

June 14-15, 2016

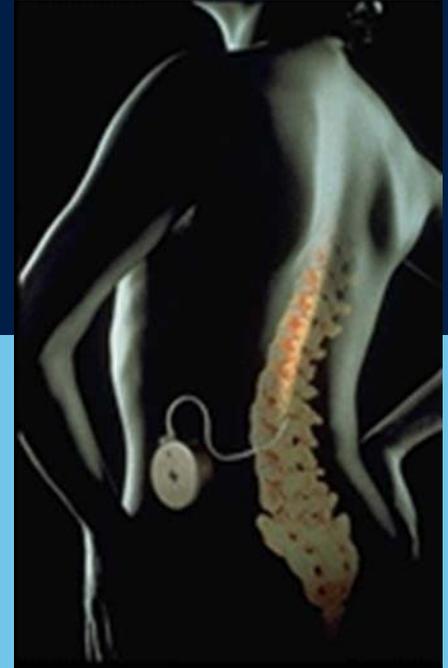
## Multimodal Therapies for Brain Disorders: A Workshop

Hosted by: Forum on Neuroscience and Nervous System Disorders

# Intrathecal Infusion Therapy for Chronic Pain: Challenges, Lessons and Opportunities

Disclaimer: Some of the solutions presented are suggestions for future research; Medtronic does not recommend or promote the off-label use of the SynchroMed Infusion Pump.

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**Medtronic**  
Further, Together

# SynchroMed® II Infusion Therapy for Chronic Pain

Catheter  
Access  
Port

Reservoir  
Refill Port



SynchroMed® II Pump

Intrathecal  
Catheter



Clinician Programmer



Morphine

Ziconotide



FDA-Approved Analgesic  
IT Monotherapies

- Mechanical method to breach the blood-brain barrier and target the CNS
- Implantable, programmable, **refillable**
- Battery-powered peristaltic mechanism,  $\leq 7$  years implant life
- CSF-delivered drug targets pain pathways in dorsal horn of the spinal cord
- Flexible dosing patterns: rates and intermittent bolusing

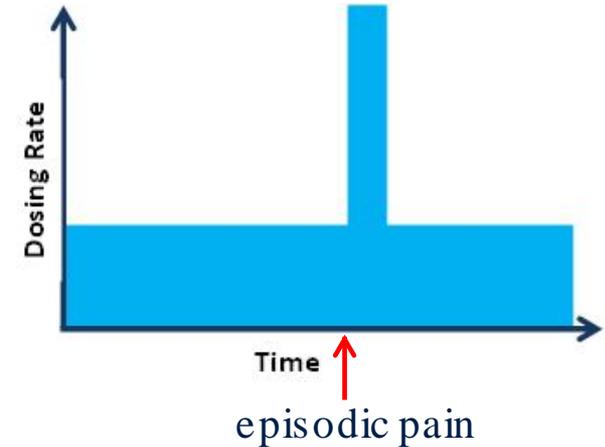
# Challenges and Solutions: Unpredictable Intermittent Pain

## The Challenge:

- Continuous infusion may not prevent or treat episodes of intermittent pain.

## The Solution:

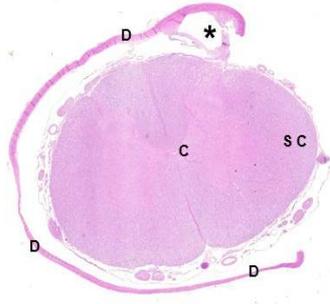
- Patient-controlled analgesia (PCA)
- Hand-held patient programmer
- Dosing restrictions by physician
- Delivers a rapid IT bolus of morphine as needed
- Increased patient engagement in therapy



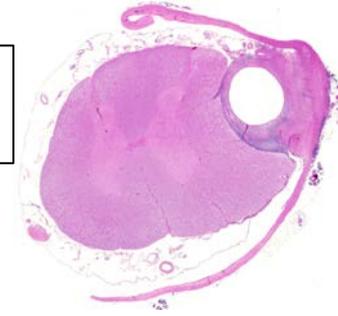
# Challenges and Solutions: Local Toxicity at the Catheter Tip

## The Challenge:

- IT morphine (high concentrations/doses) may induce catheter-tip inflammatory masses (IMs).
  - Spinal cord compression
  - Symptoms: **increased** pain, new neurological signs (leg weakness)



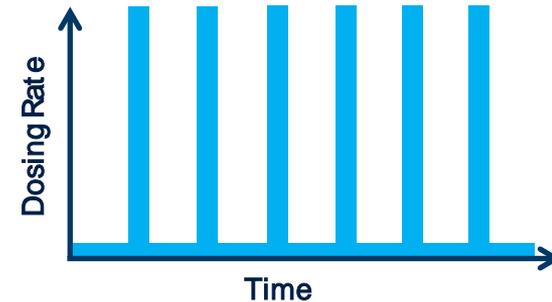
canine spinal cord  
after 28-day IT  
saline infusion



canine spinal cord  
after 28-day IT morphine  
infusion (12 mg/day @ 25  
mg/mL)

## Solutions:

- Physician education:
  - Use lowest morphine dose and concentration for as long as possible.
  - Maintain a low threshold for imaging (MRI) to detect IM early.
- Mitigation strategies under investigation:
  - Deliver morphine using intermittent boluses
  - Understand mechanisms: activation of mast cells in the dura
    - beagle and **new** guinea pig model



# Challenges and Solutions: Use of Drug Mixtures in the Pump

## The Challenge:

- Managing chronic pain over the long term may benefit clinically from using more than one analgesic in the pump.
- Using drug admixtures, off-label and compounded drugs in the pump can lead to problems:
  - Drug-drug instability
  - Drug-pump incompatibility (morphine with metabisulfite)
  - Toxicity (NMDA antagonists: ketamine)

## Solutions:

- Ideally use only agents specifically approved for the pump.
- Test clinically popular combinations in the pump under simulated clinical use conditions and publish.
- Ideally develop combination agents specifically for use in the pump.

464 *Journal of Pain and Symptom Management*

Vol. 25 No. 5 May 2003

### *Original Article*

Stability and Compatibility of Morphine-Clonidine Admixtures in an Implantable Infusion System

# Challenges and Solutions: Drug Stability/ Compatibility with the Pump

## The Challenge:

- Some drugs are not **stable** at body temperature long-term:

**Solutions:** reformulate or decrease refill interval to match.

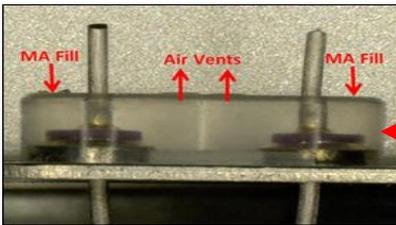
- Drug formulation may not be pump **compatible**.

## The Challenge:



Drugs and paired ions ( $\text{Cl}^-$ ) may cross silicone tubing over time and cause corrosion in the motor compartment: short circuits and gear wear.

## Solutions:



Insulation added to prevent shorts



Gear wheel replaced with corrosion-resistant gear



Coating added to motor shaft to reduce wear



# Challenges and Solutions: Sustained Analgesia

## The Challenge:

- Long-term IT morphine infusion can lead to tolerance, hyperalgesia and IMs.

## Solutions:

- Clinicians often put an additional drug(s) in the pump, e.g., bupivacaine.
- Another clinical approach: wean patients off systemic opioids and use IT morphine only/ mostly.
- Find a better drug:
  - For some patients this can be ziconotide.
  - IT gabapentin was ineffective in an RCT.
  - Consider developing a combination drug formulation.

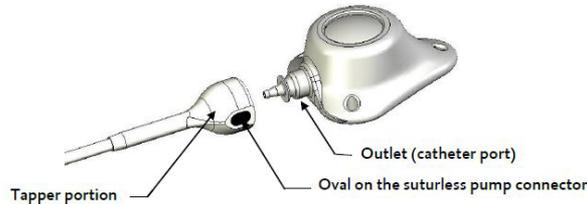
# Challenges and Solutions: Cost and Invasiveness

## The Challenge:

- Implantable pumps are expensive, complex and need to be surgically implanted/replaced.

## Solutions:

- Intermittent IT administration via a SQ port may be effective and provide: value, simplicity and repeated patient-friendly access to the IT space.



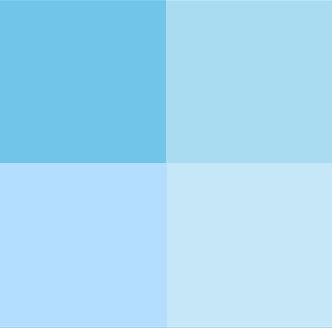
VS.



- Subcutaneous IT access ports are available in Europe (not yet in US).
  - Trialing tool before a pump
  - Early clinical testing of new IT analgesics, new IT indications
    - Pediatric neurological diseases like Niemann Pick C, intermittent IT cyclodextrin
  - IT analgesia for terminal cancer patients

# Enabling of Multimodal Therapy Development

- Understand the **science** of the interventions alone and in combination.
  - IT clonidine for refractory/neurogenic hypertension – location/response of spinal  $\alpha_2$ -adrenoceptor activation
  - Good **preclinical** research and development (safety and efficacy)
- A good/fair collaboration model for Pharma partners or use a contract pharmaceutical manufacturer (repurpose generic drugs)
- Compelling business case
  - Epidemiology and current treatment options
  - Fit with current business (sales and distribution channels)
- Engaged physician champions and collaborators
- Well-designed, small, stepwise clinical trials in carefully selected patients **BEFORE** pivotal trials



**THANK YOU**