

**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? 

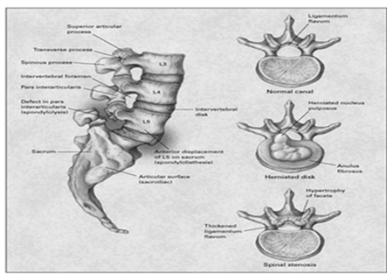
- A** Yes
- B** No

Myofascial Pain

- Nonpharmacologic therapies
- Trigger Point Injections (TPI)
 - Dry needle
 - Local anesthetic
 - +/- corticosteroid
 - Botulinum toxin
- Dry needle = saline = local anesthetic
- No benefit from adding steroid¹

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 injections¹
- ASA/ASRA guidelines state that facet joint injections are optional procedures for symptomatic relief²

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
- APS¹ 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
- ASA² 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

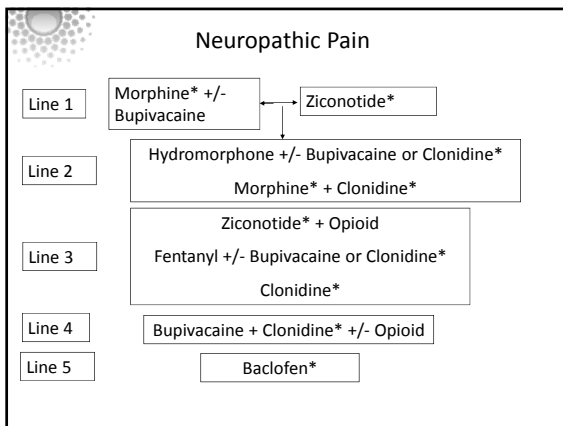
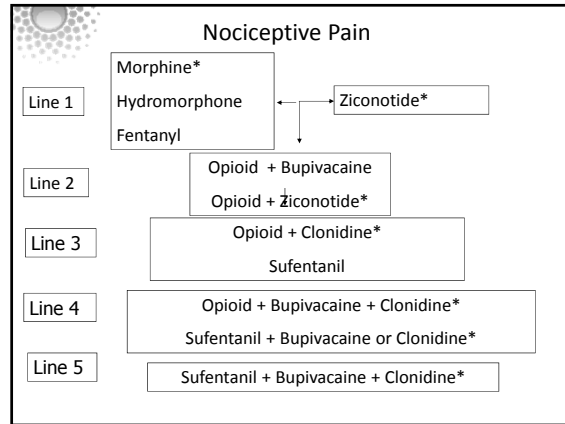
Contraindications for Implantation

- 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

*Polyanalgesic Consensus Conference 2012:
 An Update on the Management of Pain by Intraspinal Drug
 Delivery – Report of an Expert Panel*

Deer TR, et al. Neuromodulation. 2012;15(5):436-6.



- ### 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 pain¹
 - Financial break-even point at 2nd year post-implantation
 - Lifetime savings \$3,111 per patient per year
- Cost-effectiveness in select cancer pain patients²
 - 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
- APS¹ 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?