Successful Strategies in Intrathecal Pain Management

Dinner Symposium, Saturday, May 17

7:00 PM: Registration/Buffet Dinner
7:30 PM to 9:30 PM: Symposium

Waldorf Astoria – Central Park Ballroom
Supported by:

An educational grant from Jazz Pharmaceuticals, Inc.
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Disclosures

- **Research:** Jazz Pharmaceuticals, Inc.; Mallinckrodt; Medtronic, Inc.
- **Speakers Bureau:** Jazz Pharmaceuticals, Inc.; Medtronic, Inc.
- **Consultant:** Jazz Pharmaceuticals, Inc.; Medtronic, Inc.
Agenda

7:00 PM  Registration/Buffet
7:30 PM  Welcome/Introductions
7:35 PM  Patient Selection: Matching Patients to Treatment Options
8:00 PM  Trialing Methods When Initiating Therapy
8:25 PM  Titration and Dose Escalation to Optimize Outcomes
8:50 PM  Key Clinical Connections and Q&A
9:00 PM  Conclusion
Learning Objective 1

Apply evidence-based, best practice criteria for appropriate patient selection for intrathecal pain management.
Learning Objective 2

Integrate established best practice trialing strategies into the decision-making process when developing an individualized treatment approach to pain management.
Learning Objective 3

Implement an evidence-based titration strategy for the optimal treatment of chronic pain patients who are being managed with IDDS therapy to minimize potential for side effects and in alignment with the goals of the patient.
Challenges in Treating Chronic Pain

● Illness burden is high: More than 100 million Americans live with disabling chronic pain\(^1\)

● Treatment choice is complex\(^2\)
  ● Physical therapy (to what extent?)
  ● Injections (how many rounds?)
  ● Oral medication (Choice of drug, dose, long-term issues?)
  ● Spinal surgery (Rate of success?)
  ● Spinal cord stimulation (Target, frequency?)
  ● Targeted drug delivery (Drug, dose, patient selection?)

Challenges in Treating Chronic Pain

- Long-term analgesic efficacy with opioids
  - May be limited due to dose tolerance\(^1\)
  - May be variable and has led to heightened patient management requirements\(^2\)

- Diversion of oral opioids is a problem\(^3\)
  - 3 out of 4 people who misuse pain medications use drugs prescribed for someone else
  - 14,800 Americans died from prescription pain medication overdoses in 2008

Patient Reports in Treating Chronic Pain

Chronic pain patient dissatisfaction with opioids

- Breakthrough Pain: 60%
- No Control: 51%
- Limits physical activity: 81%
- Feeling Depressed: 77%
- Energy Level Impacted: 74%
- Trouble Concentrating: 70%
- Enjoyment of Life: 59%

Efficacy of Opioid Therapy

- Short-term efficacy
  - Clear efficacy in multiple RCT’s demonstrate improvement in pain

- Long-term efficacy
  - Few RCTs for longer than 12 weeks
  - Safety further declines at >50 MED, safety markedly declines at >100 MED
  - No evidence to support dosing of higher than 180 mg morphine equivalent per day
  - Studies mostly look at VAS, little evidence of improved function

Opioid Therapy in Chronic Pain

**Consensus**: Opioid therapy is first-line for moderate to severe chronic pain related to cancer and advanced medical illness of any type

**There is no consensus** on the role of opioid therapy for chronic non-cancer pain

Opioid treatment for chronic back pain

CONCLUSIONS

● Opioids have limited, if any, short-term value in chronic low back pain
● Evidence about substance abuse is too limited to draw any conclusions
● There are insufficient data to judge long-term outcomes

November 1, 2011: Dr. Thomas Frieden
Director of the Centers for Disease Control and Prevention

"For chronic pain, narcotics should be the last resort."

Changing the Route of Administration

- Intrathecal drug delivery devices are not a therapy, but are a delivery system for a therapeutic agent.
- Opioids (morphine) and ziconotide are the currently approved therapies for treating chronic pain.
Targeted Drug Delivery

- Why consider Targeted Drug Delivery (TDD)?
- What medication choices for TDD are available?
- What evidence supports such use?
- What is the role of trialing?
- How does the intrathecal route of delivery compare to systemic in terms of safety, efficacy, side effects and cost?
Why Targeted Drug Delivery?

Systemic analgesia
● Distributes drug via blood
● High blood levels of drug
● Brain receives highest proportion of drug
● High dose of drug required – High elimination load
● Increase in systemic side effects

Spinal analgesia
● Intrathecal drug distribution
● Low blood levels of drug
● Most drug binds to TARGET (spinal cord pain receptors)
● Low dose of drug is effective
● Low elimination load
  ● Minimal effect of genetic differences in metabolism
● Minimal systemic effect on brain and gut

Who Is Potential Candidate: Refractory to Oral Analgesics

- Pain History – 14 years severe chronic pain – Lumbar pain with bilateral lower extremity pain – Sedentary but capable of performing activities of daily living

- Pain Etiology and Treatment History – Failed back surgery – Failed spinal cord stimulation – Takes oral opioids, antidepressant, anticonvulsant, sleeping aid, and stool softener

- Assessment – Patient is getting limited pain relief and has become intolerant of treatment as systemic analgesics, including oral opioids
Patient Selection
Redefine Patient Selection

First Choices for Opioid-based TDD

- Elderly axial spinal pain
- Failed Back Surgery Syndrome not amenable to SCS
- Good analgesia with systemic opioids but intolerable side effects
- Cancer pain

SCS = spinal cord stimulation
TDD = targeted drug delivery
Redefine Patient Selection

Difficult choices for opioid-based TDD

- High oral opioid use with minimal perceived benefit
- Poorly defined etiology
- Poor compliance to previous therapies
- Young age
- Psychological issues which have not been successfully treated
- Positioning as a salvage therapy for opioid unresponsive patients
  - Diminished outcomes

Psychological Evaluation

- Consider recommendations and treat if indicated - *prior to trial*
- Ability to understand appropriate expectations
- Has patient come to terms with status, expected life span?
- Major active psychosis, current drug addiction, some personality disorders, cognitive deficits, progressive organic brain disorders, suicidal, homicidal behavior

Intrathecal Delivery
Advantages

- Achieves steady-state, around the clock dosing
- Reduced side effects, use of intermittent dosing to reduce tolerance
- Intrathecal Adjuvants (PACC)
- Compliance: Eliminate systemic opioids
  - Can provide patient activated rescue dosing (PCA)
  - Reduction in longitudinal costs

PACC = Polyanalgesic consensus conference
## 2012 Polyanalgesic Panel Recommended Concentrations and Doses of Intrathecal Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Maximum Concentration</th>
<th>Maximum Dose per Day</th>
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</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>20 mg/mL</td>
<td>15 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>15 mg/mL</td>
<td>10 mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>10 mg/mL</td>
<td>No known upper limit</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>5 mg/mL</td>
<td>No known upper limit</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>30 mg/mL</td>
<td>10mg</td>
</tr>
<tr>
<td>Clonidine</td>
<td>1000 mcg/ml</td>
<td>40-600 mcg/day</td>
</tr>
<tr>
<td>Ziconotide</td>
<td>100 mcg/mL</td>
<td>19.2 mcg/d</td>
</tr>
</tbody>
</table>

## 2012 Polyanalgesic Panel

### Recommended Starting Doses of Intrathecal Agents

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<tr>
<td>Morphine</td>
<td>0.1 mg/d to 0.5 mg/d</td>
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<tr>
<td>Hydromorphone</td>
<td>0.02mg/d to 0.5 mg/d</td>
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<tr>
<td>Ziconotide</td>
<td>0.1 to 0.5 mcg/d</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>25-75 mcg/day</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>1 to 4 mg/day</td>
</tr>
<tr>
<td>Clonidine</td>
<td>40-100 mcg/day</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>10 to 20 mcg/day</td>
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</table>

Intrathecal Opioids

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

Pharmacologic Considerations

- Receptors for the agents have to be at the spinal level
- Drug has to get to receptors
- Drug considerations
  - Lipid solubility
  - Density and baricity
  - Kinetics: Bolus vs. continuous

IT Opioid Doses Increased to Maintain Pain Control

Mean VAS Pain Intensity Score
Mean IT Morphine Dose (mg/d)

Baseline | Discharge/First Refill | 1 Year | 2 Years | 3 Years

Overview of Ziconotide

- Only non-opioid IT therapy approved for severe chronic pain
  - N-Type Calcium Channel Blocker
- Earlier introduction for chronic pain patients
- Option for patients with lack of efficacy despite significant doses of systemic opioids
- Non-narcotic, no respiratory depression
- No tolerance observed
- No withdrawal

Ziconotide prescribing information. Drugs@FDA.gov.
IT Ziconotide Efficacy and Safety (Pooled Studies)

- **Efficacy\(^1\)**
  - Three double-blind, placebo-controlled, multicenter studies
  - \(N = 457\)
    - 268 ziconotide
    - 189 placebo
  - Two fast titration studies; one slow titration study
  - Mixed, neuropathic, and nociceptive pain\(^2-4\)

- **Safety\(^1\)**
  - Evaluated in 1,254 severe chronic pain patients
  - Mean treatment duration = 193 days

1. Ziconotide prescribing information. [Drugs@FDA.gov](http://Drugs@FDA.gov).
IT Ziconotide Efficacy (Pooled) Results

Response in 3 Pooled Placebo Controlled Trials* (N = 453)

* From baseline to end of initial titration.

Collins R. Poster presented at AAPM Annual Meeting; 2005.
Ziconotide Patient Selection

- Ziconotide is effective in a wide range of pain etiologies\(^1\)
- Patients with a history of psychosis should be excluded from therapy\(^2\)
- Ziconotide should be used with caution in patients with preexisting depression or cognitive impairment\(^2\)

1. Ziconotide prescribing information. Drugs@FDA.gov.
Trialing
Does it Matter If and How You Trial?

● What are the goals of therapy?
● Can the trial method help achieve your clinical goals?
Drug Trial Methods

- Single injection
  - One epidural or intrathecal injection
- Multiple injections
  - Series of intrathecal or epidural injections
  - Epidural injections require a catheter
- Continuous infusion
  - Intrathecal or epidural catheter is placed and connected to external pump

## Trialing: Single Shot

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Easy, quick</td>
<td>• “Failed trial” requires multiple procedures</td>
</tr>
<tr>
<td>• Do not need to go to hospital</td>
<td>• Does not provide patient experience of alternate route of delivery</td>
</tr>
<tr>
<td></td>
<td>• May not be compliant with payor (CMS) guidelines or labeling</td>
</tr>
</tbody>
</table>

# Trialing: Continuous Infusion

## Advantages
- Best model of the pharmacodynamics of intended therapy
- Allows estimation of initial starting dose
- Compliant
- Hospital and physician are reimbursed

## Disadvantages
- Requires hospital stay and management

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Evaluate Trial Results

- Measurement tools
  - Subjective: pain diary, pain scores
  - Objective: monitor activities, monitor medications

- Assess agreed-upon goals
  - Significant pain relief
  - Increased functioning
  - Reduced side effects
  - Decreased use of systemic analgesics

- Trial outcome is positive when goals are met

Titration
PACC 2012 guidelines concluded that:

- Intrathecal drug delivery systems may be an effective pain management option for patients with moderate-to-severe intractable pain.
- The potential for adverse events caused by intrathecal therapies can be diminished with careful dosing and titration.
- And, finally, low doses with slow upward titration is the recommended method of initial dosing, and adjustments are to be made according to patient response.

Ziconotide Slow Titration Trial

IT Ziconotide Maintenance of Efficacy

Dosing
Optimal Dosing Strategies for TDD

- Terminology varies
  - Low Dose
  - Microdose
  - Dosing Strategies

- What are the main components?
  - Eliminating systemic opioids
  - Starting at low doses, physician control
  - Moderating dose escalation
  - Providing patient flexibility in dosing
  - Applying good clinical skills already in use to manage dose escalation
  - Building evidence

Start Low, Go Slow

**Ziconotide prescribing information.** [Drugs@FDA.gov](http://Drugs@FDA.gov)

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**Dose Initiation:**
No more than 2.4 mcg/day

**Dose Titration:**
Up to 2.4 mcg/day, no more than 2-3 times per week
Lower and less frequent increases may be used

**Maximum:**
19.2 mcg/day

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The lowest initial starting dose without dilution is 1.2 mcg/day.

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Adjust the dose according to:
- Pain severity
- Patient response to therapy
- Occurrence of adverse events
What is the Need for Patient-Controlled Dosing?

- **Prevalence of “Breakthrough” Pain**
  - 74% of patients
    - The percentage of patients with chronic non-cancer pain who experienced severe to excruciating intermittent pain ($n = 228$).\(^1\)
  - 2.4 episodes/day
    - The mean number of intermittent pain episodes (defined as transitory exacerbation of pain that occurs on a background of otherwise controlled pain).\(^1\)
  - 60 minutes/pain episode
    - Median duration of intermittent pain episodes.\(^1\)

TDD Requires Same Strategies as Systemic Delivery

- Early titration to achieve analgesia and therapy goals
- Careful consideration of dose increases
- Maintain moderate doses
- Monitor for side effects, efficacy
- Physician remains in control of dosing
Clinical Connections

- Patient selection is critical in recommending intrathecal therapy
- Using established trialing strategies can
- Adopting evidence-based dosing strategies can improve success in intrathecal therapy
- Establish goals of therapy with patient
Thank you.

Questions?
Reminder

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Participants can print their certificates or statement of credit immediately.