak
  - Purse string suture







- Staats. *Pain Medicine* 2008



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