

**A Trial of Conscience or Good Science:  
Compounded Analgesics**

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Wednesday, December 11, 2013  
4:00 p.m. – 5:00 p.m.

### Learning Objectives

- State the risks of intraspinal therapies, including those inherent with compounded products
- Describe the role of injectable analgesic therapies (specifically corticosteroids) in the management of chronic noncancer pain
- Determine if a given patient is a good candidate for intrathecal analgesic therapy and choose an appropriate agent for the management of noncancer or cancer pain using evidence-based literature and guidelines

### How We Got Here

↓ **SUPPLY** + ↑ **DEMAND = OPPORTUNITY**

### Drug shortages

- Good manufacturing practice concerns
  - Particulate, contamination, impurities
- Fewer manufacturers (generics)
  - Considerably more complex manufacturing processes
  - Delays or capacity issues at manufacturing facilities
  - Generic sterile injectables -74% of product shortages in 2010
- Shortage of raw materials (11%)
  - Discontinuation of drugs

<http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm277745.htm>

### Increased Demand

- Increased demand for aggressive pain management
  - “Decade of Pain Control and Research” 2000-2010
  - Baby boomers
  - Increasing number of patients seeking pain management
- Interventional pain management was officially certified as a medical specialty in 2001
- Pain clinic growth
- In 2011, 2.5 million Medicare recipients had intraspinal corticosteroid injections, as did an equal number of younger people

### Opportunity

- The rise of compounding pharmacies
  - Clinical pharmacy expansion into sterile compounding
  - Many hospitals cannot afford the facilities, staff and procedures necessary to meet USP 797 standards
  - Less expensive than FDA-approved products
  - Provided medications in time of shortage
- Regulation discrepancies, lack of oversight
  - FDA focused on “manufacturers”
  - State Board of Pharmacy regulate compounding “pharmacies”

### What are the risks?

- Sterility
  - Product
  - Procedural
  - Patient status
- Intraspinal abscess
- Osteomyelitis
- Meningitis



### What are the risks?


- Stability
  - Physical (temperature, light, etc.)
  - Chemical (pH, solubilities, compatibilities)
  - Biological (organisms)
- Medications used off-label
  - Morphine
  - Baclofen
  - Ziconotide
  - Clonidine (only epidural, not intrathecal)
  - Local anesthetics (only epidural, not intrathecal)
  - Corticosteroids NOT approved for intraspinal use

### What are the risks?

- Neurotoxicity
- Pharmaceutical preservatives
  - Benzyl alcohol, methylparaben and propylparaben, phenol, sulfites, and polyethylene glycol
- Preservative free ≠ safe for intraspinal use
  - Pyrogens and endotoxins
  - "Antioxidants" such as sodium bisulfite and sodium EDTA

### What are the risks?


- Intrathecal granuloma
- Hyperglycemia
- Respiratory depression
- Itching
- Psychiatric effects
- Hypotension



### If these products are so risky, why do we do them?

### JP

- 48 yr old male with low back, left leg pain
- "Aching" in low back with pain, down the leg into the toes
- Diffuse tenderness in low back, specifically over the left L4-5 facet joints
- Several trigger points palpated
- Activity makes pain worse
- Sleep: 3 hours at night
- Social: doesn't go out or socialize very much, used to golf but isn't able to play now due to pain
- Employed: no, but was a plumber

What kind of pain does JP have? 

- A** Myofascial Pain
- B** Radicular Pain
- C** Osteoarthritis Pain
- D** All of the above

### Corticosteroids

- Why do we use them for pain?
- Where do we use them?
- How do we choose an agent?
  - Greater particulate matter = greater/longer efficacy
  - Greater particulate matter = increased risk of embolism and occlusion of blood vessels

### Corticosteroids

Corticosteroid	Particle size (>50µ)	Indication	Preservatives/stabilizers
Methylprednisolone acetate (DepoMedrol®)	27%	IM, IA Soft tissue	Preservative free
Triamcinolone acetonide (Kenalog®)	12%	IM, IA	Benzyl alcohol
Betamethasone sodium phosphate/ acetate (Celestone Soluspan®)	3%	IM, IA Soft tissue Intra-lesional	Edetate sodium BC
Dexamethasone sodium phosphate (Decadron®)	0%	IV, IM, IA Soft tissue Intra-lesional	Preservative free

Bonzon HT, et al. Anesthesiology 2007;106(2):331-8.

JP a good candidate for injectable corticosteroid therapy? 

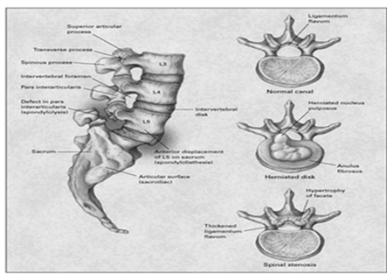
- A** Yes
- B** No

### Myofascial Pain

- Nonpharmacologic therapies
- Trigger Point Injections (TPI)
  - Dry needle
  - Local anesthetic
  - +/- corticosteroid
  - Botulinum toxin
- Dry needle = saline = local anesthetic
- No benefit from adding steroid<sup>1</sup>

1. Malanga GA, et al. Phys Med Rehabil Clin N Am 2010;21(4):711-24.

JP has diffuse tenderness in low back, specifically over the left L4-5 facet joints



Rathmell J, JAMA 2008 (17):2066-77.

### Facet Joint Injections

- Multiple studies have shown no short or long-term benefit of facet joint injections vs. placebo or home stretching.
- APS states evidence not strong enough to recommend facet joint injections<sup>1</sup>
- ASA/ASRA guidelines state that facet joint injections are optional procedures for symptomatic relief<sup>2</sup>

1. Chou R, et al. Spine 2009;34(10):1078-93. 2. Rosenquist RW, et al. Anesthesiology 2010;112:1-24.

JP has pain that radiates from his low back down his left leg to his toes

### Radicular pain (a.k.a. sciatica)



- Caused by irritation/impingement of spinal nerve root
  - Spondylolisthesis
  - Herniated disc
  - Spinal stenosis
  - Facet arthropathy

### Epidural Steroid Injections

- Usually preceded by 3-6 wks conservative tx
- Then MRI
- Cervical spine (CESI)
  - Dexamethasone
- Lumbar spine (LESI)
  - Methylprednisolone
- Caudal
  - Methylprednisolone

### Are They Safe?

- Systemic effects recently reviewed
  - Side effects dose-, duration-, location-dependent
  - Short-term blood glucose elevation
  - Flushing reaction
  - Potential HPA axis suppression
  - Rare hypercorticism
  - Rare lipomatosis
  - Central serous chorioretinopathy
- Suggest close monitoring and standard protocol

Bellini M, Barbieri M. Anaesthesiology Intensive Therapy, 2013; 45(2): 93-8.

### Are they effective?

- Majority of herniated discs resolve
- Some studies show ESI no better than saline
- May see some improvement in leg pain but no studies show improvement in back pain
- APS<sup>1</sup> Low back pain guidelines
  - Moderately effective for short-term relief of radiculopathy due to herniated disc
  - No benefit with non-radicular back pain or FBSS
- ASA<sup>2</sup> Low back pain guidelines
  - May offer temporary relief for radicular low back pain


1. Chou R, et al. Spine 2009;34(10):1078-93. 2. Rosenquist RW, et al. Anesthesiology 2010;112:1-24.

### If they're not very effective, why do them?

- Patients demand that "something" be done NOW
- Some patients **will** receive some benefit
- Got to pay the overhead
  - TPI – 1-2 muscles = \$255
  - TPI – 3 or more muscles = \$345
  - CESI = \$1060
  - LESI/caudal = \$995
- Usually only do these q 3 months

JP

- JP discusses risk-benefit with provider → ESI q3 months 3 without improvement
- Encourage nonpharmacologic management
- Continue pharmacologic management with non-opioid therapy
  - Refer to ASA guidelines
- JP undergoes spinal decompression and fusion L4-5
- Pain continues and persists at severe intensity
  - Determined he has failed back surgery syndrome

Is JP a candidate for IT therapy? 

**A** Yes

**B** No

Chronic Pain Conditions with Potential Role for Intrathecal Analgesic Administration

- Failed back surgery syndrome
- CRPS
- Spinal stenosis
- Osteoporosis with compression fractures
- Peripheral neuropathies

Limitations in Patient Selection

- Limited data evaluating long-term efficacy
- Heterogeneity of study populations and methodology
- Some studies demonstrate improvement in pain severity
- Lack of controlled studies evaluating effect on physical/mental functioning

Indications For Implantation

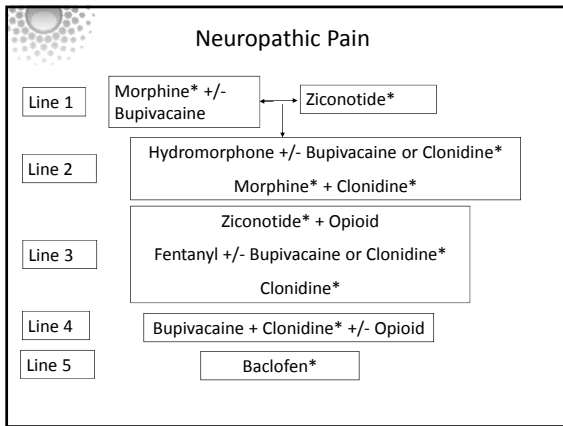
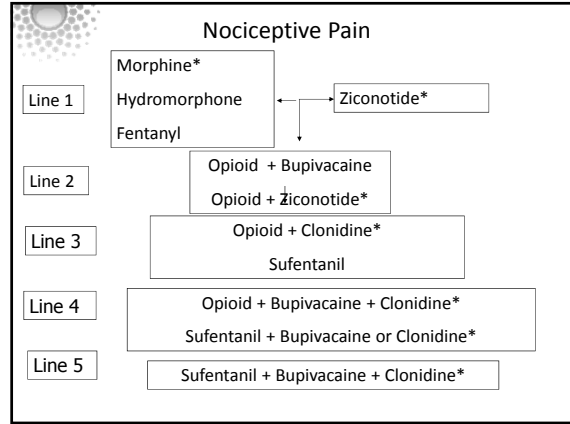
- Appropriate diagnosis of pain established
- Pain significantly interferes with activities of daily living, ability to work, and quality of life
- Pre-existing medical co-morbidities are well-controlled
- No severe or uncontrolled psychological conditions
- Trial and failure to achieve satisfactory analgesia with less invasive therapies
- Oral therapy is contraindicated

Deer TR, et al. Pain Physician 2010; 13: E175-E213

Contraindications for Implantation

- Immunocompromised patients at high risk for infection or those presenting with active infection
- Severe psychological condition
- Current or anticipated lack of insurance coverage or difficulty paying for implantation/medication
- Inability to comply with refill schedule

Deer TR, et al. Pain Physician 2010; 13: E175-E213



- ### JP Follow-up
- Imaging prior to IT pump placement reveals spinal bone lesions
  - JP diagnosed with advanced lung cancer
  - Life expectancy < 6 months

Is an IT pump still a good treatment option for JP?

**A** Yes

**B** No

- ### IT Efficacy in Cancer-related Pain
- 30-40% of patients with early disease, and 70-90% with advanced disease experience pain
    - Incidence of chronic pain after cure ~ 33%
    - Cancer patients may have pain of non-cancer origin
  - Improved pain relief and decreased adverse effects versus conventional therapies
  - Potentially improved survival
  - Patient selection should account for all attributes considered in noncancer pain **plus** life-expectancy
- Deer TR, et al. Pain Physician. 2010; 13: E175-E213.

### IT Therapy: Cost-Benefit?

- Well-documented cost-effectiveness in chronic noncancer pain<sup>1</sup>
  - Financial break-even point at 2nd year post-implantation
  - Lifetime savings \$3,111 per patient per year
- Cost-effectiveness in select cancer pain patients<sup>2</sup>
  - May become cost-beneficial within 6 months
  - Patients on high-cost opioid regimens
  - Longer life expectancy and duration of IT therapy

1. Guillemette S, et al. Pain Med 2013; 14: 504-515 2. Brogan SE, et al. Pain Med 2013; 14: 478-486.

### Other Thoughts

- Hyperalgesia
- Drug monitoring and patient follow up
- Psychological considerations
- Ability to prognosticate

### Taking the Holistic Approach

- Guidelines are there to be suggestive of best practice
- Dueling guidelines put pressure on clinical decision-making
- APS<sup>1</sup> recommends noninterventional therapies for treatment of LBP
- Injections do not address the psychological and environmental factors involved in LBP
  - Interdisciplinary rehabilitation
- Continue to study interventional techniques to allow for development of stronger evidence-based recommendations



**Welcome to the Pain Suite**

Do you have any questions before we proceed?