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Incorporating Intrathecal Treatments Into a Pain Practice

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Learning Objectives

- Describe the rationale for intrathecal drug delivery
- Explain the possible side-effects of intrathecal and oral opioid analgesics
- Discuss how “numbers need to treat calculations” help us compare analgesics

FDA Warning About Intrathecal Pumps

Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Tobacco Products

Medical Devices

Home > Medical Devices > Medical Device Safety > Safety Communications

Safety Communications

2018 Safety Communications

2017 Safety Communications

Use Caution with Implanted Pumps for Intrathecal Administration of Medicines for Pain Management: FDA Safety Communication

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Date Issued: November 14, 2018

Audience:

- Patients who have an implanted pump that delivers medicine into the spinal fluid to treat or manage pain
- Caregivers of these patients
- Health care providers who manage the care of these patients
- Compounders

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Use caution with implanted pumps for intrathecal administration of medicine for pain management: FDA safety communication Nov 14, 2018. https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm625789.htm

Only FDA Approved IT Analgesics

The only approved medicines identified in implanted pump labeling for intrathecal infusion to treat or manage pain	Examples of medicines not identified in the implanted pump labeling for intrathecal infusion to treat or manage pain
INFUMORPH® (morphine sulfate), preservative free, injectable solution ***PRIALT® (preservative free ziconotide sterile solution)**	Medicines not FDA approved for intrathecal administration or intrathecal implanted pump use (for example, hydromorphone, bupivacaine, fentanyl, clonidine) ANY mixture of two or more different kinds of medicines Any compounded medicine (for example, to achieve higher concentration or different formulation of an FDA approved medicine)
*** The current labeling (Instructions for Use) of the implanted pump should be reviewed because not all pumps are currently approved for use with PRIALT.**	

FDA Rationale

- FDA acknowledges that some patients being treated for pain may not be adequately managed by medicine approved for use with these pumps;
- However, the use of medicine not approved with the implanted pumps are associated with additional risks such as ***pump failures, dosing errors, and other potential safety issues.***
- Therefore, the FDA is sharing information and providing recommendations so that patients, caregivers, compounders, pharmacists, and health care providers can make informed treatment decisions.

HHS Integrative Treatment Plan for Chronic Pain

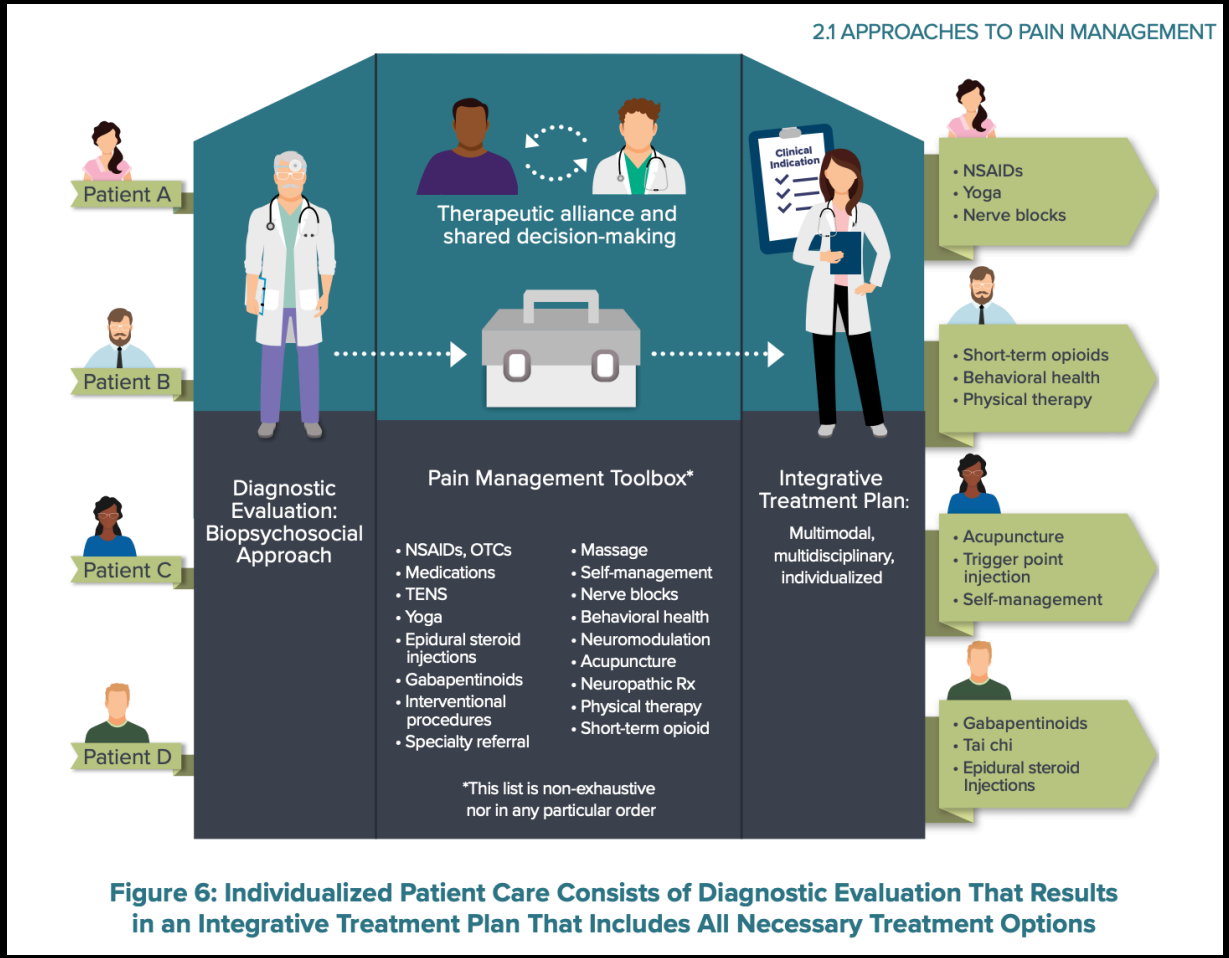
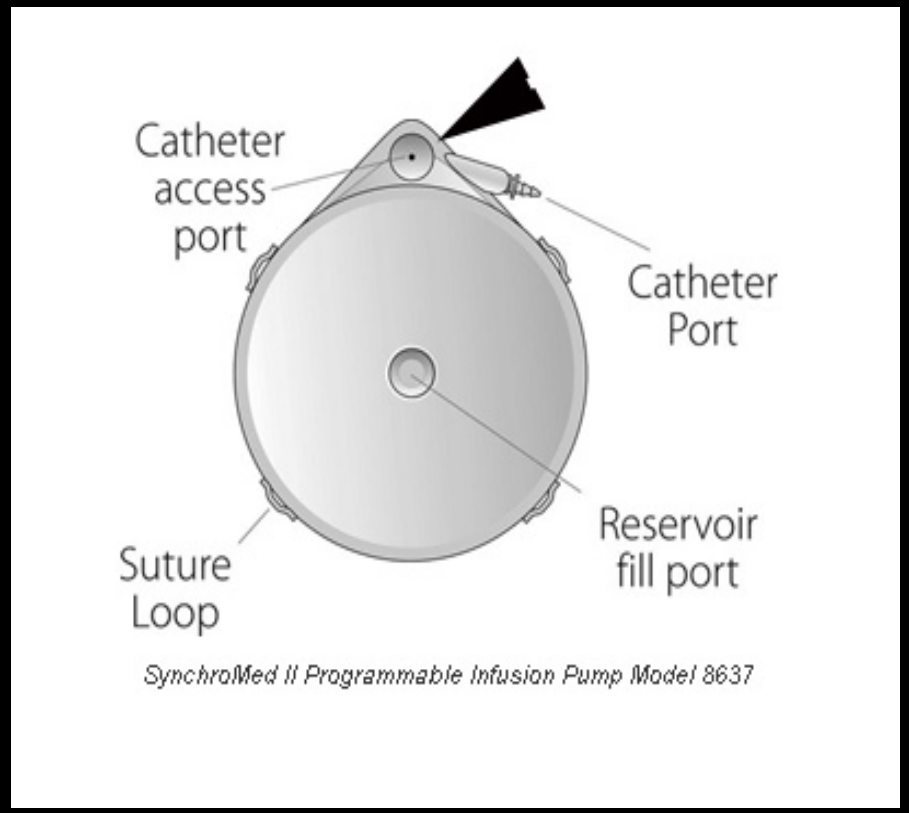


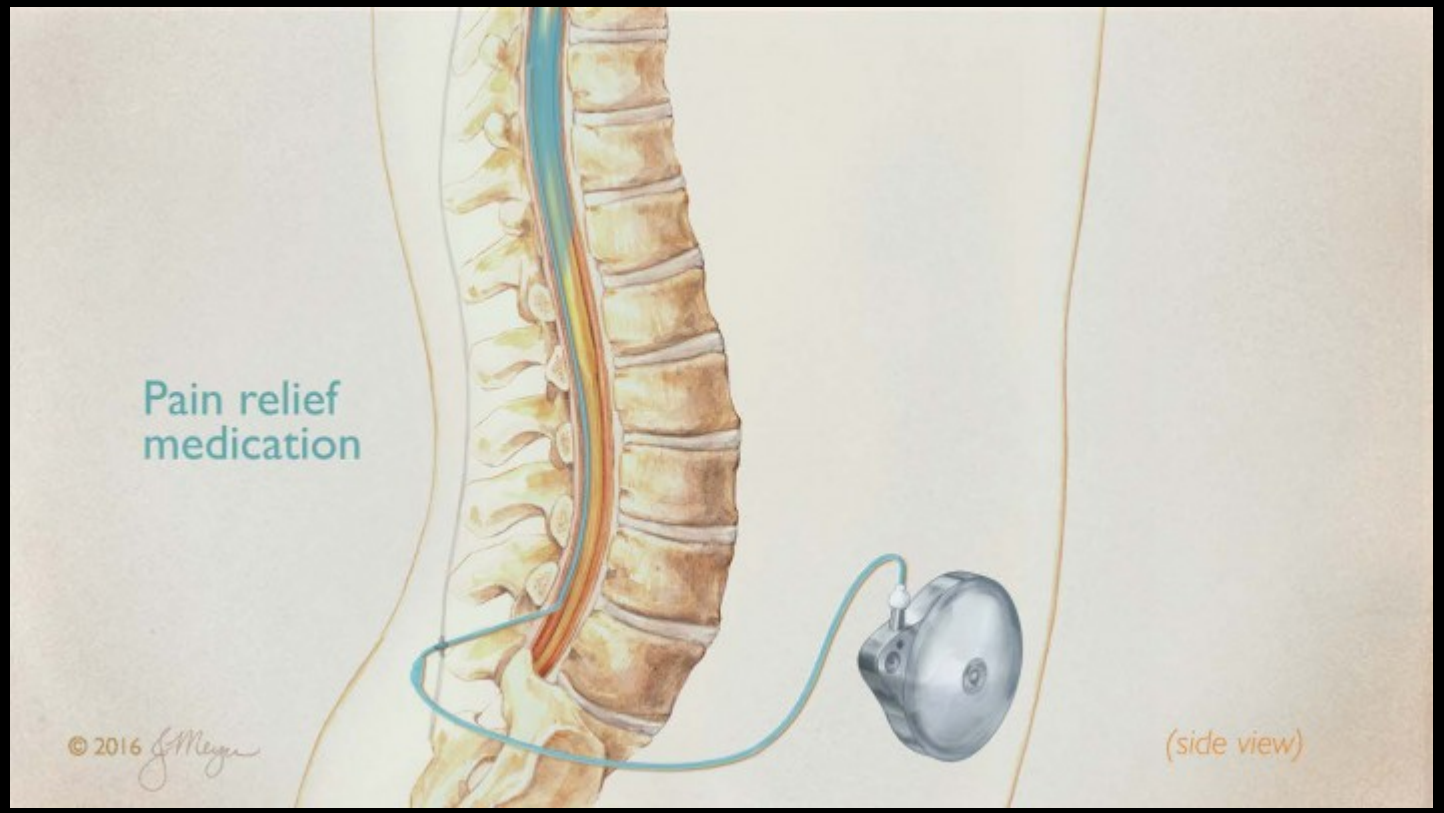
Figure 6: Individualized Patient Care Consists of Diagnostic Evaluation That Results in an Integrative Treatment Plan That Includes All Necessary Treatment Options

Rationale for use of Intrathecal Delivery

- To deliver drug to site of pain transmission
- To use smallest dose for maximal effect
- To minimize adverse effects

Intrathecal Pump Device and Placement





Successful Outcomes

Patient factors  Disease factors  Clinical team factors

IT therapy should not be used as a salvage therapy for failing systemic opioids

Treatment Outcomes

- Limited IT opioid RCTs for noncancer pain
- Cancer pain RCT compared IT opioid to comprehensive medical management
  - IT subjects more likely to achieve pain relief outcome measure
  - IT subjects had less toxicity
  - IT subjects had less fatigue and depressed level of consciousness
  - IT subjects had improved survival
- Multiple RCTs in noncancer pain with ziconotide

Smith, T. J., Staats, P. S., Deer, T., Stearns, L. J., Rauck, R. L., Boortz-Marx, R. L., ... & Pool, G. E. (2002). Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. *Journal of Clinical Oncology*, *20*(19), 4040-4049.

Rauck RL, Wallace MS, Leong MS et al. A randomized, double-blind, placebo controlled study of intrathecal ziconotide in adults with severe chronic pain. J Pain Symptom Manage 2006;31:393–406. 33.

Staats PS, Yearwood T, Charapata SG et al. Intrathecal ziconotide in the treatment of refractory pain in patients with cancer or AIDS: a randomized controlled trial. JAMA 2004;291:63–70. 34.

Wallace MS, Charapata SG, Fisher R et al. Intrathecal ziconotide in the treatment of chronic nonmalignant pain: a randomized, double-blind, placebo-controlled clinical trial. Neuromodulation 2006;9:75–86

Patient Selection for IT therapy

- Patients with severe refractory pain from cancer or noncancer etiologies
  - Localized, diffuse, global
- Patients with intolerable adverse events to systemic therapies
- Patients for whom the following have been considered:
  - Treatment history and inadequacy of alternate options
  - Psychological well being
  - Social support structure
  - Probability and capability of adherence to IT therapy requirements
  - Health care coverage and finances
- Implant following successful trial

Patient Selection for IT therapy

- Consider comorbidities:
  - Diabetes (infections)
  - Poor cardiopulmonary function (respiratory depression / hypotension)
  - Obstructive sleep apnea (respiratory depression)
  - Anticoagulant therapy (post-op bleeding)
  - Chronic infections (bacteremia)
  - History of psychosis and psychological illness
  - Substance use disorders
  - Life expectancy (min >3 months)
- Consider drug-drug interactions
  - Systemic opioids
  - Benzodiazepines
  - Anticonvulsants
  - Antidepressants
  - Muscle relaxants
  - Alcohol

Patient Education

- IT therapy aids in management of pain, not pain elimination
- Goals of success
  - Nonterminal pain generally functionally based
  - Terminal conditions generally focused on severity reduction
- Complications/Risks
  - Surgical
  - Medication risks (overdose, endocrinopathies, granuloma)
  - Device failures
  - Pharmacy errors
  - Refill errors (pocket fill)
  - Programming errors
  - MRI / Travel

Clinical Team

- Pump Managing Clinician
  - Both medical and surgical skills
  - Trial, implant, refill, complication assessment and management
  - Programming Hardware
- Psychological/Mental Health
  - Assessment and stabilization
- Clinical Staff Support
  - Pharmacy Relationship / Drug Ordering
  - Patient scheduling and transportation
- Device Technical Support
- Physical Therapy to rehabilitate to functional goals

Adler, J. A., & Lotz, N. M. (2017). Intrathecal pain management: a team-based approach. *Journal of Pain Research*, *10*, 2565.

Typical Patient Treatment Path

- Patient identified (patient/disease factors)
- Psychological Assessment (may be waived in terminal conditions)
- Trial (may be waived in terminal conditions)
- Surgical Implant
- Wound care and healing
- Titration and treatment stabilization
- Maintenance Refills (approximately every 1-6 months)
- Surgical Battery replacement approximately every 7 years

COVID19 and Disaster Preparation

- Trial/Implant/Revision/Removal
  - Ensure adequate resources available for any complications
  - Postpone if resources unavailable
- Drug Ordering
  - Submit order to pharmacy with ample time to account for shipping delays
  - Anticipate and plan for any drug shortages
- Scheduling Refills
  - Optimize time between refills through adjustment of infusion concentrations
  - Raise alarm volume to allow for flexibility in refill date if patient factors or provider factors interfere with pump refill
  - Schedule pump block of time for sequential refills of patients
- Operations Interruption Plan
  - Educate patients on withdrawal management strategies
  - Provide opioid withdrawal mitigation plan should patient unable to have pump refilled (lofexidine)

PACC Guidelines Feb 2017

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

Timothy R. Deer, MD*; Jason E. Pope, MD†; Salim M. Hayek, MD, PhD‡; Anjum Bux, MD§; Eric Buchser, MD¶; Sam Eldabe, MD**; Jose A. De Andrés, MD, PhD, EDRA††; Michael Erdek, MD‡‡; Dennis Patin, MD§§; Jay S. Grider, PhD, MBA¶¶; Daniel M. Doleys, PhD***; Marilyn S. Jacobs, PhD†††; Tony L. Yaksh, PhD‡‡‡; Lawrence Poree, MD, PhD§§§; Mark S. Wallace, MD¶¶¶; Joshua Prager, MD****; Richard Rauck, MD††††; Oscar DeLeon, MD‡‡‡‡; Sudhir Diwan, MD§§§§; Steven M. Falowski, MD¶¶¶¶; Helena M. Gazelka, MD*****; Philip Kim, MD††††††††††; Michael Leong, MD§§§§§; Robert M. Levy, MD, PhD¶¶¶¶¶; Gladstone McDowell II, MD******; Porter McRoberts, MD†††††††; Ramana Naidu, MD‡‡‡‡‡‡; Samir Narouze, MD, PhD§§§§§§; Christophe Perruchoud, MD¶¶¶¶¶¶; Steven M. Rosen, MD*******; William S. Rosenberg, MD†††††††; Michael Saulino, MD, PhD‡‡‡‡‡‡‡; Peter Staats, MD§§§§§§§¶¶¶¶¶¶¶; Lisa J. Stearns, MD********; Dean Willis, MD††††††††; Elliot Krames, MD‡‡‡‡‡‡‡‡; Marc Huntoon, MD§§§§§§§§; Nagy Mekhail, MD, PhD¶¶¶¶¶¶¶¶

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Disease Indications for IT therapy

- Axial neck or back pain; not a surgical candidate
  - Compression fractures
  - Discogenic pain
  - Spinal stenosis
  - Diffuse multiple-level spondylosis
- Failed back surgery syndrome
- Abdominal / pelvic pain
  - Visceral
  - Somatic

Disease Indications for IT therapy

- Extremity pain
  - Radicular pain
  - Joint pain
- Complex regional pain syndrome (CRPS)
- Trunk pain
  - Postherpetic neuralgia
  - Post-thoracotomy syndromes
- Cancer pain; direct invasion or chemotherapy
- Analgesic efficacy with systemic opioid delivery complicated by intolerable side effects

Comorbid Conditions

- Comorbid conditions should be well controlled
- Diabetes, sleep apnea, history of infections, or immunosuppression
- Benzodiazepines (or EtOH!) and opioids have synergistic effects
- Systemic opioids
  - Wean off all opioids 6 weeks prior to trial to assess OIH
  - Reduce opioids as much as possible
  - Keep systemic opioid dose stable

FDA APPROVED DRUGS

- USA:
  - Morphine (pain)
  - Ziconotide (pain)
  - Clonidine (pain)*
    - Epidural approval only
  - Baclofen (spasticity)

*Not approved for use in either Arrow or Medtronic pump

Noncancer-Related Pain (Localize/Diffuse) Algorithm

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.

Deer, T. R., Pope, J. E., Hayek, S. M., Bux, A., Buchser, E., Eldabe, S., ... & Doleys, D. M. (2017). The Polyanalgesic Consensus Conference (PACC): recommendations on intrathecal drug infusion systems best practices and guidelines. *Neuromodulation: Technology at the Neural Interface*, *20*(2), 96-132.

Side Effects with Intrathecal Morphine

Table 1. Incidence and Management of Side Effects Associated With Intrathecal Morphine Therapy.

Side Effect	Incidence	Treatment
Pruritus	0–100% (32) 14% for long-term ITT (33)	Treatable with mu antagonist naloxone
Nausea and vomiting	30% with acute ITT (32) ~21% in long-term ITT (33)	Antiemetics Improved by lowering dose
Urinary retention	42% (34) to 80% (35) ~3% in long-term ITT (33) Dose dependent More common in men with enlarged prostates	Cholinomimetic agents (e.g., bethanechol or distigmine [used in the UK]); catheterization if medication is ineffective
Constipation	30% (33)	Stool softener, bowel stimulant or laxatives
Edema (preexisting venous insufficiency and edema are relative contraindications to intrathecal therapy (38))	3% (33) to 16% (36)	Leg raising, elastic stockings, compressive air pumps, salt and fluid restrictions, diuretics
Mental status change (sedation and lethargy, paranoid psychosis, catatonia, euphoria, anxiety, delirium, hallucination)	10–14% in long-term ITT (33)	Lower opiate dose first Treat sedation with psychostimulants (modafinil) or neuroleptics (haloperidol)
Sexual dysfunction	68.8% in women, 95.8% in men (38) Due to opioid-induced hypogonadism	Lower opiate dose Rotate opioids Prescribe hormone replacement therapy
Respiratory depression	Cause of some fatalities soon after the start of ITT	Start ITT with low dose Monitor vulnerable patients for 24 hours after start or change of ITT (25) Readily reversed with naloxone or nalbuphine

Adapted from Ruan X. *Pain Physician.* 2007;10:357–365. ITT, intrathecal therapy.

Intrathecal Medications vs Oral Medications

- Adverse Effects:
  - Respiratory depression
  - Endocrinopathy
  - Opioid hyperalgesia
  - Addiction and diversion
- Efficacy: Numbers Needed to Treat
  - Do they exist for Intrathecal Analgesics?

Respiratory Failure after Delayed Morphine Pump Refill

Ruan in Pain Physician 2010

- 65 woman with chronic LBP; IT Codman 3000
- Titrated to 4 mg / day over 6 months
- Pump refill 10 days after empty; 10 hours later unresponsive, ED, ICU
- Conclusion: loss of opioid tolerance due to delayed pump refill may cause severe respiratory depression

Substance Abuse via an Implanted Intrathecal Pump

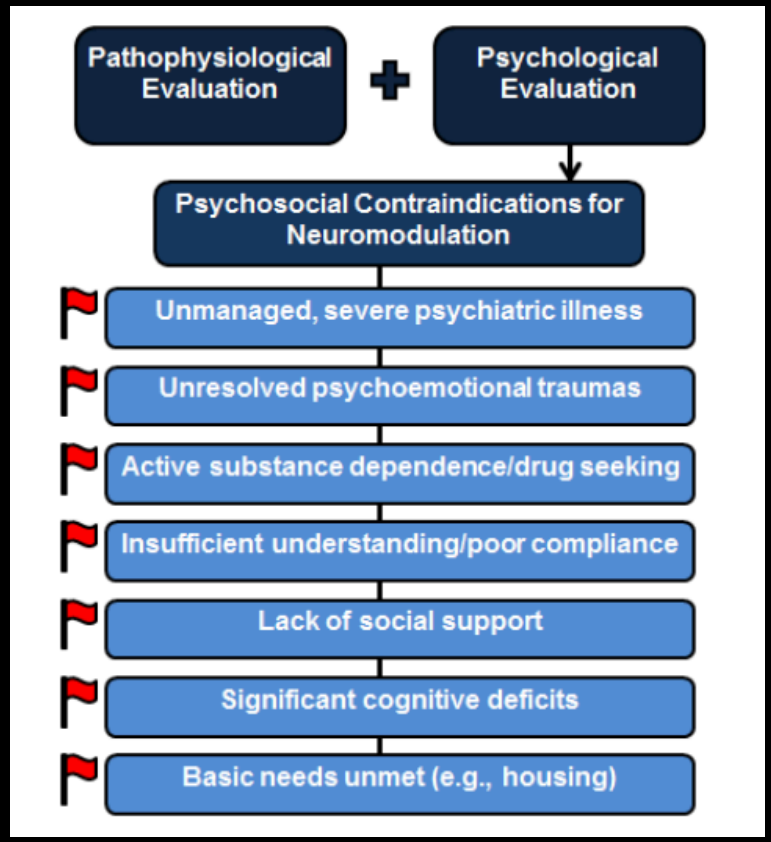
- Case report by Allen Burton 1998
- 43 male with back pain and multiple surgeries
- Incarcerated in Texas and pump maintained
- Marginal pain relief every visit, escalation from 2.5 mg to 5 mg / day over 6 months
- Pump refill cloudy; analysis = opiates plus phencyclidine, methamphetamine, and propoxyphene
- Explanted pump showed scoring near the refill aperture

Good Intentions Gone Bad: Case Study of a Patient Accessing An Intrathecal Pump 2016

UCSF Comprehensive Med / Psych Care

- Dabah, Poree, Pullins at UCSF
- 22 y/o woman after fall with spinal / pelvic fractures; IT pump place 2014 with fentanyl
- Psychiatric history of heroin abuse, bipolar, anorexia, suicide attempt
- Attempted to access fentanyl for suicide

Psychological Risk Factors for Poor Neuromodulation Outcomes



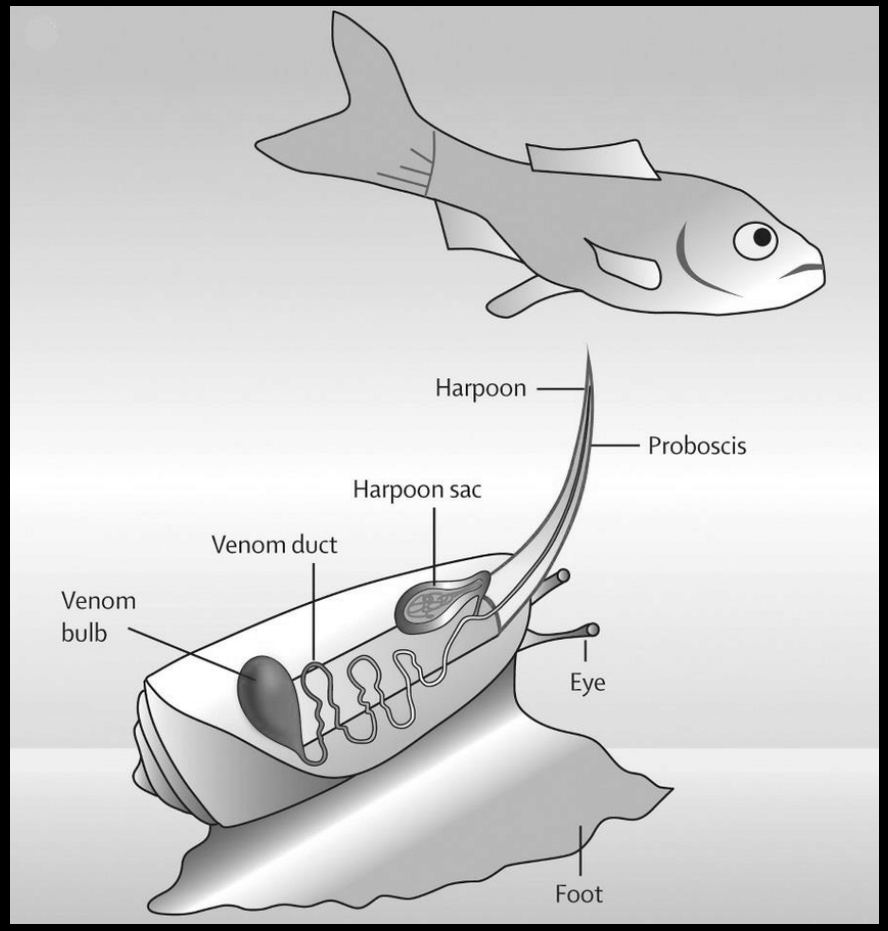
Summary of Side-effects for IT Analgesics

Side Effect	Incidence	Treatment
Respiratory depression	Biphasic with IT morphine	23 hour monitoring?
Endocrinopathy	Sexual dysfunction 69% F and 96% M with IT morphine	Testosterone supplementation
Opioid-induced hyperalgesia	Unknown	Taper
Addiction and diversion	Unknown	Psychology and non-opioid

Intrathecal versus Oral

Side Effect	Mechanism	Intrathecal vs Oral
Respiratory depression	Vascular and CSF spread to brainstem	Intrathecal can be biphasic so harder to control
Endocrinopathy	Hypogonadism	IT is 70 to 95%; IT and oral may be equal in probability
Opioid-induced hyperalgesia	Unclear	Microdosing IT opioids are effective after oral taper
Addiction and diversion	Dopamine reward system	Overall smaller dose exposure, less euphoria; pain psychology pre-implantation

Conus Magus Snail Venom Conotoxin in Action



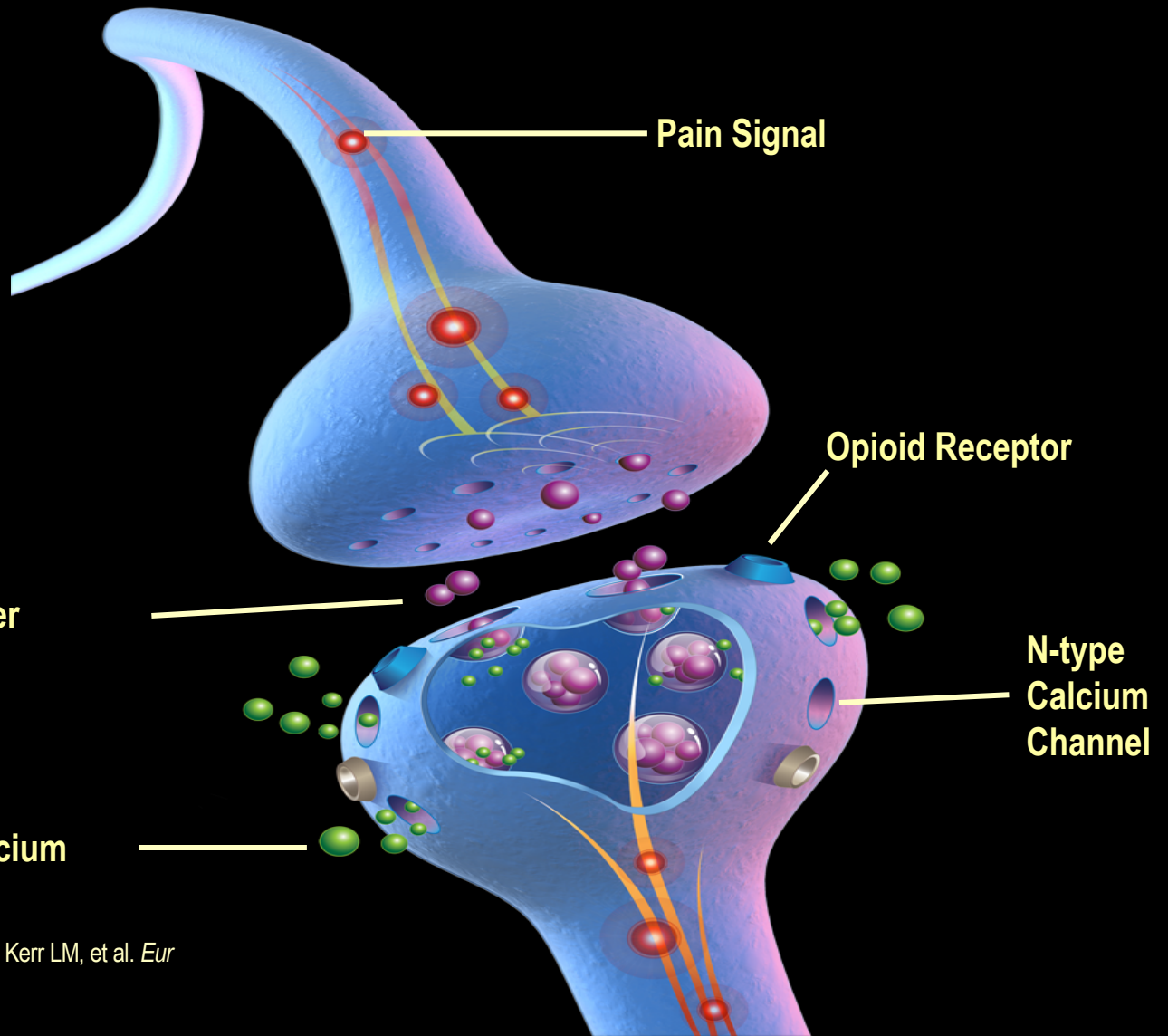
Ziconotide

- Mechanism of action: blocks presynaptic N-type calcium channels in the dorsal horn of the spinal cord; helpful for opioid tolerant patient
- Neurotoxicity: none
- More hydrophilic than morphine; inc spread in CSF
- Trialing is challenging: continuous infusion vs bolus
- Some practitioners recommend meclizine treatment
- Proper hydration is important to limit hypotension
- Black box warning for cognitive impairment and hallucinations

N-type Calcium Channels Control the Signaling of Pain to the Brain

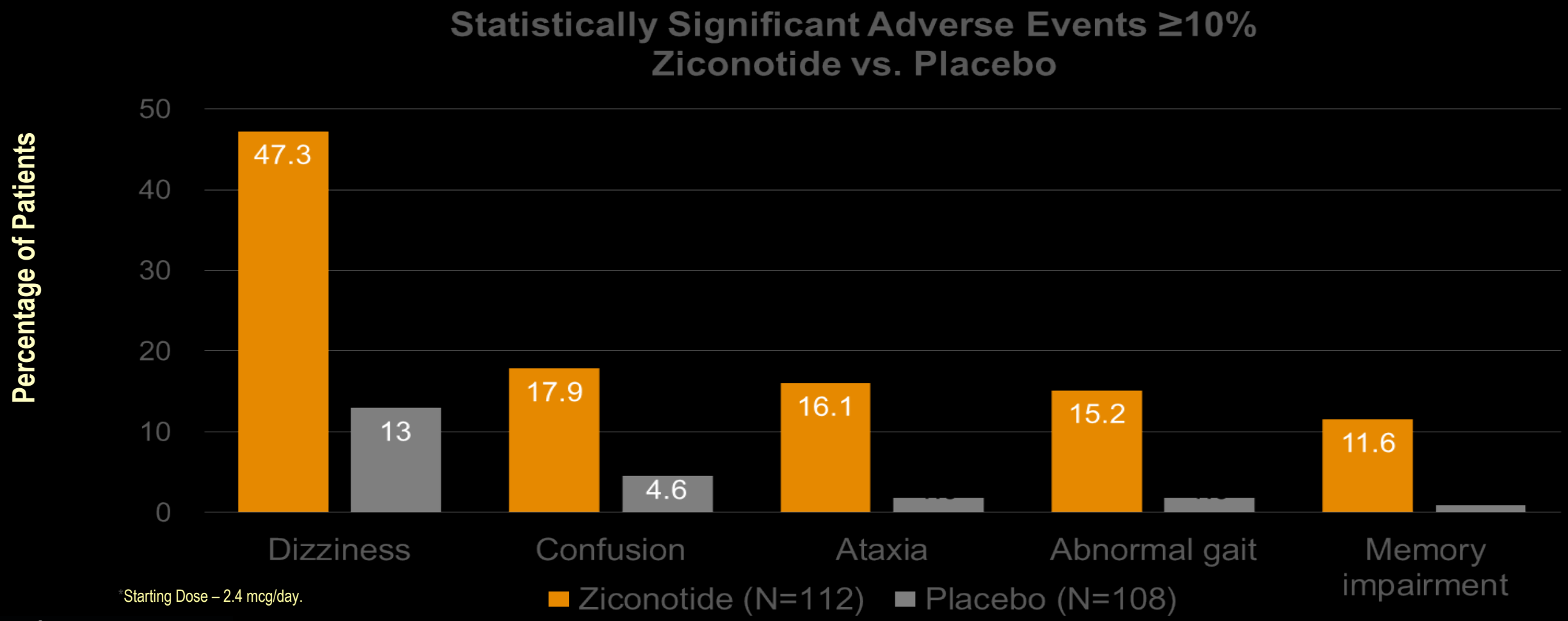
Nociceptors initiate action potentials that lead to calcium influx through N-type calcium channels.[1]

The result is neurotransmitter release into the synapses of the dorsal horn and propagation of the pain signal.[1,2]



1. Westenbroek RE, et al. *J Neurosci.* 1998;18(16):6319-6330. **2.** Kerr LM, et al. *Eur J Pharmacol.* 1988;146(1):181-183.

Slow Titration Reduces Incidence of Adverse Events*



*Starting Dose – 2.4 mcg/day.

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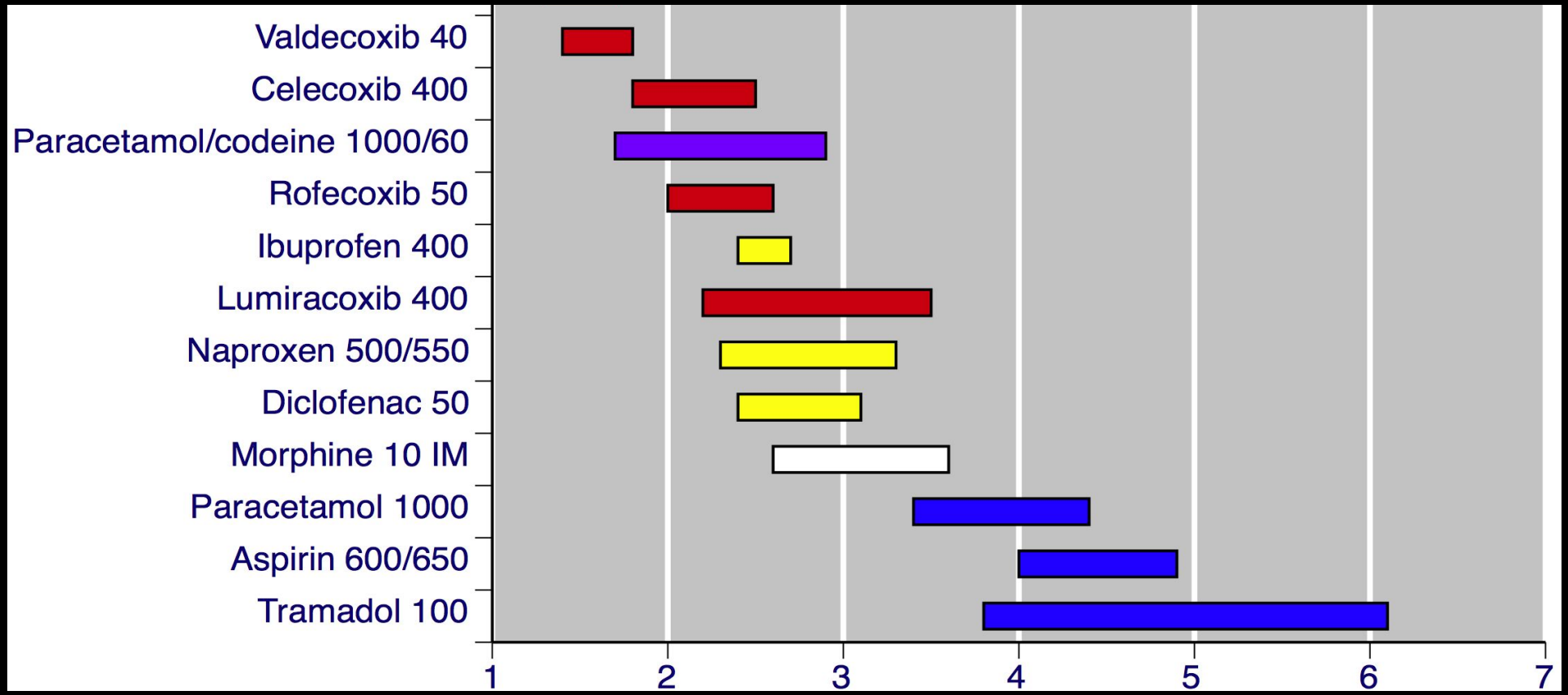
Rauck RL, et al. *J Pain Symptom Manage.* 2006;31(5):393-406.

Ziconotide and Morphine

- Wallace M 2008: stable Morphine 2 to 20 mg / day with Ziconotide (0.6 mcg to 7.2 mcg / day)
- Webster L 2008: stable Ziconotide > 4.8 mcg / day with addition of Morphine (varied doses)

Average Opioids (Oral Morphine equivalents mg / day)	Dose Week 1	Dose Week 2	Dose Week 3	Dose Week 4
< 100 mg	0.25	0.5	1.0	2.0
100 to 300 mg	0.5	1.0	2.0	3.0
> 300 mg	1.0	2.0	3.0	4.0

Oxford League Table of Analgesics



Analgesic Efficacy

- 2007 Oxford league table: at least 3 trials or 200 patients
- Numbers needed to treat are calculated for the proportion of patients with as least 50% of pain relief over 4 to 6 hours compared with placebo
- Randomised, double-blind, single-dose studies in patients with moderate to severe pain

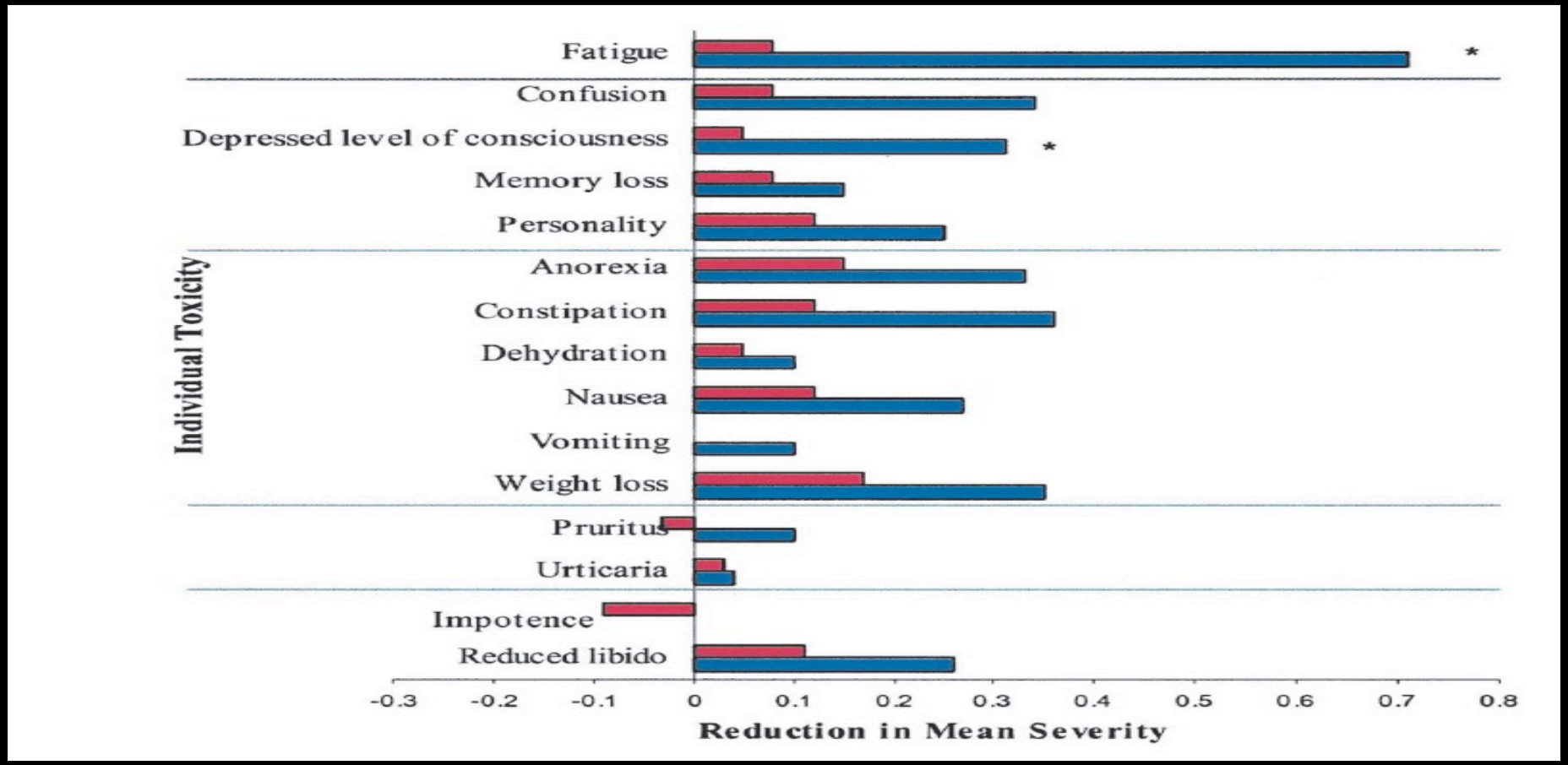
Numbers Needed To Treat

- Need 2 percentages of the same patient population
  - Either active vs placebo or active vs active
- Merged separate NNT Tables
  - Oxford Table of Analgesics for Acute Pain
  - Finnerup's Evidence-based algorithm for the treatment of neuropathic pain
  - Staats Ziconotide and Cancer / HIV treatment 2004
  - Smith / Staats IDDS vs CMM for cancer pain 2002
  - North, Deer, Slavin, Staats, Burton SUNBURST NNT Analysis

Analgesic Table: Oral, Topical, Intrathecal, SCS

Analgesic: Oral, Topical, IM, Intrathecal	NNT
Celecoxib 400	2.1
Tricyclic Antidepressants	2.1
Spinal Cord Stimulation (Burst DR)	2.2
Ibuprofen 400	2.5
Oxycodone IR 10 + Paracetamol 650	2.6
Ziconotide (Staats, Cancer and HIV)	2.8
Morphine 10 IM	2.9
Pregabalin	3.7
Gabapentin	5.1
Duloxetine	5.1
Topical Capsaicin (0.75 / 8%)	7/12
IDDS vs CMM (Smith, Staats IDDS Cancer)	7.3

IDDS vs CMM Toxicities (Smith Staats 2002)



Rational initiation of Intrathecal Treatment

- If the patient is on high dose oral opioids (>120 MEDs): taper for microdosing or ziconotide trial
- If the patient is on moderate oral opioids (50 to 110 MEDs): ideally taper opioids, then opioid or ziconotide initiation
- If the patient cannot tolerate low oral opioids: microdosing or ziconotide

Intrathecal Starting Dosages

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.

Intrathecal Bolus Trialing

Table 21. 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.

Maximum concentrations and daily dosages

Table 22. Maximum Concentrations and Daily Doses of Intrathecal Agents as Recommended by PACC 2012 (8) and 2016.

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.

For Patients on Intrathecal Therapy with Diminishing Effectiveness

- Consider an opioid rotation (may be non FDA approved)
- Add or substitute ziconotide
- Set a limit for opioid dosage and adjuvants (bupivacaine, clonidine) depending on localized or diffuse pain
- Consider patient controlled intrathecal analgesia (PCITA) for continuous + bolus or bolus-only analgesia

Draft NANS Reprogramming and Refilling Intrathecal Medication Delivery Pumps

- Lawrence Poree, Todd Sitzman, Peter Konrad, Lisa Sterns, Dave Copenhaver and others 2019
- Procedures, protocols, and policies for allied health providers performing implanted intrathecal drug pump refills
- Implantable drug delivery systems (IDDS) require maintenance by reprogramming and regular drug reservoir refills on average 30 to 90 days.
- Common practice to have allied health providers (nurses, nurse practitioners, and physician assistants) perform the refills and reprogramming

References

- Fine P and Cheatle M. Common adverse effects and complication of long-term opioid therapy. Pain Medicine Oct 2015; Vol 16, Suppl 1.
- Deer T, Pope J, et al. The polyanalgesic consensus conference (PACC): recommendations on intrathecal drug infusion systems best practices and guidelines. Neuromodulation 2016
- Use caution with implanted pumps for intrathecal administration of medicine for pain management: FDA safety communication Nov 14, 2018. https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm625789.htm

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