

Microdosing

- ⊕ Considered this form of therapy in consultation with Dr. William Martin (who first described opioid receptors and opioid-induced hyperalgesia in 1983) and his research assistant, Dr. Joe Holtman.
- ⊕ First tried this in a few patients eighteen years ago and have now made microdosing routine in my practice for all intrathecal implants since 2000.*

*Practice of Dr. Witt

“It may be that the opioid peptides play a dual role in modulating the perception of pain and not only obtund this sensation but [also] facilitate its recognition and that the balance of these two processes may differ among individuals and according to pathologic as well as physiologic states”

William R. Martin, M.D., Ph.D.

Department of Pharmacology

University of Kentucky College of Medicine

Life Sciences, 1983

Hyperalgesia

- ⊕ “...apparent opioid tolerance is not synonymous with pharmacological tolerance, which calls for opioid dose escalation, but may be the first sign of opioid-induced pain sensitivity suggesting a need for opioid dose *reduction*....”
- ⊕ “...repeated opioid administration could lead to a progressive and lasting reduction of baseline nociceptive thresholds, hence an increase in pain sensitivity....”

Dr. Witt's theory about how microdosing works

- ⊕ The theory begins with the belief that opioid-induced hyperalgesia is induced by exposure of the pontine-medullary region of the brainstem to opioids.
- ⊕ Cerebrospinal bulk fluid flow is highly variable but primarily unidirectional in a cephalocaudal direction at least at the level of the brainstem and the probable site for the induction of opioid-induced hyperalgesia is in the brainstem
- ⊕ If opioid receptors in the spinal cord can be reached without exposing the brainstem to these drugs in any meaningful concentration, then a hydrophilic drug delivered in very low doses at the T12-L1 level should result in little or no drug reaching the brainstem.

Dr. Witt's theory about how microdosing works

- ⊕ If these assumptions are correct, then analgesia without the production of opioid-induced hyperalgesia should be possible.
- ⊕ Note the kinetics of intrathecal baclofen which is also hydrophilic

Pre-Clinical Observations Regarding Nociceptive Threshold

Observations from Animal Studies:

- ⊕ There is a reduction in *nociceptive threshold* in rats receiving morphine over a seven-day period
-Mao, *ibid.*, 2002
- ⊕ Reduction in *nociceptive threshold* with continuous opioid infusion is progressive with time and has been unequivocally demonstrated
-Vanderah, *et.al.*, *J. of Neuroscience*, 2000; 20(18): 7074-79
-Mao, *ibid.* 2002

Clinical Data on Pain Sensitivity

- ⊕ In matched cohorts (25 patients in each group) patients who received intra-operative opioid infusion of remifentanyl reported *more* post-operative pain than non-opioid controls anesthetized with desfluran
 - Guignard, et.al., Anesthesiology, 2000: 93:409-17
- ⊕ Pain sensitivity is greater in opioid addicts than in a non-addicted cohort
 - Martin & Inglis, Br. J. Soc. Clin. Psychol., 1965; 4:224-9
 - Ho & Dole, Proc. Soc. Exp. Biol. Med., 1979; 162:392-5
 - Compton, et.al., Drug Alcohol Depend., 2001: 63: 139-46

Clinical observations that suggest the development of hyperalgesia

When objective tests have ruled out disease progression:

- ⊕ Pain persists or increases with increased opioid dosage
- ⊕ Pain increases on a constant opioid dosage
- ⊕ Pain is worse on opioids than prior to opioids
- ⊕ Duration of analgesia decreases with duration of therapy
- ⊕ Pain becomes increasingly diffuse anatomically and less well-defined in character with duration of therapy

Working Hypothesis

By utilizing complete opioid withdrawal for at least six weeks in non-malignant pain or cancer pain, and introducing a “sub-analgesic” infusion of a hydrophilic opioid intrathecally at T_{12} , due to the unidirectional flow of CSF, could hyperalgesia be effectively prevented or significantly reduced or delayed in onset and clinical utility significantly enhanced as a result?

Can Pain be Managed with Microdosing?

- ⊕ Intrathecal opioids delivered through the Medtronic SynchroMed® II programmable infusion pump can be effective in managing chronic pain*. However, as dosages increase, neural plasticity in the central nervous system, opioid tolerance, opioid-induced hyperalgesia, and opioid side effects become of greater concern
- ⊕ There is an emerging concept in intrathecal pain management called *microdosing* that may provide pain relief with relatively low doses of intrathecal morphine

*Kumar K, et al. Surg Neurol. 2001;55(2)79-88

Dr. Witt's Steps to Low Dosage Therapy

<i>Step 1 – Detoxify</i>	<i>Step 2 – Trialing</i>	<i>Step 3 – Implant</i>
<ul style="list-style-type: none">• Detoxify patient of all mu agonists until opioid free• Receive adjuvant therapies based on patient needs	<ul style="list-style-type: none">• Administer morphine 0.2 mg or less• Strive for at least 50% pain reduction	<ul style="list-style-type: none">• SynchroMed® II pump is implanted and set to the low dosage

Reflects the experience of Dr. Witt

There are a Number of Proposed Benefits Associated with Microdosing:

- ⊕ May reduce potential for drug interaction or accidental overdose because opioids are delivered in much smaller intrathecal increments
- ⊕ May decrease risk of respiratory depression due to the low opioid dosage
- ⊕ May reduce potential for dose-related adverse effects including lower extremity edema, hypogonadism, and fibrous catheter tip mass
- ⊕ May reduce opioid-induced hyperalgesia so there is little or no need for repeated escalation

Dr. Witt's Weaning Protocol

- ⊕ Most patients are weaned in one month
- ⊕ This is usually the most difficult portion of the process and is the source of considerable anxiety in some patients

Dr. Witt's Weaning Protocol

- ⊕ Patients need to be motivated, psychologically prepared and usually treated with adjuvant medication
- ⊕ If there are significant co-morbid medical conditions or massive opioid doses, we pursue inpatient weaning
- ⊕ When opioids are stopped, abstinence is maintained for six weeks to eliminate any opioid-induced hyperalgesia

Trialing

- ⊕ Trialing is done on an inpatient basis with an intrathecal catheter and continuous infusion of morphine
- ⊕ Morphine infusion starts at 0.0125 mg (12.5 mcg) per 24 hours diluted as necessary depending on the capabilities of the trial pump
- ⊕ The dose is doubled every 12 hours for up to three days
- ⊕ Maximum trialing dose is 0.4 (400 mcg) mg of morphine per day
- ⊕ In my practice, this dose is rarely reached

Patient Response

- ⊕ We have the best results applying this protocol to elderly patients with spinal stenosis and neuropathic rest pain
- ⊕ Intrathecal infusion is ideal for the elderly because they have an increased risk of drug interactions, slowed metabolism and/or excretion, organ toxicity, patient confusion, and complex dosing schedules

Complications

- ⊕ With microdosing, if the patient receives a systemic opioid, the analgesia quickly fades and can only be recaptured with ever-increasing dosages or by weaning the patient again
- ⊕ The only complications I have seen are patients with progressive disease such as osteoporosis who do require dosage escalation on the basis of disease progression and then it seems that once a critical dosage is reached, hyperalgesia begins to develop
- ⊕ As with any implant, there still may be catheter and pump complications or surgical and anesthetic complications
- ⊕ Post-implant complications may include an inverted pump, catheter issues such as leaking, dislodgement, or kinking, or drug-related side effects. Refer to package insert for full list of possible side-effects

Experience

- ⊕ I have treated approximately 200 patients with this protocol since 2003
- ⊕ I have approximately 100 patients on this protocol that are still in my practice
- ⊕ After one year, some patients are on dosages as low as 0.05 mg per day
- ⊕ I expect at least 70% reduction in pain and a corresponding improvement in function wherein function is otherwise pain-limited

Experience

- ⊕ All patients have agreed to enroll in a medical and behavioral modification program
- ⊕ Self-administered opioids are not used in my practice with the exception of end-of-life situations in the absence of an implanted pump

Case Studies

Case Study #1- Patient Profile

- ⊕ Failed Back Surgery
- ⊕ 56-year-old male
- ⊕ Experiencing chronic pain from cervical spondylosis, degenerative disc disease of the cervical spine and cervicalgia, as well as lumbar radiculopathy and lumbago

Case Study #1- Initial Course of Therapy

- ⊕ In March 1992, the patient sustained a neck and back injury at work
- ⊕ Neuropathic medications and opioids were orally administered
- ⊕ The patient did not have adequate pain relief with opioids and he experienced significant intolerance as well
- ⊕ Multiple epidural injections in the cervical and lumbar spine were performed with minimal relief
- ⊕ The patient underwent several courses of physical therapy utilizing a TENS unit and traction, chiropractic, and acupuncture, again without improvement

Case Study #1- Treatment with Intrathecal Drug Delivery

Screening Test:

- ⊕ In September 2000, the patient underwent a complete psychological evaluation and pain inventory complaining of pain at 10/10 on a numerical pain score. He was considered an optimal candidate for implantation of an intrathecal drug delivery device
- ⊕ The patient was weaned off all opioids for six weeks, and utilized only adjuvant therapy in the form of biofeedback, anti-inflammatory medications, anticonvulsants, and acetaminophen
- ⊕ In January 2001, the patient underwent a 72-hour continuous intrathecal trial with admission to the hospital
- ⊕ The patient had an excellent response to the trial and his pain was reduced to a 5/10 on a numerical pain scale with functionality increasing 70% according to evaluation by physical and occupational therapy

Case Study #1- Treatment with Intrathecal Drug Delivery

Implant:

- ⊕ In June 2001, a 20-ml Synchroned® EL pump was implanted with preservative-free morphine sulfate at a starting daily dose of 0.05 mg/day, with a simple continuous infusion
- ⊕ Over seven months, the infusion rate was gradually increased to a total daily dose of 1.2 mg/day of morphine by simple continuous infusion

Case Study #1- Treatment with Intrathecal Drug Delivery

Patient Response:

- ⊕ The patient's functionality improved and his pain level remained approximately a 3/10 on a numeric pain scale, throughout his titration, up to 1.2 mg/day. There was no "tolerance" manifesting as hyperalgesia
- ⊕ In November 2006, the pump was replaced with a Synchromed II pump due to battery depletion
- ⊕ The pump was set at the same previous infusion rate of preservative-free morphine sulfate. After seven years, his current daily dose is 1.58 mg/day, with a numeric pain scale of 2/10
- ⊕ He is receiving no oral or transdermal opioids; he denies any adverse reactions to the morphine
- ⊕ He is very happy with his infusion device

Case Study #2- Patient Profile

- ⊕ Complex Regional Pain Syndrome, Type I
- ⊕ 46-year-old female
- ⊕ Experiencing chronic pain secondary to CRPS-I of the right upper extremity

Case Study #2- Initial Course of Therapy

- ⊕ In 1998, the patient had an automated Cardiac defibrillator placed secondary to chronic atrial-fibrillation
- ⊕ She subsequently developed increasing right shoulder and arm pain refractory to medical management rating her pain a 10/10 on a numeric pain scale
- ⊕ She was diagnosed with Complex Regional Pain Syndrome, Type I of the right upper extremity. Neuropathic medications and opioids were orally administered
- ⊕ The patient did not have adequate pain relief with opioids and she experienced significant intolerance as well
- ⊕ In 2001, she underwent a right thoracic sympathectomy with no improvement
- ⊕ She had minimal improvement with right stellate ganglion blocks
- ⊕ In 2003, she had a cervical spinal cord stimulator implanted
- ⊕ Initially, she had good relief with the stimulator, but shortly thereafter her pain returned and she had difficulty maintaining good stimulation coverage

Case Study #2- Treatment with Intrathecal Drug Delivery

Screening Test:

- ⊕ In August 2004, the patient underwent a complete psychological evaluation and pain inventory and was considered to be an optimal candidate for implantation of an intrathecal drug delivery device
- ⊕ The patient was weaned off all opioids for six weeks, and utilized only adjuvant therapy in the form of biofeedback, anti-inflammatory medications, anticonvulsants and acetaminophen
- ⊕ In December 2004, the patient underwent a 72-hour intrathecal trial with admission to the hospital
- ⊕ The patient had an excellent response to the trial with at least 70% improvement in functionality and a commensurate decrease in pain score

Case Study #2- Treatment with Intrathecal Drug Delivery

Implant:

- ⊕ In January 2005, a 40-ml Synchroned® II pump was implanted with preservative-free morphine sulfate at a starting daily dose of 0.05 mg/day by simple continuous infusion
- ⊕ Over a 12-month course, the infusion rate was increased to a total daily dose of 0.2199 mg/day of morphine by simple continuous infusion

Case Study #2- Treatment with Intrathecal Drug Delivery

Patient Response:

- ⊕ The patient's functionality improved and her pain level remained approximately a 4/10 on a numeric pain scale, throughout the titration, up to 0.2199 mg/day
- ⊕ There was no "tolerance" manifesting as hyperalgesia
- ⊕ After two years, her current daily dose is 0.2426 mg/day, with a numeric pain scale of 3/10.
- ⊕ She is not taking any oral or transdermal opioids and she only takes ibuprofen 600 mg, on an as-needed basis
- ⊕ She denies any adverse reactions to the morphine
- ⊕ She is not utilizing the spinal cord stimulator and has it turned off
- ⊕ She is very happy with her infusion pump

Case Study #3- Patient Profile

- ⊕ Post-laminectomy syndrome (atypical neuropathic lower extremity pain complicating Charcot-Marie Tooth Disease)
- ⊕ 40-year-old female
- ⊕ Experiencing chronic back and bilateral lower extremity neuropathic pain

Case Study #3- Initial Course of Therapy

- ⊕ Neuropathic medications and anti-inflammatories were orally administered without significant benefit
- ⊕ The patient did not have adequate pain relief with opioids and she experienced significant intolerance as well
- ⊕ In September 2004, she had a percutaneous lumbar spinal cord stimulator trial performed and she had greater than 70% improvement in neuropathic symptoms during the trial
- ⊕ In November 2004, she had a two lead, lumbar spinal cord stimulator system implanted
- ⊕ Initially, she had good success with the stimulator, but subsequently had difficulty maintaining good stimulation coverage
- ⊕ She underwent several lead and pocket revisions without the ability to regain the original coverage during the trial and in February 2007, the leads and impulse generator were explanted at her request

Case Study #3- Treatment with Intrathecal Drug Delivery

Screening Test:

- ⊕ In July 2007, the patient underwent a complete psychological evaluation and pain inventory and was considered an optimal candidate for implantation of an intrathecal infusion device
- ⊕ She was weaned off all opioids for six weeks, utilizing only adjuvant therapy prior to her intrathecal trial
- ⊕ In August 2007, the patient underwent a 72-hour intrathecal trial with admission to the hospital
- ⊕ The patient had an excellent response to the trial with at least a 70% improvement in functionality and a commensurated decrease in pain during the trial.

Case Study #3- Treatment with Intrathecal Drug Delivery

Implant:

- ⊕ In September 2007, a 40-ml Synchroned® II pump was implanted with preservative-free morphine sulfate at a starting daily dose of 0.05 mg/day by simple continuous infusion

Case Study #3- Treatment with Intrathecal Drug Delivery

Patient Response:

- ⊕ The patient's functionality improved and her pain level remains approximately a 4/10 on a numeric pain scale with a simple continuous infusion of preservative-free morphine sulfate at 0.951 mg/day
- ⊕ She has not developed any "tolerance" manifesting as hyperalgesia
- ⊕ She is not taking any oral or transdermal opioids and she takes celecoxib on an as-needed basis
- ⊕ She denies any adverse reactions to the morphine
- ⊕ She is happy with the results of the implant

Case Study #4- Patient Profile

- ⊕ Spinal Stenosis
- ⊕ 71-year-old female
- ⊕ Experiencing chronic neck and back pain secondary to cervical and lumbar spinal stenosis, with lumbar spondylosis and cervical myofasciitis

Case Study #4- Initial Course of Therapy

- ⊕ In 2001, the patient underwent a cervical fusion
- ⊕ Neuropathic medications, and anti-inflammatories were orally administered without significant benefit
- ⊕ The patient did not have adequate pain relief with opioids and she experienced significant intolerance as well
- ⊕ She has also had epidural injections, trigger point injections, and facet injections without any significant improvement in her pain
- ⊕ Prior to implantation, her pain score was rated 10/10 on the numeric pain scale

Case Study #4- Treatment with Intrathecal Drug Delivery

Screening Test:

- ⊕ In March 2007, the patient underwent a complete psychological evaluation and pain inventory and was considered an optimal candidate for implantation of an intrathecal infusion device
- ⊕ She was weaned off all opioids for six weeks prior to her trial, and utilized only adjuvant therapy in the form of biofeedback, anti-inflammatory medications, anticonvulsants, and acetaminophen
- ⊕ In June 2007, the patient underwent a 72-hour intrathecal trial with admission to the hospital
- ⊕ The patient had an excellent response to the trial

Case Study #4- Treatment with Intrathecal Drug Delivery

Implant:

- ⊕ In July 2007, a 40-ml Synchroned® II pump was implanted with preservative-free morphine sulfate at a starting daily dose of 0.05 mg/day, with a simple continuous infusion
- ⊕ She reported a pain score of 1/10 postoperatively and had complete return of functionality

Case Study #4- Treatment with Intrathecal Drug Delivery

Patient Response:

- ⊕ The patient continues to have full functionality and her pain level remains a 0/10 on a numeric pain scale and she has not had any increase in infusion rate since the initial implant
- ⊕ There was no “tolerance” manifesting as hyperalgesia
- ⊕ She is not taking any oral or transdermal opioids and she takes acetaminophen on an as-needed basis
- ⊕ She denies any adverse reactions to the morphine
- ⊕ She is extremely pleased with her new device