Non-CME Webinar Series
designed with the trainee in mind

second Tuesdays of odd-numbered months

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Intrathecal Drug Delivery

Tuesday, March 9, 2021

7-8:15 pm ET

Disclosures – Michael Leong, MD

- Board of Directors (Secretary), Pacific Spine and Pain Society
- Board of Directors, American Society of Pain and Neuroscience
- Co-director of Advocacy and Legislative Fellowship, North American Neuromodulation Society
- Consultant/Independent Contractor
  - Sorrento Therapeutics – Resiniferatoxin
- Grant/Research Support
  - Wex Pharmaceuticals – Halneuron (tetrodotoxin)

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

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.**	

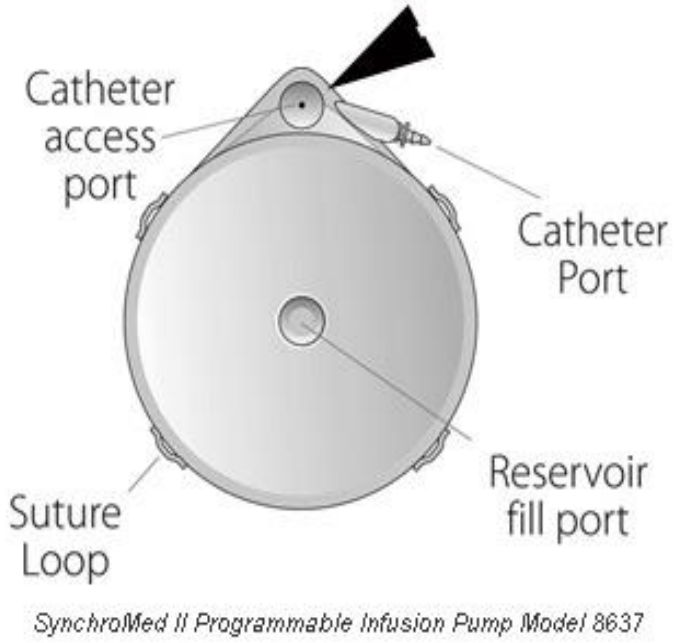
FDA rationale

- 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.

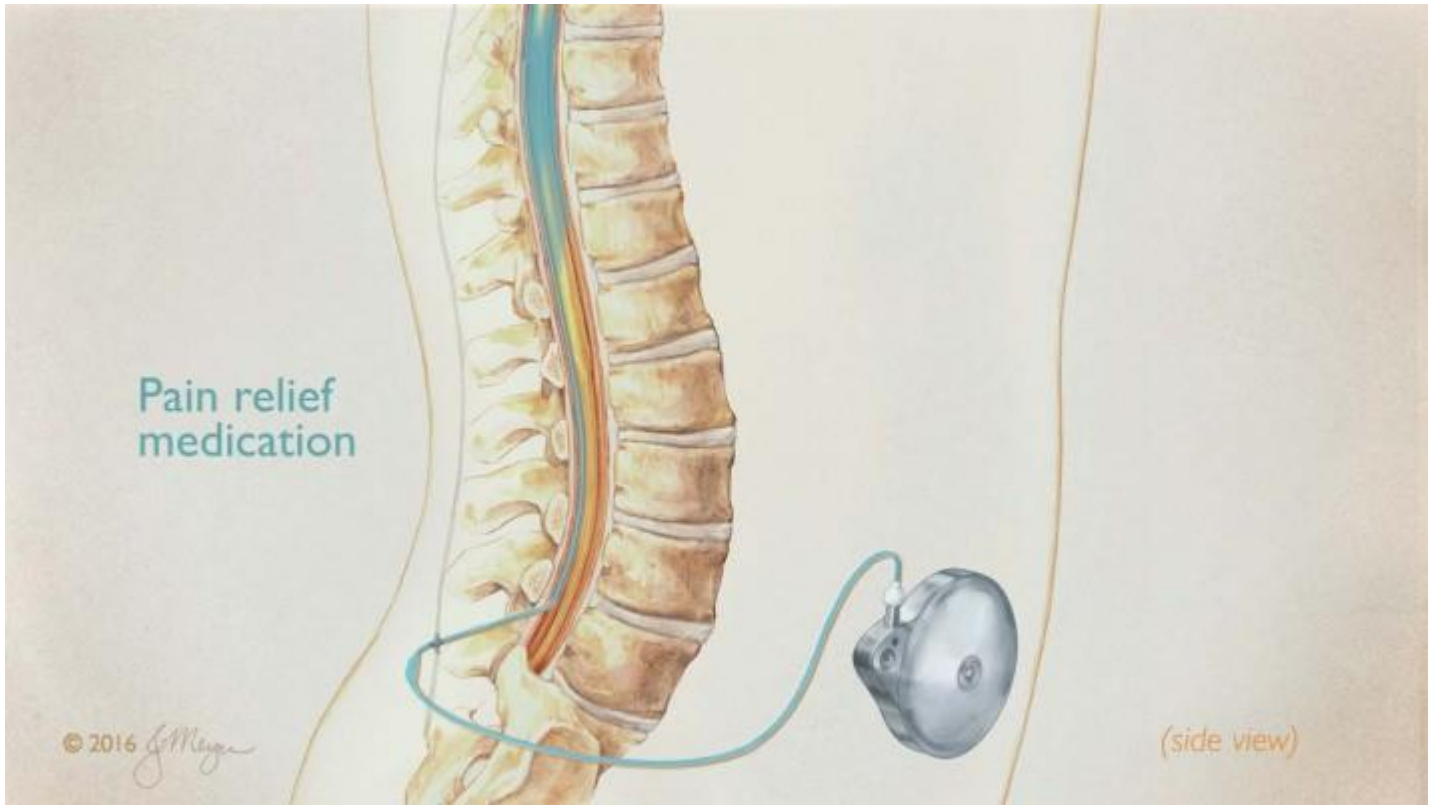
Rationale for use of Intrathecal delivery:

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

Intrathecal Pump Device and Placement



Smyth, C., Ahmadzai, N., Wentzell, J. et al. Intrathecal Analgesia for Chronic Refractory Pain: Current and Future Prospects. *Drugs* 75, 1957–1980 (2015).



Adler JA, Lotz NM. Intrathecal pain management: a team-based approach. *J Pain Res*. 2017;10:2565-2575.

Intrathecal Diffusion Factors

- Catheter positioning – place as close to area of pain
- Infusion volume and flow rate
- Biochemical characteristics of drug
- Cerebrospinal Fluid Dynamics
  - blood pressure
  - heart rate
  - respiratory movement
- Consideration for pulsatile intrathecal drug delivery vs standard continuous infusion

PACC Guidelines Feb 2017

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

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Morphine

- Mechanism of action: mu opioid agonist
- Neurotoxicity: granuloma formation
- Studies from 1983 to 2000 show efficacy with long term infusion for chronic cancer and noncancer pain
- Prospective studies (open label) for chronic pancreatitis, vertebral fractures
- One retrospective study showed responder rates higher in men than women – Reig Neuromodulation 2000

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.

Summary of Side-effects for IT Morphine

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 Microdosing

- Decreased efficacy with increasing duration of therapy but in the absence of disease progression
- Opioid Induced Hyperalgesia – controversial
- Grider Pain Physician 2011: 6 wks opioid free then trial of IT morphine 25, 50, 100, 200, 400 mcg
- Hamza Pain Medicine 2012: n = 61, 6+ yrs of intractible noncancer pain, over 3 -5 weeks tapered to 50% opioids > IT trial, if + trial, taper all opioids 7 days prior to IT pump implant; decreased pain and improved function at 1.4 mg IT morphine per day
- Hayek critique: no dose response 0.25 or 0.5 mg IT morphine trial, IT implant under GA

HYDROMORPHONE

- More potent than morphine (5:1 ratio)
- Mechanism of action: mu opioid agonist
- Neurotoxicity: granuloma formation
- Mallinckrodt – formal FDA approval studies
  - Controlled two arm parallel-group randomized withdrawal study
- Side-effect of peripheral edema: 61 woman with LE edema on IT morphine, switched to IT HM same edema after 2 months

FENTANYL and SUFENTANIL

- Mechanism of action: lipophilic mu agonist
- Neurotoxicity: no granulomas as a single agent
- Recommend to place the tip of the catheter near the painful region
- Maximum dosage recommendation 1000 mcg per day

- Mechanism of action: potent mu agonist
- Neurotoxicity: not in canine bolus model
- Lower incidence of peripheral edema
- Maximum dosage recommendation of 500 mcg per day

BACLOFEN

- Treatment of intractible spasticity: SCI, MS, CP, CVA, dystonia
- Mechanism of action: GABA-B agonist
- Neurotoxicity: possible in monotherapy
- 1:100 spinal to oral ratio
- Excessive sedation from oral administration

Recommendations for baclofen

- Consider usage at IT medication to treat spasticity
- Can be used as an adjuvant to treat pain
- Care regarding mitigating withdrawal from baclofen
- Physical therapy to aid titration and assessment is recommended
- Consider using bolus or flex dosing strategies to improve spasticity rather than continuous infusion

Baclofen Withdrawal

per Joey Sclafani, MD

- Itchy
- “Bitchy” – mental status changes, confusion
- Twitchy – NOT dystonia, Velocity dependent
- Modified Ashworth Scale

Grade	Description
0	No increase in muscle tone
1	Slight increase in muscle tone, catch, minimal resistance at end of motion
1+	Slight increase in muscle tone, catch, minimal resistnace throughout the remainder (less than half) of ROM
2	Marked increase in muscle tone through most ROM but affected part easily moved
3	Considerable increase in muscle tone, passive mvt difficult

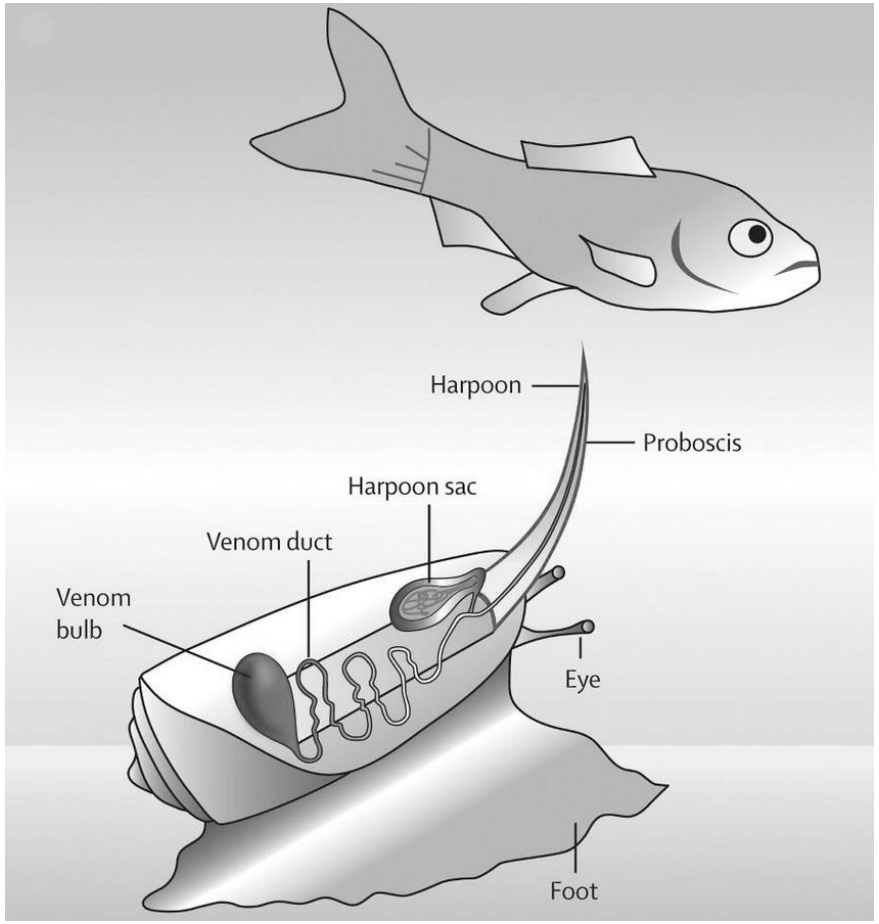
clonidine

- Mechanism of action: alpha 2 adrenergic agonist; may inhibit glial cell activation and proinflammatory cytokines
- Neurotoxicity: no granuloma and in dogs with clonidine and morphine, decrease in granuloma
- CRPS: decrease pain, allodynia, hyperalgesia, and mean arterial blood pressure
- Increases analgesia duration and decreases morphine usage for postoperative pain
- May precipitate hypotension in patients with baseline hypertension
- Decreases Ziconotide concentration in mixture

BUPIVACAINE

- Mechanism of action: amide local anesthetic
- Neurotoxicity: safe at clinical doses alone or with morphine
- Not FDA approved for continuous IT use
- Typical doses: 3.8 mg/day to 15 mg/day
- High lipid solubility so need to place the catheter in the posterior IT space

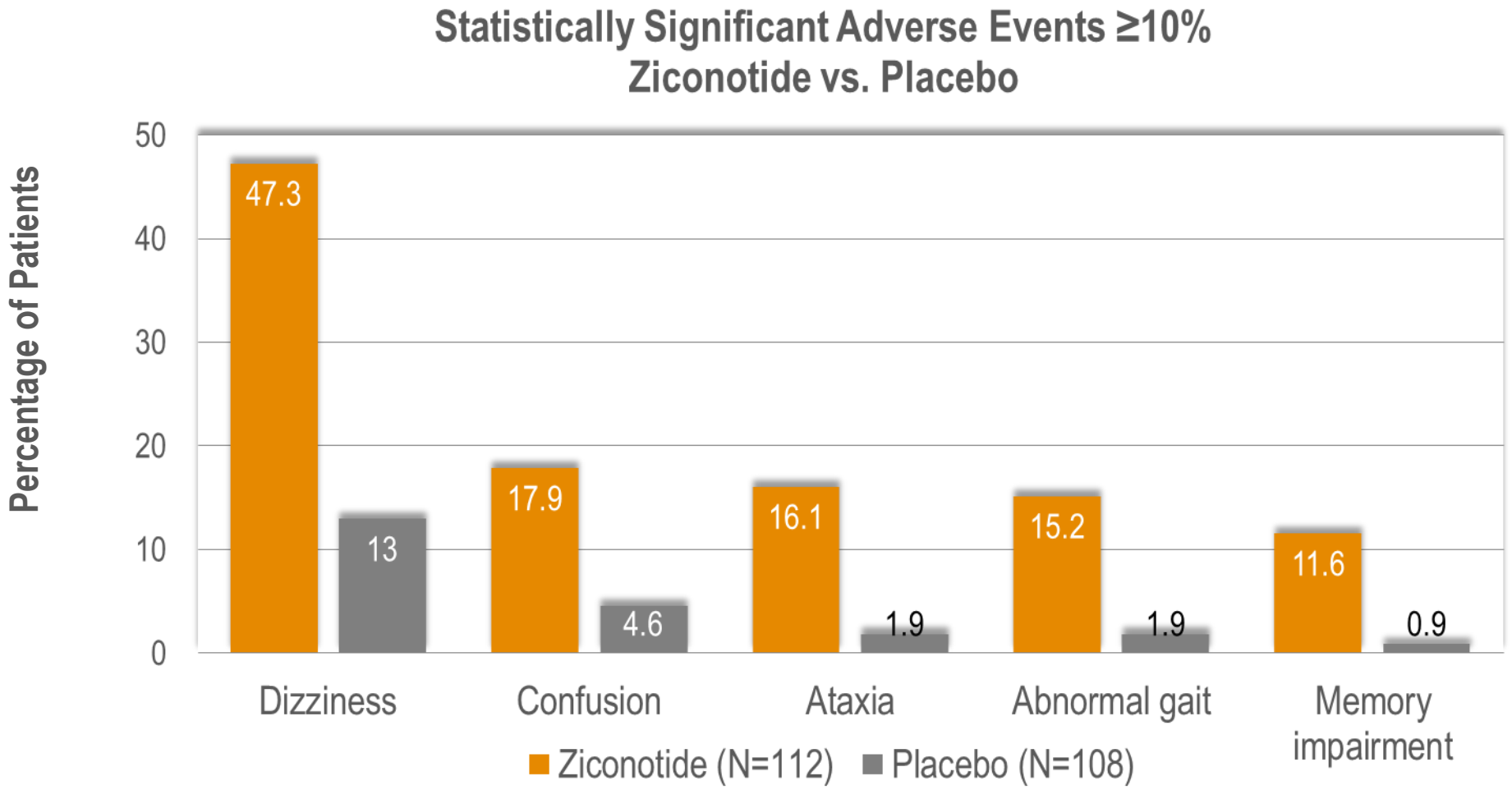
Conus Magus Snail Venom Conotoxin in Action



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; increased spread in CSF
- Trialing: bolus vs continuous infusion
- Some practitioners recommend meclizine treatment
- Proper hydration is important to limit hypotension
- Black box warning for cognitive impairment and hallucinations

Slow Titration Reduces Incidence of Adverse Events*



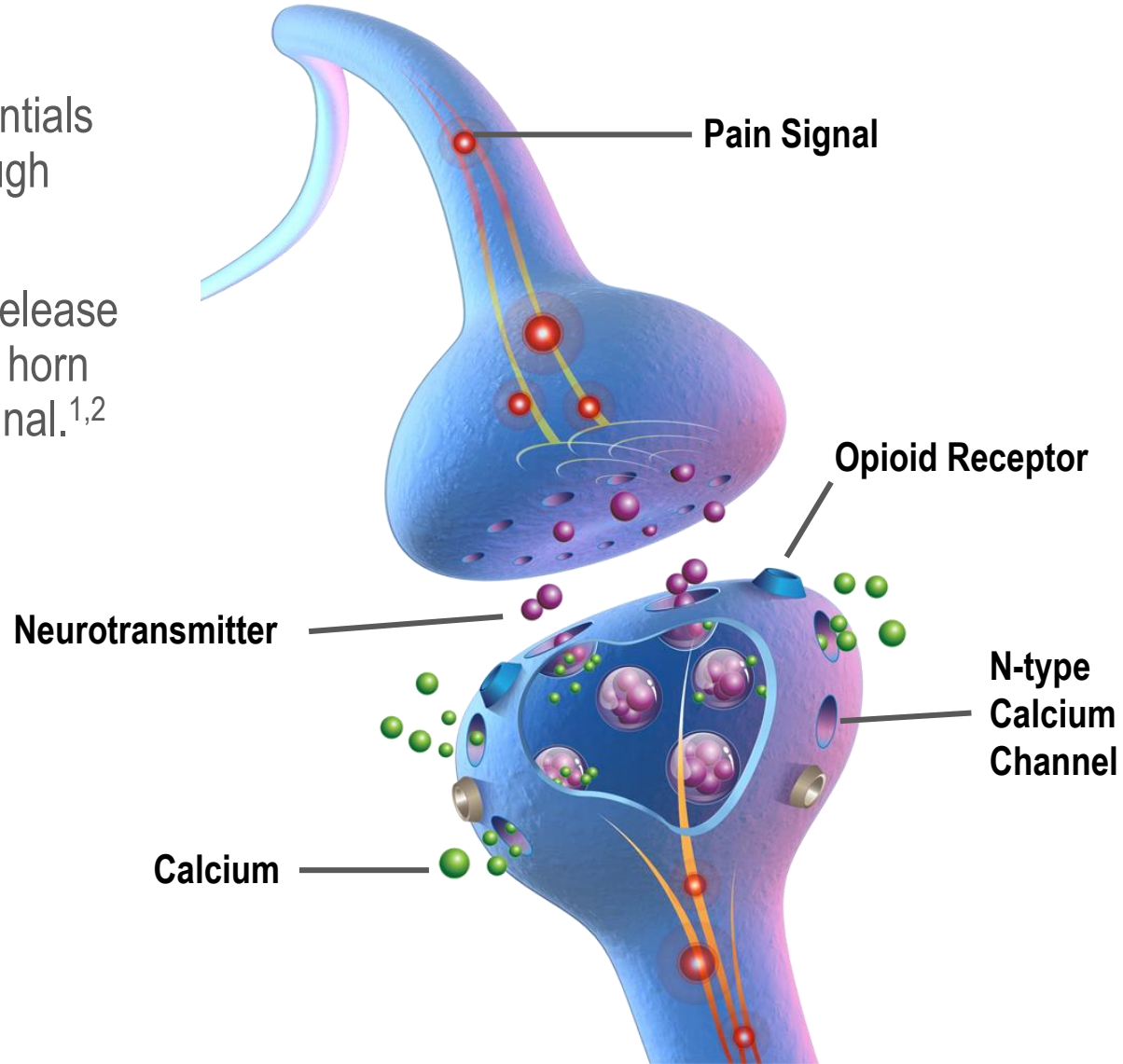
*Starting Dose – 2.4 mcg/day.

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

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.

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

Neurotoxic Drugs – not recommended

- Not recommended except in special cases
- Opioids (Meperidine, Methadone, Tramadol)
- Local Anesthetics - Tetracaine
- Adrenergic Agonist – Dexmedetomidine
- NMDA Antagonists – all agents
- Nonopioids (Droperidol, Midazolam, Methylprednisone, Ondansetron)

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.

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.

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

Rational initiation of Intrathecal Treatment

1. If the patient is on high dose oral opioids (>120 MEDs): taper for microdosing or ziconotide trial
2. If the patient is on moderate oral opioids (50 to 110 MEDs): ideally taper opioids, then opioid or ziconotide initiation
3. If the patient cannot tolerate low oral opioids: microdosing or ziconotide
4. Consider addition of combination agents: clonidine, bupivacaine

For patients on intrathecal therapy with diminishing effectiveness

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

HHS Integrative Treatment Plan for Chronic Pain

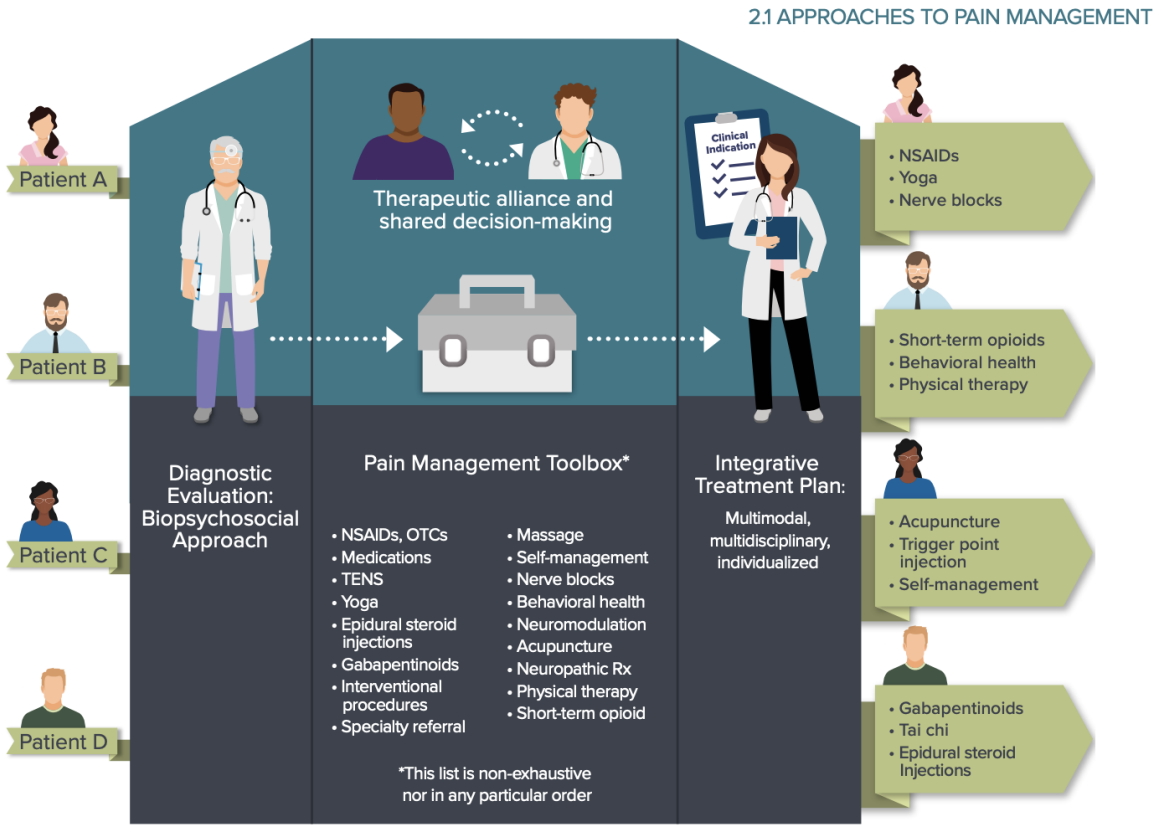


Figure 6: Individualized Patient Care Consists of Diagnostic Evaluation That Results in an Integrative Treatment Plan That Includes All Necessary Treatment Options

https://kcmedicine.org/dr_singh_comments/

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Thank You For Listening

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