Washington State Health Care Authority

Health Technology Assessment Program

Health Technology Clinical Committee
IDDS Pumps

1

Washington's Health Technology Assessment Program Background

- **Part of Governor's 2006 Five point health strategy for state to lead by example**
  - **Emphasize evidence-based health care**

    http://www.hca.wa.gov/contf/doc/GovGregoireHealthBrief.pdf

- **Program Purpose: Achieve better health by paying for technologies that work**
  - Better health with better information: investigate what works and maintain a centralized website.
  - Open and transparent process: publish process, criteria, reports, and committee decisions in public meeting.
  - Eliminate Bias: contract for independent evidence report and independent clinical committee.
  - Promote consistency: state agencies rely on a single, scientifically based source.
  - Flexible: review evidence regularly to ensure update information is included.

2

Why Health Technology

Health Care Context

- **Part of an overall strategy**
- **Medical technology is a primary driver of cost**
  - The development and diffusion of medical technology are primary factors in explaining the persistent difference between health spending and overall economic growth.
  - Some health experts arguing that new medical technology may account for about one-half or more of real long-term spending growth.
    Kaiser Family Foundation, March 2007: **How Changes in Medical Technology Affect Health Care Costs**
- **Medical Technology has quality gaps**
  - Medical technology diffusing without evidence of improving quality Highly correlated with misues, overutilization, underutilization.
    Cathy Schoen, Karen Davis, Sabrina K.H. How, and Stephen C. Schoenbaum, "U.S. Health System Performance: A National Scorecard," *Health Affairs*, Web Exclusive (September 20, 2006): w459

3

Washington State Health Care Authority

HTA Goal

Outcome: Pay for What Works

- Coverage decisions:
  - scientifically based
  - use transparent process, and
  - consistent across state health care purchasing agencies
- Formal, systematic process to identify, review, and cover appropriate health care technologies.
  - Is it safe?
  - Is it effective?
  - Does it provide value (improve health outcome)?

4

Washington State Health Care Authority

Process Overview

1. HCA Administrator Selects Technology

Nominate, Review, Public Input, Prioritize

Semi-annual

2. Vendor Produce Technology Assessment Report

Key Questions and Work Plan, Draft, Comments, Finalize

2-8 Months

3. Clinical Committee makes Coverage Determination

Review report, Public hearing

Meet Quarterly

4. Agencies Implement Decision

Implements within current process unless statutory conflict

5

Hierarchy of Evidence

Best: Meta-analysis of large randomized head-to-head trials.

Large, well-designed head-to head randomized controlled clinical trials (RCT):

- Long-term studies, real clinical endpoints
- Well accepted intermediates
- Poorly accepted intermediates

Smaller RCTs, or separate, placebo-controlled trials

Well-designed observational studies, e.g., cohort studies, case-control studies

Safety data without efficacy studies

Case series, anecdotes

Least: Expert opinion, non-evidence-based expert panel reports, and other documents with no direct clinical evidence

6

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Evidence for use in Policy Decisions

Different Data Sources

- Efficacy
  - How technology functions in "best environments"
    - Randomized trials-distinguish technology from other variables
    - Meta-analysis
- Effectiveness
  - How technology functions in "real world"
    - Population level analyses
    - Large, multicenter, rigorous observational cohorts (consecutive pts/objective observers)
- Safety
  - Variant of effectiveness
    - Population level analyses
    - Case reports/series, FDA reports
- Cost
  - Direct and modeled analysis
    - Administrative/billing data (charge vs cost)
- Context
  - Mix of historic trend, utilization data, beneficiary status, expert opinion

7

Chronic Non-Cancer Pain (CNCP)

- CNCP is an important and common medical concern worldwide defined as pain lasting beyond the normal time of healing, and three months or longer. International Association for Study of Pain (IASP)
- Most common source is low back pain
- prevalence rates of chronic pain (any severity) to be as high as 55% and an estimated 9% of Americans have moderate to severe CNCP (ECRI Review)
- Most find adequate relief from conservative therapy or treatment of underlying/co-morbid condition (ECRI Review)
- Estimated 1% to 20% have pain resistant to treatment or unacceptable side effects ((Williams et al. INHATA Review, 2000)

8

Chronic Non-Cancer Pain

- Chronic pain is burdensome – discomfort, decrease in quality of life, daily activities, function, and employment
- Chronic pain is costly due to high prevalence, chronicity, co-morbidities present, multiple modalities and clinician supervision often needed
- CNCP treatment goal to reduce pain, improve quality of life, and resume daily activities without substantial side effects

9

Intrathecal Drug Delivery Systems (IDDS)

- IDDS first introduced for CNCP treatment in late1970's with realization that spinal cord was important in pain transmission. (Williams et al. INHATA Review, 2000)
- Improvements in intrathecal drugs and pump systems to modern IDDS occurred throughout 1980 and 1990s (Williams et al. INHATA Review, 2000)
- IDDS includes catheter and totally implantable, externally programmable pump

10

IDDS Technology

- IDDS used for diabetes, spasticity, and cancer pain not at issue and fully covered by all agencies
- IDDS for CNCP seeks to replace the route of opioid administration to achieve better pain control with fewer adverse effects (Williams et al. INHATA Review, 2000)
- IDDS treatment is invasive, prone to side-effects and complications, costly, and requires a large amount of technical support (Williams et al. INHATA Review, 2000)
- For patients with pain resistant to all conventional therapies this treatment may be beneficial (Williams et al. INHATA Review, 2000)

11

IDDS Potential Benefits

- Lower dose and effective pain relief by delivery of opioids direct to spinal cord (instead of systemic oral/injected)
- Fewer side effects due to lower dose/direct administration
- Better pain control leads to:
  - Improved quality of life
  - Improved functional status
  - Improved employment status
- Reduced addiction/tolerance
- Patient convenience

12

Potential Drawbacks

- Invasive procedure that is an additional method to deliver opioids
  (not replacement or different treatment mechanism for individuals with chronic pain)
- Tolerance and dose escalation of infused and adjudavent oral medications
- Safety Issues
  - Overdose of infused medications
  - Infused drug side effects
  - Device/ Mechanical pump complications
  - Surgical Complications
- Permanent implantation implications
  - Non-life threatening condition with unknown resolution
  - Generally middle age candidates
  - Maintenance and revisions required –risks with each surgery; long term patient and provider commitment
- Costs and specialty provider availability for long term

13

Agency Prioritization

- **Safety concern: High**
  - Drug tolerance and drug-related side effects
  - Device related complications
  - Multiple follow-up services
  - Overdose and surgical complications
- **Efficacy concern: Medium**
  - Many patients still experience chronic moderate to severe pain even with implant.
  - No improvement in disability or employment status
  - Removal rate for intolerance or lack of effect
- **Cost Concern: Low**
  - Individual cost for technology is relatively high, but implantation for chronic pain utilization is currently very low.
  - However, current utilization/dissemination may change if widely permitted and
  - population with chronic pain is significant

14

Medicare Coverage Policy

Medicare has a national coverage decision for infusion pumps (manual section 280.14) that covers all uses (permanent and temporary, cancer, diabetes, non-cancer pain).

Under this policy, permanent intrathecal pump implantation is covered with criteria:

- Life expectancy of at least three months
- Unresponsive to less invasive medical therapy, such as systemic opioids and attempts to correct underlying physical and psychological abnormalities
- Successful intraspinal opioid trial, defined by acceptable pain relief and side effects and their impact on daily living, and patient acceptance

A national coverage decision for infusion pumps (manual section 280.14) was issued in February 1994 as durable medical equipment. The latest version of the policy was implemented December 17, 2004, and made effective February 18, 2005. This determination included implantable infusion pumps for epidural or intrathecal administration of opioid drugs for chronic non-cancer pain.

This NCD; however, was based on a technology assessment completed in 1994 by the Office of Health Technology Assessment (OHTA) and used the only available literature which was from 1984-1992.

15

IDDS Clinical Practice Guidelines

Organization	Date	Outcome	Evidence Cited?
American Society of Interventional Pain Physicians (Boswell et. al)	2007	"Evidence for implantable intrathecal infusion systems is strong for short term improvement in pain of malignant or neuropathic pain. The evidence is moderate for long term management of chronic pain."	Y
Sisken Hospital for Physical Rehabilitation (Sanders et. al)	2005	"Studies and systematic reviews regarding the efficacy of infusion pumps and spinal cord stimulators have increased. Thus far, they have not met the current criteria for adequate supportive evidence to recommend the application to CPS (chronic pain syndrome) patients".	Y
International Research Foundation for RSD/CRPS (Kirkpatirck et. al)	2003	No conclusion offered, however authoirs note that "morphine pumps" have not been clinically shown to be superior to oral morphine.	Not reported

16

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IDDS Pumps

Questions?

17

Washington State Health Technology Assessment
Intrathecal Drug Delivery Discussion

August 15, 2008

William Fehrenbach, John Loeser, MD, David Caraway, MD

Mary Owens, MD, Mike Baca, Scott Guillemette

Agenda

- **Contextual Overview, Request for Subcommittee** (1 minute) — **W. Fehrenbach**
  - Unique complexities, legislative intent, focus on safety questions, request for Pain Subcommittee
  - "Presumption of Correctness" of Medicare, National Medical Society/Patient Group Guidelines, Insurance Covg.
  - Unique and sick population that has exhausted all other treatment options
- **Mitigating Risk Strategies and Status**
  - Dr. John Loeser Experience, Thoughts (5 minutes via teleconference) — **J. Loeser, M.D.**
  - Dr. Caraway Experience, Thoughts, How to Collaborate to Best Ensure Patient Safety (15 minutes) — **D. Caraway, M.D.**
- **Medical and Data Issues** (3 minutes) — **M. Owens, M.D.**
  - Unique and sick population that has exhausted all other treatment options
  - FDA MAUDE Database Limitations
  - Industry "event" increases overall
  - ISPR – Highlights of Updated Information
  - Patient Deaths, Educational Brief, Adverse Outcomes
- **FDA Warning Letter, Product Issues, Safety Alerts and Solutions** (3 minutes) — **M. Baca**
- **Cost Effectiveness** (3 minutes) — **S. Guillemette**
  - New actuarial analysis from Reden & Anders in Response to ECRI Questions

Introductions and Contextual Overview

William Fehrenbach, Medtronic Director State Government Affairs
(One Minute)

- **Context**
  - Provide background and context. There are three areas that we want to cover:
    - Therapy Importance, Impact for Patients with No Other Options
    - Mitigating Risks – Ensuring Patient Safety
    - Medtronic's Commitment to Quality and Safety
  - Through an extensive review process (Pre-Market Approval) the FDA has determined the benefits outweigh the risks of this therapy. We agree there are associated risks - most productive discussion is to substantively focus on how to mitigate and minimize risks wherever possible.
  - We believe that given both the unique complexities involved in this discussion, and with the fact that HTA leadership acknowledges that the legislative intent of this program did not envision these types of discussions, that an Interventional Pain "Advisory Group" should be convened to best sort through these complexities and to establish how to best ensure patient safety moving forward, and are requesting same be convened and stand ready to assist in any appropriate manner. RCW 70.14.110 (2)(c); WAC 182-55-045
  - Will do our best to directly answer any and all questions to the best of our ability but time is very limited for public testimony today so we would ask that questions be deferred until after panel presentation and all public testimony is complete. We are willing to stay all day, or to be involved in any Advisory Group discussions, to answer any and all questions.

3

Medicare and National Expert Society Guidelines "Presumed Correct"

- **RCW 70.14.110 (3) states that HTA's reviews and determinations "shall be consistent with decisions made under the federal Medicare program and in expert treatment guidelines, including those from specialty physician organizations and patient advocacy organizations unless the committee concludes, based on its review of the systematic assessment, that substantial evidence regarding the safety, efficacy, and cost-effectiveness of the technology supports a contrary determination."**
  - **POSITIVE NATIONAL MEDICARE COVERAGE DECISION: CMS has issued an affirmative National Coverage Decision (NCD) for coverage of IDDS for non cancer pain.**
  - **We believe this is the first therapy, intervention, test that HTA is reviewing that has a positive National Medicare Coverage Decision as well as support from national expert medical societies and patient advocacy groups through position statements, guidelines and other work.**
  - **Overwhelming support for this therapy in appropriate situations.**
  - **For patients that have no other options, this therapy is the standard of care.**

4

Supported by Societies and Patient Organizations

- ***Evidence Based Treatment Guidelines***
  - *American Society of Interventional Pain Physicians (3,000 members)*
  - *Official Disability Guidelines (used in at least 19 states), continually updated*
  - *Workers Compensation State Regulations*
    - *Washington and all other 49 state currently provide coverage*
    - *California DWC Proposal to be adtoped in September, supporting appropriate coverage for IDDS for non-cancer pain*
    - *Minnesota in midst of updating and adopting new EBM supported IDDS coverage policy for non-cancer pain*
    - *Delaware adopted EBM guidelines June 2008 including apropriate coverage for IDDS for non-cancer pain*
  - *Millman, Interqual*
- ***Other physician organizations whose members are actively involved in the implantation of IDDS for non-cancer pain:***
  - *American Academy of Pain Medicine*
  - *International Spine Intervention Society*
  - *North American Neuromodulation Society*
  - *International Spine Society*
  - *American Society of Anesthesiologists*
  - *American Association of Neurological Surgeons/CNS Section of Pain*
  - *American Society or Regional Anesthesia and Pain Medicine*
  - *American Pain Society*
- *Patient advocacy groups that support appropriate coverage of IDDS for non-cancer pain:*
  - *American Pain Foundation (86,000 members) (Patient Organization)*
  - *Washington Alaska Pain Initiative (Patient Organization)*
- ***Additional government and private payor coverage policies, additional attached national list***
  - *Civilian Health and Medical Program of the Department of Veterans Affairs*
  - *TRICARE*
  - *Premera, Regence Coverage Policies; Group Health Case-by-Case Coverage*

Therapy, Evidence, Patient Safety

(5 minutes)

John Loeser, MD, University of Washington

Calling in from Europe via Teleconference

Phone number to call:

Dial the country code (00) and then 1 plus 309 946 5000

Code: 9461464

Risk Mitigation Strategies

(15 minutes)

David L. Caraway, MD, PhD

Center for Pain Relief Tri-State

Saint Mary's Regional Neuroscience Center

Huntington, WV

AMDG *3/2007*

Interagency Guideline on Opioid Dosing for Chronic Non-Cancer Pain

- **Reasonable Guidelines are in place**
- **No discussion regarding impact of route of delivery**
- **Long acting, sustained release, non-compounded opioids generally recommended with referral to pain management at does exceeding 120 MED**

Intrathecal Opioids

- **Requires same strategies as systemic delivery**
  - Early titration to achieve analgesia and goals of therapy
  - Careful consideration of dose increases
  - Maintain moderate doses
  - Physician remains in control of dosing
  - Monitor for side effects, efficacy
  - Adjuvants

9

Intrathecal Opioids

Advantages:

- **Achieves steady-state, around the clock dosing**
- **Reduced side effects**
  - Hormonal effects and edema may be exceptions
- **Adjuvants**
- **May result in reduction in longitudinal costs**
- **Compliance**
  - Can provide patient activated rescue dosing
  - Eliminate systemic opioids

10

AMDG

- **L&I data shows that between 1996 and 2002 there were 32 deaths among injured workers where an accidental overdose of prescription opioids, or narcotics, was confirmed.**
- **Statewide, deaths involving prescription opioids — sometimes used illegally — increased by more than 800 percent from 1995 to 2004.**
- **Prescription opioid related deaths now exceed non-prescription opioid related deaths.**

Franklin AMDG 3/2007

11

IDD – Risk Mitigation

- **Early in 2006, Medtronic became aware of an apparent increase in the rate of spontaneous reports of patient death with intrathecal drug therapy**
- **A total of nine patient deaths within three days after the initiation – or re-initiation following interrupted use – of intrathecal opioid therapy for pain.**

12

Risk Mitigation

"The available evidence indicates that the infusion systems operated normally."

- Relatively high initial doses

- Respiratory depressant effects of intrathecal opioids All nine deaths involved patients who were just started on intrathecal opioid therapy, or for whom the therapy was restarted after weeks of interruption.

13

Risk Mitigation

- Insufficient patient monitoring: **Seven of the patients were released from the hospital within 24 hours after *initiation* of intrathecal opioid therapy for pain or after *re-initiation* of intrathecal therapy following interrupted use.**
- Concomitant medications: **Seven patients were prescribed, administered in-hospital, or self-administered systemic opioid and/or sedative drugs. Those concomitant medications may have amplified the respiratory depressant effects of the intrathecal opioids.**
- Co-morbid risk factors: **Several patients had risk factors for respiratory depression that included pulmonary disease, severe obesity, and/or advanced age.**

14

White Paper Recommendations

Co-administration of medications

Closely monitor patients at initiation or

re-initiation of intrathecal therapy***.***

"Patients should be monitored in an adequately equipped facility for sufficient time"

The Infumorph package insert states, "*The facility must be equipped with resuscitative equipment, oxygen, naloxone injection, and other resuscitative drugs."*

15

AMDG

Principles for prescribing opioids

"Do not combine opioids with sedative hypnotics, benzodiazepines, or barbiturates"

16

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Principles for prescribing opioids:

"Be cautious about using opioids with conditions that may potentiate opioid adverse effects (including COPD,CHF,sleep apnea, alcohol or substance abuse, elderly,or history of renal or hepatic dysfunction"

17

White Paper Recommendations

"Physicians also should be aware of the complexity and uncertainty involved in converting a systemic opioid dose to an equianalgesic intrathecal dose"

18

Infumorph package insert

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**

Do we need oral opioids after pump implant?

- **Vertebral Compression Fractures, N=24**
- **Failed systemic opioids**
- **Compare before implant to one year follow up**
  - VAS, DW, ambulation, PHS
- **Results**
  - None required systemic opioids
  - All showed significant improvement

Neuromodulation
Volume 10 Issue 2 Page 167-176, April 2007

Dose Escalation

- **Tolerance**
  - Physiological, role of age
- **Opioid Induced Hyperalgesia**
  - Solid evidence in animal models
  - Emerging clinical data
- **Perception**
  - Goals of therapy
- **Disease progression**

21

QUALITY OF PAIN

Patient Selection – positive factors

- Cancer
- Diffuse pain, eg Rh. Arthritis
- Elderly axial spinal pain
- Mechanical, nociceptive back pain, documented etiology
- Good analgesia with systemic opioids but intolerable side effects

22

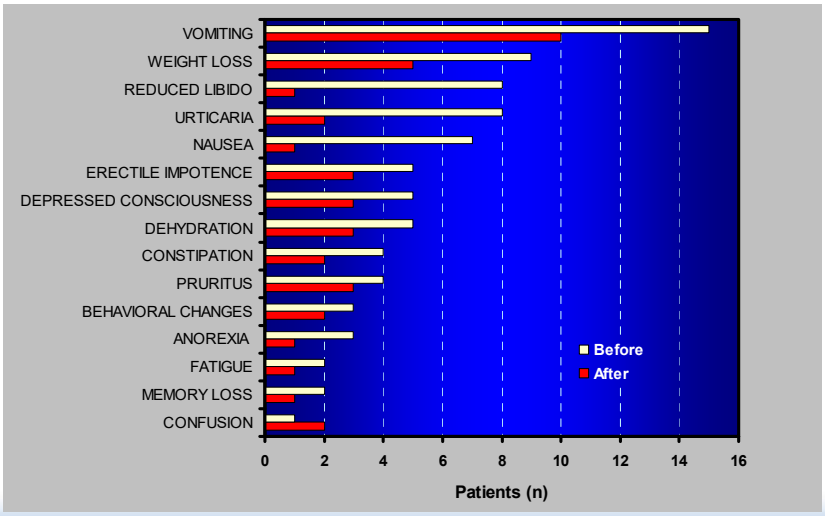
Results of Change in Route of Opioid Administration

Parameter	At Crossover	Crossover + 1 Month	% Change
Pain			
VAS	5.78 ± 2.92	4.89 ± 2.77	15.4
Pain on Average	6.39 ± 1.85	4.94 ± 2.24	22.7
Patient Quality of Life			
SF-12 mental	36.45 ± 6.16	37.13 ± 7.54	-1.9
SF-12 physical	24.25 ± 4.38	24.9 ± 6.86	-2.7
$BPI_{Interference\ with\ life}$	6.83 ± 1.44	6.37 ± 2.50	6.7
$BPI_{Enjoyment\ of\ life}$	6.83 ± 2.18	6.39 ± 2.77	6.4
Caregiver QOL			
Caregiver QOL	5.6 ± 1.41	5.66 ± 1.70	-1.1
Opioid Toxicity			
NCI Toxicity	7.06 ± 4.87	3.71 ± 4.43	47.5

23

Smith, T. J Clin Oncology, 2002

Prevalence of Opioid Side Effects



Smith, T. J Clin Oncology, 2002

QUALITY OF PAIN

Patient Selection – negative factors

Minimal baseline pain with intermittent severe pain

Poorly defined etiology

Poor compliance to previous therapies

Poor response to escalating doses of opioids

Young age

25

Goals of Therapy

- **Create a written document with specific goals *eg:***
  - Manageable constipation
  - Gardening, shopping, holding grandchildren
  - Increased range of motion, ambulation
  - Reduced hospital, ER visits

26

Psychological Evaluation

- **Consider recommendations and treat if indicated - *prior to trial***
- **Ability to understand and perceive benefits -- appropriate expectations**
- **Major active psychosis, current drug addiction, some personality disorders, cognitive deficits, progressive organic brain disorders, suicidal, homicidal behavior**

27

Continuous vs single shot and intermittent bolus

- **Titration**
- **Interpreting adverse events**
- **Multiple procedures**
- ***Does not model steady-state characteristics of intended therapy***

28

Continuous Epidural vs Continuous Intrathecal Screening

	Advantages	Disadvantages
Intrathecal	More closely approximates pharmacodynamics of system to be implanted Does not require epidural space (fusion, mets)	Increased risk of: PDPH CSF leak Serious infection Overdose Neurological complication during placement
Epidural	May allow outpatient Management Extended trials Less risks	Less predictive? Risk of migration to SAS

29

Polyanalgesia Consensus Conference 2007

2007 POLYANALGESIC ALGORITHM FOR INTRATHECAL THERAPIES

Line #1:	**(a)** morphine	↔ **(b)** hydromorphone	↔ **(c)** ziconotide
Line #2:	**(d)** fentanyl	↔ **(e)** morphine/hydromorphone + ziconotide	↔ **(f)** morphine/hydromorphone + bupivacaine/clonidine
Line #3:	**(g)** clonidine	↔ **(h)** morphine/hydromorphone/fentanyl bupivacaine +/clonidine +ziconotide	
Line #4:	**(i)** sufentanil	↔ **(j)** sufentanil + bupivacaine +/ clonidine +ziconotide	
Line #5:	**(k)** ropivacaine, buprenophine, midazolam meperidine, ketorolac		
Line #6	***Experimental Drugs*** gabapentin, octreotide, conpeptide , Neostigmine, Adenosine, XEN2174, AM336, XEN, ZGX 160		

30

Neuromodulation Vol 10 Issue 4 page 300 – 328
October 2007

Recommended Maximum Intrathecal Dosages and Concentrations*

Drug	Dosage (mg/day)	Concentration(mg/ml)
Morphine	**15**	**20**
Hydromorphone	**4**	**10**
Fentanyl	**2**	**No known upper limit**
Bupivacaine	**30**	**40**
Clonidine	**1.0**	**2.0**

These represent general recommendations and are dependent upon the specific patient and the clinical experience of the physician and thus, maximum dosage and/or concentrations may vary from these.

31

Neuromodulation Vol 10 Issue 4 page 300 – 328 October 2007

Special Cases in Chronic Pain Management

- **Single-agent therapy insufficient**
  - Bupivacaine plus opioid
  - Clonidine plus opioid
  - Ziconotide plus opioid
- **End of Life (Cancer, AIDS)**
  - Midazolam
  - Ketamine
  - Tetracaine
  - Droperidol
- **Spasticity as a major component of pain**
  - Baclofen

32

Special Cases in Chronic Pain Management

- **Adjuvant Medications**
  - Requires reformulation to change dosing of single component
  - Addition of single agent at a time recommended
  - Complex mixtures are generally not well studied
  - Requires compounding to achieve therapeutic dose
    - Formulation errors
    - Contamination
    - Dosing errors, increased complexity
    - Side effects / toxicities

33

An Approach

- **Perform and document history and PE**
- **Document reasonable etiology**
- **Document failure of conservative therapy**
- **Psychological evaluation**
- **Create written goals of therapy**
- **Consider discontinuation of systemic opioids prior to trial**

34

An Approach

- **Perform inpatient catheter trial**
  - Consistent with Medicare guidelines
  - Discontinue or dramatically reduce systemic opioids during trial
  - Trial with single opioid
    - Generally morphine or hydromorphone
  - Document achievement of goals of therapy
  - Document tolerable side effect

An Approach

- **Perform implant as overnight stay**
  - Start with lower than anticipated analgesic dose
- **Discontinue systemic opioids**
- **Titrate to achieve goals within 6- 8 weeks of initiation of opioid therapy**
  - 20 – 30% dose increases
- **Document attainment of goals**

An Approach

- **Failure to achieve moderate stable dose warrants re-examination of treatment plan**
  - Trial of adjuvant while holding opioid dose steady
  - Episodic pain and “rescue dosing”
  - Rotation of opioids
  - Reduction or discontinuation
  - Surveillance
    - Progression of disease
    - Complications eg: IM, catheter failure

37

INTRATHECAL THERAPY FUTURE

- **Novel Agents**
  - Improved efficacy
  - Elimination of tolerance and withdrawal
- **Improved devices**
- **IT activity related rescue doses**
- **Ultra low dose IT therapy**
  - Potential for decreased tolerance, OIH
  - Enhanced patient satisfaction
  - Elimination of all oral agents

38

Context: Patient Population for IDSS

Mary Owens, MD, Medtronic Regulatory Medical Director
(Three Minutes)

- **Extremely sick patient population with intractable pain**
  - These treatments must be balanced against the unreasonable alternative of no further treatment which would leave these very ill patients in chronic, intractable pain or with severe untreated spasticity. In fact, to put these illnesses in perspective, a study by Brown[1] et al demonstrated that IDDS candidates have poorer physical functioning and lower health-related quality of life scores than patients with congestive heart failure, Type II diabetes, rheumatoid arthritis, and patients actively suffering a migraine headache.
- **Already tried and exhausted all other treatment**
  - Pain is not responsive to over the counter analgesics, oral systemic analgesics, antidepressants and membrane stabilizing drugs
  - Unsatisfactory response to systemic opioids due to lack of therapeutic effect or intolerable side effects
  - Medtronic's own data base shows that these patients also tend to have multiple medical conditions in addition to the condition requiring therapy for pain

[1]*Brown J. Klapow J, Doleys D, et al. Disease-specific and generic health outcomes: A model for the evaluation of long-term intrathecal opioid therapy in non-cancer low back pain patients. Clin J Pain 1999; 15:122-131.*

39

IDDS Nonmalignant Pain Patient Population

(Rauck R, Wallace M, Leong M et al. J Pain and Symptom Management. 2006;31:393-406)

- **Medical History**
  - 58% with depression
  - 25% with anxiety
  - 24% with respiratory disease
    - 6% with bronchitis
    - 7% with COPD
    - 8% with dyspnea
    - < 1% with emphysema
    - < .05% with pulmonary fibrosis diffuse interstitial
    - < .1% with decreased lung capacity
  - 14% with muscle spasms
  - 11% with back pain
  - 11% with laminectomy
  - At least 10% of patients screened reported a medical condition
- **Drug History**
  - Average of 12 oral non-opioid drugs
  - 98% (216/220) with oral opioid use (patients may have > 1 prescription)
    - 41% oxycodone + acetominophen
    - 34% oral morphine
    - 28% hydrocodone + acetominophen
    - 24% methodone
    - 18% fentanyl
    - 13% hydromorphone
  - 51% with transdermal opioids
  - 48% with parenteral opioids
  - 86% muscle relaxants
  - 62% on anxiolytics
  - 81% on antidepressants

40

Databases used to Evaluate Safety of IDDS

- **MAUDE**

  FDA Disclaimer says: "MAUDE data is not intended to be used either to evaluate rates of adverse events or to compare adverse event occurrence rates across devices."
  www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM

  - Voluntary reporting is incomplete
  - Limited or no drug or medical history – prevents valid analysis
  - MAUDE counts adverse events only, no total implant count for perspective
  - "Expected" mortality is unknown for this population
  - Trending can't be done reliably due to reporting changes. (Change in regulation caused a 77% increase in MDR reporting filed industry-wide in 2006 (see The Gray Sheet August 27, 2007 Vol 33 (035) p 10))

- **Medtronic Implantable System Performance Registry (ISPR)**
  - Standardized prospective data collection of real world practice
  - Long-term follow-up
  - 50 centers, 3256 pump patients for all indications (1767 non-malignant pain) with approximately 4-years follow up
    - No device related deaths
  - Pump "survival" for nonmalignant pain = Percentage of devices that remain operational
    - 36 months: 97.5%*
    - 42 months: 97.1%*

*Means 2.5% / 2.9% risk of being removed for incurring a device failure since the time of implant. (See written submission for more detailed description)

41

Summary of Mortality Data for IDDS Patients

- **Medtronic Educational Brief Nov. 2006 due to cluster of spontaneous reports of deaths within 3 days of implant (or re-initiation following interrupted use) caused us to do additional investigation**
  - Cluster was purely coincidence, there was no product or drug problems, but Medtronic's investigation resulted in the communication to physicians (Educational Brief).
    - Etiology was multi-factorial – most likely caused was opioid and/or sedative drug overdose.
    - Infusion system operated normally – device malfunction was not the cause.
- **Since then Medtronic continues to monitor reports of mortality and conduct trending analysis**
  - Spontaneous reports
  - Scientific literature
  - Internal Database
- **No additional clusters of death reports since 2006**
- **Trending analysis shows that rates of death post Nov 2006-2008 are similar to those pre Nov 2006**
- **We are actively engaged on an ongoing basis with experts in the community to determine if other steps need to be taken to mitigate risks including physician communication and education, training and awareness/mitigation of patient risks**

42

FDA Warning Letters and Status

Mike Baca, Medtronic Director of Quality
(Three Minutes)

- **In summer 2006 and 2007 Medtronic received two warning letters from the FDA regarding various process and product-specific issues.**
- **Areas cited**
  - **A number of quality system elements many of which were based on our system 6-7 years ago.**
  - **The design specifications change related to one specific catheter model**
  - **Pump motor stalls on one old model (Newer SynchroMed II has displaced SynchroMed EL model)**
  - **Infusion system "inflammatory mass" – a drug effect associated with intrathecal morphine**
- **FDA conducted a comprehensive re-inspection of Medtronic's quality system during June 17, 2008 – July 25, 2008. At the conclusion of the inspection, the FDA investigator reported to Medtronic that no citations or observations would be issued. (FDA Form 483)**

Field Advisories and Recalls

- **<u>SynchroMed® EL Gearshaft Wear (Motor Stalls)</u>**
  - **Safety Alert concerning a sub-set of (SynchroMed EL only) pump motors produced prior to September, 1999 that exhibited a higher than historical incidence of motor shaft wear. Engineered out of SynchroMed II.**
  - **Product has been displaced by newer SynchroMed II.**
- **<u>Product Code 8540 / 8551 Catheter Kit</u>**
  - **68 units recalled due to mis-printed product labels (Rx symbol missing).**
- **<u>Product Code 8590 Refill Kit</u>**
  - **11 units recalled due to mis-printed product labels (Rx symbol missing).**
- **<u>Inflammatory Mass (IM)</u>**
  - **The third in a series of updates to customers related to an adverse drug effect associated with intrathecal morphine. Communication provided latest rate of occurrence and updated associated technical manuals and other documentation.**
  - **Estimated occurrence: 0.49%**

Field Advisories and Recalls (cont.)

- **SynchroMed® II Missing Propellant**
  - 11,920 pumps possibly manufactured without propellant
    - Confirmed incidence 8 pumps (.06 incidence)
    - Returned to Medtronic if not implanted
    - Instructions to physicians if implanted
- **Catheters with Sutureless Connectors (Models 8709SC, 8731SC, 8596SC, 8578)**
  - Sutureless connectors were a significant improvement over the previous technology
  - Learned that physicians were not following our technical manuals and connecting them properly so we issued a Safety Alert to inform them of the problem.

45

Medtronic's Commitment to Quality and Safety

- 97.5% reliability on pumps at 36 months
- Improvements to systems to drive higher quality, reliability and manufacturability to enhance effective and safe use. Recent example can be seen in SynchroMed II with redesigned motor, elimination of gear shaft issue, and improved catheter design.
- We are dedicated to continuous improvement in our products and committed to continuous communication with physicians when issues are identified.
- Therapy-related issues are much greater than the product-related issues and are addressed by Drs. Loeser and Caraway related to risk mitigations and patient access for a patient population without any other options, making this a late, if not last, resort.
  - Risks are preventable and management
  - Medtronic recognizes that there are risks associated with any interventional therapy. They must be understood within context and risk of all interventional therapies.

46

Effects of IDD on Non-Malignant Pain Sufferers
Reden & Anders Analysis in Response to ECRI Questions

Scott Guillemette, Reden & Anders Lead Project Actuary
(Three Minutes)

- **Produces savings per individual per year ≈ $7,400** (PV-basis; 7/1/2006 fee levels)
  - Assumes 3% discount rate per annum
  - Assumes implantation occurs every 7 years over a 30-year time horizon from the month of implant
- **Savings are negatively correlated to the rate of re-implantation**
  - 4-year re-implantation rate ≈ $1,600 savings per individual per year
  - 6-year re-implantation rate ≈ $4,900 savings per individual per year
  - Payback period ≈ 3.7 years
- **Savings are materially derived from lower utilization in:**
  - Inpatient facility admissions (54% of total savings); and
  - Prescription drug order rates (23% of total savings)
- **Level of annual savings varies on:**
  - Duration from implantation
  - Frequency of re-implantation
  - Type of pain sufferer (i.e., Spasticity, Malignant and Non-Malignant)

PV = Present Value