

Intrathecal Drug Delivery

How Did We Get Here?

A Journey from Macro to Micro Dosing

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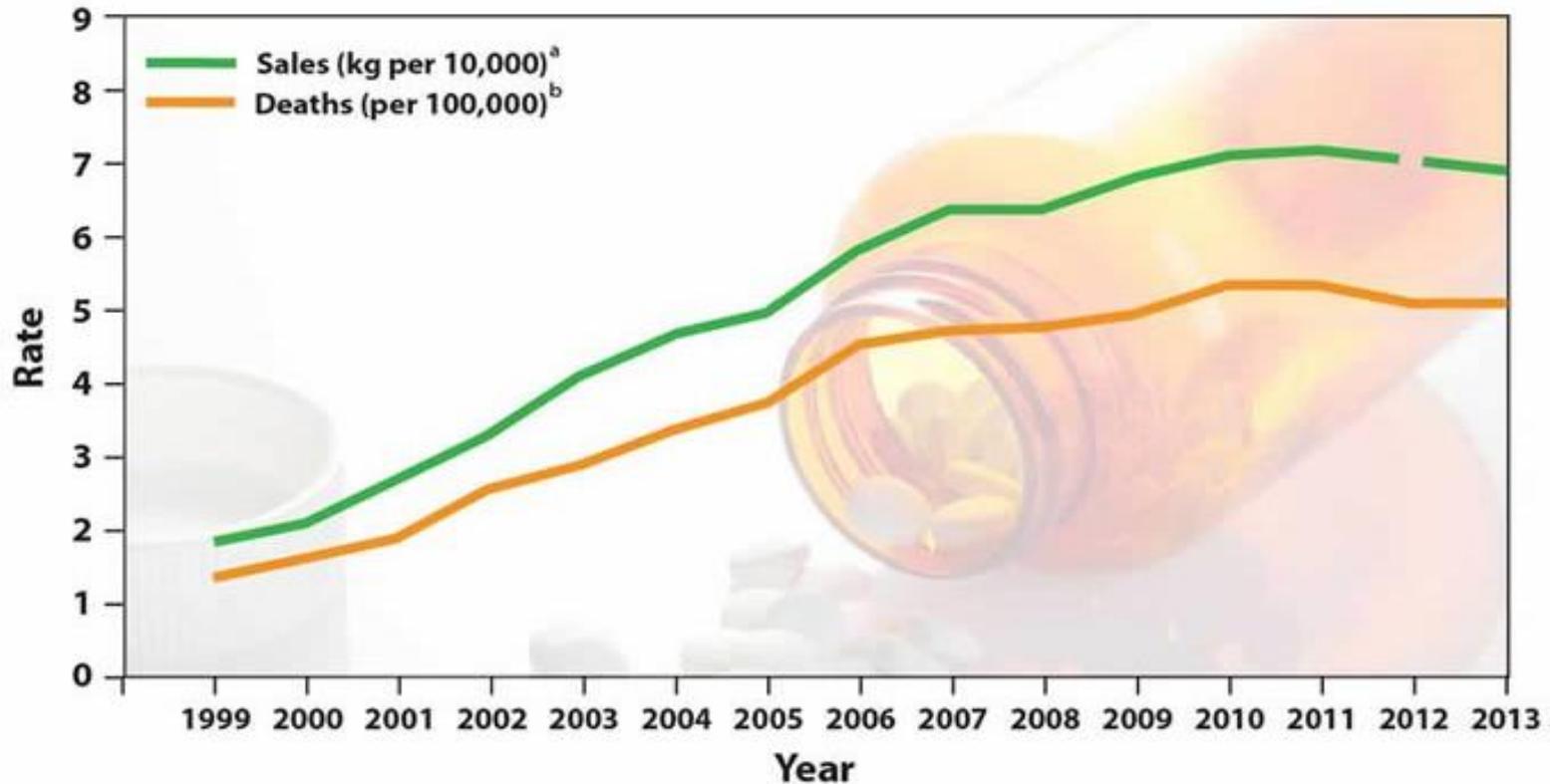
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Summary

- Opioid Overdose Epidemic
- The Past: *Macro dosing*
- The Need: More options
- Opioid Induced Hyperalgesia (OIH)
- Intrathecal Opioids
- Patient Selection
- Low dose clinical studies
- CSF Flow
- Optimal dosing strategy for intrathecal drug delivery, in general
- Optimal dosing strategy for Micro-dosing intrathecal drug delivery
- OIH Case Study (in cancer)
- Micro-Dosing Case Study

Prescription Painkiller Sales and Deaths



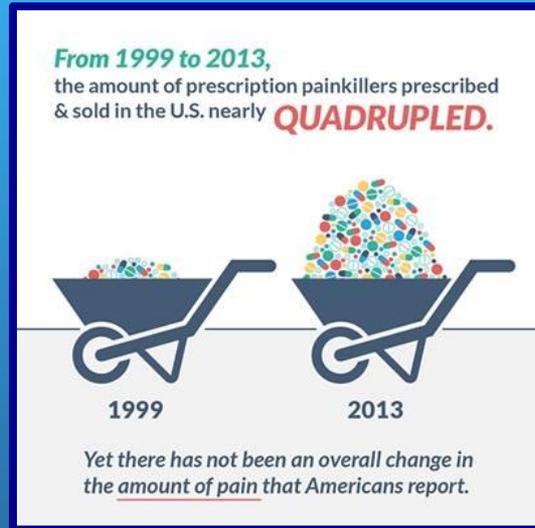
Sources:

^aAutomation of Reports and Consolidated Orders System (ARCOS) of the Drug Enforcement Administration (DEA), 2012 data not available.

^bCenters for Disease Control and Prevention. National Vital Statistics System mortality data. (2015) Available from URL:

<http://www.cdc.gov/nchs/deaths.htm>.

Prescription Painkiller Sales and Deaths



- Deaths from prescription painkillers have also quadrupled since 1999.⁴
- 16,000 people died in the United States from prescription painkillers in 2013.⁴
- Nearly 2 million Americans aged 12 years and older either abused or were dependent on opioids in 2013.⁵

Deaths from Prescription Opioid Overdose

- Every day in the United States, 44 people die as a result of prescription opioid overdose.
- Between 1999 and 2013:
 - Most were ages 25-54
 - The overdose rate for ages 55-64 increased more than 7 fold
 - The large majority were non-Hispanic whites
 - 1.6 per 100,000 in 1999
 - 6.8 per 100,000 in 2013
 - The rate more than doubled for non-Hispanic blacks
 - The rate only slightly increased for Hispanics
 - The rate increased nearly four fold for American Indian or Alaska Natives.

Centers for Disease Control and Prevention. National Vital Statistics System mortality data. (2015) Available from URL: <http://www.cdc.gov/nchs/deaths.htm>.

Deaths from Prescription Opioid Overdose

- Men are more likely to die from painkiller overdose than women
- However, deaths increased more than 400% in women compared to 237% among men²
- Drug overdose death was the leading cause of injury death in 2013
- Among individuals 25-64, drug overdose caused more deaths than MVA's³
- There were 43,982 drug overdose deaths in 2013
 - 22,767 (51.8%) were related to prescription drugs.¹
 - 16,235 (71.3%): Opioids¹
 - 6,973 (30.6%): Benzodiazepines¹
 - *Often a combination of opioids and benzodiazepines¹

¹Centers for Disease Control and Prevention. National Vital Statistics System mortality data. (2015) Available from URL:

<http://www.cdc.gov/nchs/deaths.htm> ²Centers for Disease Control and Prevention. Vital Signs: Overdoses of Prescription Opioid Pain Relievers and Other Drugs Among Women – United States, 1999-2010. MMWR 2013; 62(26);537-542. ³Centers for Disease Control and Prevention. Web-based Injury Statistics Query and Reporting System (WISQARS) [online]. (2014) Available from URL: <http://www.cdc.gov/injury/wisqars/fatal.html>.

Cost of Drug Misuse and Abuse

- 5.1 million drug related E.R. visits in 2011
 - 49% (2.49 million) related to drug misuse/abuse
 - 1.42 million related to prescription drugs (28%)
 - 420,040 related to opioid analgesics (8.2%)
 - 1.25 million related to illicit drugs (25%)
- In the United States prescription opioid abuse costs were about 55.7 billion in 2007
 - 46% due to lost productivity
 - 45% due to healthcare costs
 - 9% due to criminal justice costs

Substance Abuse and Mental Health Services Administration. Highlights of the 2011 Drug Abuse Warning Network (DAWN) findings on drug-related emergency department visits. The DAWN Report. Rockville, MD: US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration; 2013. Available from URL: <http://www.samhsa.gov/data/2k13/DAWN127/sr127-DAWN-highlights.htm>

Sources of Prescription Opioids

for people using opioids non-medically 200 or more days per year

- 27%: Using their own prescriptions
- 26%: From friends or relatives for free
- 23%: Buying from friends or relatives
- 15%: Buying from a drug dealer
- Those at highest risk for an overdose are about 4 times more likely than the average user to buy drugs from a dealer or other stranger.¹

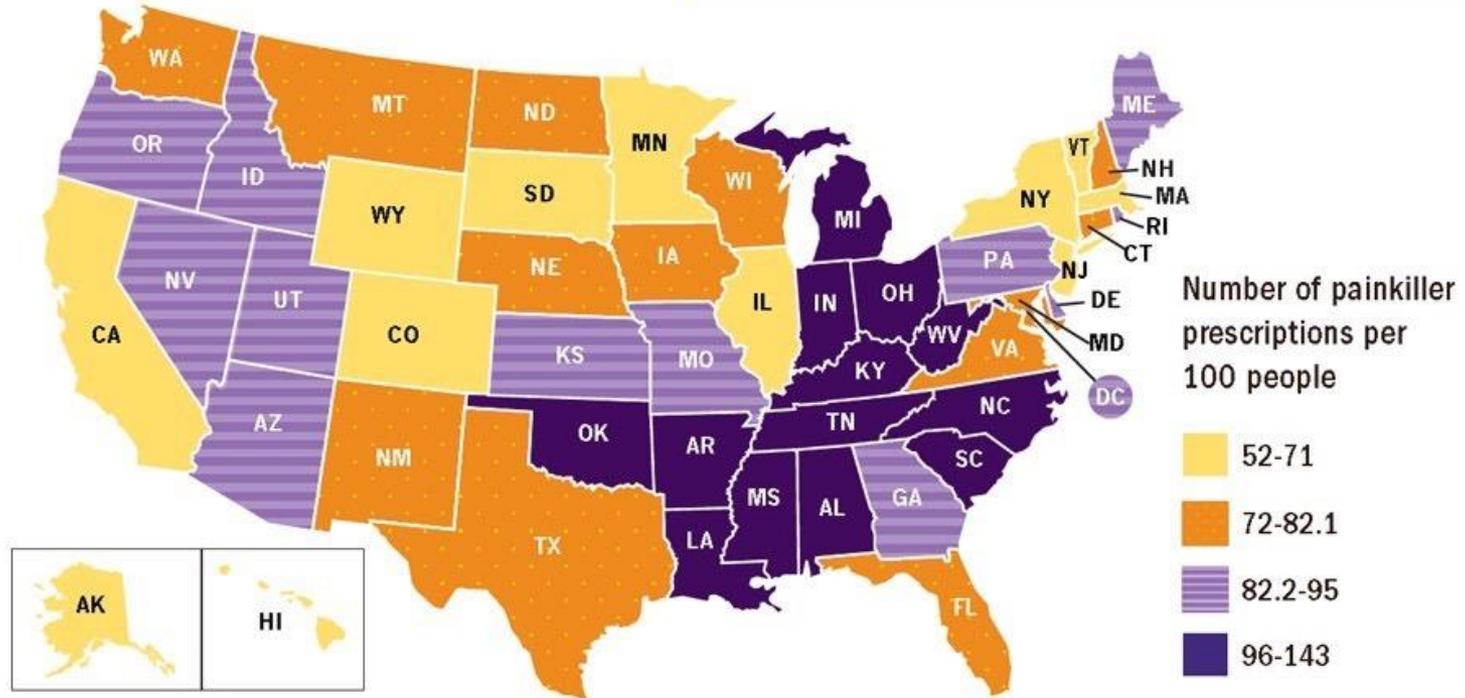
¹Jones C, Paulozzi L, Mack K. Sources of prescription opioid pain relievers by frequency of past-year nonmedical use: United States, 2008-2011. *JAMA Int Med* 2014; 174(5):802-803.

State Prescription Variability

- Prescribing rates for opioids vary widely across different states.
- Healthcare providers in the highest prescribing state wrote more than 3 times as many opioid painkiller prescriptions than the lowest prescribing state.¹
- Health issues that cause people pain do not vary much from place to place and do not explain this variability in prescribing.
- Health care providers in different parts of the country do not agree on:
 - When to prescribe
 - How much to prescribe
- Some of the increase in demand is from people who:
 - Use the medications non-medically
 - Use drugs without a prescription
 - Sell them
 - Obtain them from multiple prescribers
- Many states report problems with for-profit, high volume pain clinics (“pill mills”) that prescribe large quantities of painkillers to people who don’t need them medically.

State Prescription Variability

Some states have more painkiller prescriptions per person than others.



SOURCE: IMS, National Prescription Audit (NPA™), 2012.

Risk Factors for Prescription Painkiller Abuse and Overdose



Risk Factors for Prescription Painkiller Abuse and Overdose



Obtaining overlapping prescriptions from multiple providers and pharmacies.



Taking high daily dosages of prescription painkillers.



Having mental illness or a history of alcohol or other substance abuse.



Living in rural areas and having low income.

Risk Factors for Prescription Painkiller Abuse and Overdose

- Medicaid
 - Inappropriate provider prescribing practices and patient use are substantially higher among Medicaid patients than among privately insured patients.
 - In a 2010 study 40% of Medicaid enrollees with painkiller prescriptions had at least one indicator of potentially inappropriate use or prescribing.
 - Overlapping painkiller prescriptions
 - Overlapping painkiller and benzodiazepine prescriptions
 - Long acting or extended release prescription painkillers for acute pain and high daily doses

Efficacy of Systemic Opioids

- Among 70 randomized trials on opioids
 - Nearly all were short-term efficacy (16 weeks or less)
 - Most excluded high-risk patients
 - Substance abuse, medical or psychiatric co-morbidities
- Patients are not uniform in response to opioids
 - Dosages
 - Analgesia
 - Intolerable side effects
 - Non-response
- Side effects can limit efficacy

The past: *Macro-dosing*

- High dose intrathecal pumps
- Multiple intrathecal medications
- Combination systemic therapy
 - High dose oral/transdermal opioids
- Escalating doses
- High Pain Scores
- Side effects
- High maintenance therapy

The past: *Macro-dosing*

- Reimbursement went down substantially
- Pain providers largely lost interest in the therapy
- Spinal Cord Stimulation became the implantable therapy of choice
 - Better reimbursement
 - Lower maintenance therapy
- Less and less pumps implanted for chronic non-malignant pain

The need: *More Options*

- Failed SCS trials and implants.
- Back pain not well controlled with SCS.
- Declining reimbursement for SCS and more difficult insurance authorization.
- Escalating doses of systemic opioids
 - Side effects
 - Worsening pain
 - No functional improvement
 - No objective evidence of better pain relief
 - Physician liability
- Other options needed for these patients.
- Evolving concept of Opioid Induced Hyperalgesia (OIH)

Opioid Induced Hyperalgesia

- **Definition**: A state of nociceptive sensitization caused by exposure to opioids.
 - A patient who receives opioids for pain, paradoxically has worsening pain.
 - May explain loss of opioid efficacy in some patients.

Opioid Induced Hyperalgesia

- Several observational, cross-sectional, & prospective controlled trials have examined the expression and potential clinical significance of OIH.
 - Former opioid addicts (Methadone maintenance therapy)
 - Modality-specific increased sensitivity to cold pressor pain
 - Hyperalgesia to electrical pain was weak
 - Hyperalgesia to mechanical pain was weak
 - Perioperative exposure in patients undergoing surgery
 - Increased postoperative pain despite increased postoperative opioids use in patients who were exposed to high dose opioids intraoperatively
 - Other studies show no difference

Opioid Induced Hyperalgesia

- Healthy human volunteers after acute opioid exposure using human experimental pain testing
 - Multiple investigators have shown direct evidence of OIH in humans using models of secondary hyperalgesia and cold pressor pain.
- Chronic Pain Patients
 - Patients being tapered off opioids that were on a greater baseline morphine equivalent to begin with, were associated with higher hyperalgesia values
 - Chronic pain patients on opioids were hyperalgesic when exposed to the cold pressor test.
 - Patients on a steady dose of opioids were more likely to find a subcutaneous local anesthetic injection for an interventional procedure more painful.

Opioid Induced Hyperalgesia

- Mechanism: generally thought to result from neuroplastic changes in the peripheral and central nervous system that lead to sensitization of pro-nociceptive pathways.
 - Central glutaminergic system
 - NMDA receptors
 - Spinal dynorphins
 - Descending facilitation
 - Genetic mechanisms
 - Decreased reuptake and enhanced nociceptive response.

Opioid Induced Hyperalgesia

- Central Glutaminergic System (CGS)
 - The most common proposed etiology
 - Current data suggests a common cellular mechanism in part mediated through activation of CGS with:
 - Opioid induced desensitization
 - Pharmacological Tolerance
 - Opioid Induced Hyperalgesia
- The excitatory neurotransmitter NMDA plays a central role in the development of OIH
 - NMDA antagonists can reverse opioid enhanced nociception through the CGS
 - NMDA receptors (NMDAr) become activated and when inhibited, prevent the development of tolerance and OIH
 - The glutamate transporter system is inhibited, increasing the amount of glutamate available to the NMDAr
 - Calcium regulated intracellular protein kinase C is likely a link between the cellular mechanisms of tolerance and OIH
 - Cross talk of neural mechanisms of pain and tolerance may exist
 - Prolonged morphine administration:
 - Induces neurotoxicity via the via NMDAr mediated cell death in the dorsal horn
 - Elicits increased levels of the pro-nociceptive peptide CGRP and Substance P within the DRG ganglia

Opioid Induced Hyperalgesia

- Spinal Dynorphins
 - Levels increase with continuous infusions of μ -receptor agonists
 - Leads to release of CGRP from primary afferents
 - OIH is a pro-nociceptive process facilitated by the synthesis of excitatory neuropeptides and their release upon peripheral nociceptive input
 - Increased activity of the excitatory peptide neurotransmitter CCK in the RVM activates spinal pathways that up-regulate spinal dynorphins
 - Enhances nociceptive input at the spinal level

Opioid Induced Hyperalgesia

- Descending Facilitation
 - OIH activates facilitative descending pathways from the RVM
 - Subsets of neurons (on and off cells within the RVM) have a unique response to opioids
 - Lesioning of the descending pathway to the spinal cord (dorsolateral funiculus) prevents the increase in excitatory neuropeptides seen in OIH

Opioid Induced Hyperalgesia

- Genetic Mechanisms
 - Murine (mice and rats) genetics are used to identify genomic loci linked to OIH
 - A growing collection of literature supports that genetics influence pain sensitivity, analgesic responses and potentially OIH

Opioid Induced Hyperalgesia

- Decreased reuptake and enhanced nociceptive response.
 - Decreased re-uptake of neurotransmitters from the primary afferent fibers & enhanced responsiveness of spinal neurons to nociceptive neurotransmitters have been considered the common mechanism among those used to explain OIH
 - Enhanced expression of β_2 adrenergic receptors occurs during chronic exposure to opioids

Opioid Induced Hyperalgesia

- Should be suspected when:
 - Waning of opioid treatment effect without disease progression
 - Unexplained pain reports
 - Diffuse allodynia not associated with original pain
 - Increased levels of pain despite increasing dosages
 - Treatment:
 - Reduction of opioid dosage
 - Tapering off of opioids
 - Supplementation with NMDA receptor modulators

Redefine Patient Selection

First Choices for Intrathecal Drug Delivery

- Elderly
 - Axial Pain
 - Spinal Stenosis
- Failed Back Surgery Syndrome
- Good analgesia with systemic opioids but intolerable side effects
- Cancer pain



Redefine Patient Selection

Difficult choices for Intrathecal Drug Delivery

- High oral opioid use with minimal perceived benefit
- Poorly defined etiology of pain
- Poor compliance to previous therapies
- Young age
 - Not an absolute contraindication
- Positioning as a salvage therapy
 - Diminished outcomes

Redefine Patient Selection

Some conditions have not experienced good outcomes:

- Headache
- Fibromyalgia
- Atypical facial pain
- Non-cancer head-neck pain
- Borderline personality

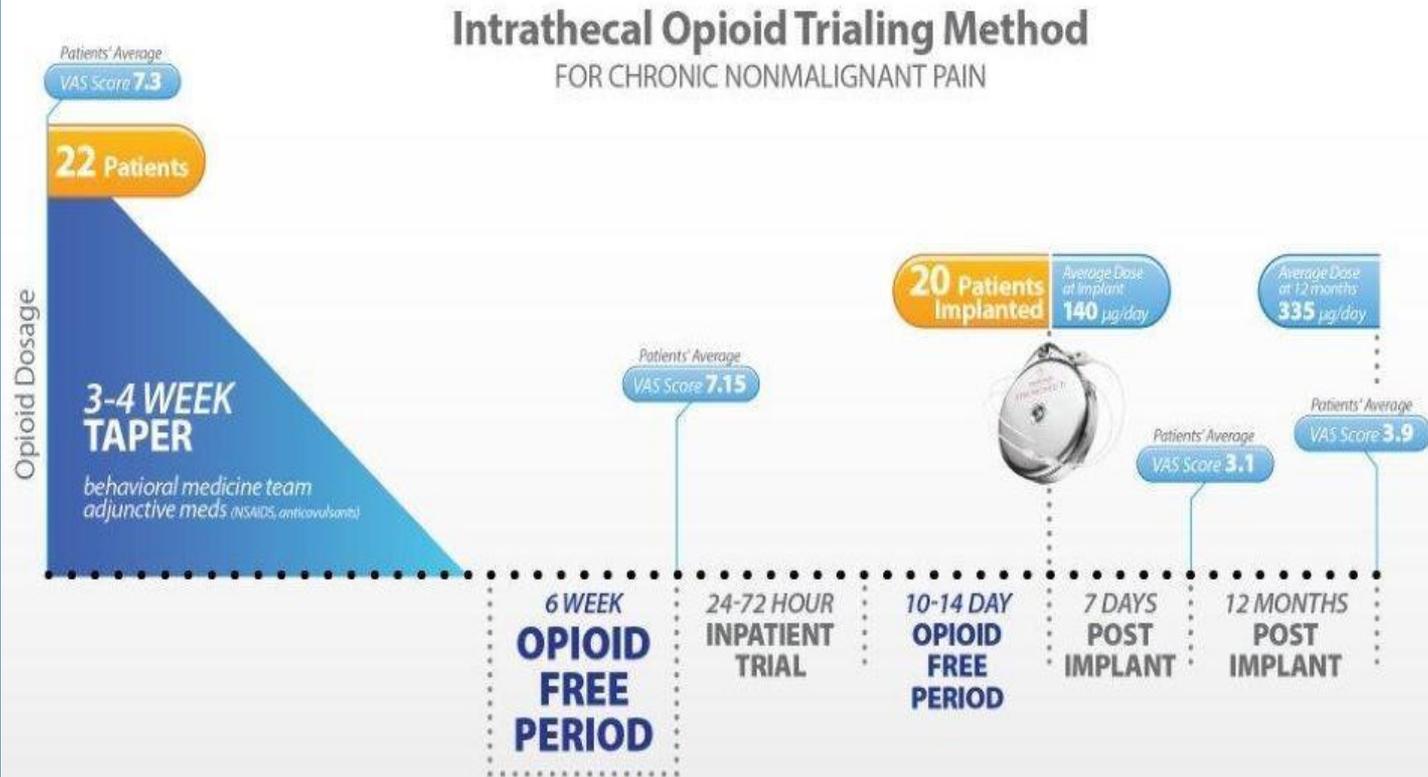
Dosing Strategies Publications

- Patient Selection and Outcomes Using a Low-Dose Intrathecal Opioid Trialing Method for Chronic Nonmalignant Pain (Grider, et. al)
 - *Pain Physician* 2011

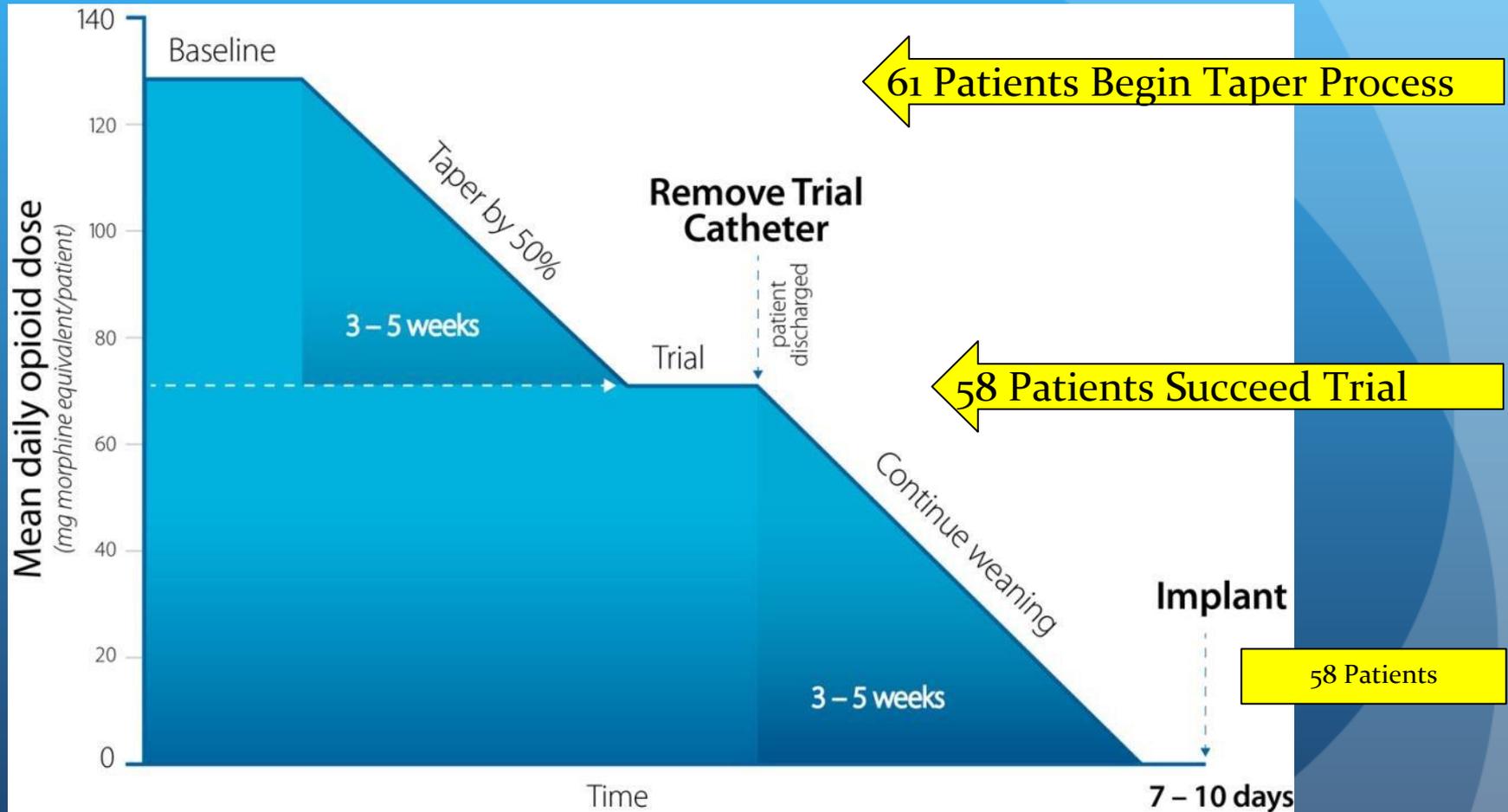
- Prospective Study of 3-Year Follow-Up of Low-Dose Intrathecal Opioids in the Management of Chronic Nonmalignant Pain (Hamza, et. al)
 - *Pain Medicine* 2012



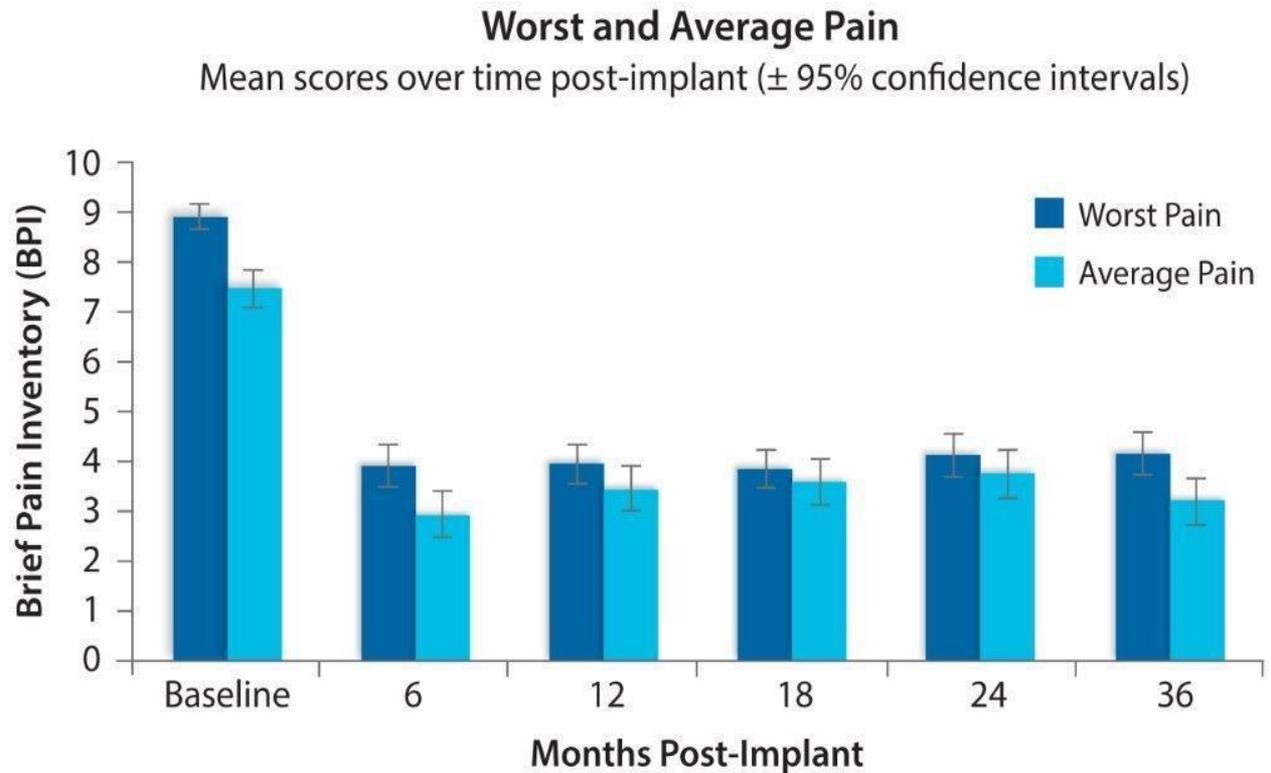
Grider et al. Method and Results



Hamza et al: Tapering and Trialing Protocol

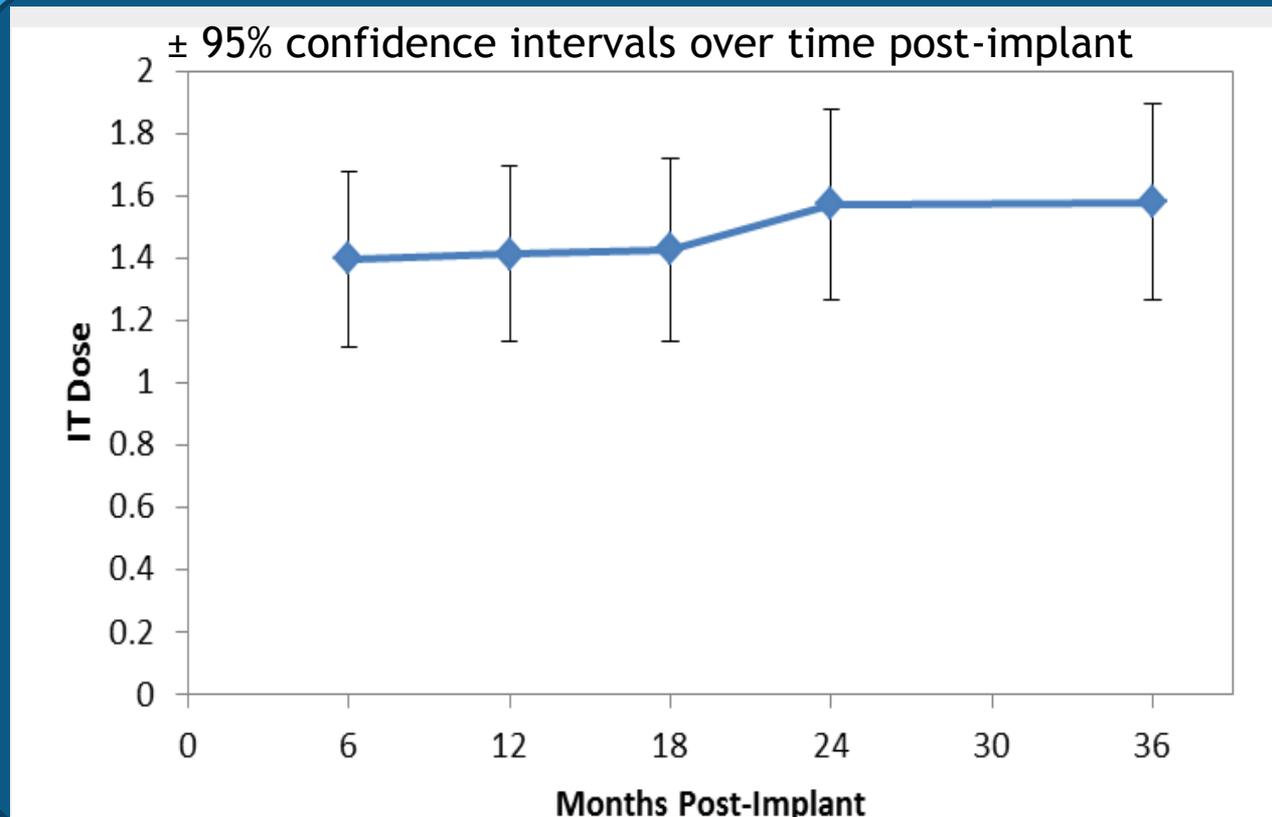


Hamza et al. Pain Score Results



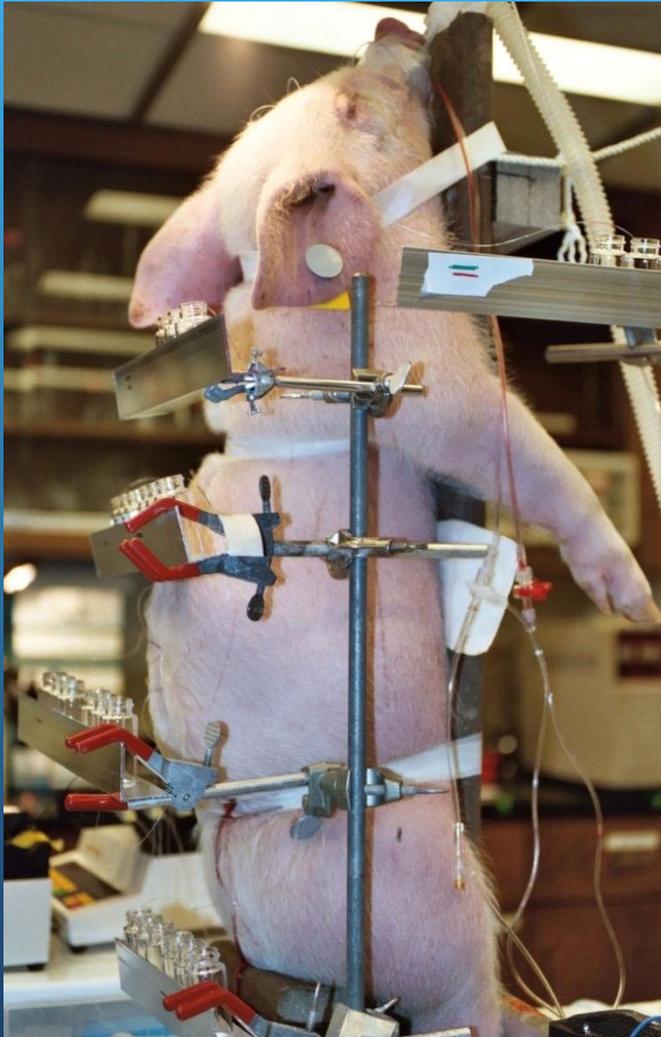
Hamza M, Doleys D, Wells M, et al. Prospective study of 3-year follow-up of low-dose intrathecal opioids in the management of chronic nonmalignant pain. *Pain Med.* 2012;13(10):1304-1313.

Hamza et al : Mean IT Dose



Hamza M, Doleys D, Wells M, et al. Prospective study of 3-year follow-up of low-dose intrathecal opioids in the management of chronic nonmalignant pain. *Pain Med.* 2012;13(10):1304-1313.

Spinal Drug Distribution: CM Bernards



- Posterior T12 catheter
- 8-hr infusion
- Infusion rates: .02 ml/hr; 1.0ml/hr; 1.0 ml bolus
 - ^3H -bupivacaine
 - ^{14}C -baclofen
- Drugs
 - Baclofen - more hydrophilic
 - Bupivacaine - more lipophilic
- CSF - Microdialysis probes
 - Anterior and posterior
 - T12 (0 cm), 5 cm caudal, 5 and 10 cm cephalad, cerebral (parietal lobe)
- Tissue - Spinal cord sections
 - 1 cm segments
 - Anterior and posterior

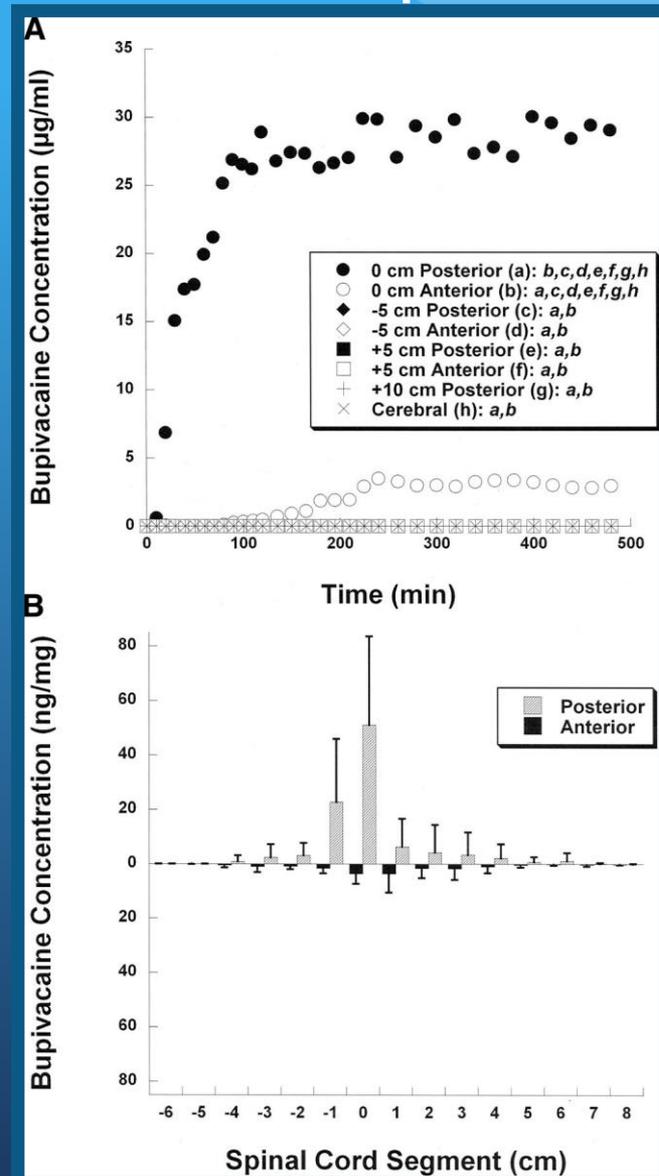


CSF and Spinal Cord Tissue Bupivacaine Levels

CSF

Low Infusion Rate
20 μ l/hr

Spinal Cord Tissue



CSF Drug Levels Low Infusion Rate

- No bupivacaine was detected in any of the cerebral CSF microdialysis probes
- The highest average peak CSF bupivacaine concentration and the highest AUC were obtained from the dorsal probe at the catheter tip
- The second highest concentration was from the site directly anterior
- Minimal bupivacaine was measured above or below the catheter tip
- Baclofen behaved similarly
- There was no difference between bupivacaine and baclofen in terms of the number of samples containing measurable drug quantities

Spinal Cord Tissue Drug Levels Low Infusion Rate

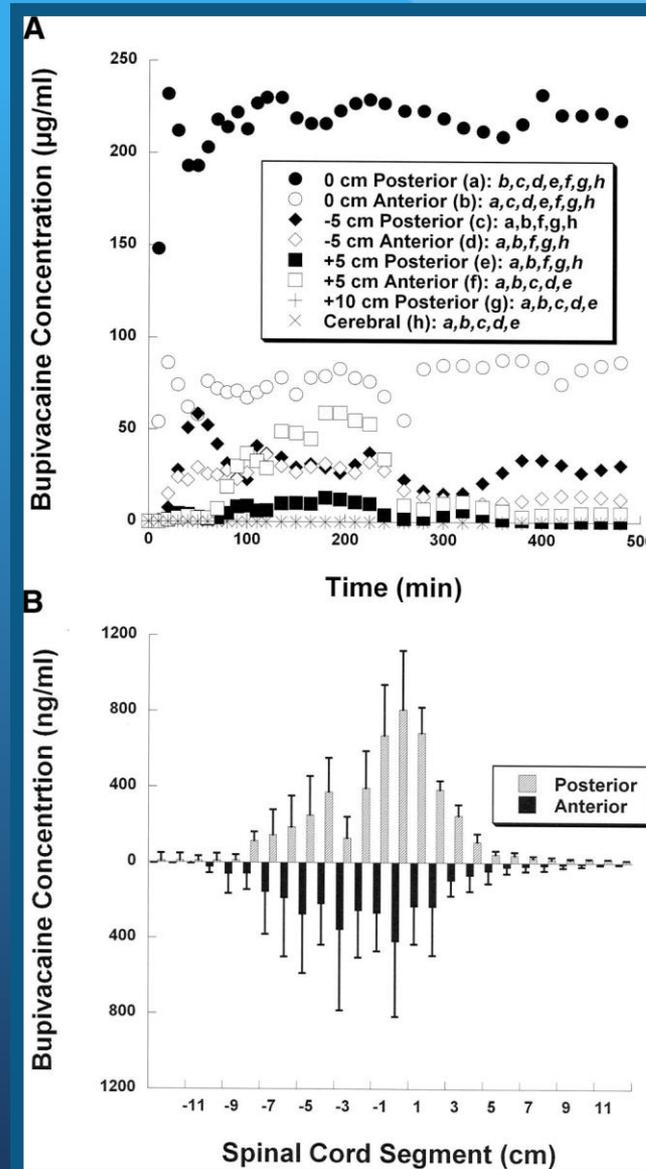
- Baclofen and Bupivacaine were highly concentrated in the posterior segment of the cord at the catheter tip level
- 56% +/- 17% of the baclofen recovered from the spinal cord was from the catheter tip site
 - 8 times greater than the next closest, the adjacent anterior site
- 58% +/- 19% of the bupivacaine recovered from the spinal cord was from the catheter tip site
 - 14 times greater than the next closest, the adjacent anterior site

CSF Bupivacaine Levels

CSF

High Infusion Rate
1000 $\mu\text{l}/\text{h}$

Spinal Cord Tissue



CSF Drug Levels High Infusion Rate

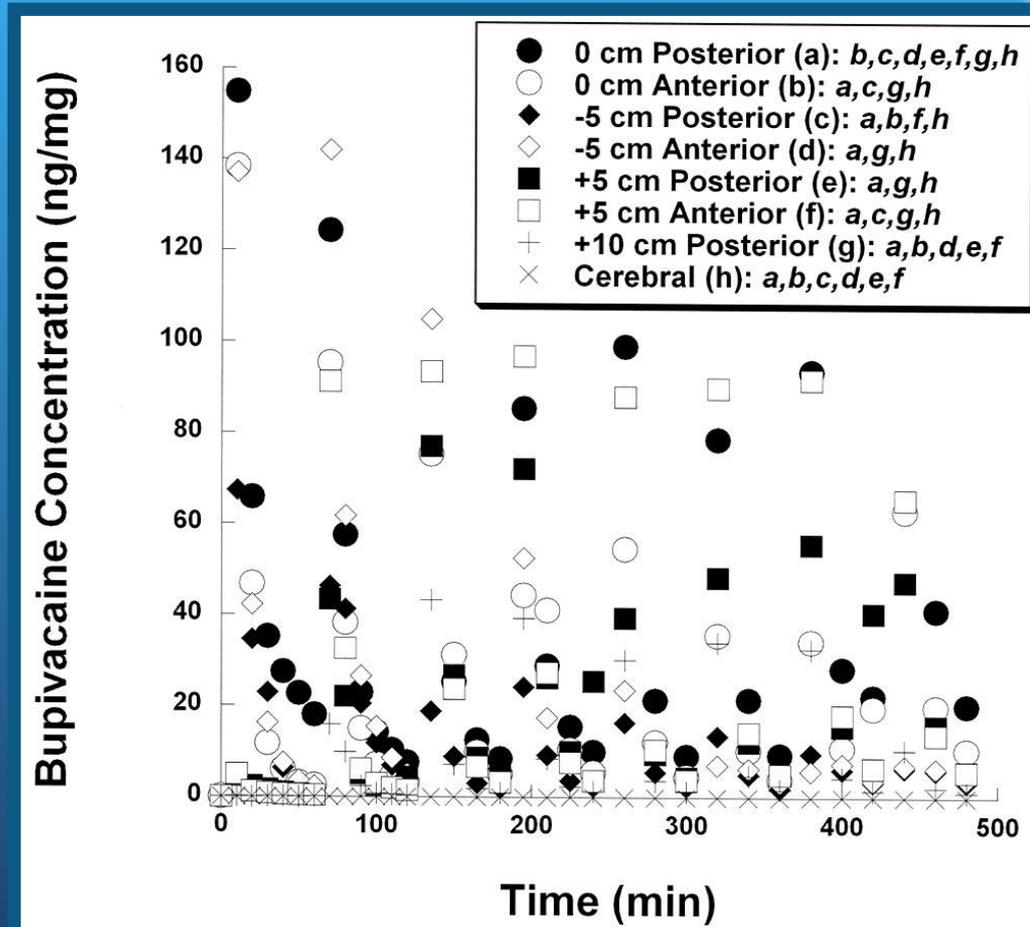
- Average peak concentration and AUC of both drugs was highest at the catheter tip.
- There were measurable concentrations at many more sampling sites than the 20 μ l/hr group
- CSF concentrations reached steady state earlier
- The second highest average peak drug concentration was from the site below the catheter tip not directly anterior

Spinal Cord Tissue Drug Levels High Infusion Rate

- The highest concentration for both drugs occurred at the segment adjacent to the catheter tip
- For Bupivacaine, the drug concentration at the posterior catheter tip segment was significantly greater than the segment directly anterior and as a function of the distance from the site of drug administration
- Baclofen concentration differed significantly only as a function of distance from the site of administration, but not anterior and posterior

CSF Bupivacaine Levels

Bolus

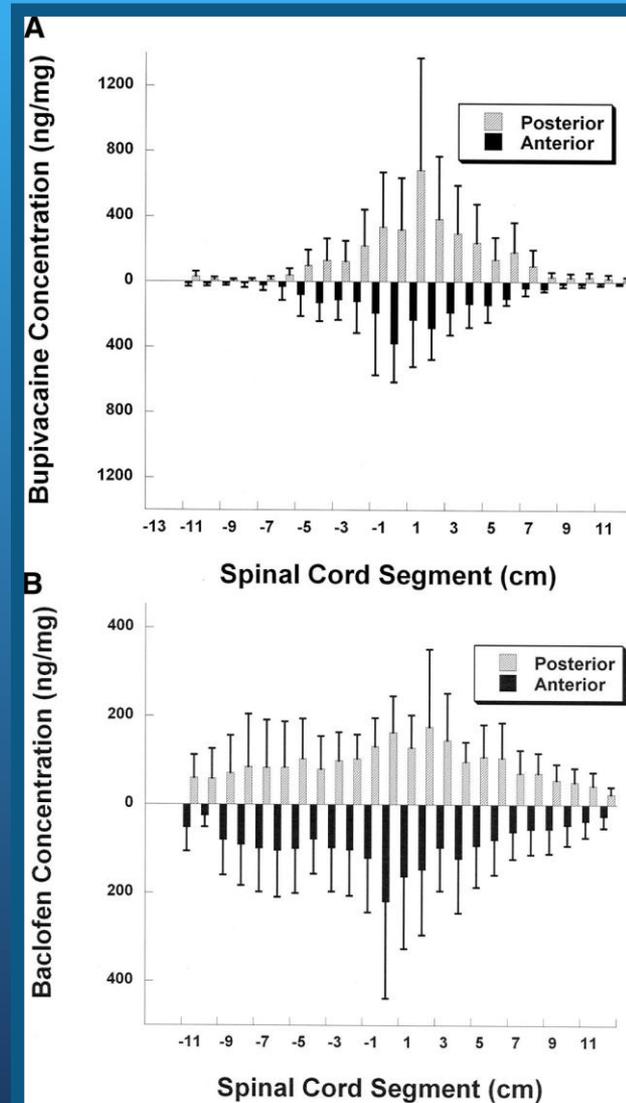


CSF Drug Levels Bolus

- Like the other two groups, there was significant differences in concentration of both drugs over time among the different sampling sites
- Unlike the other two groups, there were few differences in average peak concentrations among the different sampling sites
 - The only significant difference was between the catheter tip site and the cerebral site
- There were no differences between the AUC's of the different sampling sites
- There were no differences in the number of sites with measurable concentrations

Drug Concentrations in Spinal Tissue Bolus Group

Bupivacaine

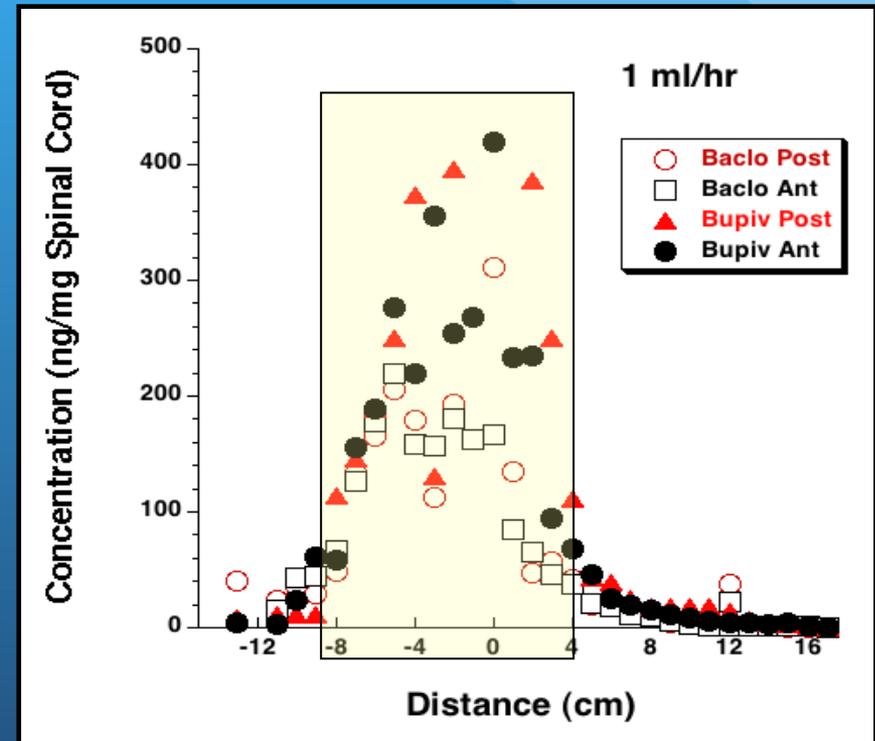
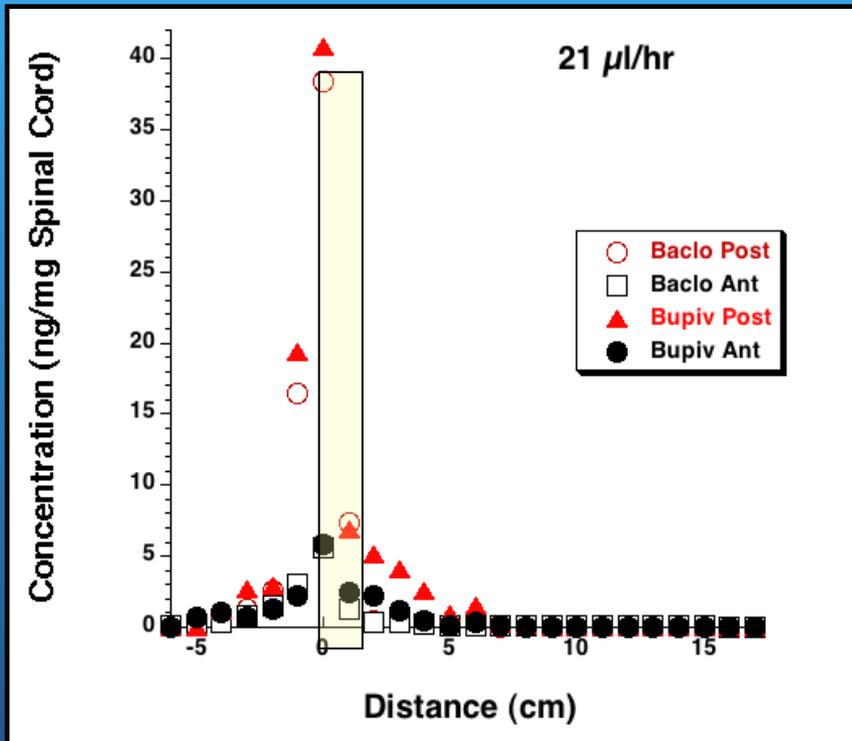


Baclofen

Spinal Cord Tissue Drug Levels Bolus

- Highest concentration for both drugs occurs in the catheter tip segment
- Bupivacaine concentration was significantly different between the catheter tip segment and the segment directly anterior and as a function of distance from the administration site (same as 1000 $\mu\text{l/hr}$ group)
- Baclofen only significantly differed as a function of the distance from the administration site

Spinal Tissue Drug Levels



- Low flow - narrow longitudinal distribution pattern vs. high flow (greater distribution)
- Low flow - posterior to anterior ratio is large vs. high flow narrow

Bernards CM. Cerebrospinal fluid and spinal cord distribution of baclofen and bupivacaine during slow intrathecal infusion in pigs. *Anesthesiology*. 2006;105(1):169-78

Spinal Drug Distribution Conclusions

- Evidence that the bolus group had better drug distribution
- There were few differences between the lipophilic and hydrophilic drug
- Location of the infusion catheter tip may be critical
 - dorsal catheter placement
 - dermatomal catheter placement
- Developing ways of improving drug distribution may decrease the incidence of granuloma

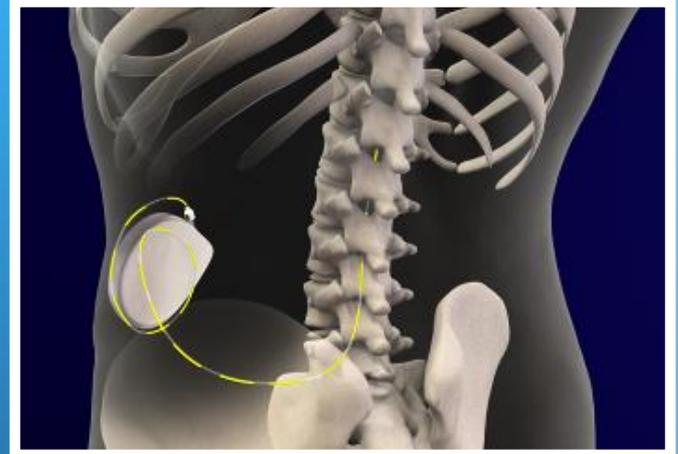
Optimal Dosing Strategies for Intrathecal Drug Delivery

- Terminology varies
 - Low Dose
 - **Microdose**
 - Dosing Strategies
- What are the main components?
 - Eliminating systemic opioids
 - Starting at low doses, physician control
 - Minimizing/Eliminating dose escalation
 - Patient flexibility
 - Bolus dosing
 - Applying good clinical skills already in use to manage dose escalation

Optimal Dosing Strategies for Intrathecal Drug Delivery

Advantages:

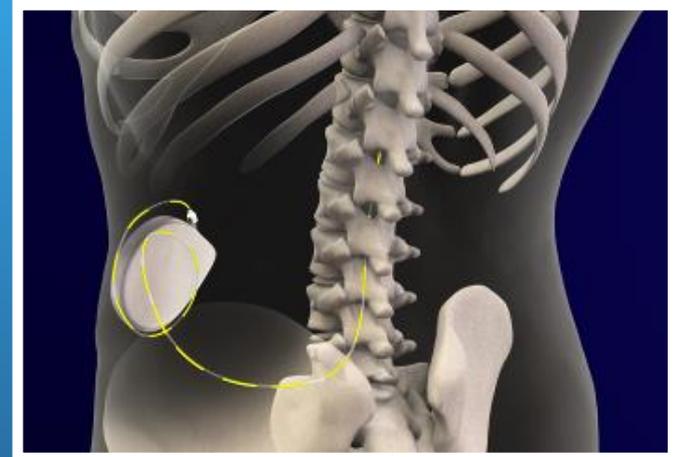
- Achieves steady-state, around-the-clock dosing
- Reduced side effects
- Use of intermittent dosing
- Compliance: Eliminate systemic opioids
- Reduction in longitudinal costs



Optimal Dosing Strategies for Intrathecal Drug Delivery

Disadvantages:

- More invasive
- More difficult to discontinue therapy
- Acquisition costs
- If positioned as a salvage therapy for patients who have failed but remain on high-dose systemic opioids, outcomes are diminished



Optimal Dosing Strategies for Intrathecal Drug Delivery

- Trial Goals
 - Assess efficacy of intrathecal medication administration for pain management
 - Allow physician to assess potential of achieving goals set during patient selection
 - Sufficient pain relief
 - For cancer patients, may be only goal assessed
 - Increased functioning

Optimal Dosing Strategies for Intrathecal Drug Delivery

- Trial Considerations
 - Inpatient or outpatient
 - Length of drug trial
 - Compliance with payor guidelines
 - Medicare requirement for catheter trial
 - Are you prepared for possible complications?

Optimal Dosing Strategies for Intrathecal Drug Delivery

- Trial Methods
 - Epidural catheter
 - Intrathecal catheter
 - Single shot intrathecal trial
 - Intermittent bolus trialing (intrathecal and epidural)
 - Continuous Infusion Trial

Optimal Dosing Strategies for Intrathecal Drug Delivery

- Continuous vs Single Shot/Intermittent Bolus
 - Titration
 - Interpretation of adverse events
 - Multiple procedures
 - Does not model steady-state characteristics of intended therapy
 - Does medication reach the correct level?

Optimal Dosing Strategies for Intrathecal Drug Delivery

	Advantages	Disadvantages
Intrathecal	<ul style="list-style-type: none">• More closely approximates pharmacodynamics of system to be implanted• Does not require epidural space (fusion, mets)	<p>Increased risk of:</p> <ul style="list-style-type: none">• PDPH• CSF leak• Serious infection• Overdose• Neurological complication during placement
Epidural	<ul style="list-style-type: none">• May allow outpatient management• Extended trials• Less risks	<ul style="list-style-type: none">• Less predictive?• Risk of migration to subarachnoid space

Optimal Dosing Strategies for Intrathecal Drug Delivery

- Trial Result Evaluation
 - Measurement tools
 - Subjective: Pain diary, pain scores, side effects
 - Objective: Specific activities of daily living, job tasks, medication use
 - Assess results against goals established before trial
 - Sufficient pain relief
 - Improved functioning
 - Reduced side effects
 - Decreased use of systemic analgesics
 - Trial outcome is positive when goals are met

Optimal Dosing Strategies for Micro-Dosing Intrathecal Drug Delivery

- Patient must be weaned off systemic opioids
 - 10-20% every 3-5 days
- Patient must remain opioid free for 2-6 weeks
- Pre-surgical psychological clearance
- 3 day outpatient trial
- Some patients may require inpatient trial

Optimal Dosing Strategies for Micro-Dosing Intrathecal Drug Delivery

- Patient education
 - Explain Hyperalgesia to the patient in terms they can understand
 - Explain the purpose of Intrathecal Drug Delivery
 - Point out high pain scores
 - Point out low activity levels
 - Explain to the patient the available options if the trial fails
 - Long acting opioids at a much lower dose
 - Better pain relief than high dose oral medication
 - Less side effects
 - Partner with the Primary Care Physician
 - Make sure PCP's are aware of the therapy and its reasoning
 - More likely accepted if the patient hears about it from someone else
 - Expectations
 - Will not completely eradicate pain
 - Explain that 50-70% relief is substantial
 - Explain that IDD will be the **ONLY** opioid therapy

Optimal Dosing Strategies for Micro-Dosing Intrathecal Drug Delivery

- Trial
 - 3- 4 days
 - A patient receives 1-3 small bolus doses of spinal morphine
 - 0.050 mg
 - 0.100 mg
 - 0.200 mg
 - 8 hours of direct observation
 - Pain scores collected
 - Activity level assessed
 - If the patient has a significant response to any of the above doses, a placebo is given to further assess candidacy
 - If response to placebo is significantly less than active drug then trial is a success
 - Permanent implant scheduled for two weeks later

Optimal Dosing Strategies for Micro-Dosing Intrathecal Drug Delivery

- Permanent Implant
 - The procedure is performed at the hospital
 - The pump is filled with sterile saline
 - The patient is discharged on the same day of implant
 - Well tolerated superficial surgery
 - Small midline subcutaneous posterior incision
 - Catheter placement is percutaneous through incision
 - Small right or left postero-lateral buttock incision for pump placement
 - Catheter placed in dorsal intrathecal space
 - Catheter placed at dermatomal level of pain
 - No opioids given for postoperative pain
 - NSAIDS
 - Tylenol
 - Postoperative visit with wound check at 1 week
 - Infusion started 2 weeks after implant at low dose and slowly titrated upward (every 2 weeks)

Intrathecal Drug Delivery for Non-Cancer Pain

- Retrospective Database study 1/2006-1/2009 involving 555 non-malignant pain patients that received an intrathecal drug delivery system
- A conventional pain therapy group was simulated assuming the same slope in costs prior to implantation
- Intrathecal Drug Delivery was more cost effective than Conventional Pain Therapy
- Break even point occurred at 27 months post-implant

Systemic Opioid Elimination After Implantation of an Intrathecal Drug Delivery System Significantly Reduced Health-Care Expenditures

- 389 patients from commercial and Medicare databases who had an intrathecal drug delivery system implanted from 2008-2011.
 - Used systemic opioids prior to implant
 - 12 months pre-implant continuous medical and pharmacy coverage
 - 13 months post-implant continuous medical and pharmacy coverage
- 51% completely eliminated systemic opioid in the year after implant
- 10-17% reduction in yearly inpatient, outpatient and drug expenditures

Opioid Induced Hyperalgesia Case Study

- 50 year old with Metastatic Prostate Cancer to the thoracic spine
- Severe, debilitating thoracic spine pain
- Initially treated with:
 - Radiation
 - Laminectomy
 - Short term relief only
- Unable to sleep/exhausted
- Pain Medicine consultation requested

Opioid Induced Hyperalgesia Case Study

- Opioids were rapidly increased to try and improve pain by oncology team
- 6 mg of hydromorphone IV per hour
 - 42 mg/hr Morphine equivalents
- 4mg of Hydromorphone Q 8 minutes prn
- 325 mcg/hr fentanyl patches
- 100 mg oral methadone per day
- Not amenable to intrathecal opioids due to high dose of systemic opioids

Opioid Induced Hyperalgesia Case Study

- Rapidly weaned off hydromorphone over 4 days
- Fentanyl decreased to 150mcg/hr
- Methadone continued at 100 mg per day
- Neurontin titrated to 600mg po tid
- Elavil titrated to 75 mg po qhs

Opioid Induced Hyperalgesia Case Study

- After Taper
 - Patient sleeping several hours
 - Increased activity level
 - Pain improved dramatically

Opioid Induced Hyperalgesia Case Study

- Intrathecal Trial Commenced
 - 5 mg of intrathecal morphine per 24 hours
 - Morphine PCA
 - No continuous
 - 2 mg incremental dose
 - 6 minute lockout
 - IV medication use converted to intrathecal
 - All other systemic opioids discontinued

Opioid Induced Hyperalgesia Case Study

- Morphine slowly increased to 8mg per 24 hours
- IV PCA use drastically reduced
- Excellent pain relief
- No significant side effects
- Permanent pump implant scheduled

Opioid Induced Hyperalgesia Case Study

- Permanent Implant performed
 - Intravenous PCA use discontinued after 24 hours
 - Intrathecal PCA allowed 0.4 mg q 6 hours
- No significant side effects
- Discharged home 3 days later
- Walking on his own
- Minimal breakthrough medication
- Neurontin and Elavil continued

Micro-dosing Case Study

- 55 year old caucasian male
- Low Back Pain with bilateral LE Radicular Pain
- Bilateral LE Peripheral Neuropathy
- Medications prescribed by PCP
 - MS Contin 15 mg po bid
 - Forgetfulness
 - Dulls his personality
 - Ultram ER 200mg per day
 - Lyrica 150mg po bid
- Taper instructions given
 - Started taper 3/28/2011

Micro-dosing Case Study

- Finished 6 week opioid holiday on 5/19/2011
- Taper/Holiday was very difficult for the patient and his wife
 - Payer on the floor in the fetal position within at night
- 8-9/10 average pain
- 3 day inpatient continuous intrathecal trial 5/25-5/27
 - 0.4 mg per day
 - 0/10 back pain, 2-3/10 overall pain
 - Urinary retention requiring Urecholine and temporary catheterization
- Permanent Implant on 6/24/2011
 - Catheter to Mid T-11 level in the dorsal intrathecal space
 - Left postero-lateral buttock 20cc infusion pump placed
 - Started on 0.2mg of PF morphine per day

Micro-dosing Case Study

- Dose titrated up to 0.33 mg of intrathecal morphine per day
- In March 2012, increased pain (5/10) after traveling to Africa and riding on very bumpy roads.
- Chronic pain behavior started to return
- Unable to draw CSF from catheter access port
 - Total Drug in catheter calculated to be 0.4137 mg
 - Dye study performed
 - Minimal dye at catheter tip
 - Substantial dye at catheter entry point
 - Tear in catheter assumed
 - Patient monitored for four hours after dye study in the office.
 - Priming bolus set to start to redeliver drug 24 hours later for safety purposes

Micro-dosing Case Study

- MRI of the thoracic and lumbar spine revealed no abnormalities
- At 24 hours patients pain spiked substantially and decreased to 5/10 after infusion restarted
 - Even small amount of medicine was providing some pain relief
- Catheter replaced
- Pain returned to 2-3/10
- Last seen 10/01/2015
 - Continues on 0.4 mg/day of intrathecal morphine with 2/10 pain

Benefits of Micro-dosing

- Better pain relief
 - Medication is placed at dermatomal level of the pain
- Reduced incidence of Opioid Induced Hyperalgesia (OIH)
- Less side effects
 - Itching and urinary retention more common with intrathecal opioids
 - Usually abate over 2 weeks
- More provider control
 - Less risk of addiction and diversion
- Lower concentration of intrathecal medication
 - May allow for dye study when unable to aspirate from catheter access port.
 - Less risk with a pocket fill
- Cost Effective
- Can be an effective *Maintenance Free* therapy for chronic pain

The End