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INTERVENTIONAL PAIN MANAGEMENT III

Neuroaxial Drug Delivery

British-Polish-Ukrainian Project for Anaesthetists and Pain Medicine Specialists

Pain Medicine:
Present and Future

KYIV May 2010

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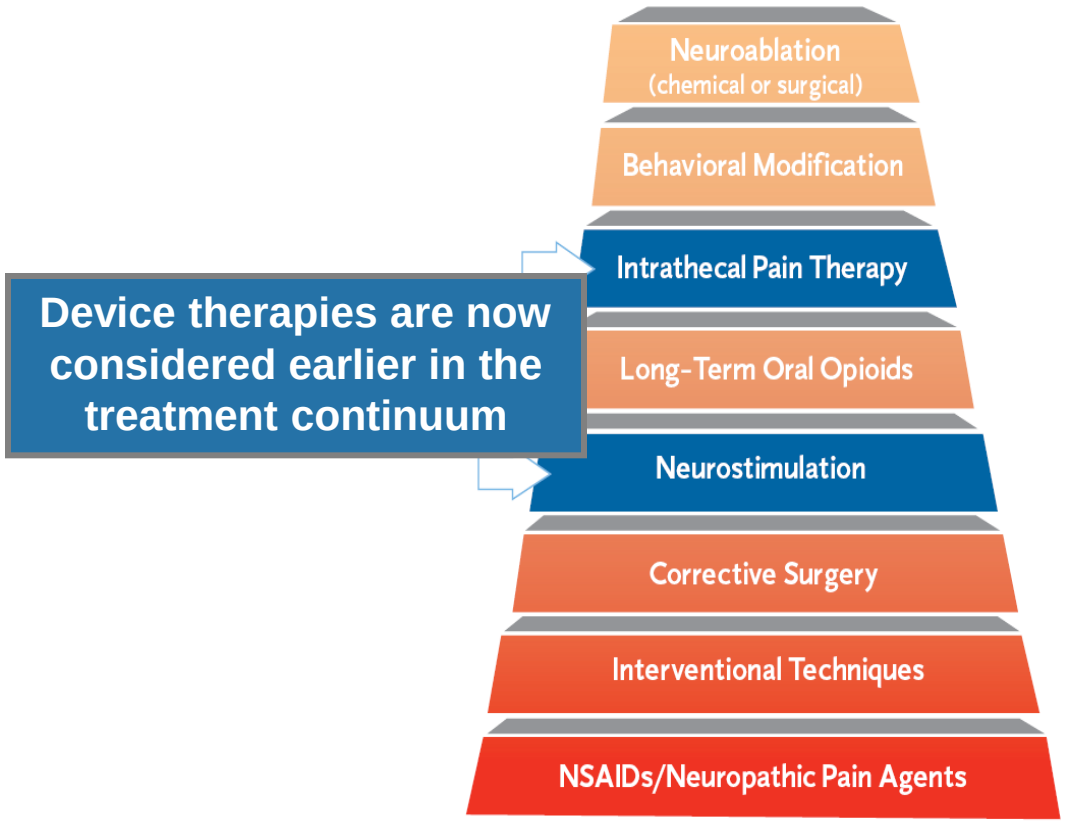
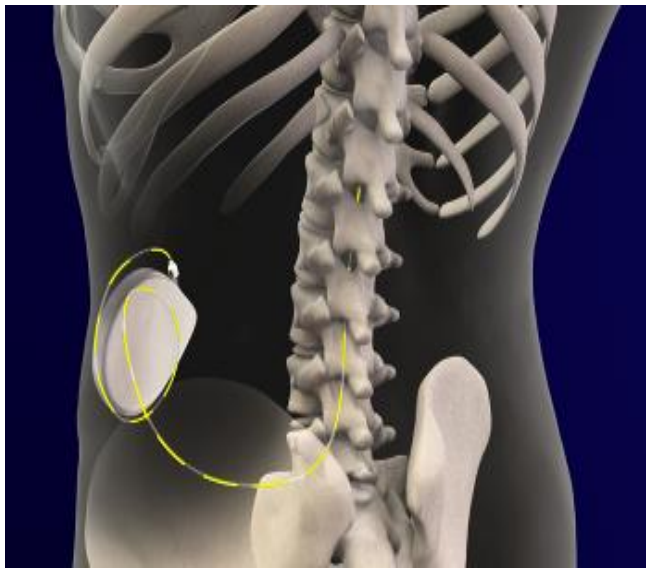
Pain Treatment Ladder

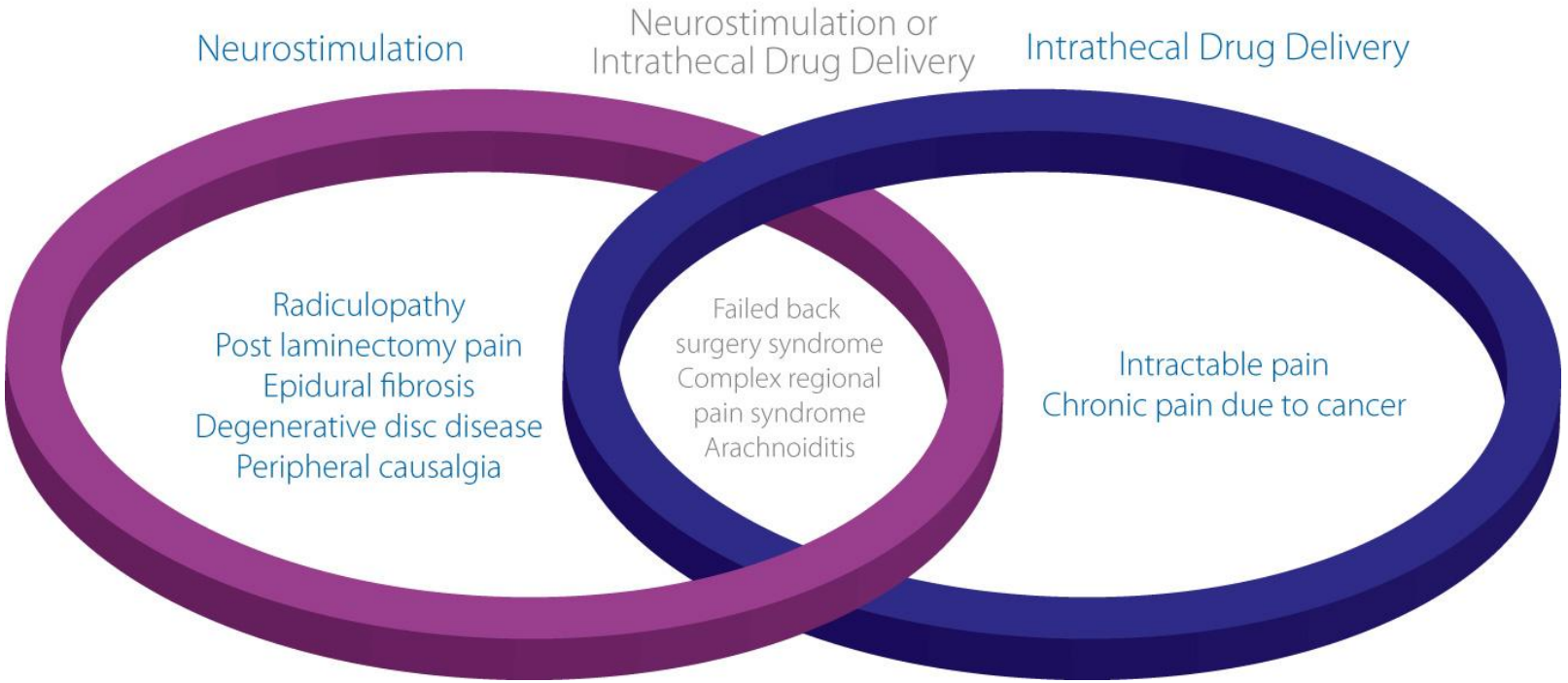


Intrathecal Drug Delivery Therapy

- IDD therapy involves the delivery of pain medicine in the intrathecal space
- The pump is connected to a thin, flexible catheter; both are implanted under the skin
- Smaller doses of medication are needed for effective pain relief because drug is delivered directly to the pain receptors



Indications for Neurostimulation and Intrathecal Drug Delivery Therapy



Scientific Basis of Spinal Opioids

Application of morphine into the substantia gelatinosa was demonstrated to induce a naloxone-reversible reduction in activity in dorsal horn neurons following noxious skin heating. **Nature 1976;264:456** ***Duggan et al***

Dose dependent, stereospecific, naloxone-reversible analgesia after intrathecal morphine in rats. **Science 1976;192:1357** ***Yaksh & Reddy***

SPINAL OPIOIDS

1973 Opioid receptors spinal cord

1976 Yaksh → intrathecal opioids
→ **intense analgesia**

1979 Intrathecal opioids man
→ **pain relief**

EQUIPOTENT DOSES MORPHINE

ORAL / RECTAL	300mg
↓	
PARENTAL	100mg
↓	
EPIDURAL	10mg
↓	
INTRATHECAL	1mg

Provisional

THE BRITISH PAIN SOCIETY

Intrathecal drug delivery for the management of pain and spasticity in adults; recommendations for best clinical practice

Prepared on behalf of the British Pain Society
in consultation with the Association for Palliative Medicine and
the Society for British Neurological Surgeons.

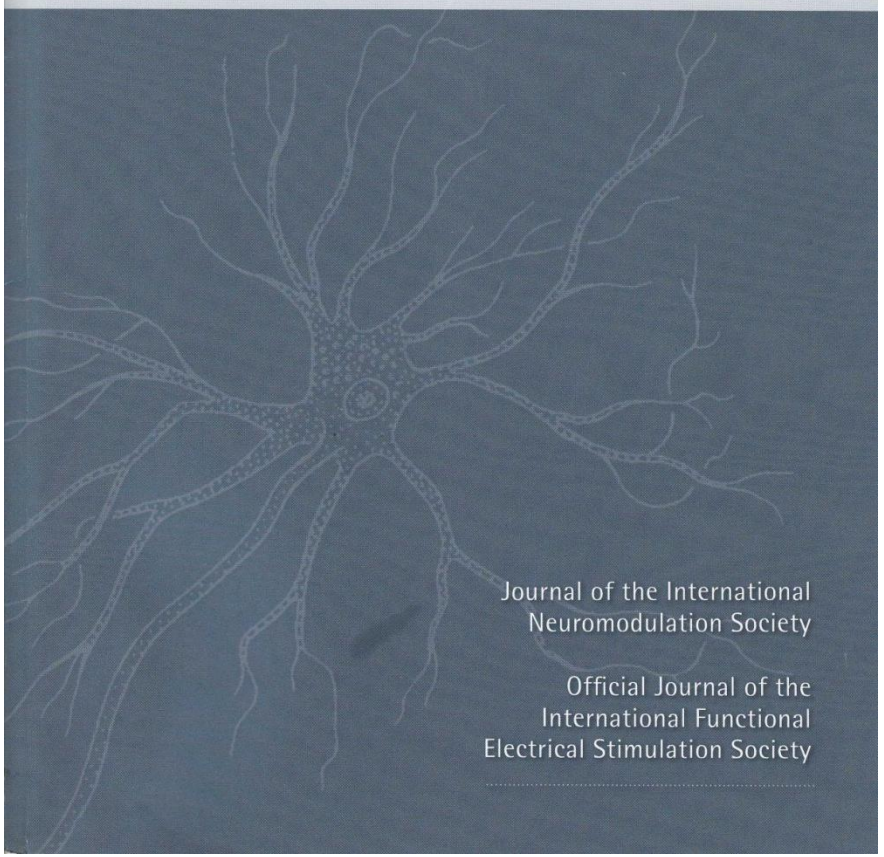
April 2006

Final document April 2007
To be reviewed April 2010

Neuromodulation

Technology at the Neural Interface

VOLUME X • NUMBER 4 • OCTOBER 2007



Journal of the International
Neuromodulation Society

Official Journal of the
International Functional
Electrical Stimulation Society

NEUROMODULATION: TECHNOLOGY AT THE NEURAL INTERFACE

Volume 10 • Number 4 • 2007
http://www.blackwell-synergy.com/loi/ner

ORIGINAL ARTICLE

Polyanalgesic Consensus Conference 2007: Recommendations for the Management of Pain by Intrathecal (Intraspinal) Drug Delivery: Report of an Interdisciplinary Expert Panel

Timothy Deer, MD • Elliot S. Krames, MD • Samuel J. Hassenbusch, MD, PhD • Allen Burton, MD • David Caraway, MD • Stuart Dupen, MD • James Eisenach, MD • Michael Erdek, MD • Eric Grigsby, MD • Phillip Kim, MD • Robert Levy, MD, PhD • Gladstone McDowell, MD • Nagy Mekhail, MD • Sunil Panchal, MD • Joshua Prager, MD • Richard Rauck, MD • Michael Saulino, MD • Todd Sitzman, MD • Peter Staats, MD • Michael Stanton-Hicks, MD • Lisa Stearns, MD • K. Dean Willis, MD • William Witt, MD • Kenneth Follett MD, PhD • Marc Huntoon, MD • Leong Liem, MD • James Rathmell, MD • Mark Wallace, MD • Eric Buchser, MD • Michael Cousins, MD • Anne Ver Donck, MD

ABSTRACT

Background. Expert panels of physicians and nonphysicians in the field of intrathecal therapies convened in 2000 and 2003 to make recommendations for the rational use of intrathecal analgesics based on the preclinical and clinical literature known up to those times. An expert panel of physicians convened in 2007 to update previous recommendations and to form guidelines for the rational use of intrathecal opioid and nonopioid agents. **Methods.** A review of preclinical and clinical published relevant studies from 2000 to 2006 was undertaken and disseminated to a convened expert panel of physicians and nonphysicians. Focused discussions were held on the rational use of intrathecal agents and a survey asking questions regarding intrathecal therapies management was given to the panelists. **Results.** The panelists, after review of the literature from 2000 to 2006 and discussion, created an updated algorithm for the rational use of intrathecal opioid and nonopioid agents in patients with nonmalignant and end-of-life pain. Of note is that the panelists felt that ziconotide, based on new and relevant literature and experience, should be updated to a line one intrathecal drug.

KEY WORDS: *Analgesics, consensus, guidelines, intrathecal, polyanalgesia.*

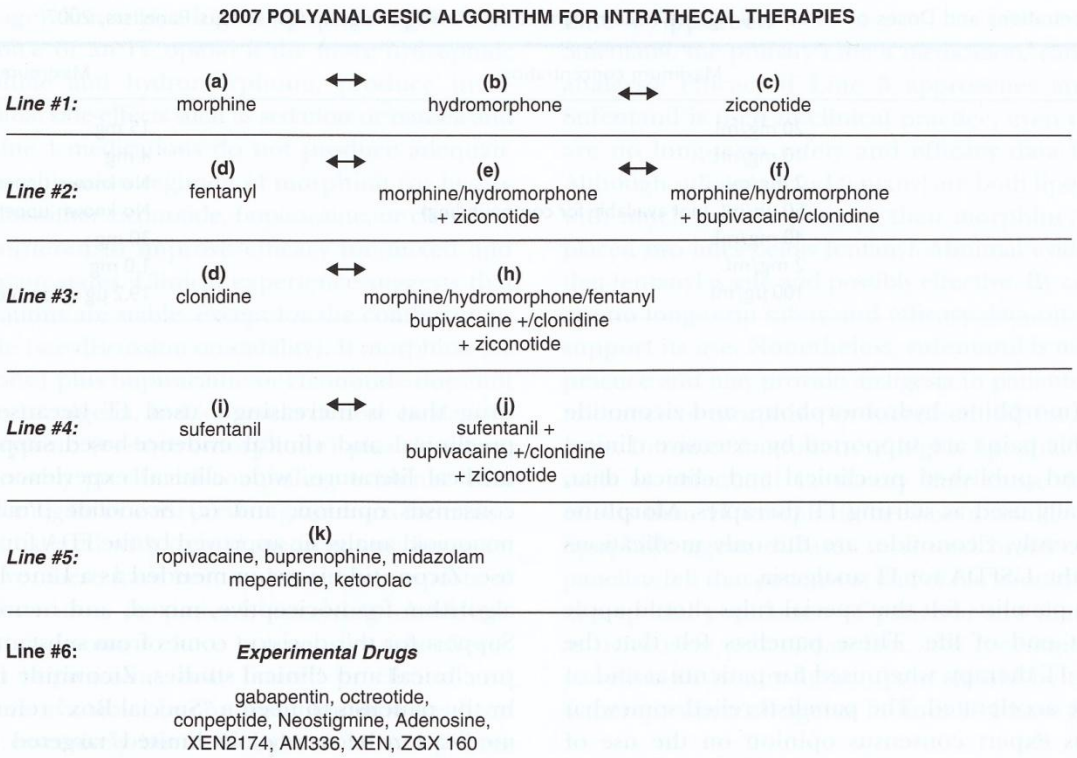
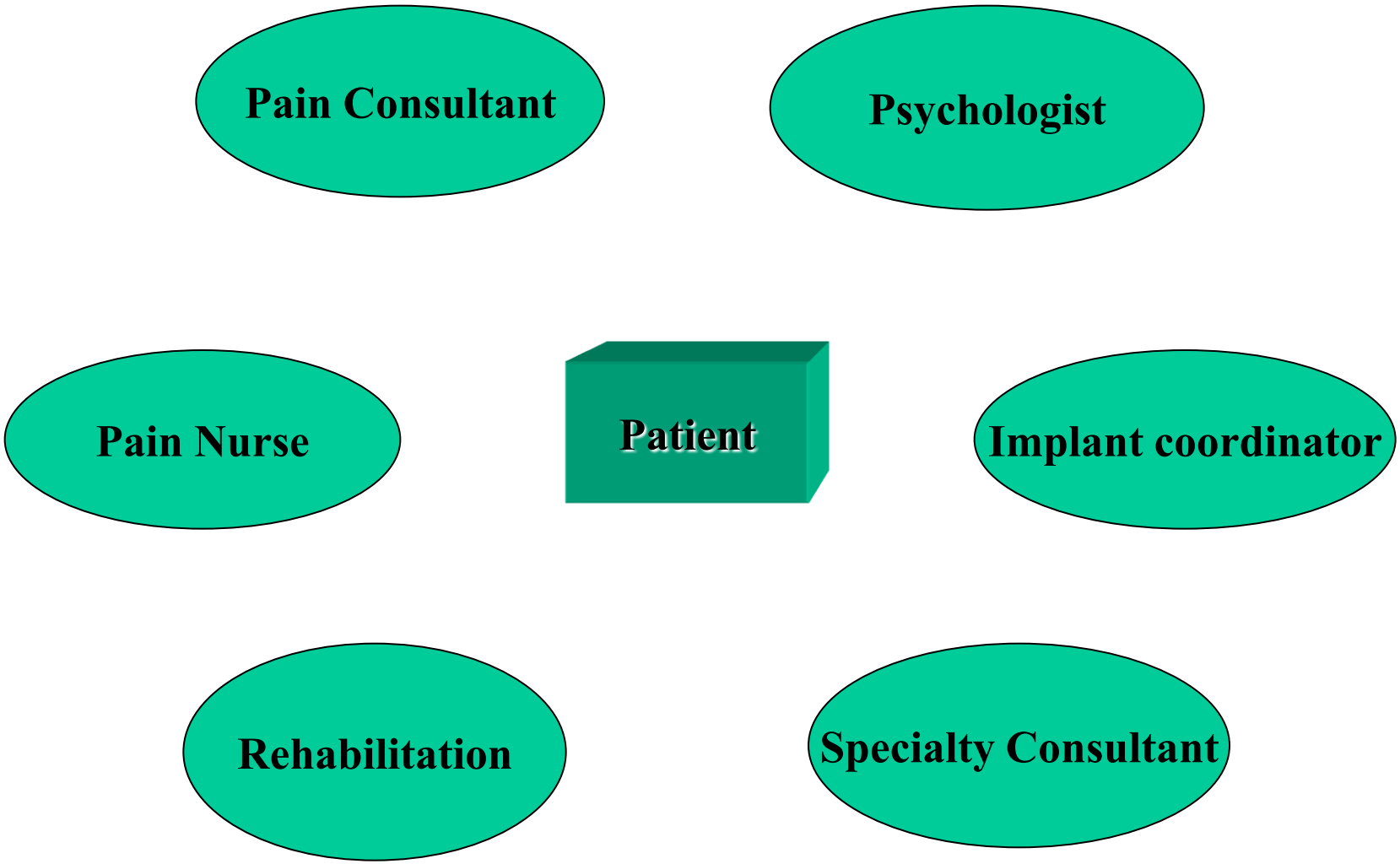


FIGURE 1. Recommended algorithm for intrathecal polyanalgesic therapies, 2007. Line 1: Morphine (a) and ziconotide (c) are approved by the Food and Drug Administration of the United States for intrathecal analgesic use and are recommended for first line therapy for nociceptive, mixed, and neuropathic pain. Hydromorphone (b) is recommended based on clinical widespread usage and apparent safety. Line 2: Because of its apparent granuloma sparing effect and because of its wide apparent use and identified safety, fentanyl (d) has been upgraded to a line 2 agent by the consensus conference when the use of the more hydrophilic agents of line 1 (a,b) result in intractable supraspinal side-effects. Combinations of opioid + ziconotide (e) or opioid + bupivacaine or clonidine (f) are recommended for mixed and neuropathic pain and may be used interchangeably. When admixing opioids with ziconotide, attention must be made to the guidelines for admixing ziconotide with other agents. Line 3: Clonidine (g) alone or opioids such as morphine/hydromorphone/fentanyl with bupivacaine and/or clonidine mixed with ziconotide (h) may be used when agents in line 2 fail to provide analgesia or side-effects occur when these agents are used. Line 4: Because of its proven safety in animals and humans and because of its apparent granuloma-sparing effects, sufenta alone (i) or mixed with bupivacaine and/or clonidine plus ziconotide (j) is recommended in this line. The addition of clonidine, bupivacaine, and or ziconotide is to be used in patients with mixed or neuropathic pain. *In patients with end of life, the panelists felt that midazolam and octreotide should be tried when all other agents in lines 1–4 have failed. Line 5: These agents (k), although not experimental, have little information about them in the literature and use is recommended with caution and obvious informed consent regarding the paucity of information regarding the safety and efficacy of their use. Line 6: Experimental agents (l) must only be used experimentally and with appropriate Independent Review Board (IRB) approved protocols.

Patient Selection & Workup

Team Approach - MDT



Patient Selection Considerations

- Patients who have neuropathic pain in a concordant anatomic distribution respond best to neurostimulation therapy
- Patients who have nociceptive pain in a concordant distribution respond best to Intrathecal Drug Delivery
- Patients who do not respond well to NS may be candidates for IDD therapy

Patient Selection Checklist

Failure of oral/transdermal opiate use or undesirable side effects

More conservative therapies have failed

An observable pathology exists that is concordant with the pain complaint

Further surgical intervention is not indicated

No serious untreated drug habituation exists

Psychological evaluation and clearance for implantation has been obtained

No contraindications to implantation exist

EVIDENCE

- **In Chronic Non Malignant pain**
  - No RCTs
  - >100 open studies

    Anderson et al 1999, Hassenbusch et al 1996, Tutak et al 1996, Winkelmuller et al 1996
- **Cancer pain**
  - Numerous case reports
  - RCT multicentre, Smith et al
  - Comparative efficacy of epidural, subarachnoid and intracerebroventricular opioids in pain due to cancer.

    The Cochrane Database of Systematic Reviews 2006, issue 1, art no. CD 005178
- **Spasticity**
  - Multiple sclerosis, cerebral palsy, spinal cord injury

EVIDENCE

- Implantable drug delivery systems study group. International multicentre RCT of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain; impact on pain, drug related toxicity and survival.

  Smith et al J Clin Oncol. 2002; 20: 4040-9
  Smith et al Ann Oncol 2005: 16: 82-83

- Improved QOL
- Significantly less drug toxicity
- Improved survival @ 6/12, 53% of ITDD were still alive vs 32% for conventional medical management

ITDD - Indications in Cancer Pain

- Pathological fractures
- Movement pain
- Visceral pain (secondary to gut distension)
- Cutaneous / mucocutaneous ulceration
- Neuropathic pain
- Tumour invasion of nerve plexuses

Poor responders to oral / parental opioids

Evidence

Cost effectiveness

- Cost modelling
- Cost utility analysis

ITDD is more cost effective than systemic Mx

For Cancer pain at 3 - 6 months

For CNMP 11 - 22 months

Spasticity - acceptabe cost/benefit ratio

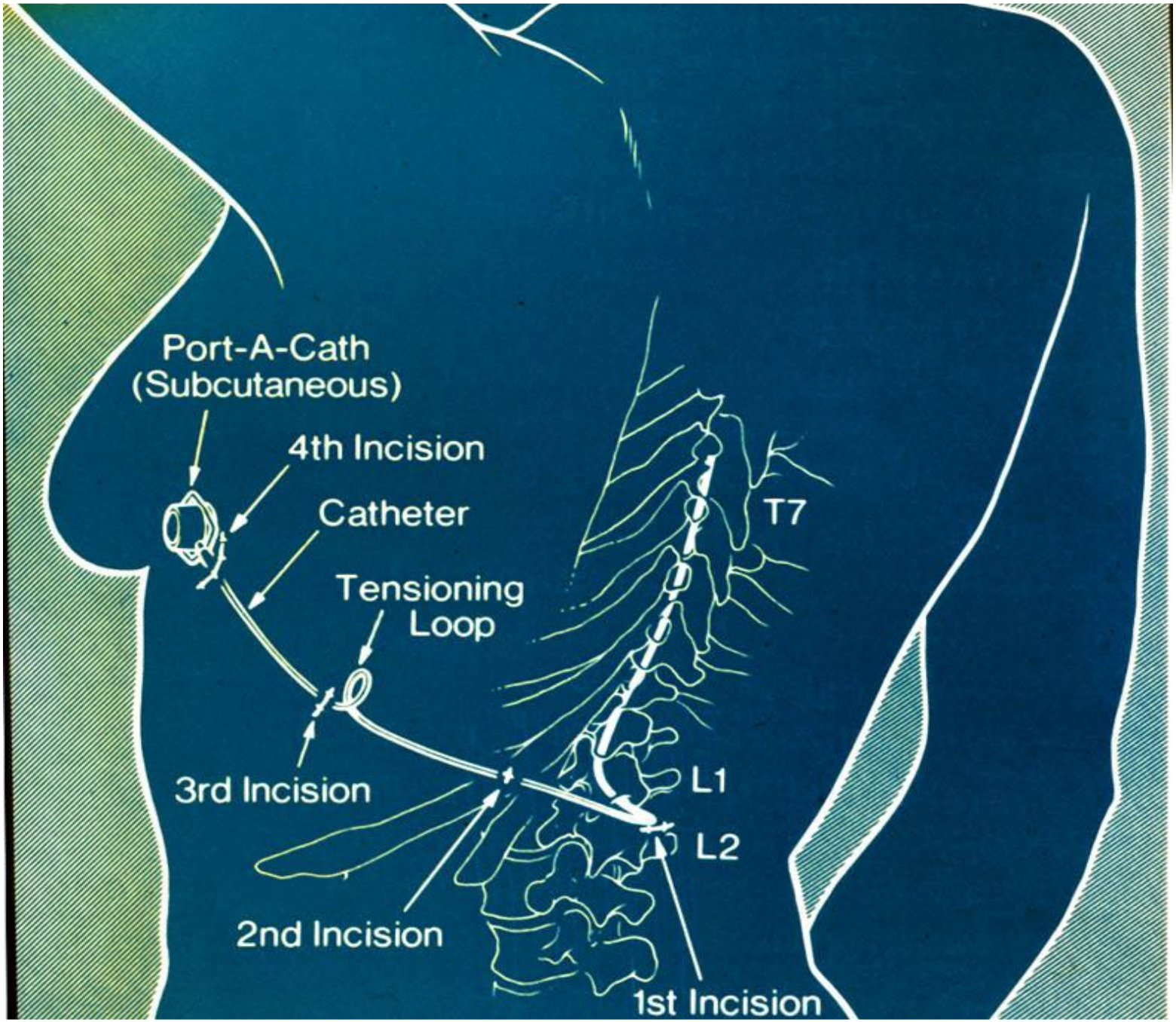
Delivery Systems

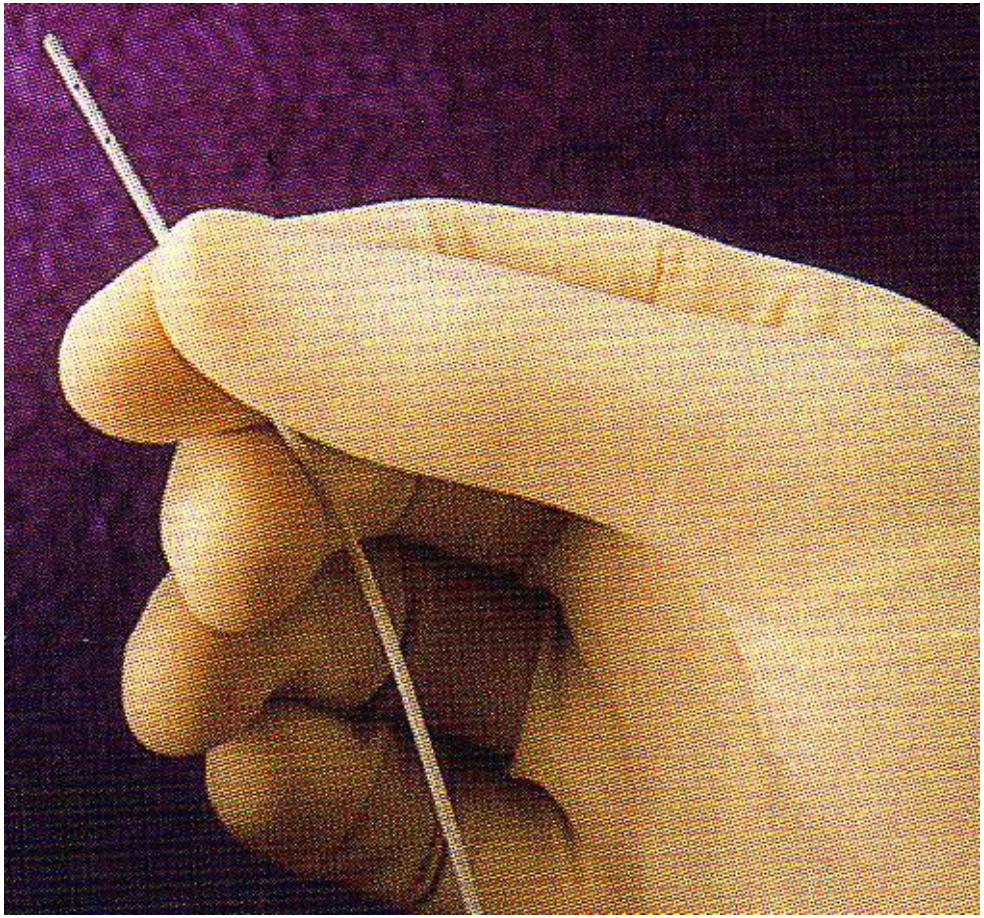
Exteriorised (short term)

- Standard ‘epidural’± tunnelling

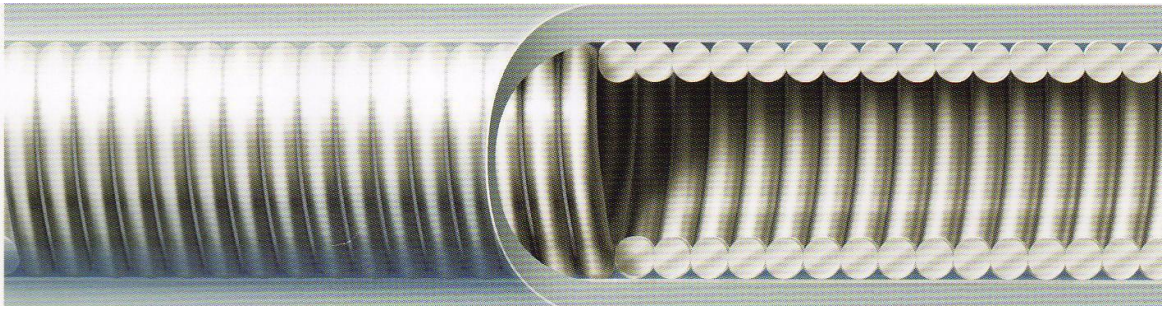
Implanted (long term)

- Subcutaneous injection port
- Patient activated reservoir
- Programmable variable flow systems
- Constant flow systems

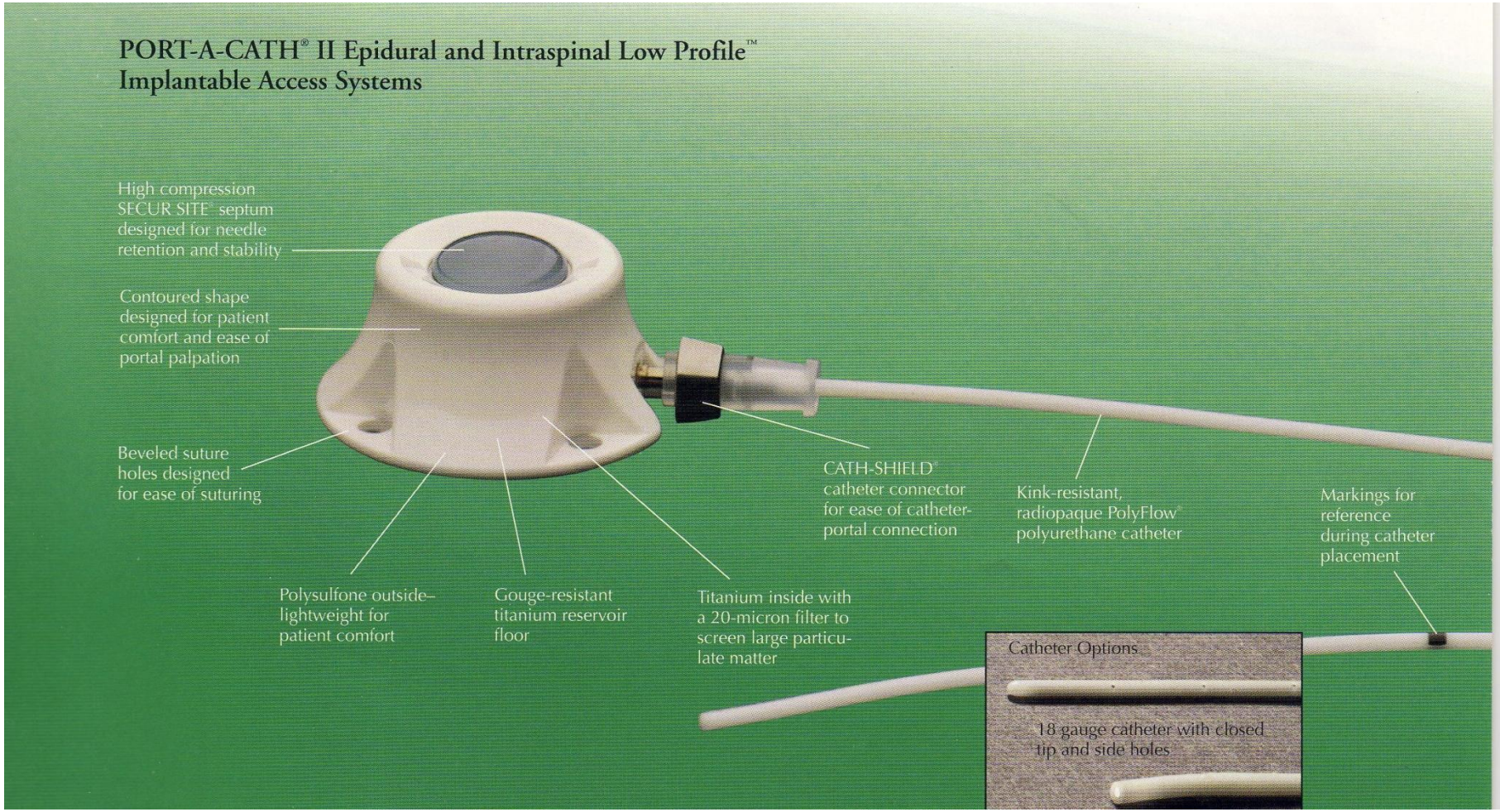

Port-A-Cath
(Subcutaneous)
4th Incision
Catheter
Tensioning
Loop
3rd Incision
2nd Incision
1st Incision
T7
L1
L2



A coiled titanium spring wire keeps the catheter lumen open and maintains flow - even when knotted!



PORT-A-CATH® II Epidural and Intraspinal Low Profile™ Implantable Access Systems

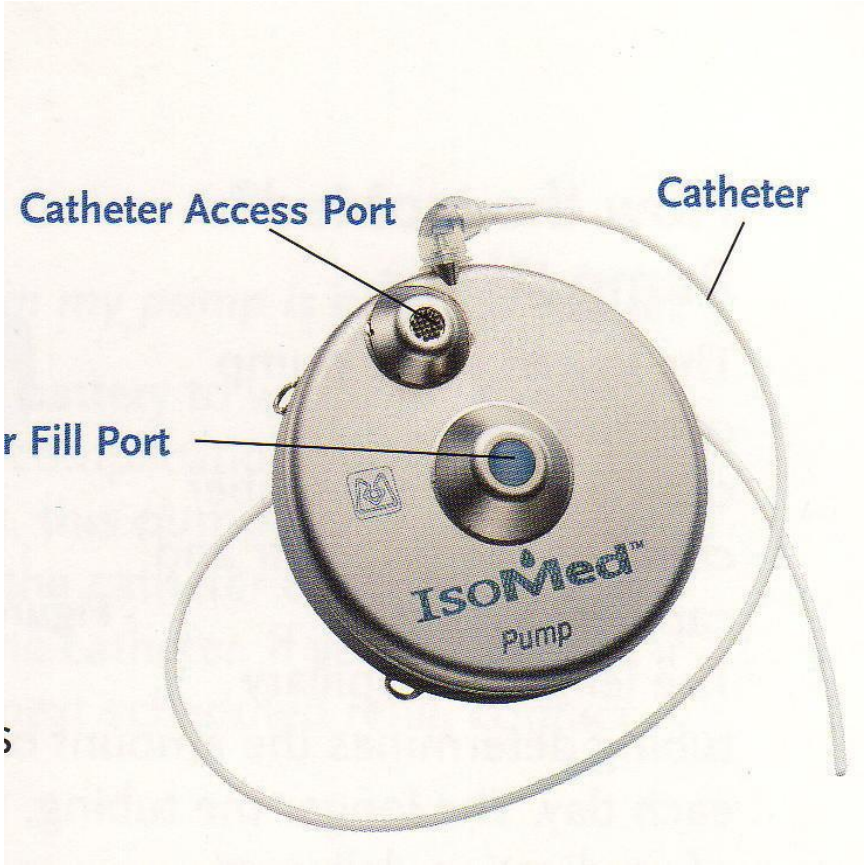


CADD-MS 3® External pump
Reservoir volume 3mls
Range from 0.002-1mls/hr

Features of implantable pumps

- Drug storage reservoir
- Percutaneous refill system
- Flow control system
- Power source
- Delivery catheter

Constant Flow Pumps



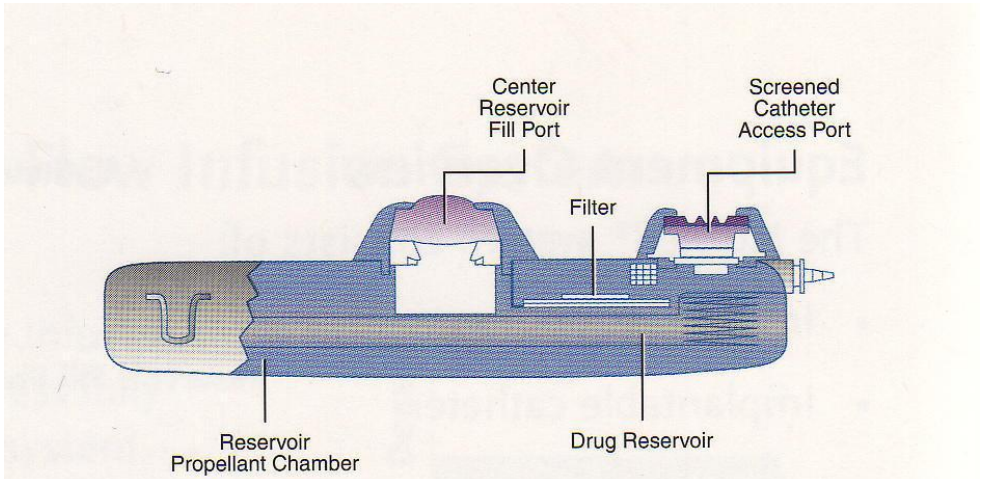


Figure 6: Internal components of the IsoMed pump

Programmable Pumps

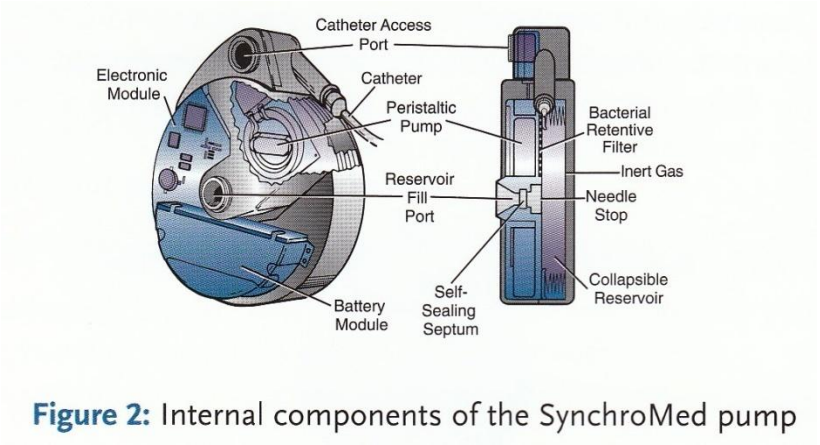


Figure 2: Internal components of the SynchroMed pump

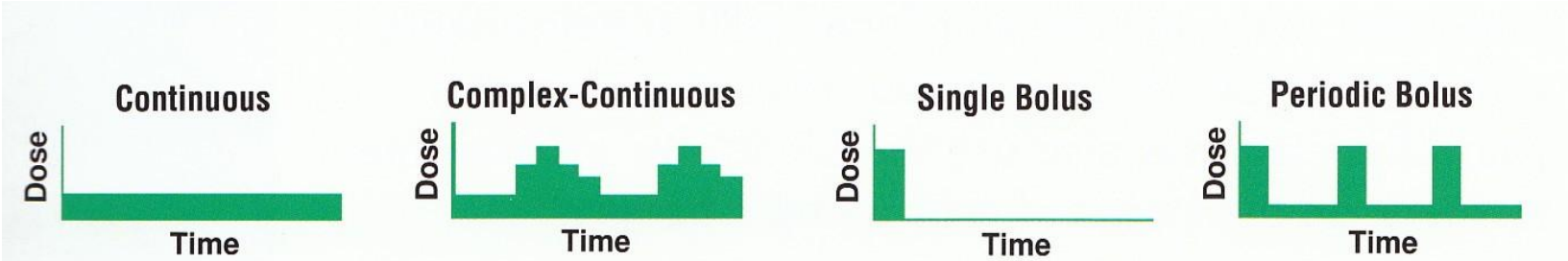
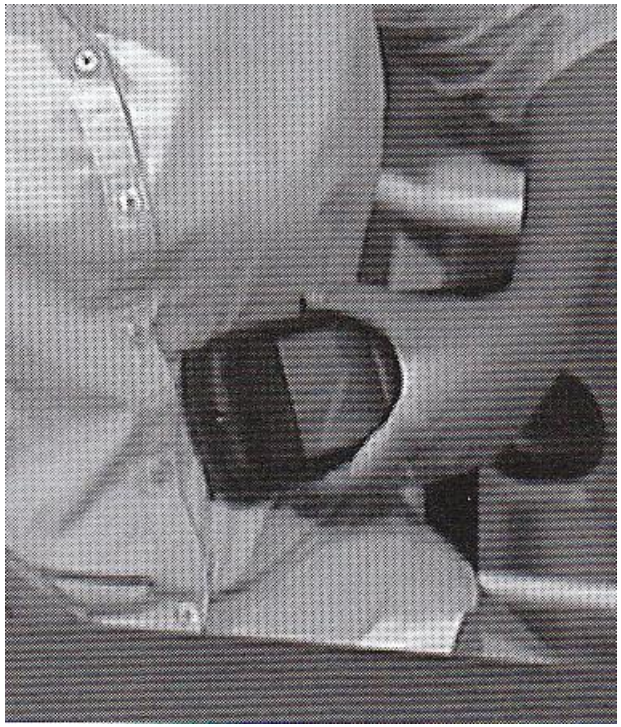


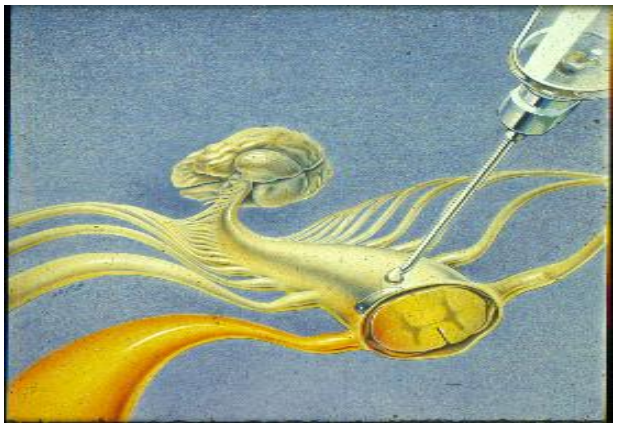
Figure 4: Programmable dosing modes offered by the SynchroMed pump


1
PA infusion programmed parameters are stored in the memory of the **SynchroMed II Implantable Pump** (Model 8637).
Using telemetry, these devices establish a 2-way, radio-frequency link with the implanted pump to transmit signals to and receive status information from the pump.
2
Patient Activation is enabled using the **N'Vision Clinician Programmer** (Model 8840).
3
SynchroMed II Personal Therapy Manager (Model 8832) requests PA doses from the pump and interrogates the pump for information when needed.



Intrathecal Drug Delivery Systems
Complications

- **Drug related**
  - Drug-specific side-effects
    - Endocrine disturbance
    - Hyperalgesia
- **Procedure related**
  - Infection of system ± meningitis
  - Spinal haematoma
  - CSF leak
  - Spinal cord trauma
- **Catheter related**
  - Kinking, knotting, occlusions, breaks, migration, disconnection
  - Intrathecal granuloma
- **Pump related**
  - Pump failure
  - Pump torsion
  - Refill errors
  - Reprogramming errors



Kamran S, Wright BD. Neuromodulation 2001
Naumann C, et al. Neuromodulation 1999

External Tunnelled IT Catheters

- N=200
- refractory cancer pain
- 1-575 days, median 33 days
- Normal functioning system in 93%
- PDPH in 15.5%
- Infections - minimal
  - Epidural abscess, Meningitis, Catheter tracking, Systemic, local skin
- Haematoma 0.5%
- Catheter migration 5.5%
- External CSF leak
- Skin breakdown
- Pain on injection
- No granuloma

Nitescu et al J Clinical Pain 1995

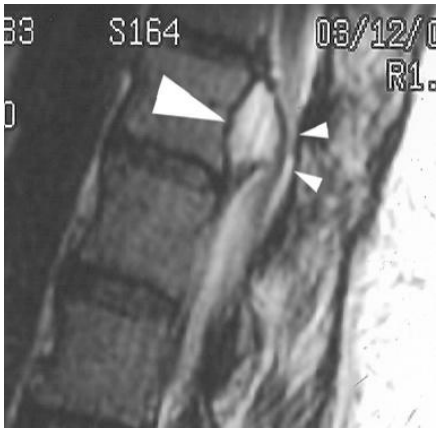
Endocrine effects of long term IT Opioids

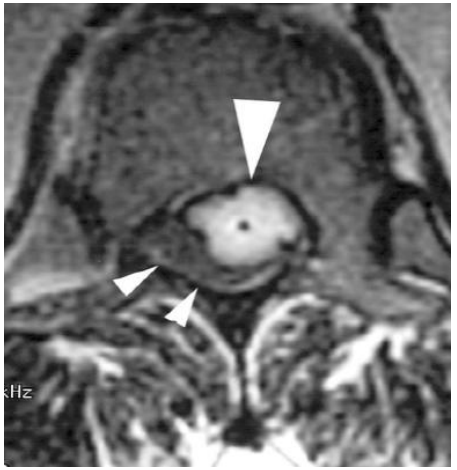
- Endocrine dysfunction
  - Hypogonadotropic hypogonadism (M>60%,F100%)
  - Central hypocorticism 15%
  - GH deficiency 10%
- No relationship to dose of opioids & duration of administration
- IT > oral opioids
- Treatment
  - Replacement therapies
  - Withdrawal of opioids

Abs R et al. J Clin Endocrinol Metab 2000;85:2215-2222

Catheter related Complications
Intrathecal granuloma

- **Prevalence**
  - 3% in a surveillance series(80% asymptomatic)
- **Duration of infusion**
  - 25 months (0.5-120 months)
- **Presentation**
  - Loss of analgesia
  - Frequent need for dose escalation
  - New onset radicular pain
  - Paraesthesia
  - Spinal cord neurlogical deficits
- **Drugs implicated**
  - Morphine ±adjuvants
  - ≥10mg/day (70%)
  - ≥25mg/mL (85%)
  - Hydromorphone
  - Fentanyl, Sufentanil, tramadol





Yaksh TL et al. Pain Medicine 2002;3:300-312.
Deer TR. Pain Physician 2004;7:225-228.

SUMMARY
Benefits of IDD Therapy

- Pain relief for patients who have not received adequate relief with conventional therapies
- Reduction in adverse effects from oral opioids such as nausea, vomiting, sedation, and constipation
- Decreased or elimination of oral analgesics
- Increased ability to perform activities of daily living
- Patient control within physician-set limits
- May be effective for patients who do not experience relief from neurostimulation therapy

Lamer TJ: ***Mayo Clin Proc*****. May 1994;69(5):473-80; Paice JA, et al:** ***J Pain Symptom Manage.*****1996;11(2):71-80**.

SUMMARY
Clinical Evidence

Neurostimulation

- Clinically significant leg pain relief
- Significant improvement
  - Function
  - Quality of life
- High satisfaction
- Long-term pain relief
- Most effective when considered early
- More effective than repeat surgery

Intrathecal Drug Delivery

- Back and leg pain relief
- Successful disability reduction
- Decreased use of pain medication
- Overall pain relief

Thank you

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Thank you

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