NON-OPIATE MEDICATION OPTIONS: COMPOUNDING, TOPICALS, AND MORE

NATALIE GUSTAFSON, PHARMD
DISCLAIMER I

Compounding pharmacist and owner of Lloyd Center Compounding Pharmacy
DISCLAIMER II: I LIKE CATS.

Pain is natures way of saying "Don't do that."

Painkillers are mankind's way of saying "Just watch me."
OBJECTIVES

• Analyze compounded non-opiate alternatives such as topical analgesics, LDN and ULDN in pain management

• Discuss designing topical analgesics to best target pain and help transition off opiates

• Evaluate clinical evidence of LDN and ULDN for pain and opiate management

• Differentiate between dosage and therapeutic uses of naltrexone, LDN and ULDN
I found pills
and ate them

WHAT WE’RE TRYING TO AVOID
TRANSITIONING FROM OPIATE USE

• Opiates are used in many chronic pain conditions
  • Fibromyalgia
  • Low back pain
  • Diabetic neuropathy
  • Osteoarthritis

• How do you transition a patient from opiates?
  • Consider alternate analgesic therapies
NON-OPIATE ANALGESICS

• Acetaminophen or NSAIDs (e.g. ibuprofen, naproxen)
• Muscle relaxants (e.g. cyclobenzaprine)
• Neuropathy agents (e.g. SNRIs, TCAs)
• Natural supplements (e.g. MSM, ALA, herbs)
• Topical analgesics
• Low dose naltrexone (LDN)
COMPOUNDED ALTERNATIVES

• Topical analgesics

• Low dose naltrexone (LDN)

• What if patient cannot completely wean from opiates?
  • Ultra low dose naltrexone (ULDN)
HOW TO DESIGN A TOPICAL ANALGESIC FOR TRANSITION PLAN

• 1) Determine type(s) of pain – any muscle spasms or inflammation?

• 2) How diffuse is the pain? Is a more localized therapy possible?

• 3) Has the patient previously tried oral therapy or other topicals with any success?
THE BASE IS IMPORTANT: LIPOSOMAL BASES ARE BEST

• Liposomes allow enhanced penetration through skin even for hydrophilic drugs

• Elastic liposomal vesicles are able to fit between stratum corneum cells to deliver drug intact to deeper tissues

• Effect is comparable to subcutaneous injection

Shipton Anesthesiol Res Pract 2012:546409
# Common Agents Used in Topical Analgesics

<table>
<thead>
<tr>
<th>Type of Pain Relief</th>
<th>Some Topical Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal analgesic</td>
<td>Ketoprofen, Ibuprofen, Diclofenac</td>
</tr>
<tr>
<td>Muscle relaxant</td>
<td>Cyclobenzaprine, Baclofen, Guaifenesin</td>
</tr>
<tr>
<td>Neuropathic agent</td>
<td>Amitriptyline, Clonidine, Ketamine, Gabapentin, NSAIDs</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>Ketoprofen, Ibuprofen, Diclofenac, MSM</td>
</tr>
<tr>
<td>Topical anesthetic for fast relief</td>
<td>Lidocaine, Tetracaine, Bupivacaine</td>
</tr>
</tbody>
</table>

LITERATURE ON TOPICAL ANALGESICS

• Various agents in topical analgesics have been studied individually and in combination

• Not enough time to delve into today!

CASE STUDY: STACY

• Stacy is a 37 yo woman with fibromyalgia

• Her main complaint is fatigue and pain

• Current Medications:
  • Vicodin (hydrocodone/APAP) 5/325mg Q6H prn pain
  • Lyrica (pregabalin) 150 mg PO BID
  • Ambien (zolpidem) 10 mg PO QHS prn

• How would you design a topical analgesic to help her stop the Vicodin?
HOW TO DESIGN A TOPICAL ANALGESIC FOR STACY

1) Determine type(s) of pain
   - Fibromyalgia – muscular, inflammation with some neuropathic pain

2) How diffuse is the pain? Is a more localized therapy possible?
   - Multiple trigger points – use topical
     - Continue Lyrica - could add oral cyclobenzaprine or NSAID
     - Physical and psychological therapy and support
HOW TO DESIGN A TOPICAL ANALGESIC FOR STACY

3) Has Stacy previously tried oral therapy or other topicals with any success?

- Had little pain relief with amitriptyline and failed duloxetine (Cymbalta)
- Hasn’t tried topical analgesics other than menthol OTC cream
<table>
<thead>
<tr>
<th>Type of Pain Relief</th>
<th>Some Topical Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal analgesic</td>
<td>Ketoprofen, Ibuprofen, Diclofenac</td>
</tr>
<tr>
<td>Muscle relaxant</td>
<td>Cyclobenzaprine, Baclofen, Guaifenesin</td>
</tr>
<tr>
<td>Neuropathic agent</td>
<td>Amitriptyline, Clonidine, Ketamine, Gabapentin, NSAIDs</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>Ketoprofen, Ibuprofen, Diclofenac, MSM</td>
</tr>
<tr>
<td>Topical anesthetic for fast relief</td>
<td>Lidocaine, Tetracaine, Bupivacaine</td>
</tr>
</tbody>
</table>
STACY: FIBROMYALGIA

• First choice for spasms and neuropathy:
  • Cyclobenzaprine/gabapentin/ketoprofen 2/6/10%

• Alternate option without neuropathy agent:
  • Cyclobenzaprine/ketoprofen/MSM 2/10/10%

• If minimal response or severe pain consider:
  • Amitriptyline/baclofen/ketamine/lidocaine 4/2/5/5%

• Sig: Apply 0.5-1gm to affected areas up to four times daily

• Typically recommend 30gm to start but can get up to 120gm
You gots a lil something there
CASE STUDY: MYLES

- Myles is a 67 yo man with diabetic neuropathy in his feet
  - Previously tried amitriptyline without success

- Current medications:
  - Gabapentin 600 mg PO BID
  - Oxycodone CR 30mg daily

- How would you handle transitioning him off the oxycodone?
MYLES: TRANSITIONING OFF OPIATES

• Need to taper off – can start by tapering in 10mg increments

• Can switch to an immediate release oxycodone or try tramadol for breakthrough pain

• Add topical analgesics and alpha lipoic acid orally to completely taper off opiates
HOW TO DESIGN A TRANSITION PLAN FOR MYLES

• 1) Determine type(s) of pain – any muscle spasms or inflammation?
  • Neuropathic pain with inflammation

• 2) How diffuse is the pain? Is a more localized therapy possible?
  • Fairly localized pain in feet for topical
    • Continue gabapentin
    • ALA 600mg orally daily
HOW TO DESIGN A TRANSITION PLAN FOR MYLES

3) Has Myles previously tried oral therapy or other topicals with any success?

- Good success with gabapentin
  - Side effects problematic

- Poor response to amitriptyline
  - Should ask him what that means
    - Did it not work?
    - Side effects intolerable?
## WHAT WOULD YOU GIVE MYLES?

<table>
<thead>
<tr>
<th>Type of Pain Relief</th>
<th>Some Topical Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal analgesic</td>
<td>Ketoprofen, Ibuprofen, Diclofenac</td>
</tr>
<tr>
<td>Muscle relaxant</td>
<td>Cyclobenzaprine, Baclofen, Guaifenesin</td>
</tr>
<tr>
<td>Neuropathic agent</td>
<td>Amitriptyline (maybe), Clonidine, Ketamine, Gabapentin, NSAIDs</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>Ketoprofen, Ibuprofen, Diclofenac, MSM</td>
</tr>
<tr>
<td>Topical anesthetic for fast relief</td>
<td>Lidocaine, Tetracaine, Bupivacaine</td>
</tr>
</tbody>
</table>
MYLES: DIABETIC NEUROPATHY

• First choice:
  • Gabapentin/Ketamine/Ketoprofen/Lidocaine 6/5/10/5%

• If don’t want to use ketamine:
  • Gabapentin/Lidocaine 6/5%
  • Gabapentin/Ketoprofen/Lidocaine 6/10/5%

• Can consider if others fail:
  • Amitriptyline/Gabapentin/Ketamine/Ketoprofen/ Lidocaine 4/6/5/10/5%

• Sig: Apply 0.5-1gm to affected areas up to four times daily

• Typically recommend 30gm to start but can get up to 120gm
Owww

"bite me" is just an expression, dude
CASE STUDY: HANNAH

• 70 yo with severe osteoarthritis in her knees and hips
  • Acetaminophen not very helpful
  • Limited NSAID use due to hypertension and GERD

• Current medications:
  • Acetaminophen/codeine 300/30mg 1-2 tabs PO Q4-6H prn
  • Tramadol 50mg PO TID prn
  • Lisinopril 10mg PO daily
  • Omeprazole 20mg PO daily

• How would you transition Hannah off opiate medications?
HOW TO DESIGN A TRANSITION PLAN FOR HANNAH

1) Determine type(s) of pain
   • Osteoarthritic joint pain with inflammation

2) How diffuse is the pain? Is localized therapy possible?
   • Localized to joints for a topical

- Antioxidant/anti-inflammatory alternatives
  • MSM 1000mg BID
  • Curcumin SR 500mg QD-BID
  • Glucosamine/chondroitin 500/400mg TID
  • Enzymatic preparations BID

- Exercise, physical therapy, weight loss, orthoses
HOW TO DESIGN A TRANSITION PLAN FOR HANNAH

3) Has Hannah previously tried oral therapy or other topicals with any success?

- NSAIDs helped but cannot take
- OTC MSM cream helped somewhat
### WHAT WOULD YOU GIVE HANNAH?

<table>
<thead>
<tr>
<th>Type of Pain Relief</th>
<th>Some Topical Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal analgesic</td>
<td>Ketoprofen, Ibuprofen, Diclofenac</td>
</tr>
<tr>
<td>Muscle relaxant</td>
<td>Cyclobenzaprine, Baclofen, Guaifenesin</td>
</tr>
<tr>
<td>Neuropathic agent</td>
<td>Amitriptyline, Clonidine, Ketamine, Gabapentin, NSAIDs</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>Ketoprofen, Ibuprofen, Diclofenac, MSM</td>
</tr>
<tr>
<td>Topical anesthetic for fast relief</td>
<td>Lidocaine, Tetracaine, Bupivacaine</td>
</tr>
</tbody>
</table>
HANNAH: OSTEOARTHRITIS

- First choice due to hip joint:
  - Ketoprofen/MSM/DMSO 10/10/10%

- Alternative with penetration enhancing properties:
  - Ketoprofen/Lidocaine/MSM 10/5/10%

- Including ketamine for NMDA receptor:
  - Ibuprofen/ketamine/lidocaine 10/5/5%

- Sig: Apply 0.5-1gm to affected areas up to four times daily

- Typically recommend 30gm to start but can get up to 120gm
QUICK REFERENCE GUIDE

- Muscle spasms and pain
  - Cyclobenzaprine/ketoprofen/MSM 2/10/10%

- Neuropathy or neuralgia
  - Gabapentin/ketoprofen/lidocaine 6/10/5%
  - Gabapentin/ketamine/ketoprofen/lidocaine 6/5/10/5%

- Muscle or joint pain
  - Ketoprofen/lidocaine/MSM 10/5/10%

- Combination muscle spasm + neuropathy
  - Cyclobenzaprine/gabapentin/ketoprofen 2/6/10%
LET'S TALK LDN

I'VE NEVER BEEN SO INSULTED

HOW DARE YOU SAY I'M INBRED
NALTREXONE

• Commercially available drug

• Pure opioid receptor antagonist
  • Binds to mu opioid receptors to block euphoria
  • 50mg blocks receptors for 24 hours

• Traditionally used to treat alcohol and heroin dependence

NALTREXONE VS. LDN

• Standard dosing for **commercial** naltrexone:
  • 50mg tablet once daily

• Standard dosing for **compounded** LDN:
  • 1.5mg, 3mg and 4.5mg capsule QHS most common
  • Any dosage is possible

LDN: PAIN CONDITIONS

• Pain is an area getting more attention

• Two studies on fibromyalgia

• Case reports on refractory chronic low back pain, diabetic neuropathy and complex regional pain syndrome

• Clinically, used in neuropathy, osteoarthritis and rheumatoid arthritis

SO HOW DOES LDN WORK IN PAIN?
LDN: DUAL MECHANISM

- Opioid Receptors
  - ↓ Inflammation
  - ↓ Pain
  - Δ Immune Response

- Filamin A, Adenosine, Toll-Like Receptor 4
  - ↓ Inflammation
  - ↓ Pain
  - ↑ Neuroprotection

LDN: MECHANISM OF ACTION I

CNS Opioid Receptors

↑ Beta-endorphins
↑ Met-5-enkephalin

↓ Inflammation
↓ Pain
Δ Immune Response

OPIOID & BETA-ENDORPHIN ACTIONS

- Neurotransmitter release
  - Substance P, norepinephrine, serotonin, acetylcholine, dopamine

- Analgesia

- Gastrointestinal function and appetite

- Learning and memory

- Autonomic responses

- Immune system function

LDN: MECHANISM OF ACTION II

Filamin A Adenosine Toll-Like Receptor 4 (TLR4)

\[ \downarrow \text{oxide synthase} \]
\[ \downarrow \text{Superoxide} \]
\[ \downarrow \text{Glutamate} \]
\[ \downarrow \text{Microglial activity} \]

\[ \downarrow \text{Inflammatory cytokines} \]
\[ \downarrow \text{Neurotoxicity} \]
\[ \downarrow \text{Neuropathic Pain} \]

IMPORTANCE OF MOA II

- Modulation of pain and inflammation response
- Important protective effect in MS lesions
  - Microglial activation and nitric oxide key contributors
  - Prevents neurodegeneration
- Controversy whether main mechanism for treating fibromyalgia

RHEUMATOID ARTHRITIS & BETA-ENDORPHINS

• Met-5-enkephalin is present in bone and joint tissues and decreased in arthritic conditions

• Beta-endorphins have anti-inflammatory effects on joint cartilage
  • Mu-opioid receptors are present on chondrocytes and within osteoarthritic cartilage

• Bihari reported good results in 10 patients

### LDN: FIBROMYALGIA TRIAL

<table>
<thead>
<tr>
<th><strong>Trial Design</strong></th>
<th>Placebo-controlled, double-blind, cross-over</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Subjects</strong></td>
<td>31 women</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>4.5mg PO QHS</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>12 weeks LDN, 4 weeks placebo</td>
</tr>
<tr>
<td><strong>Result</strong></td>
<td>28.8% (LDN) vs 18.0% pain reduction</td>
</tr>
<tr>
<td></td>
<td>57% sx reduction by &gt;30% from placebo</td>
</tr>
<tr>
<td></td>
<td>Improvement in QOL and mood</td>
</tr>
<tr>
<td><strong>Adverse Effects</strong></td>
<td>Vivid dreaming (37% vs 13%)</td>
</tr>
<tr>
<td></td>
<td>Headache (16% vs 3%)</td>
</tr>
</tbody>
</table>

Younger et al Arthritis Rheum 2013
NEUROPATHY TREATMENT

• Charcot-Marie-Tooth (CMT) disease
  • Rare inherited neuropathy with axonal loss and muscle wasting
  • No approved treatment

• 80 patients in Phase II RCT over one year
  • LDN, baclofen and sorbitol combination
  • Most effective dosage was 0.7 mg LDN daily

Attarian et al Orphanet J Rare Dis 2014 Dec
COMPLEX REGIONAL PAIN SYNDROME

- May be mediated by microglial activation
- Inflammation often a trigger
- Relationship to GI disorders
- LDN has been shown to put long-term CRPS into remission in several case reports
  - Added for both MOAs

Weinstock et al A A Case Rep 2016 May
TOLERABILITY & DOSING
LDN ADVERSE EFFECTS

• Vivid dreaming
  • Not necessarily nightmares or frightening
  • Third of patients experience – decrease with time

• Sleep disturbances

• Commonly resolves within a week

• Anecdotal reports of nausea and headaches

Coffee

cannot fix this kind of tired.
DOSING

• Common dosing 1.5, 3 & 4.5 mg PO QHS
  • Most studies have used 4.5 mg
  • Caution about dosing at levels too high: more is not necessarily better
  • Opioids most effective between 2-6 am

• May need to dose QAM due to adverse effects or interactions

Moore and Wilkinson 2009, Junker and Wirz J Oncol Pharm Pract 2010
DOSAGE RAMPING

• Titration helps to reduce vivid dreaming

• Careful ramping, especially for rheumatoid arthritis

• Patients with RA can have a flare triggered by initiation of LDN or quickly increasing dose
TYPICAL RAMPING SCHEDULE

• LDN 1.5mg PO QHS for 1-2 weeks

• If well tolerated, increase to LDN 3mg for another 1-2 weeks

• Depending on condition and response, increase LDN to 4.5mg
  • If well tolerated, leave at this dose to evaluate response → can take up to several months
CAUTIONS & INTERACTIONS
FULL DOSE NALTREXONE: CONTRAINDICATIONS

• Hypersensitivity to naltrexone

• Concomitant use of opioid analgesics or opioid dependency
  • Can precipitate withdrawal

• Acute opioid withdrawal
FULL DOSE NALTREXONE: PRECAUTIONS

• Hepatic or renal impairment or dysfunction
  • No change in hepatic enzymes or toxicity issues seen with LDN

• Pregnancy Category C
  • No studies done in pregnancy

• Breastfeeding
  • Infant risk cannot be ruled out

LDN CONSIDERATIONS

• Ensure appropriate fillers are used
  • Recommend inert, hypoactive fillers like microcrystalline cellulose
  • Calcium carbonate may interfere with absorption
  • Avoid dyes since many patients are sensitive to chemicals

• LDN should NEVER be sustained release (SR)

• Typically not used twice daily

NALTREXONE DRUG INTERACTIONS

• LDN should **NOT** be taken at the same time as an opiate since it is an opiate antagonist

• NEVER give a patient LDN who is on an extended release opiate

• If possible, wean patient off opiate before initiating LDN therapy
  • Consider topical analgesics or ULDN

CONTRAINDICATED DRUG EXAMPLES

- Transdermal
  - Butrans (buprenorphine)
  - Duragesic (fentanyl patches)

- Oral extended release products
  - Avinza (morphine ER)
  - Dolophine (methadone)
  - Embeda (morphine/naltrexone)
  - Exalgo (hydromorphone ER)
  - Kadian (morphine SR)
  - MS Contin (morphine CR)
  - Nucynta ER (tapentadol)
  - Opana ER (oxymorphone)
  - Oxycontin (oxycodone CR)
  - Palladone (hydromorphone hcl)

DRUG INTERACTION MANAGEMENT

• If patient cannot completely wean off opioid analgesic some practitioners will initiate LDN
  • Dosing MUST be separated from LDN
  • Use EXTREME caution with this strategy
  • Should not attempt unless opiate is immediate release

• Use muscle relaxants, NSAIDs or topical analgesics to help patient to transition off of opioids

• Consider starting with ULDN 1 mcg PO BID
WHAT IF WEANING OFF OPIATES ISN’T AN OPTION YET?
ULTRA-LOW-DOSE NALTREXONE (ULDN)
Acute opioids

+ 

Gi/Go Proteins

Analgesia

Chronic opioids

+ 

Gs Proteins

Hyperalgesia

ANALGESIA ↔ HYPERALGESIA

• Chronic opioid treatment shifts mu opioid receptor protein binding from $G_i/G_o$ to $G_s$
  • Shifts from analgesia to hyperalgesia
  • May contribute to excitatory neurotransmission in neuropathic pain

• Spinal cord injury induces $G_s$ protein coupling
  • Chronic oxycodone use enhances effect
  • ULDN attenuates effect

Largent-Milnes et al The J of Pain 2008
Opioids

↓ cAMP levels

↓ Ca\(^{2+}\) influx

↑ K\(^+\) outward

Shorter APD

↓ Substance P

Analgesia

G\(_i\)/G\(_o\) Proteins

G\(_s\) Proteins

Adenylyl cyclase stimulation

↑ Ca\(^{2+}\) influx

Prolonged APD

↑ Neuronal excitability

Hyperalgesia

Chronic opioids

↓ cAMP levels
↓ Ca²⁺ influx
↑ K⁺ efflux
↓ Substance P

Analgesia

+ Gₛ Proteins

Adenylyl cyclase stimulation
↑ Ca²⁺ influx
Prolonged APD
↑ Neuronal excitability

Hyperalgesia


Gi/Go Proteins

Gs Proteins

Gi/Go Proteins + Chronic opioids + Gₛ Proteins

Shorter APD
Neuronal excitability
The diagram illustrates the effects of Opioids + ULDN on neuronal excitability.

- **Gi/Go Proteins**
  - $\downarrow$ cAMP levels
  - $\downarrow$ Ca$^{2+}$ influx
  - $\uparrow$ K$^+$ efflux
  - Shorter APD
  - $\downarrow$ Substance P

- **Gs Proteins**
  - Adenylyl cyclase stimulation
  - $\uparrow$ Ca$^{2+}$ influx
  - Prolonged APD
  - Neuronal excitability

**Analgesia**

**Hyperalgesia**

# ULDN + Oxycodone: Chronic Treatment

<table>
<thead>
<tr>
<th>Trial Design</th>
<th>Placebo-controlled, randomized, double-blind</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects</td>
<td>360 adult patients with osteoarthritis of knee or hip</td>
</tr>
<tr>
<td>Dosage</td>
<td>Oxycodone 10mg + 1mcg ULDN QID vs Oxycodone 20 mg + 1mcg ULDN BID</td>
</tr>
<tr>
<td>Duration</td>
<td>3 weeks</td>
</tr>
<tr>
<td>Result</td>
<td>Oxy 20 mg + 1 mcg ULDN BID showed best level and duration of analgesia</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>No significant difference between groups Nausea, constipation and dizziness seen in active treatment groups</td>
</tr>
</tbody>
</table>

Chindalore et al, The J of Pain 2005
Chindalore et al. The J of Pain 2005
OPIOID TOLERANCE & SPINAL GLIOSIS

- Chronic opioid use causes spinal gliosis
- Inhibiting activation of spinal glia prevents tolerance
- Increased immunolabeling of astrocytes and microglia in rats completely attenuated by ULDN
- ULDN stopped increase in volume of astrocytes though still larger than controls
Saline

Morphine + ULDN

ULDN

Morphine

Astrocyte Hypertrophy

Mattioli et al
Molecular Pain 2010
## ULDN: OPIOID ABUSE

<table>
<thead>
<tr>
<th>Trial Design</th>
<th>Double-blind, cross-over, placebo-controlled, randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects</td>
<td>14 adult opioid abusers</td>
</tr>
<tr>
<td>Dosage</td>
<td>7 dosages: 20mg and 40mg oxycodone, 1mcg and 0.1 mcg ULDN and placebo</td>
</tr>
<tr>
<td>Duration</td>
<td>7 randomized 4hr test sessions 5 days apart</td>
</tr>
<tr>
<td>Result</td>
<td>ULDN + Oxy did not decrease abuse liability in acute dosing</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>86 AEs → highest number in placebo followed by Oxy 20 + ULDN</td>
</tr>
</tbody>
</table>

Tompkins et al Psychopharmacol 2010
### Trial Design
- Placebo- and active-controlled, randomized, double-blind

### Number of Subjects
- 719 adults with chronic low back pain

### Dosage
- Oxy vs. Oxy 10-80mg + 2-4mcg ULDN

### Duration
- 12 weeks once dose optimized

### Result
- Oxycodone + 1 mcg ULDN BID provided adequate analgesia with lower oxycodone doses and less physical dependence

### Adverse Effects
- ↓ constipation by 44%, ↓ somnolence by 33%, ↓ pruritus by 51%
  (Oxy + 1mcg ULDN vs Oxy)

---

Webster et al The J of Pain 2006
A

Day 1 SOWS Scores

SOWS Score

Placebo  oxycodone QID  Oxytrex QID  Oxytrex BID

B

SOWS Scores in Patients > 50

SOWS Scores

Day 1  Day 2  Day 3  Day 4

Placebo  oxycodone QID  Oxytrex QID  Oxytrex BID

Withdrawal Severity

Webster et al The J of Pain 2006
# ULDN: OPIOID WITHDRAWAL

<table>
<thead>
<tr>
<th>Trial Design</th>
<th>Double-blind, randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Subjects</strong></td>
<td>174 opioid dependent patients</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>125mcg or 250 mcg ULDN daily</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>6 day methadone taper</td>
</tr>
</tbody>
</table>
| **Result**       | Reduced craving and withdrawal sxs  
                             More negative drug tests 1 week out |
| **Adverse Effects** | Fewer withdrawal symptoms in patients on  
                        ULDN during taper and 1 week after |

ULDN DOSING: RAT STUDIES

• Rats do not absorb naltrexone well orally
  • When studied, found best results at ULDN 3mcg/kg

• Most studies conducted with intrathecal dosing

• Best responses found with ratio of NTX:oxycodone of $10^8$ and NTX:morphine of $10^6$
  • Corresponded to ULDN 1pg/kg infusion 5ng/kg

ULDN DOSING: HUMAN STUDIES

- Wide range in studies from 5ng-250mcg
- Positive results with 1 mcg BID → reasonable starting dose
- Clinically, often dose BID and taper up by 1-3 mcg every 3-4 days as tolerated
  - Often coincides with decreasing opioid dose

QUESTIONS?

Thanks for coming!
If you have further questions, please feel free to contact me at:

natalie@lcrx.com
Phone: 503-281-4161
Fax: 503-281-1990