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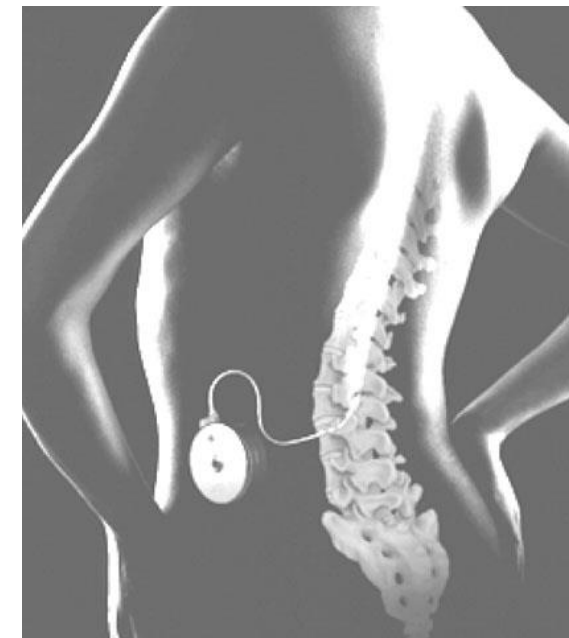


# Targeted Intrathecal Drug Delivery: *Outcomes*



Salim Hayek, MD, PhD  
Dept of Anesthesiology  
Division of Pain Medicine

University Hospitals Cleveland Medical Center





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# Disclosures

No disclosures to report relative to this activity

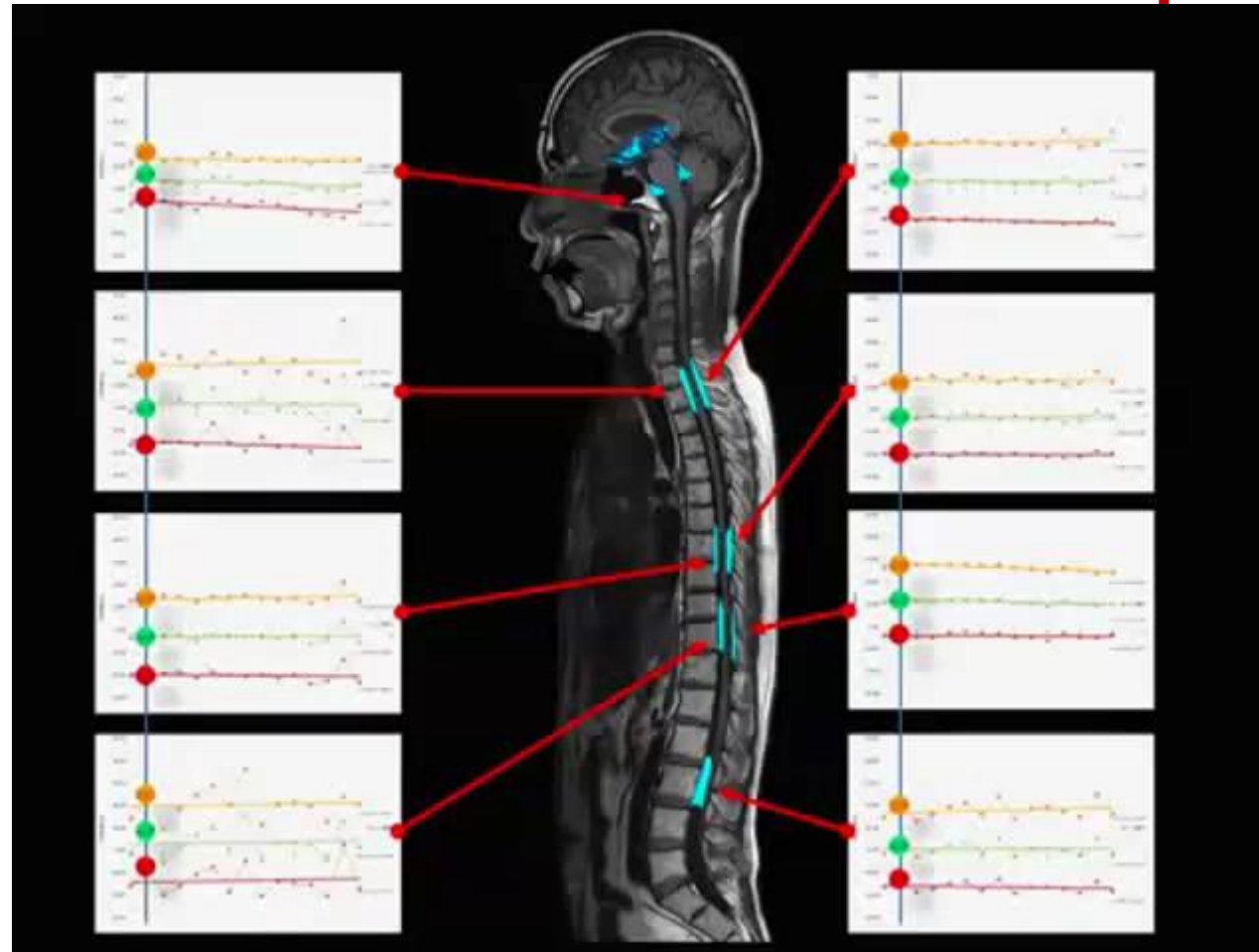


# Objectives

- How to best adjust the therapy to the patient?
  - ❑ What are the patient characteristics that affect TIDD?
    - Cancer vs. noncancer pain
    - Diffuse vs. localized pain
    - Neuropathic vs. Nociceptive pain
    - Old vs. young
  - ❑ Starting dose of opioids
  - ❑ Combination of opioids and local anesthetics



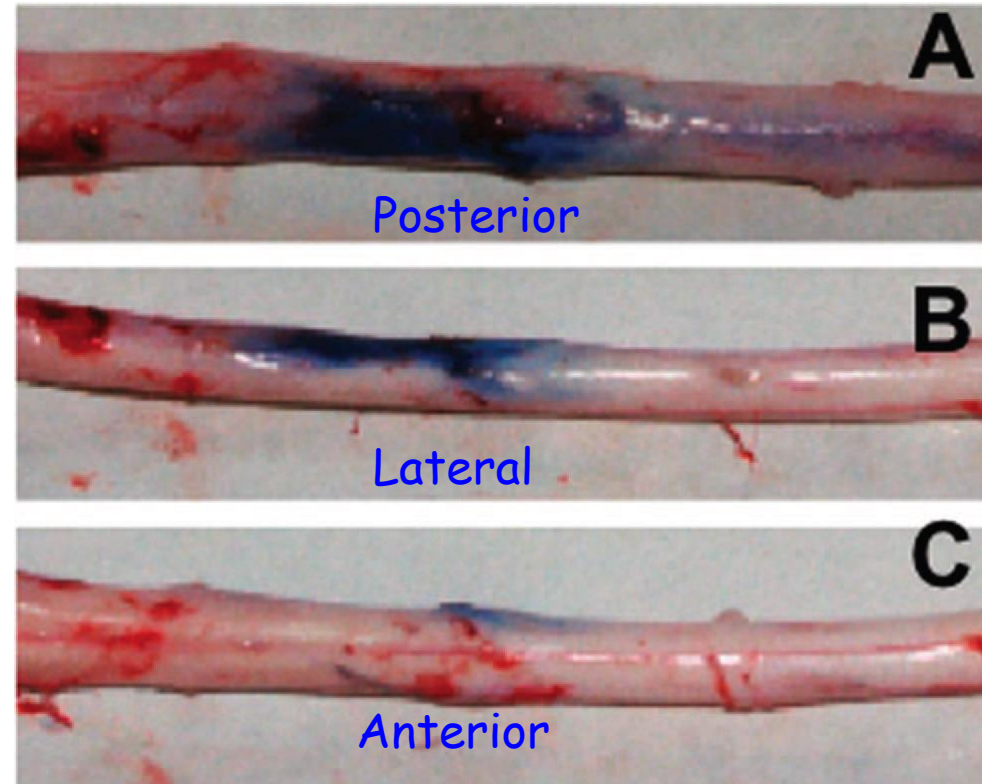
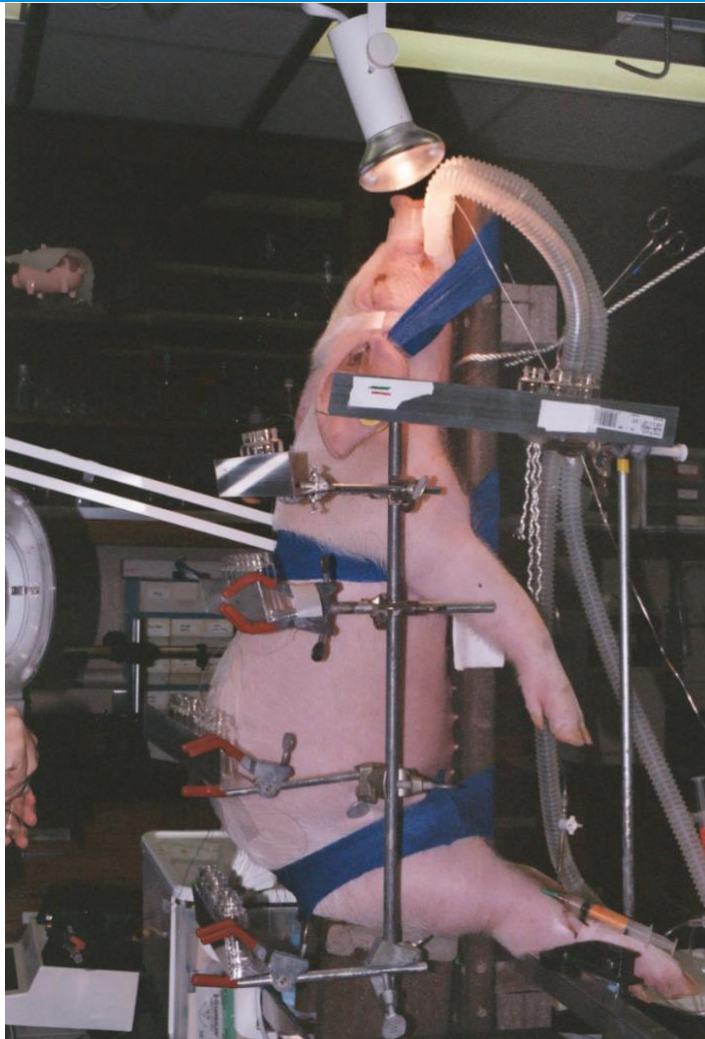
# Pulsatile CSF Flow in the Spine



Yamada S. Cerebrospinal fluid physiology: visualization of cerebrospinal fluid dynamics using the magnetic resonance imaging Time-Spatial Inversion Pulse method. *Croat Med J.* 2014 Aug 28;55(4):337-46



## In vivo Porcine Pilot Study



**Christopher M Benards, MD**  
**1958-2012**

**Bernards, CM.** Cerebrospinal Fluid and Spinal Cord Distribution of Baclofen and Bupivacaine during slow intrathecal infusion in Pigs.  
*Anesthesiology* 2006;105:169-78.



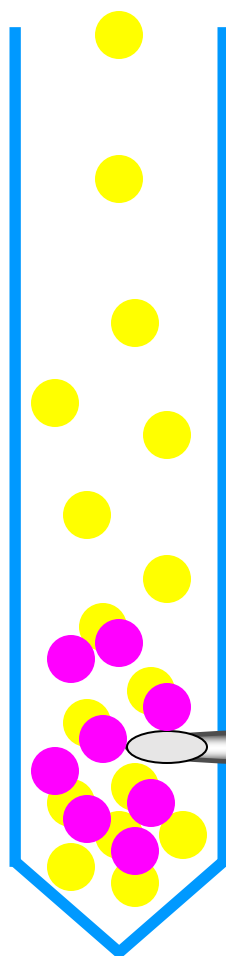
# Intrathecal Medication Characteristics

- ❖ Receptors for the agents have to be at the spinal level
- ❖ Drug considerations
  - **Lipid solubility** → Location of catheter/receptors
  - Density and baricity
  - Bolus vs. continuous





# Pharmacokinetics-Lipophilicity



- ❖ Moderately hydrophilic agents (e.g. morphine, baclofen or clonidine) → concentration gradient in the CNS
  - cisternal CSF drug concentration is 1/3 to 1/7 that in the lumbar CSF
- ❖ Bupivacaine, Fentanyl-lipophilic

*Kroin JS et al: The distribution of medication along the spinal canal after chronic intrathecal administration. Neurosurgery 33:226-230, 1993*



# Patient & Clinical Characteristics







# TIDD Patient Selection

- ❖ Objective evidence of pathology
- ❖ Failure to achieve adequate results from oral opioid therapy/AE's
- ❖ Psychological evaluation
- ❖ Demographics: Old vs. Young patient
- ❖ Neuropathic vs. Nociceptive pain
- ❖ Cancer vs. non-cancer pain
- ❖ Localized vs. diffuse pain
- ❖ Starting dose of opioids: low vs. high

Krames E. Journal of Pain and Symptom Management;1996, Vol 11, No 6: 333-352

Hayek SM, Veizi E, Narouze S, Mekhail N. Pain Med, 2011 Aug;12(8):1179-89

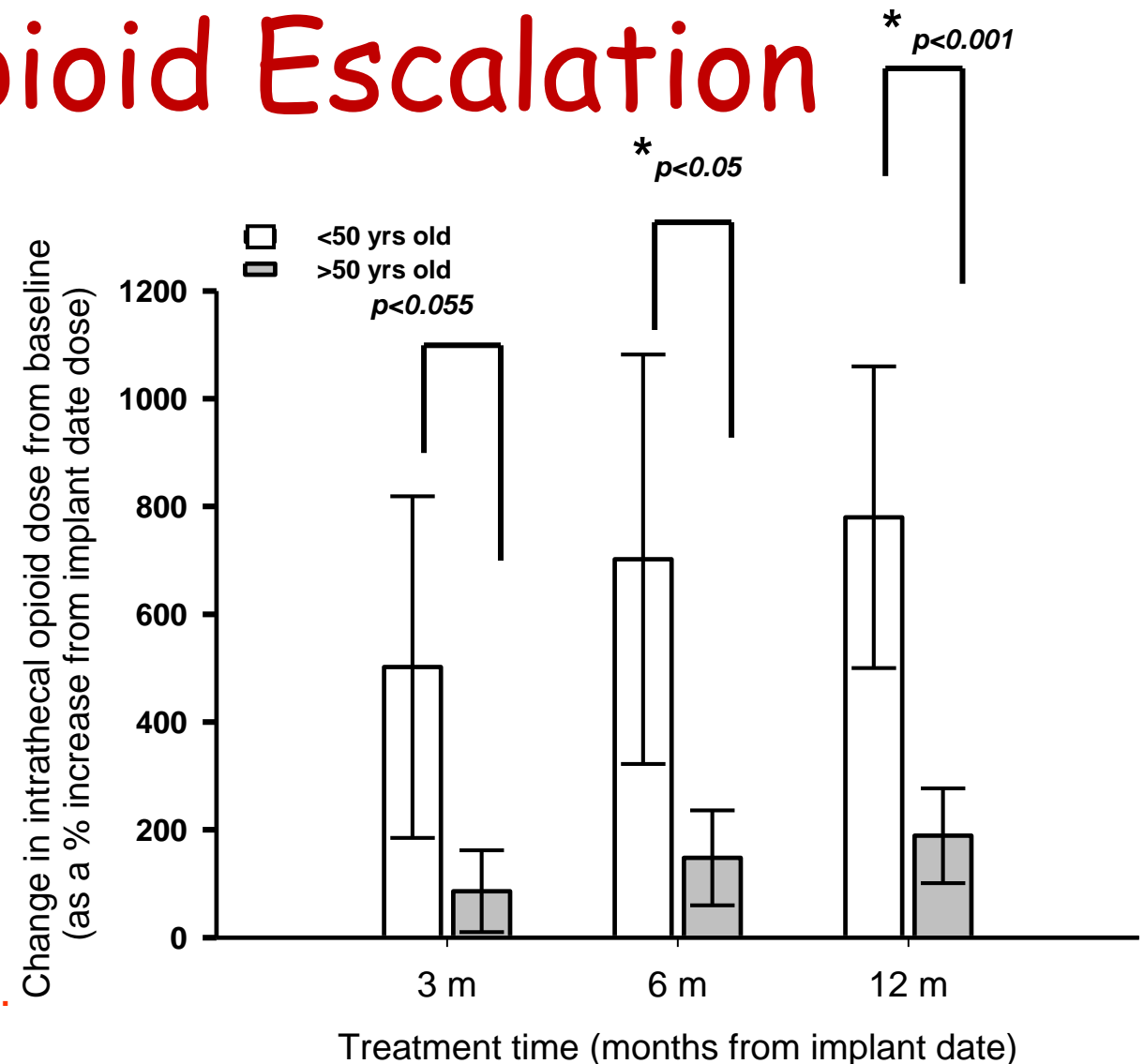
Veizi E, Hayek SM, Narouze S, Mekhail N. Pope, JE. Pain Med, 2011 Oct;12(10):1481-9

Grider J Harned ME, Etscheidt MA, Pain Physician 2011; 14:343-351

	Younger (≤ 50 years old) (n=50)	Older (>50 years old) (n=85)	P value
Age (yrs)	41.6 ±5.5	64± 11	<0.01
Male (n in %)	29 (58%)	45 (53%)	<0.01
Female (n in %)	21 (42%)	40 (47%)	<0.01
<b>NRS</b>			
Baseline	7.2± 1.4	7.36± 2.2	NS
12 m post implant	5.6±2.1†	5.5± 2.4†	NS
NRS decrease >50% (at 12 m)	5 (10%)	21 (25%)	<0.01



# ↑ Age: ↓ IT Opioid Escalation <sup>\*p<0.001</sup>

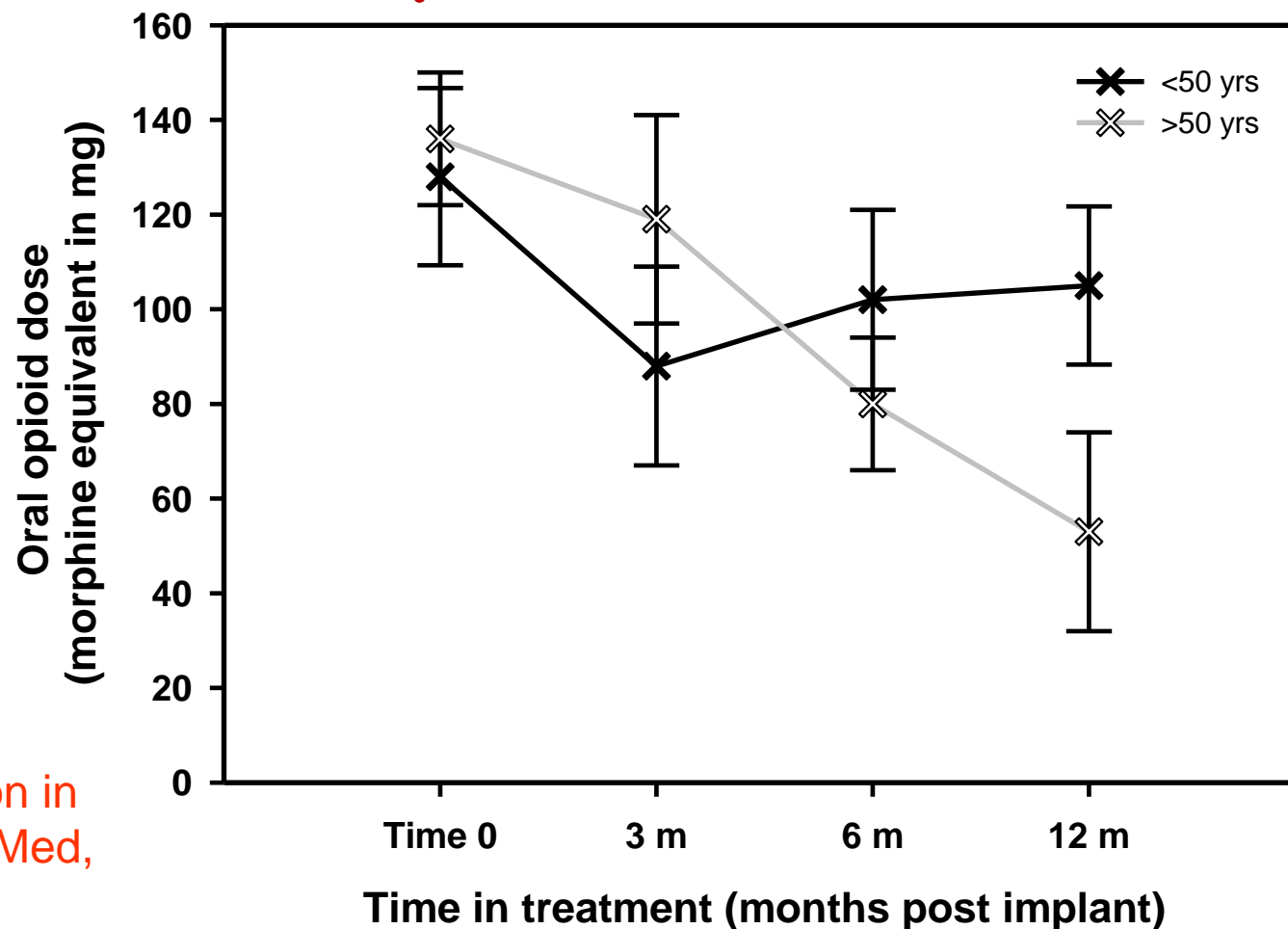


Hayek SM et al., Age-dependent intrathecal opioid escalation in chronic noncancer pain patients. *Pain Med.* 2011 Aug;12(8):1179-89.





# ↑ Age: ↓ Oral Opioid Dose



Hayek SM, Veizi E, Narouze S, Mekhail N.  
Age-dependent intrathecal opioid escalation in  
chronic non-malignant pain patients. *Pain Med*,  
2011 Aug;12(8):1 179-89



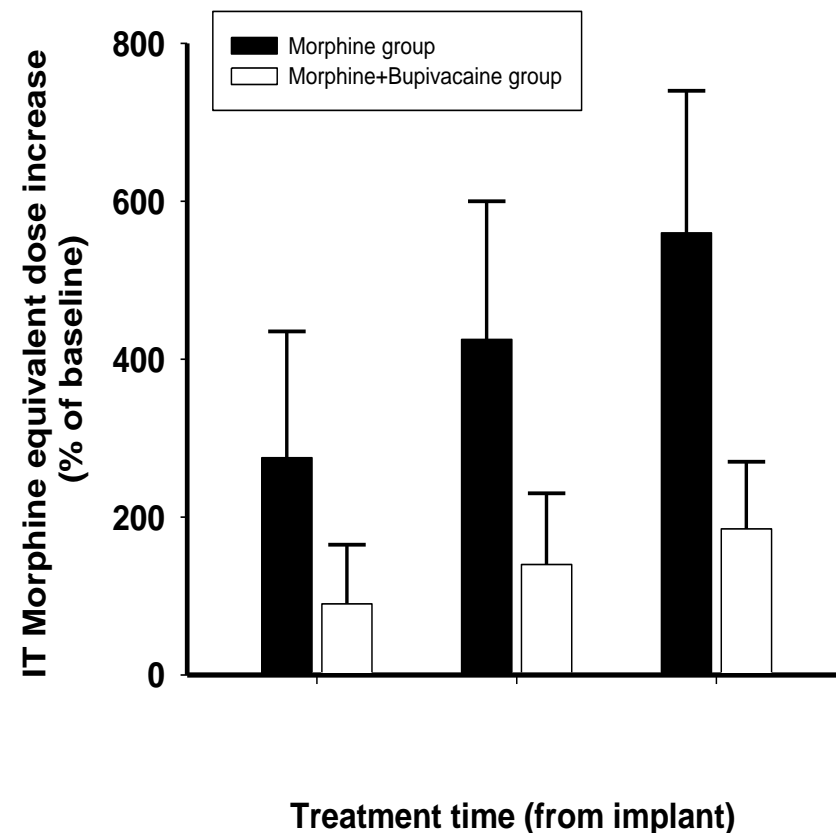
# Demographics

## ❖ AGE: Older is better

- Animal data<sup>1</sup>
- Dominguez et al., >65<sup>2</sup>
- Hayek et al., >50<sup>3</sup>
- Kim et al., + correlation<sup>4</sup>
- Grider et al., + but NS<sup>5</sup>

## ❖ GENDER: No difference

- F < M<sup>2</sup>
- No Difference<sup>3,4,5</sup>



1. Wang Y et al., *Anesth Analg*, 2005;100(6):1733-9
2. Dominguez E et al., *Pain Practice*, 2002; 2(4): 315–325
3. Hayek SM et al., *Pain Med*, 2011 Aug;12(8):1179-89
4. Kim D et al., *Neuromodulation*, 2011;14(2):165-75
5. Grider JS et al., *Neuromodulation*. 2016;19(2):206-19



# TIDD Patient Selection

- ❖ Objective evidence of pathology
- ❖ Failure to achieve adequate results from oral opioid therapy/AE's
- ❖ Psychological evaluation
- ❖ Old vs. Young patient
- ❖ Neuropathic vs. Nociceptive pain
- ❖ Starting dose of opioids: Low vs. High
- ❖ Cancer vs. non-cancer pain
- ❖ Localized vs. diffuse pain

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Veizi E, Hayek SM, Narouze S, Mekhail N. Pope, JE. Pain Med, 2011 Oct;12(10):1481-9

Grider J Harned ME, Etscheidt MA, Pain Physician 2011; 14:343-351





# Pain Type: Neuropathic vs. Nociceptive

- ❖ Controversial if TIDD is more effective for one > other
  - Neuropathic > Nociceptive<sup>1\*,2,3</sup>
  - Nociceptive > Neuropathic<sup>4,5</sup>
  - No Correlation<sup>6</sup>
- ❖ None of the above studies used objective measures to diagnose/follow neuropathic pain/response to TIDD

1. Kumar K et al., *Surg Neurol*, 2001;55(2):79-86
2. WinkelMuller M & W, *J neurosurgery*, 1996;85(3):458-67
3. Dominguez E et al., *Pain Practice*, 2002; 2(4): 315–325
4. Mekhail N et al., *Pain Practice*, 2014;14(4):301-8
5. Grider JS et al., *Neuromodulation*. 2016;19(2):206-19
6. Kim D et al., *Neuromodulation*, 2011;14(2):165-75



# TIDD Patient Selection

- ❖ Objective evidence of pathology
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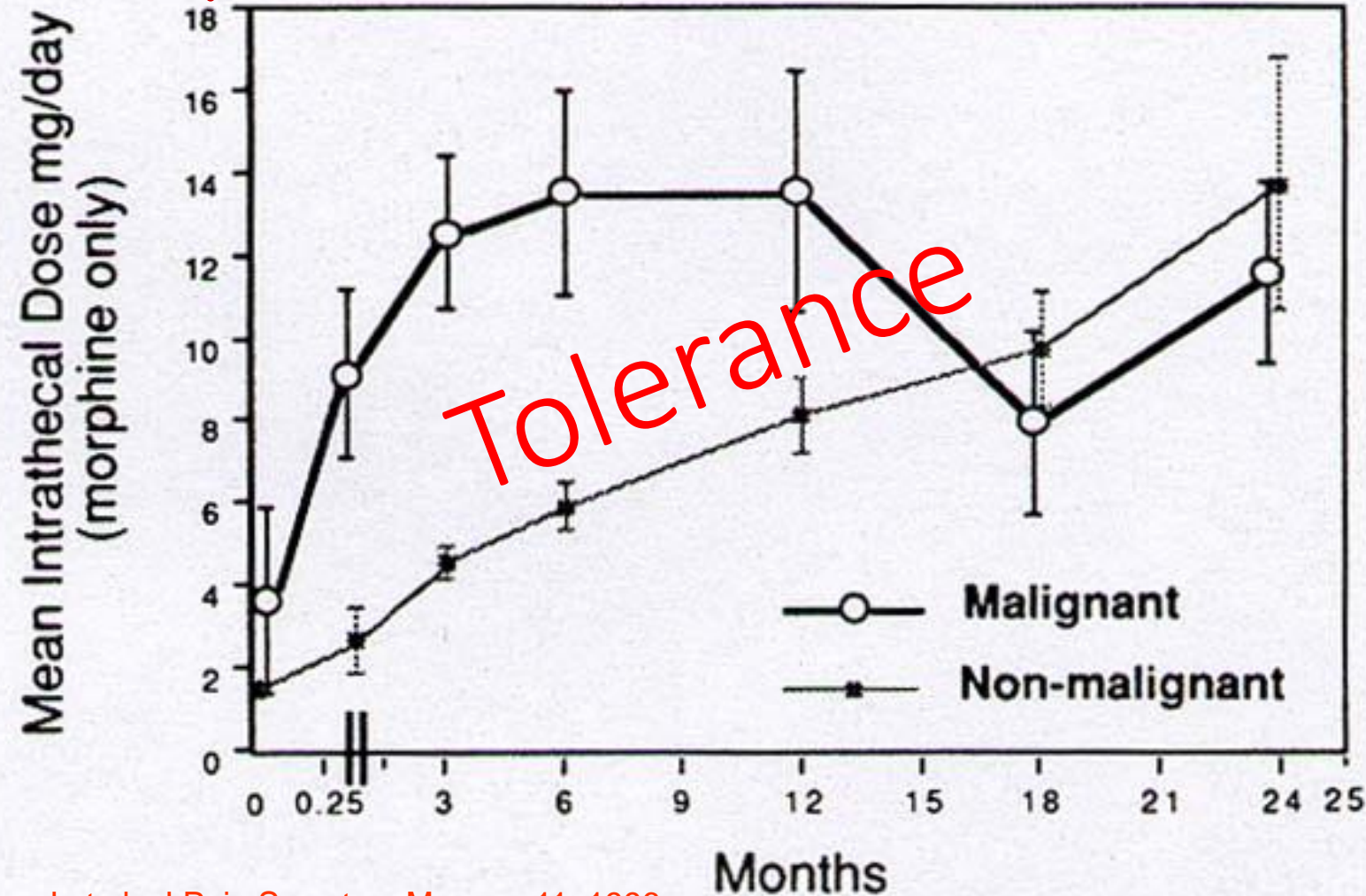
Hayek SM, Veizi E, Narouze S, Mekhail N. Pain Med, 2011 Aug;12(8):1179-89

Veizi E, Hayek SM, Narouze S, Mekhail N. Pope, JE. Pain Med, 2011 Oct;12(10):1481-9

Grider J Harned ME, Etscheidt MA, Pain Physician 2011; 14:343-351



# IT Opioid Dose Escalation



Paice J et al., J Pain Symptom Manage 11, 1996





# Cancer vs. Non-Cancer: Limited by Survival

Long-Term Intrathecal Opioid Therapy With a Patient-Activated,  
Implanted Delivery System for the Treatment of Refractory  
Cancer Pain

Richard L. Rauck,<sup>\*,†,‡</sup> David Cherry,<sup>‡</sup> Michael F. Boyer,<sup>‡</sup> Peter Kosek,<sup>‡</sup> Joseph Dunn,<sup>‡</sup>  
and Kenneth Alo<sup>‡</sup>

❖ Of the 119 patients implanted, only 15 survived at 13 months post-implant



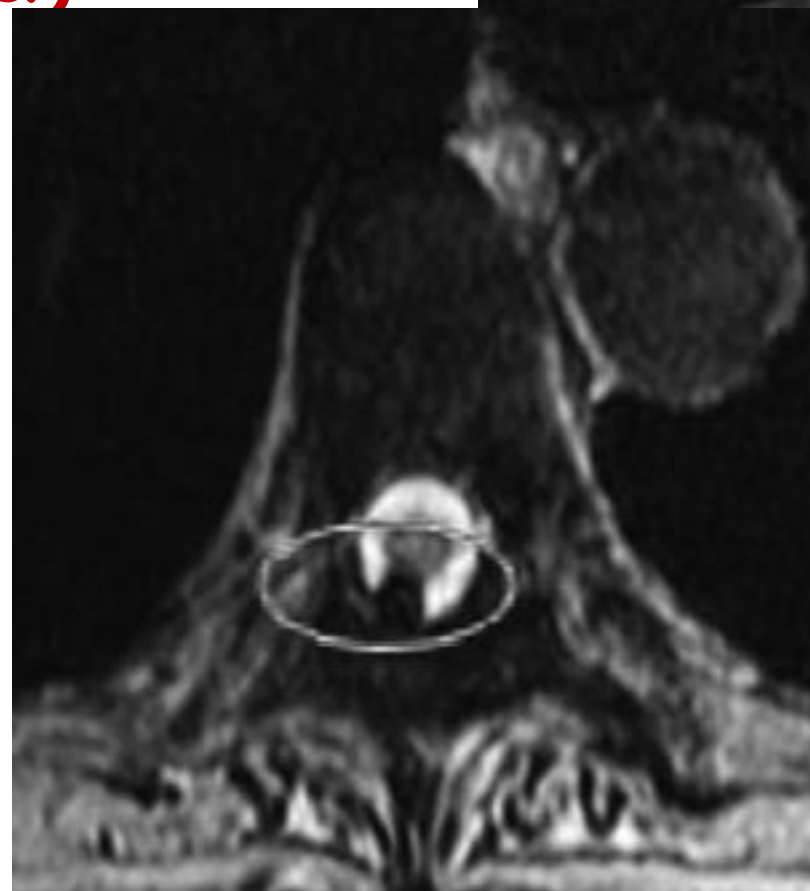
# Why important to ↓ IT Opioids? ICTG (Granuloma)

## ■ Risk Factors

- Morphine or hydromorphone
- ↑Concentration
- ↑Amount
- ↑Duration

## ■ Occurs in 3-9% of implanted pts

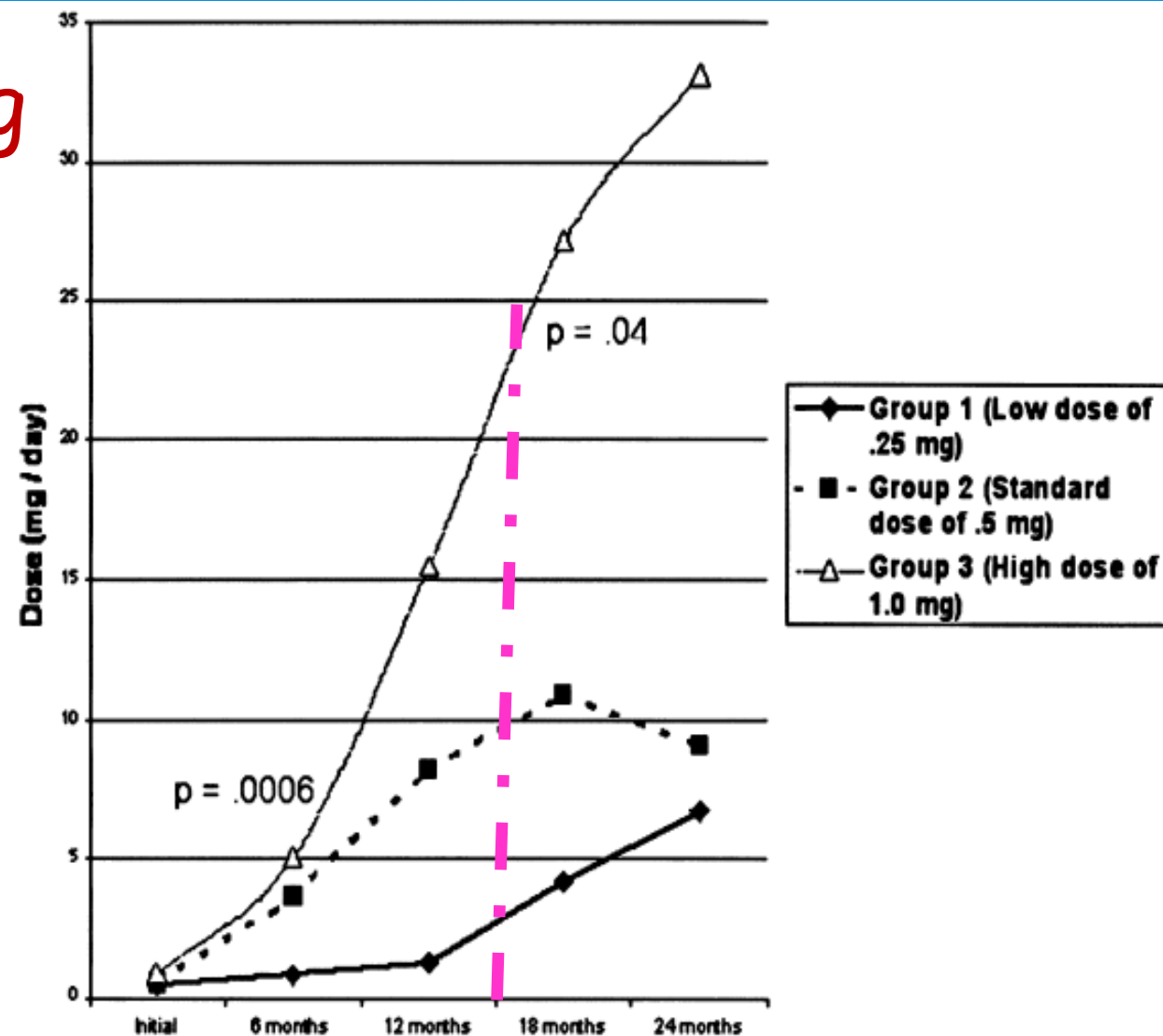
## ■ May be partly reversible with removal of the opiate/saline replacement





## Predictive Value of Trialing

- ❖ Dose of opioids at trial is an important determinant of
  - Opioid dose escalation
  - Need for adjuvants
- ❖ Responders to 1mg IT morphine bolus dose at trial → >25 mg/day by 18 months post-implant







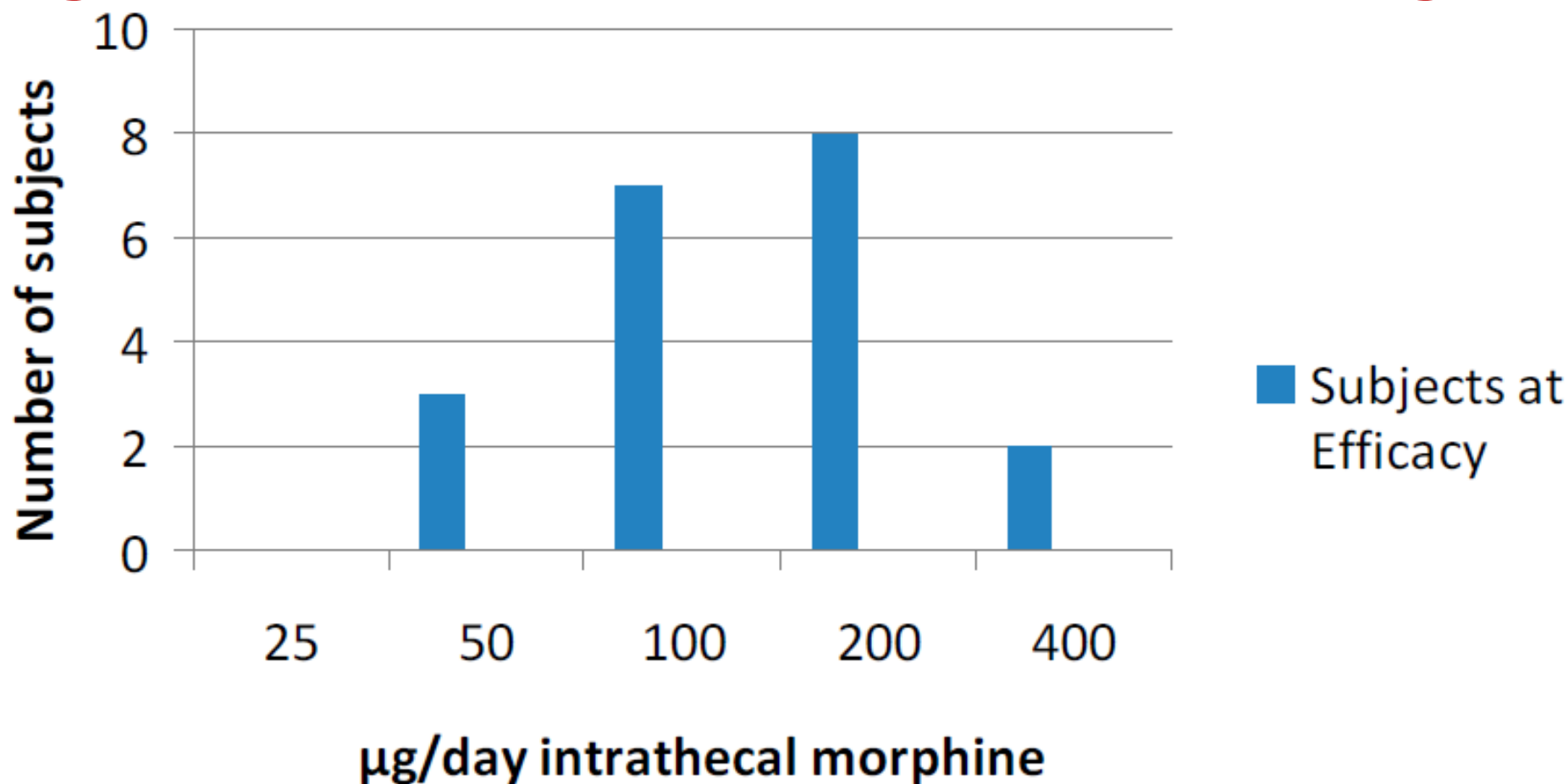
## IT "Microdosing"

- ❖ Oral opioid taper to 0 over 3-4 weeks
- ❖ Opioid-free for 5 weeks → trial
- ❖ 22 patients, retrospective

Trial Day 1 6 am	25 mcg/day morphine
Trial Day 1 6pm	50 mcg/day morphine
Trial Day 2 6am	100 mcg/day morphine
Trial Day 2 6pm	200 mcg/day morphine
Trial Day 3 6am	400 mcg/day morphine



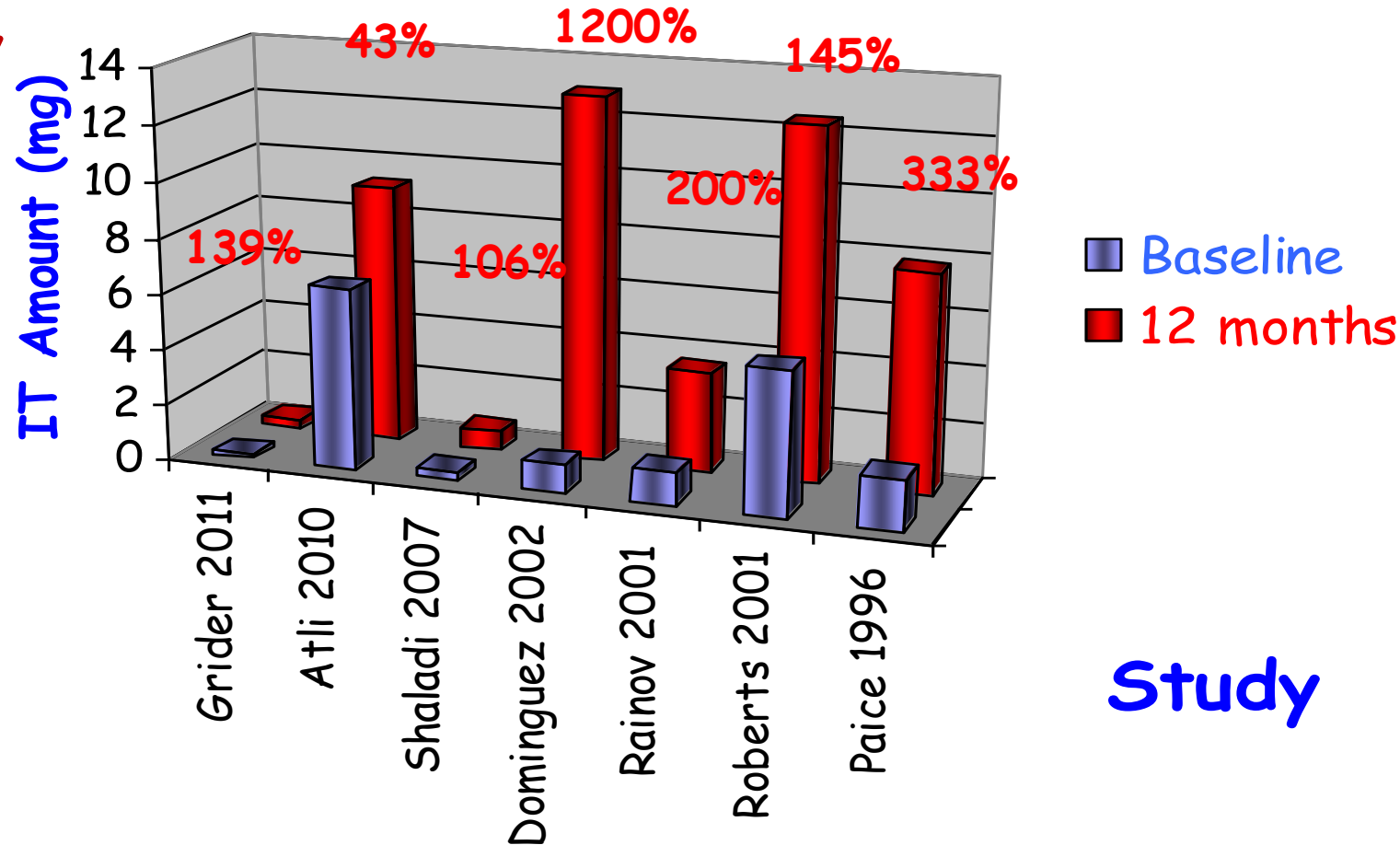
## Average Effective Dose at Trial = 140 mcg





## IT Morphine Eq. Dose Escalation

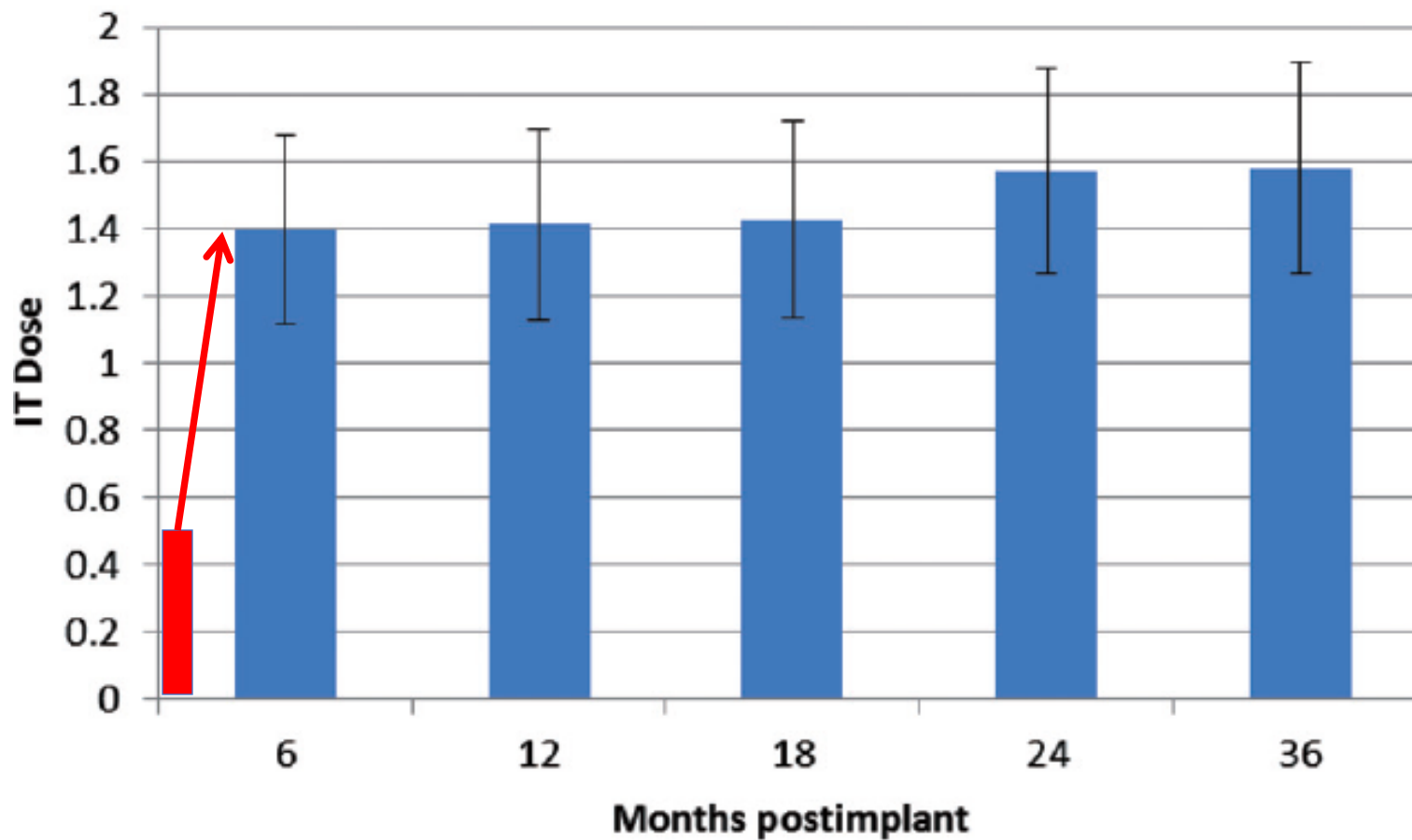
At Implant →  
335 mcg/day







# Prospective “Microdosing” Study



Hamza 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 Jul 30.



## → Reduction in Oral Opioids

**Table 3** Mean opioid dose (mg/day) from baseline to 3 months postimplant

	N	Estimate	SE	95% CI
Baseline	58	126.71	12.92	(100.83, 152.58)
3 months	58	3.80	0.90	(2.01, 5.60)
Decrease		122.91	12.61	(97.65, 148.16)

SE = standard error; CI = confidence interval.

Hamza 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 Jul 30.



## ❖ Prospective study

### ➤ 58 Patients

□ 20 FBSS

□ 23 LDD

□ 11 LSS

### ➤ VAS 7.8 → 4.6

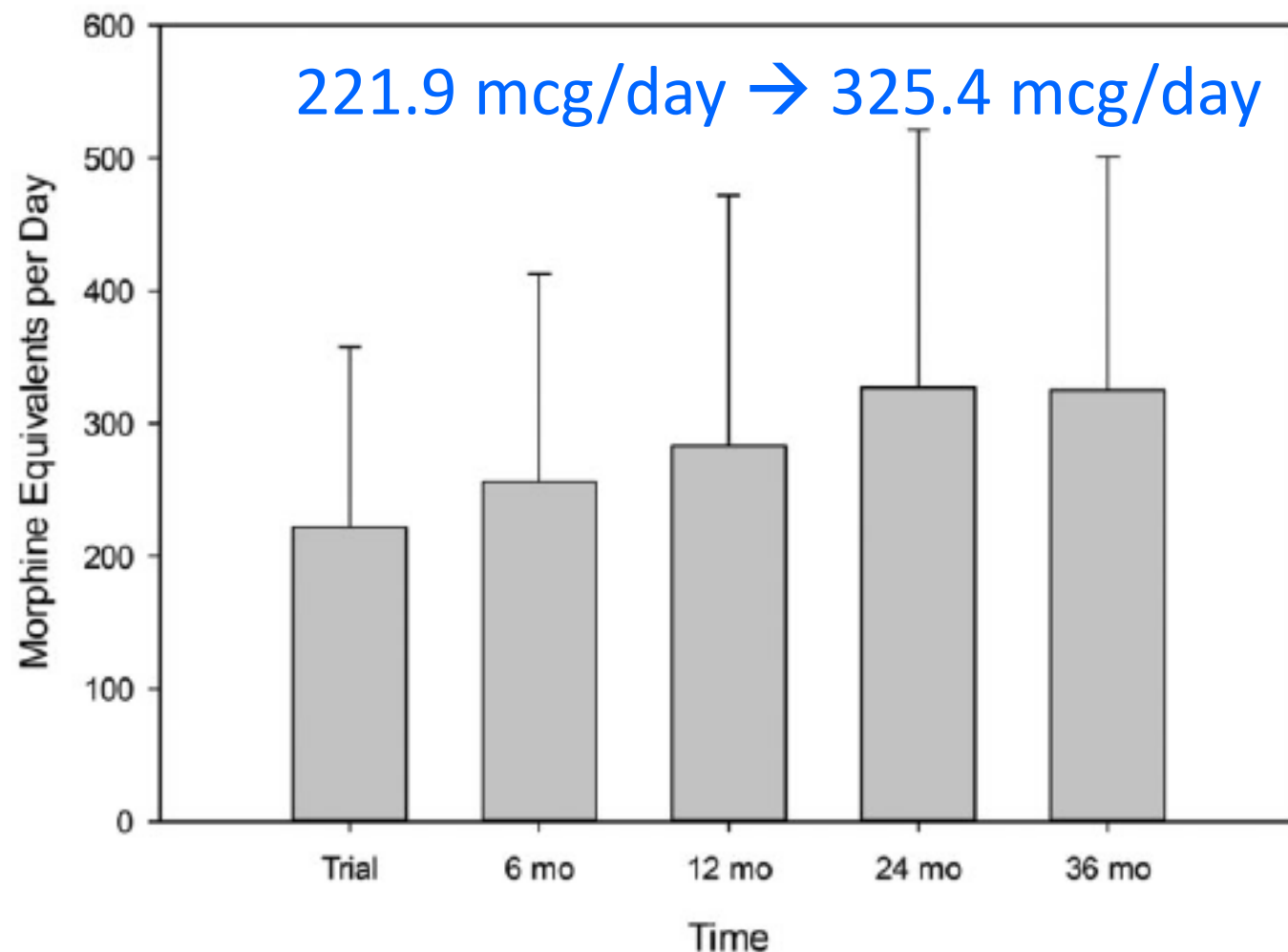
## ❖ 73 trialed

### ➤ 13 failed

□ Urinary retention: 3

□ Ineffective: 10

- 8 returned to oral opioids
- VAS 8.1 → 6.9



Grider JS, Etscheidt MA, Harned ME, et al. Trialing and Maintenance Dosing Using a Low-Dose Intrathecal Opioid Method for Chronic Nonmalignant Pain: A Prospective 36-Month Study. *Neuromodulation*. 2016;19(2):206-19





# Opioid Challenges

## ❖ Intrathecal Opioids

- Pruritus: IT>>oral
- Peripheral edema
- Urinary retention
- Hypogonadotrophic hypogonadism
- **IT granuloma**
- Opioid-induced hyperalgesia
- Death as a result of respiratory depression
- → **same AE/tolerance issues as systemic opioids**

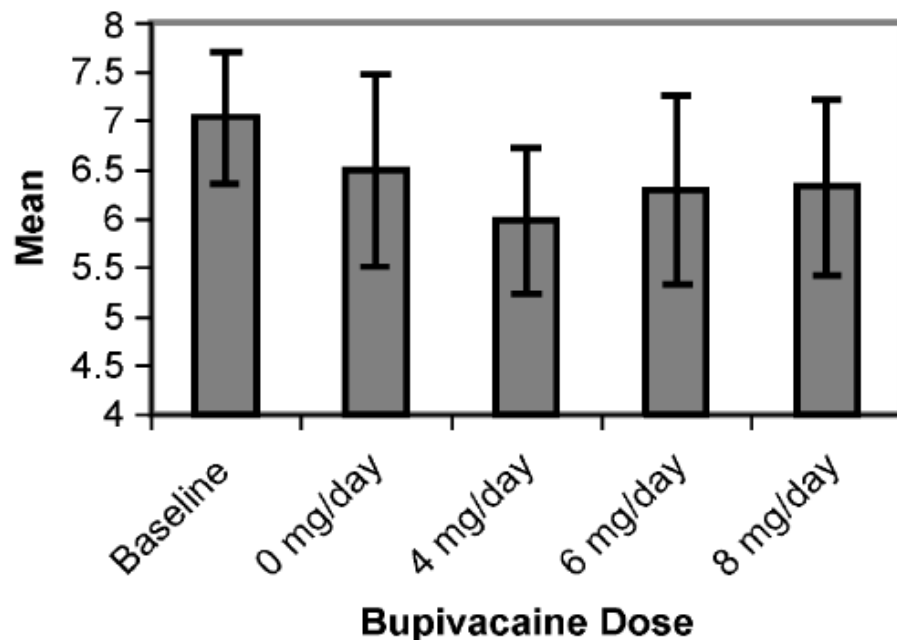
Hayek, S. et al., *Seminars in Pain Medicine* 1(4):238-253

Coffey RJ et al., *Anesthesiology*. 2009 Oct;111(4):881-91



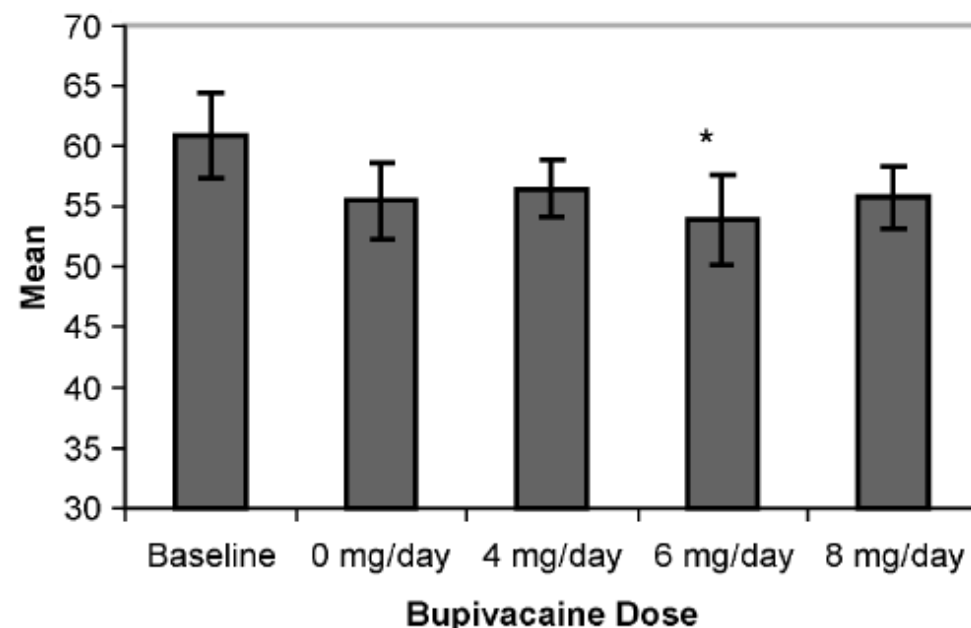
# Bupivacaine Added to Existing IT Opioids

**Pain Scores at Different Dosages**



Error Bars are +/- 2 Standard Errors

**Quality of Life at Different Dosages**



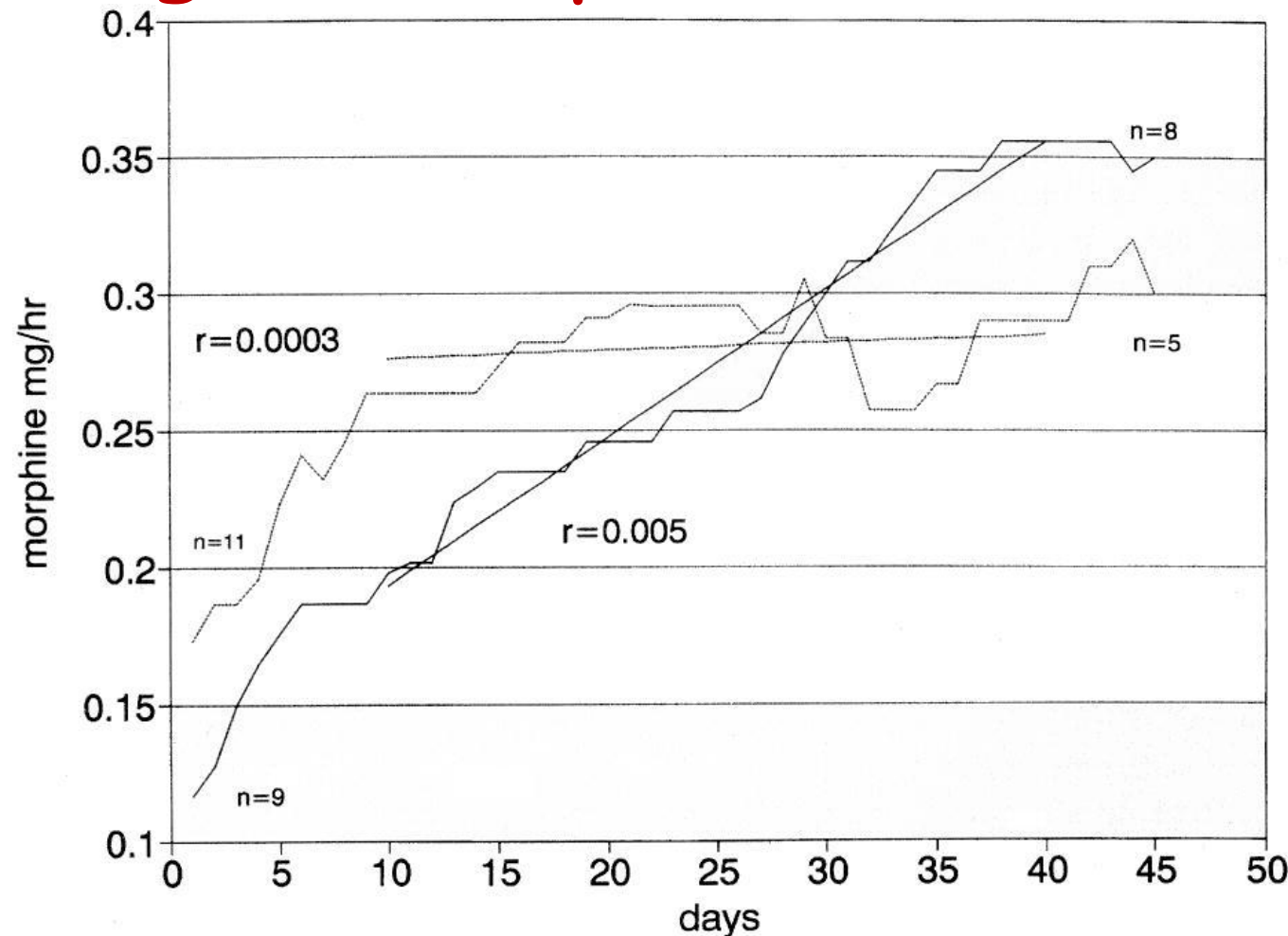
Error Bars are +/- 2 Standard Errors

\*=statistically significant

- ❖ Addition of Bupivacaine to pumps infusing IT opioids → No Statistically significant ↓ in pain scores (defined as 1.5 point on VAS)
- ❖ QOL improved only @ 6 mo.



# Blunting of Morphine Escalation Rate

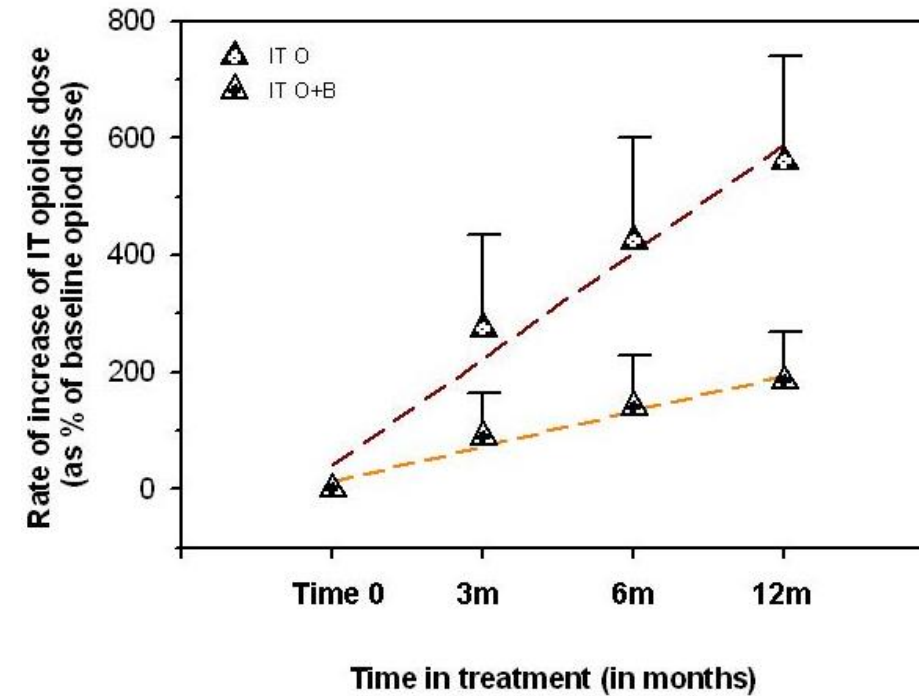
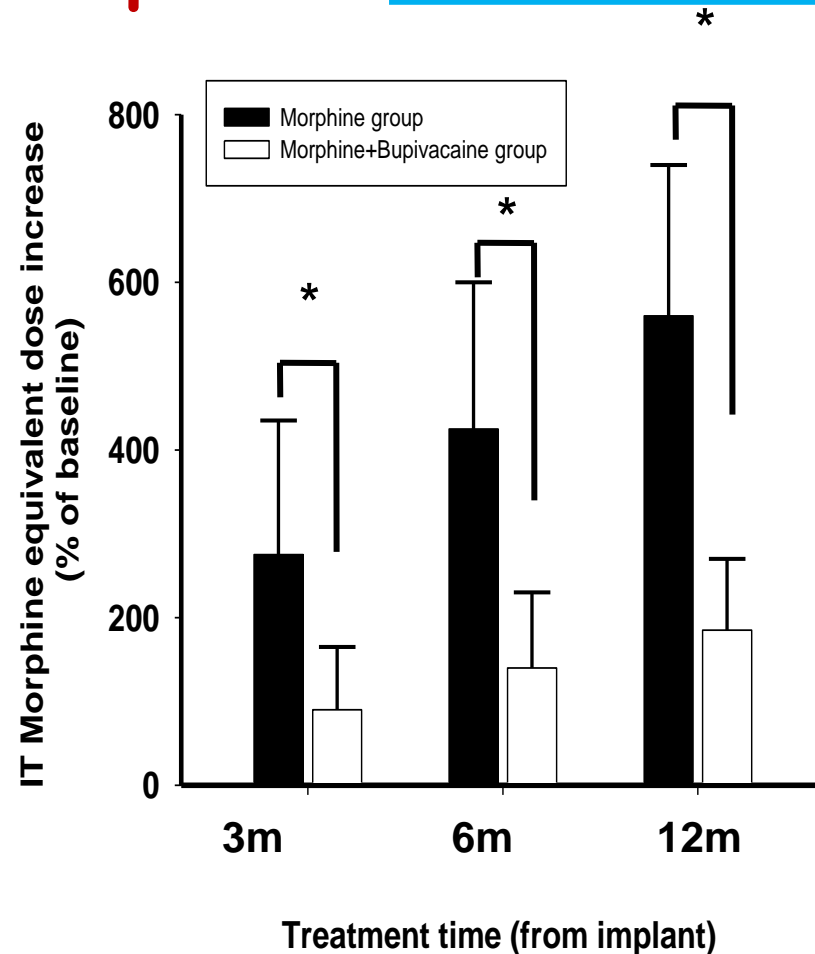


Van Dongen et al., *Clin J Pain*. 1999 Sep;15(3):166-72.





# Bupiv+Opioid from Outset = ↓ IT Opioid Escalation



Curve 1: coefficients:  
b[0] -142.5  
b[1] 183  
r<sup>2</sup> 0.968

Curve 2: coefficients:  
b[0] -47.5  
b[1] 60.5  
r<sup>2</sup> 0.969



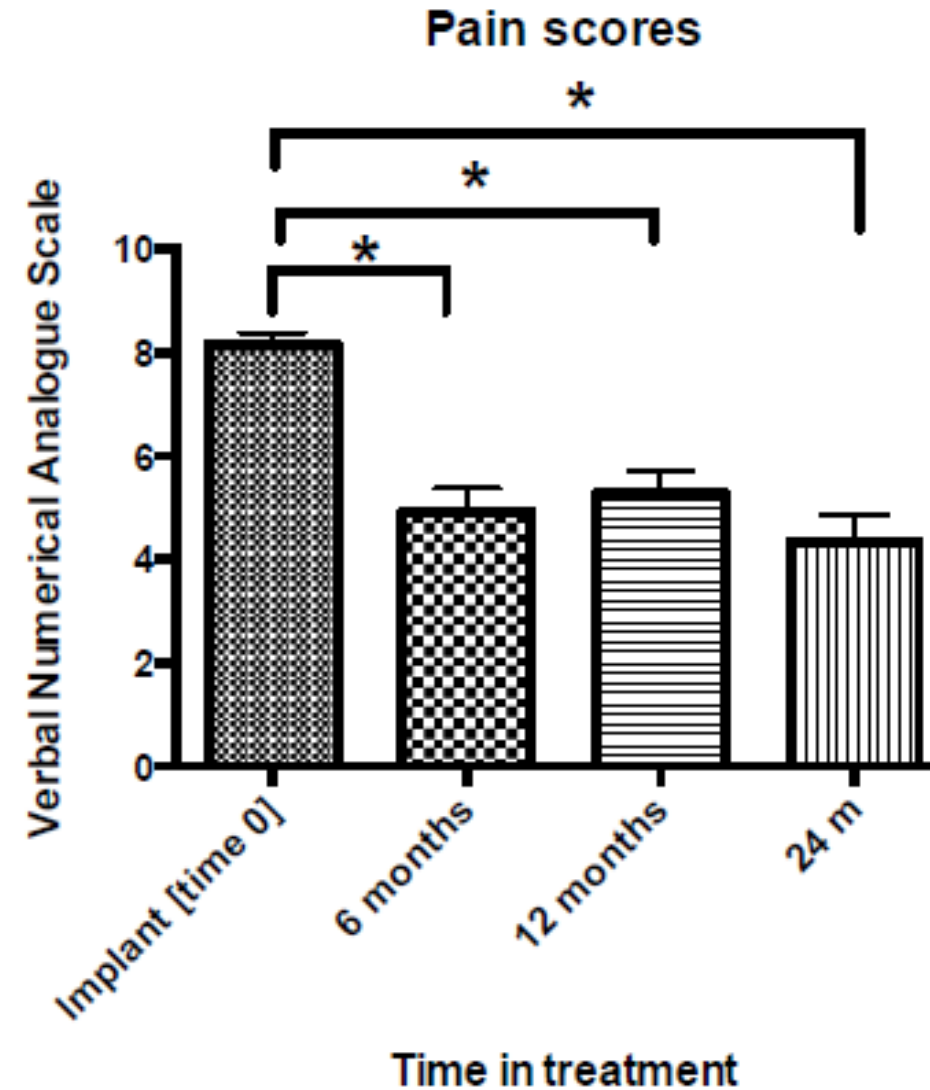
# Combination TIDD for LBP in FBSS

Subjects:	Male	26	46%
	Female	31	54%
	Mean age at implant	64.4 [median 66]	Range: 38-84
	Mean symptom duration	7.5 years	Range: 0.9-24
Etiology of Pain:			
	Post-laminectomy syndrome	57	100.00%
Oral opioids	MEDD [mg /day]	55.7± 67	95% CI ± 18.3
Average VAS Score:		8.42± 1.76	95% CI ± 0.42

- ❖ All: hydromorphone + bupivacaine
- ❖ All: PTM device



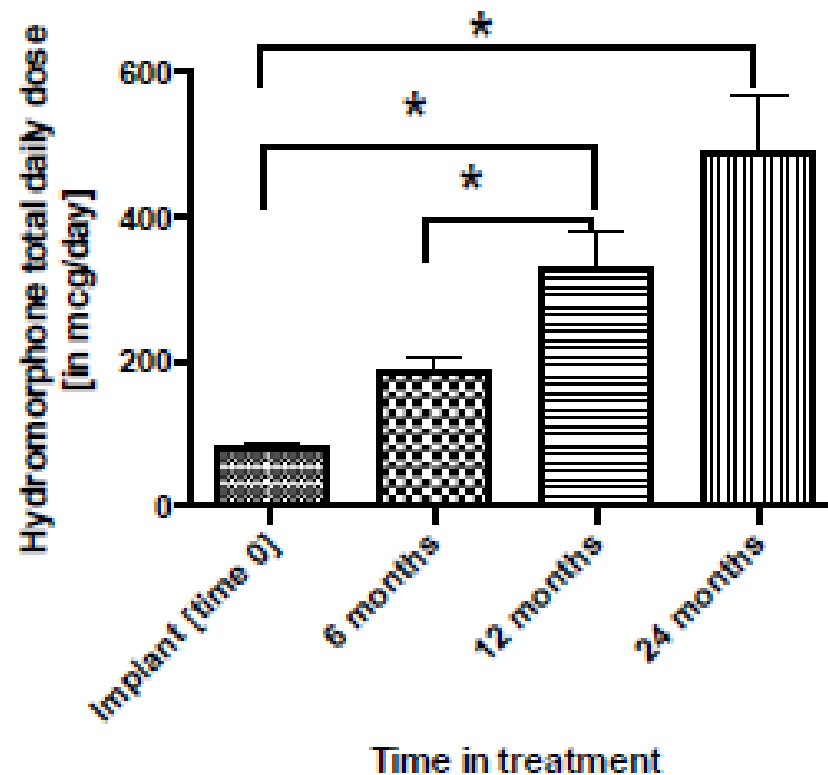
# 24-Month Follow up



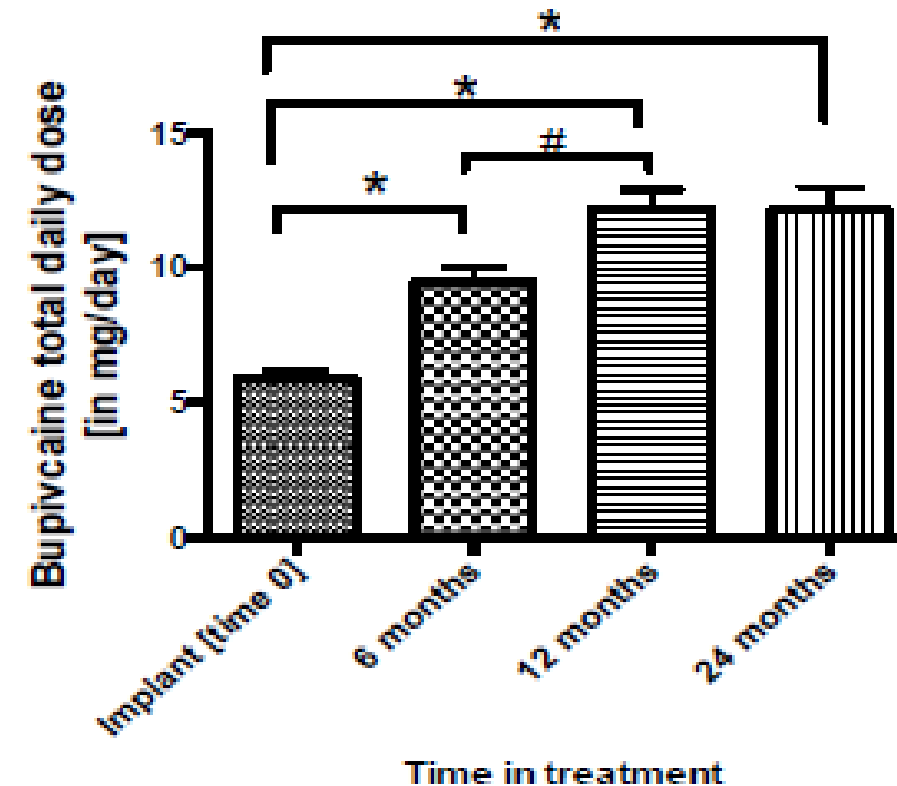




**Hydromorphone total dose**

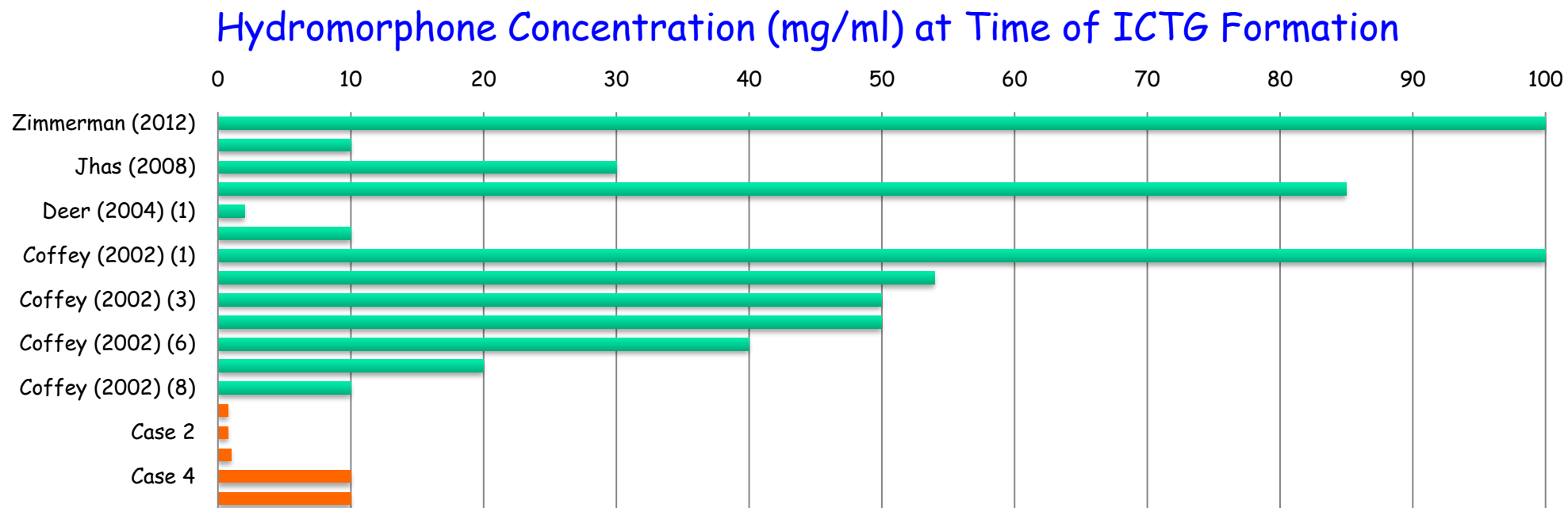


**Bupivacaine T daily dose**



(onlinelibrary.wiley.com) DOI: 10.1111/ner.12481

**I. Elias Veizi, MD, PhD<sup>\*†</sup>; Salim M. Hayek, MD, PhD<sup>\*‡</sup>; Michael Hanes, MD<sup>‡</sup>;  
Ryan Galica, MD<sup>‡</sup>; Sivakanth Katta, MD<sup>‡</sup>; Tony Yaksh, PhD<sup>§</sup>**

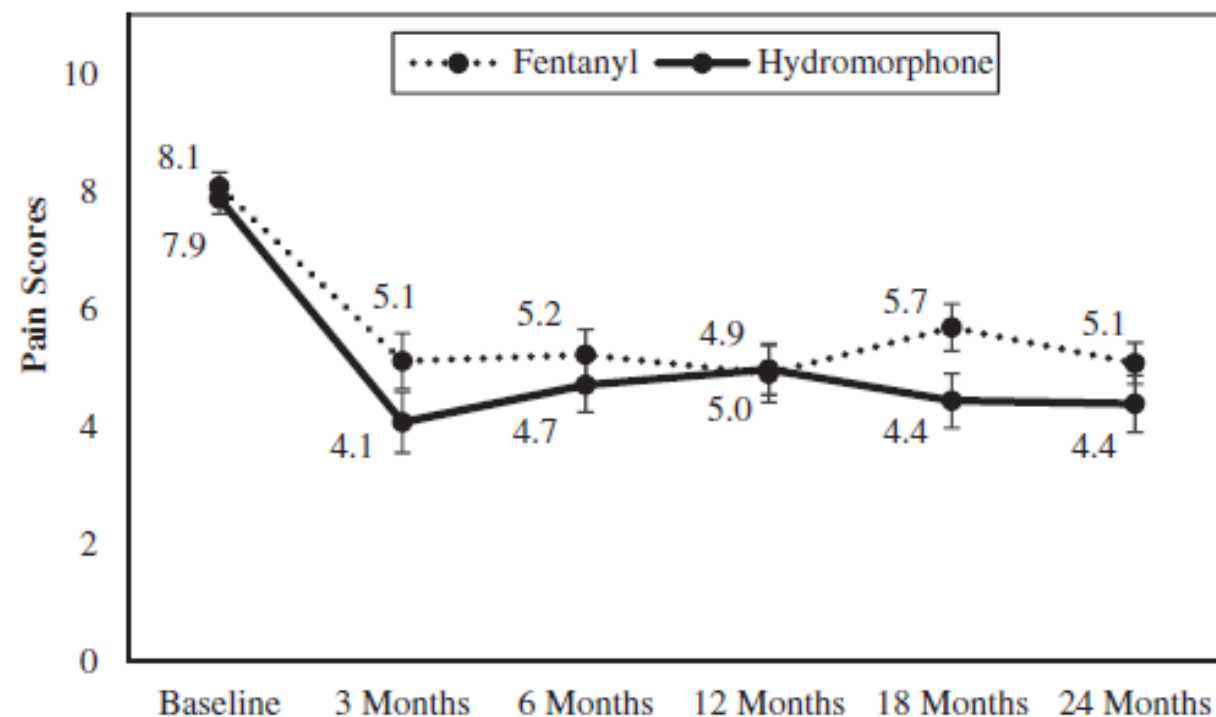




## Combination Rx: Fentanyl vs. Hydromorphone in FBSS

❖ Given risk of granuloma with hydromorphone →

- 28 pt fentanyl/bupivacaine vs.
- 30 pt hydromorphone/bupiv



Ade T, Roh J, Sharma G, et al. Comparative Effectiveness of Targeted Intrathecal Drug Delivery Using a Combination of Bupivacaine with Either Low-Dose Fentanyl or Hydromorphone in Chronic Back Pain Patients with Lumbar Postlaminectomy Syndrome [published online ahead of print, 2020 May 11]. *Pain Med*.



# TIDD Patient Selection

- ❖ Objective evidence of pathology
- ❖ Failure to achieve adequate results from oral opioid therapy/AE's
- ❖ Inability to tolerate the side effects of oral opioids
- ❖ Psychological evaluation
- ❖ Demographics: Old vs. Young patient
- ❖ Nociceptive vs. Neuropathic pain
- ❖ Starting dose of opioids: low vs. high
- ❖ Cancer vs. non-cancer pain
- ❖ Localized vs. diffuse pain

Krames E. Journal of Pain and Symptom Management;1996, Vol 11, No 6: 333-352

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Grider J Harned ME, Etscheidt MA, Pain Physician 2011; 14:343-351





## PACC Guidelines 2017 Recommendations for First Line Therapy in CANCER-RELATED Pain

### **Localized** Nociceptive or Neuropathic Pain

<b>Line 1 A</b>	Ziconotide	Morphine
<b>Line 1B</b>	Fentanyl	Morphine or Fentanyl + Bupivacaine

### **Diffuse** Nociceptive or Neuropathic Pain

<b>Line 1 A</b>	Ziconotide	Morphine
<b>Line 1B</b>	Hydromorphone	Morphine or Hydromorphone + Bupivacaine

Deer TR, Pope J, Hayek SM et al., **The Polyanalgesic Consensus Conference (PACC):** Recommendations on Intrathecal Drug Infusion Systems Best Practices and Guidelines. *Neuromodulation*. **2017** Feb;20(2):96-132.



## PACC Guidelines 2017 Recommendations for First Line Therapy in NONCANCER Pain

### Localized Nociceptive or Neuropathic Pain

Line 1 A		Ziconotide	Morphine
Line 1B		Fentanyl	Fentanyl + Bupivacaine

### Diffuse Nociceptive or Neuropathic Pain

Line 1 A		Ziconotide	Morphine
Line 1B		Hydromorphone	Hydromorphone or Morphine + Bupivacaine

Deer TR, Pope J, Hayek SM et al., **The Polyanalgesic Consensus Conference (PACC):** Recommendations on Intrathecal Drug Infusion Systems Best Practices and Guidelines. *Neuromodulation*. **2017** Feb;20(2):96-132.



# Conclusions

- ❖ TIDD provides lasting relief when tailored appropriately
- ❖ TIDD is optimized by
  - Targeting the catheter to the appropriate location
  - Weaning off opioids to low doses prior to implant (noncancer)
  - Choosing older patients
  - Combination with bupivacaine
  - Use of safer medications



*Thank You!!*

