PainWeek®

How Low Can You Go?
The Low-Down on Low Dose Analgesics

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Disclosure

- Stephanie Abel
  - Nothing to disclose
- Annabelle Hood
  - Nothing to disclose
- Tanya Uritsky
  - Consulting Fee (e.g., Advisory Board): AcelRx

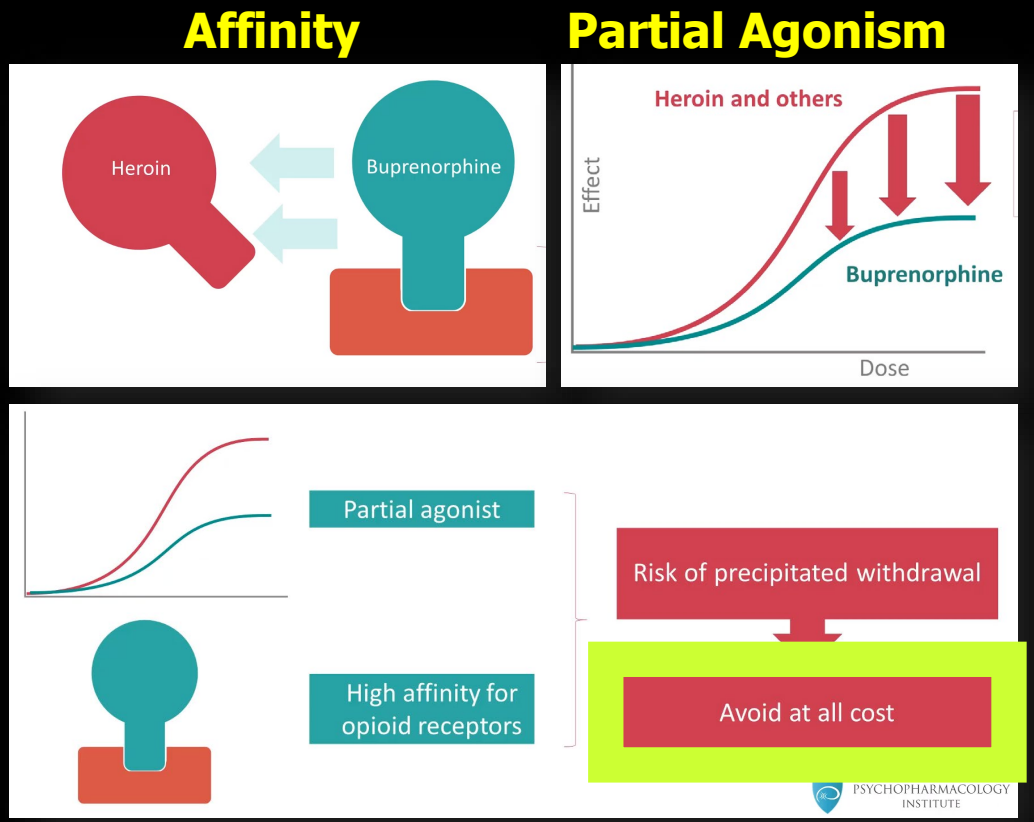
Learning Objectives

- Summarize the rationale for microdosing as a strategy for initiation of buprenorphine
- Discuss low-dose methadone as an adjuvant analgesic for refractory pain management
- Describe the use of low-dose naltrexone as an alternative treatment for chronic pain
- Using a patient case, explain principles of unique low-dose management strategies

Low Dose Buprenorphine

Background

- Buprenorphine is a partial opioid agonist with high affinity for opioid mu receptors
- Indicated for pain management and the treatment of opioid use disorder (OUD)
- Partial Agonism + High Receptor Affinity → In the setting of a full opioid agonist, buprenorphine at higher doses (mg) will precipitate withdrawal
- Traditional buprenorphine initiation requires a patient to begin opioid withdrawal prior to the first dose



Buprenorphine Formulations

- Sublingual film/tablet (Buprenorphine/naloxone (Suboxone) or buprenorphine (Subutex™)
  - 2/0.5 mg, 4/1 mg, 8/2 mg of buprenorphine/naloxone (Bup/Nal)
  - Dosing based on craving control

- Transdermal Patch (Butrans™)
  - 10 mcg/h and 20 mcg/h patch
  - 72-h to steady state

- Buccal film (Belbuca™)
  - 75 mcg, 150 mcg, 450 mcg, 600 mcg, 900 mcg
  - Manufacturer-provided Dosing is dependent on prior exposure to opioid therapy
    - <30 mg Oral Morphine Equivalents (OME): 75 mcg daily or q12
    - 30-89 OME: 150 mcg q12h
    - 90-160 OME: 300 mcg q12

Buprenorphine Absorption

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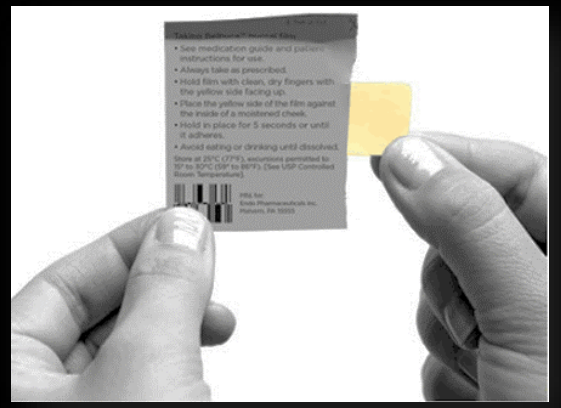


1 mg IV Buprenorphine

4 mg Suboxone™ (buprenorphine/ naloxone sublingual film/tablet)

1800 mcg Belbuca™ (buprenorphine buccal film)

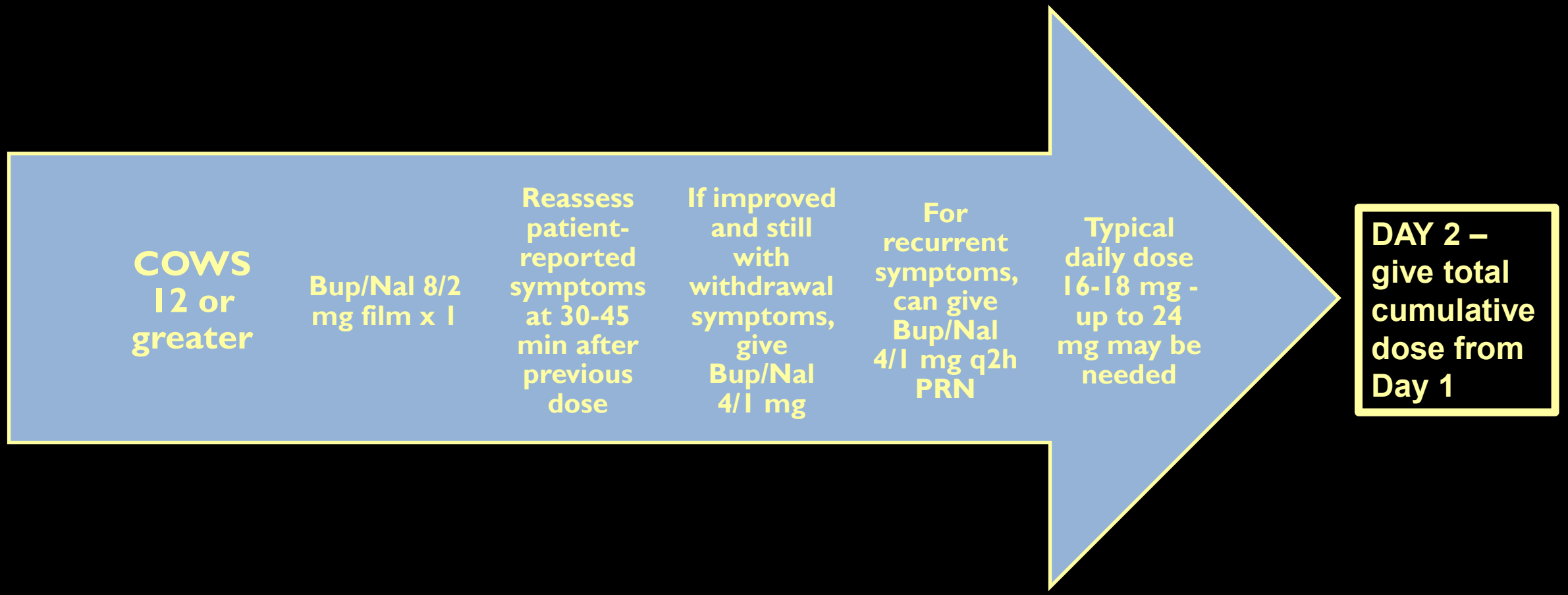
COWS

Talk to nurse!

- *COWS should be documented throughout the process to monitor for precipitated withdrawal*
- *Nursing should document a COWS score at least every 12 hours (e.g. every other buprenorphine administration) & PRN*
- *Is patient upset/irritable? They might be in withdrawal!*
- *If COWS scores begin to elevate, go back to previous dosing scheme and consider a pain consult (if available)*

Clinical Opiate Withdrawal Scale (COWS)	
Heart Rate	<80 = 0 81-100 = 1 101-120 = 2 >120 = 4
Sweating	Subjective report = 1 Flushed or moist face = 2 Beads of sweat on face = 3 Sweat streaming off face = 4
Restlessness	Able to sit still = 0 Subjective reports of restlessness = 1 Frequent shifting or extraneous movements = 3 Unable to sit still for longer than a few seconds = 5
Pupil size	Normal or small = 0 Pupils possibly larger than appropriate = 1 Pupils moderately dilated = 2 Pupils so dilated that only rim or iris visible = 5
Bone or joint aches	Mild diffuse discomfort = 1 Subjective reports= 2 Patient actively rubbing joints or muscles = 4
Rhinorrhea or lacrimation	Congestion or moist eyes = 1 Rhinorrhea or lacrimation = 2 Nose constantly running or tears streaming = 4
Yawning	1-2 times = 1 >3 times = 2 Several times/minute = 4
Anxiety or irritability	Subjective report = 1 Appear anxious = 2 Too irritable to participate in assessment = 4
Gooseflesh	Smooth skin = 0 Piloerection can be felt = 3 Prominent piloerection =5
If any of the above symptoms are not present = 0	

Traditional Buprenorphine Induction



PPT Withdrawal literature

- Increased risk with:
  - Higher initial doses of buprenorphine
  - Shorter time interval between full agonist and buprenorphine administration
  - Higher levels of physical dependence
- Need for withdrawal prior to induction is a barrier to success
- Higher dropout rates for buprenorphine vs. methadone induction
- Small frequent doses of partial agonist in setting of full agonist are NOT associated with precipitated withdrawal

Rosado J, et al. Drug Alcohol Depend. 2007; 90(2-3): 261-269.

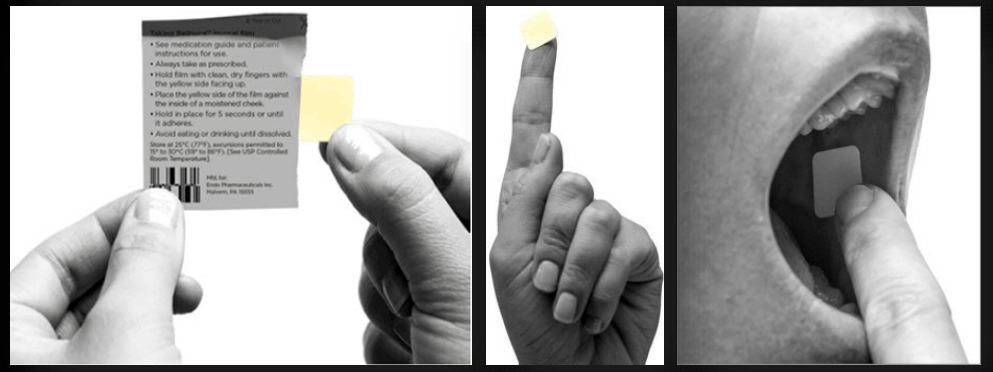
Buprenorphine Micro-dosing

Micro-dosing of buprenorphine uses mcg dosing of buprenorphine

Buprenorphine/naloxone strips (cut strips) OR buccal films (Belbuca™) which:

1. Allows initiation of buprenorphine without the need to first experience withdrawal
2. Minimizes risk of precipitated withdrawal given the very small doses

Micro-doses are increased over 3-4 days to achieve full maintenance dose in milligrams of buprenorphine (Subutex™ or Suboxone™)



Micro-dosing literature

- Many approaches published in case reports and case series. All have varying:
  - Timelines
  - Formulations of Buprenorphine (SL, transdermal, buccal, IV)
  - Patient populations (OUD, chronic pain, inpatient vs outpatient)
  - Approaches:
    - Taper full agonist before starting buprenorphine
    - Taper full agonist while increasing buprenorphine
    - Continue full agonist at full dose until buprenorphine ~12 mg/day, then discontinue full agonist

Intended Patient Populations

Group A: *OUD*

- Starting buprenorphine treatment for OUD + hx of illicit opioid use (i.e. fentanyl)

- *Examples:*
  - Patients wishing to transition from methadone to buprenorphine
  - Patients with chronic, heavy use of IV or intranasal fentanyl
  - Patients who have experienced prior precipitated withdrawal

Group B: *OUD + Pain*

- Hx of OUD + on full agonist for pain, to initiate buprenorphine while cross-tapering full agonist

- *Examples:*
  - Patients admitted with acute pain and concomitant OUD, requiring full agonist therapy for analgesia but wishing to initiate buprenorphine
  - Patients on chronic opioids for analgesia and diagnosed with OUD who would like to be transitioned to buprenorphine for MOUD (e.g. sickle cell)

Standard Micro-dosing
Regimen using Belbuca® and Suboxone® (Buprenorphine/naloxone)

Day 1 Belbuca 150 mcg buccal film q6h *(450 mcg total ≈ 1 mg Suboxone)*

Day 2 Belbuca 450 mcg buccal film q6h *(1800 mcg total ≈ 4 mg Suboxone)* → Start here if not cross-tapering full agonist

Day 3 Buprenorphine/naloxone (Suboxone™) 2 mg SL q6h*

Day 4 Buprenorphine/naloxone (Suboxone™) 4 mg SL q6-8h**

If NOT requiring full opioid agonists, go straight to 4 mg q6h

***If patient is also experiencing acute pain/requiring full opioid agonists– consider q8h dosing.*

*

- *Prior to discharge, consolidate total daily dose into once daily dosing as buprenorphine/naloxone once on a stable dose*

Standard Micro-dosing

Regimen using Intravenous Buprenorphine

For patients who cannot tolerate or take anything in the oral cavity

Day 1	Buprenorphine 150 mcg IV q6h
Day 2	Buprenorphine 300 mcg IV q6h → Start here for patient not requiring a cross-taper of full agonist
Day 3	Buprenorphine/naloxone 2 mg SL q6h*
Day 4	Buprenorphine/naloxone 4 mg SL q6-8h*

***If patient is also experiencing acute pain/requiring full opioid agonists– consider q8h dosing.*

Prior to discharge, consolidate total daily dose into once daily dosing as buprenorphine/naloxone once on a stable dose

Michael: Acute Pain

32 y.o. male HIV, Hep C admitted for b/l LE osteomyelitis, pyomyositis

- –IV fentanyl 20-30 bags daily (2-3 bundles) + xylazine (“tranq”)
- –Maintained on high dose oxycodone ER 40 mg PO q8h and oxycodone 60 mg PO q4h
- –GOAL: Stabilize on buprenorphine while maintaining full-agonist for acute pain

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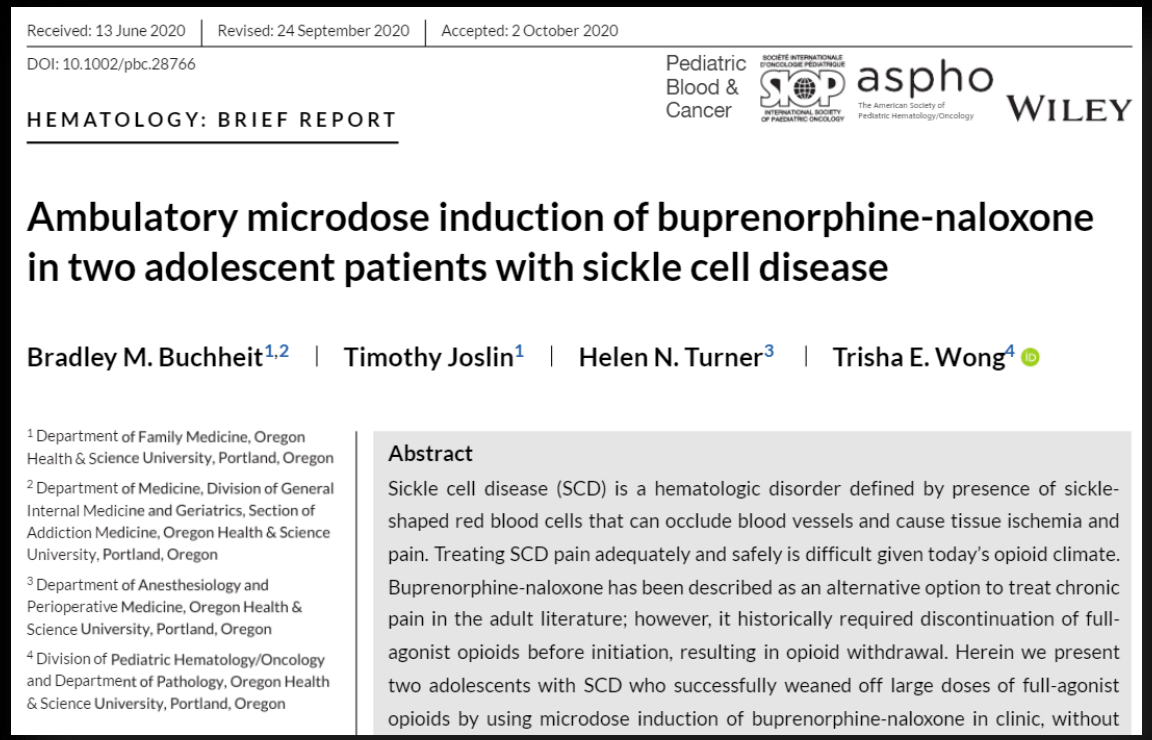
Buprenorphine Micro-dosing Schedule

Day	Cross-taper		Daily Dose	
	Full-agonist	Buprenorphine	Full-agonist	Buprenorphine
Baseline	Oxycodone: 60 mg q4h Oxycontin: 120 mg daily	-	Oxycodone 720 mg	-
Day 1	Oxycodone 60mg q4h	75 mcg buccal x 1 150 mcg buccal q6h	360 mg	526 mcg = 0.5 mg
Day 2		450 mcg buccal q6h	360 mg	1800 mcg = 1.8 mg
Day 3	45mg q4h OR 90mg q8h	2mg Bup/nal q12h	270 mg	4 mg
*Day 4	*Self-directed discharge*	2mg Bup/nal q6h	270 mg	12 mg
Day 5		4mg Bup/nal q6h		6 mg
Day 6	30 mg q4h OR 60 mg q8h	8mg Bup/nal q8h	180 mg	24 mg
…				
Day 9		8mg Bup/nal q8h	90 mg	24 mg

Chronic Sickle Cell Pain

31yo F with sickle cell disease previously treated with exchange transfusions, c/b ESRD s/p LRKT in 2015, with frequent inpatient admissions for complex pain syndrome.



Received: 13 June 2020 | Revised: 24 September 2020 | Accepted: 2 October 2020

DOI: 10.1002/pbc.28766

Pediatric Blood & Cancer

HEMATOLOGY: BRIEF REPORT

Ambulatory microdose induction of buprenorphine-naloxone in two adolescent patients with sickle cell disease

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Abstract

Sickle cell disease (SCD) is a hematologic disorder defined by presence of sickle-shaped red blood cells that can occlude blood vessels and cause tissue ischemia and pain. Treating SCD pain adequately and safely is difficult given today's opioid climate. Buprenorphine-naloxone has been described as an alternative option to treat chronic pain in the adult literature; however, it historically required discontinuation of full-agonist opioids before initiation, resulting in opioid withdrawal. Herein we present two adolescents with SCD who successfully weaned off large doses of full-agonist opioids by using microdose induction of buprenorphine-naloxone in clinic, without

- Prior opioids: gabapentin, oxycodone, hydrocodone/APAP, fentanyl patch, morphine, codeine, oxycodone/APAP, hydromorphone, methadone
- Prior nonopioids: tizanidine, cyclobenzaprine, pregabalin, amitriptyline, nortriptyline
- ER admission 4/5/21, family meeting 4/6/2021, new pain plan 4/7/2021
- **GOAL: Trial buprenorphine for pain, as well as a consistent opioid to avoid withdrawal in between admissions.—amenable to trying buccal buprenorphine (Belbuca™)**

Buprenorphine Micro-dosing Schedule

Day	Cross-taper Order		Daily Dose	
	Full-agonist	Buprenorphine	Full-agonist	Buprenorphine
Baseline	Hydromorphone PCA 0 mg/h / 0.8 mg demand / 30 min	-	336mg MEDD*	
Day 1	PCA 0.8mg demand/30 min (used 0.7mg/h)	75mcg q6h	336mg	300mcg
Day 2	No change	150mcg q6h	336mg	600mcg
Day 3	PCA 0.8mg demand/60 min	450mcg q12h	76.8mg	900 mcg
Day 4	PCA 0.8mg demand/60min	450mcg q6h	17.1mg	1800 mcg (1.8 mg)
Day 5	Oxycodone 5mg q6h	450mcg q6h		-
Day 6	Oxycodone 5mg	450mcg q6h		-

Pocket Guide

- Patient populations
- Sample dosing regimen
- Cross-tapering recs
- Important reminders

Buprenorphine Micro-Dosing

Intent: For use as an alternative to standard or lower-dose buprenorphine induction strategies

Intended Patient Population

- Patients requesting buprenorphine treatment for OUD who have had recent use of illicit opioid use (within 16-24 hours).
- Who wish to avoid the usual withdrawal that is required prior to induction with higher doses of buprenorphine.
- On full opioid agonist for treatment of pain but also with OUD, as means to initiate buprenorphine for treatment of OUD while maintaining full agonist therapy for pain control.

Microdosing regimen using Belbuca®:

Day 1 - 150 mcg buccal film (may need to be two 75 mcg films based on availability) q6h.

Day 2 - 450 mcg buccal film q6h

Day 3 – Buprenorphine/naloxone 2 mg q12h

Day 4 – Buprenorphine/naloxone 2 mg q6h

Day 5 – Buprenorphine/naloxone 4 mg q6-8h*

*If patient is also experiencing acute pain requiring full opioid agonists– consider q8h dosing. If patient is not also experiencing acute pain requiring full opioid agonists, go straight to 4 mg q6h. Consolidate total daily dose into once daily dosing as Suboxone® (Buprenorphine/naloxone) once stable and prior to discharge.

ALTERNATIVE using IV Buprenorphine (for patients who cannot tolerate or take anything in the oral cavity):

Day 1 – Buprenorphine 50 mcg IV q6h

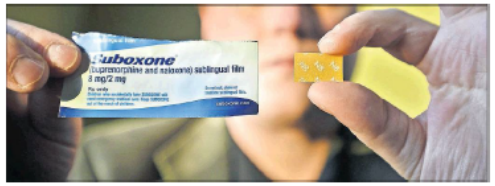
Day 2 – Buprenorphine 150 mcg IV q6h

Day 3 – Buprenorphine 300 mcg IV q6h

Day 4 – Buprenorphine/naloxone 2 mg SL q6h

Day 5 – Buprenorphine/naloxone 4 mg SL q6-8h*

*If patient is also experiencing acute pain requiring full opioid agonists– consider q8h dosing. If patient is not also experiencing acute pain requiring full opioid agonists, go straight to 4 mg q6h. Consolidate total daily dose into once daily dosing as Suboxone® (Buprenorphine/naloxone) once stable and prior to discharge.



Pertinent Resources for Inpatient:

- All patient's should have SW consults AND CORE consult
- MEND team consult if applicable
- Pharmacy Help with Questions: Tanya Uritsky,
-

Opioid taper:

Chronic opioids: Initially decrease dose by 30-50% and then 25% every 3 days thereafter as indicated based on expected acute pain trajectory.

Acute pain: continue to provide PRN opioid analgesic. Can provide more rapid full agonist taper (over 3-5 days) as acute pain resolves.

Important Reminders:

- All patient's started on Suboxone SHOULD be discharged with NARCAN and SUBOXONE, even if there is no prescriber outpatient to DECREASE risk of overdose
- Involve the patient in the plan and allow them to take ownership of their plan

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Buprenorphine Micro-dosing Pearls

- Based on clinical evidence
- Try to start as soon as possible! No need to wait for acute pain resolution.
- Flexibility is built in, don’t sweat a missed dose.
- Monitor for pain relief.
- Utilizing co-analgesics is important to optimize pain control in patients on BUP.
- Aggressively monitor and manage any withdrawal symptoms with supportive care.

Low-dose Methadone

Methadone Background

- Synthetic opioid
- Multiple mechanisms of action
- Complex pharmacokinetics
- Most common indications
  - Pain management
  - Detoxification
  - Medication for opioid use disorder

Patient Case – Mr. Thompson

- Metastatic prostate cancer
- Refractory pain
  - Not improved with ↑ oxycodone
- Current (relevant) meds:
  - Oxycodone ER 80 mg TID
  - Oxycodone 30 mg Q4H PRN
  - Sertraline 100 mg QD

Background – Methadone Mechanism of Action

Mu Agonist

- Re-sensitization
- Central & peripheral antinociception
- Synergy

NMDA Receptor Antagonist

- NMDA activation
  - –Partially mediates central sensitization
  - –Hypothesized to play a role in opioid tolerance

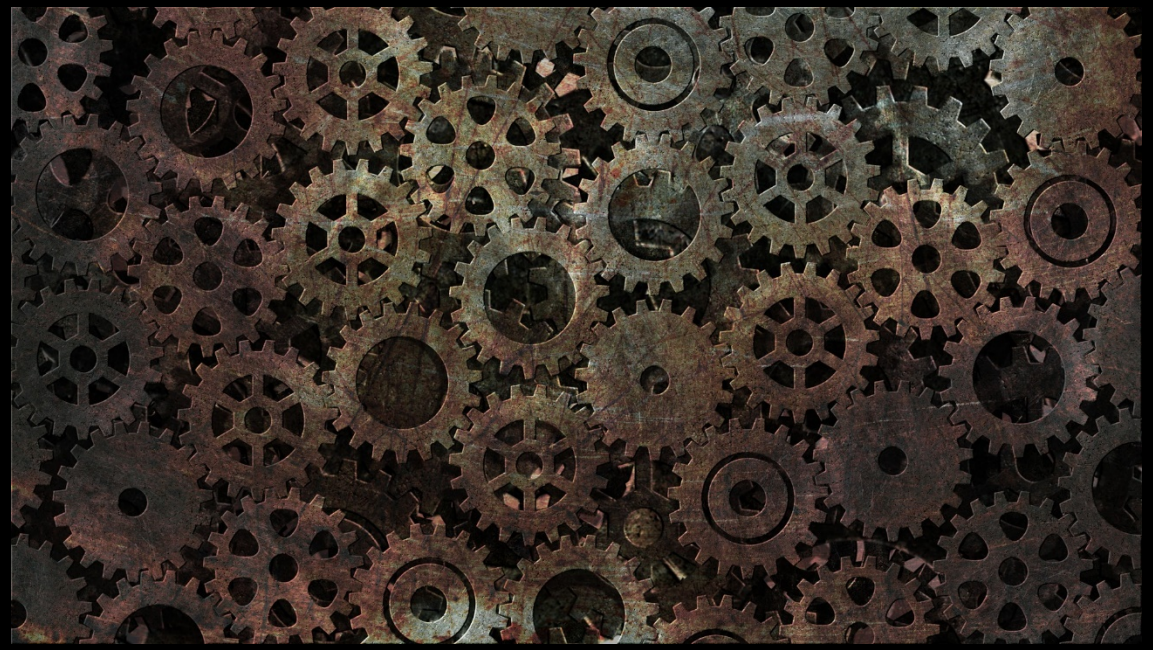
Background – Methadone Mechanism of Action

- Serotonin/Norepinephrine Effects
  - Potent inhibitor of the 5-HT transporter (SERT)
  - Also inhibits noradrenaline transporter (NET)

Drug	NET IC_{50} [μM]	SERT IC_{50} [μM]
Methadone	4.1	0.23
Duloxetine	0.12	0.044
Venlafaxine	0.41	N/A
Citalopram	>20	0.038

Table adapted from Table 1: Br J Pharmacol. 2018 Feb;175(3):532-543

Methadone Background



- Mechanisms preventing tolerance
  - Intrinsic activity
  - Endocytosis
  - Delta opioid receptor
- Hyperalgesia
  - Role of central glutaminergic system
- Role as a co-analgesic

Indications in the Literature

- Palliative pain management and prevention of OIH
  - Low-dose adjuvant methadone
    - 1 – 20 mg / day (some with other adjuvants such as haloperidol)
  - Conversion to methadone
    - 2.5 – 15 mg/day + scheduled haloperidol
  - Ultra-low dose adjunct methadone with slow titration for cancer pain
- Improved pain control when low doses used individually or as co-analgesic
- Mild adverse effects

Indications in the Literature

- Perioperative
  - Intraoperative
    - ↓ postop opioids, ↓ pain scores, ↑ patient satisfaction with analgesia, no difference in AE
  - Intraoperative + ketamine
    - Significantly ↓ IV & oral opioid usage, pain scores 1/3 less
    - Effects far greater than previous studies of ketamine + other opioids
  - Postoperative
    - PCA's or infusion at low doses
      - Improved analgesia, ↓ opioid consumption, no difference in adverse events
  - Multidose
    - 3 – 5 doses in adolescent patients (0.1 mg/kg intraop and Q12H for 3 – 5 doses)
      - Improved pain control, ↓ opioid usage, minimal adverse events

Indications in the Literature

- Refractory pediatric pain
  - Nociceptive pain unresponsive to other opioids
  - Severe, refractory neuropathic pain
  - Facilitation of opioid weaning
  - End-of-life pain management
- Median starting dose 0.32 mg/kg/day
- Efficacy
  - Nociceptive pain → 52.9%
  - Neuropathic pain → 40%

Low-dose Methadone Adverse Effects (AE)

- Cancer pain
  - Dry mouth, somnolence, constipation, nausea, vomiting
  - Sedation or somnolence reported for both morphine and methadone
- Postoperative use
  - No difference in respiratory depression or hypoxemia events in RCTs
    - Not powered to assess safety outcomes
    - 2 retrospective reviews have shown ↑ respiratory depression in methadone group
  - No difference in sedation, nausea, or vomiting
  - No adverse cardiac events described
    - Not powered to assess safety outcomes

Clinician Considerations for Low-dose Methadone

- Patient considerations
  - Pathology of pain
  - Current / previous regimen
  - Comorbidities
  - Concomitant medications
- AE considerations
  - Potential for serotonin toxicity
  - Pharmacokinetics
  - Pharmacogenomics / drug interactions
  - Cardiac toxicity

Low-Dose Naltrexone

Meet Mrs. Payne

Mrs. Payne is a 58 year old female presents to your clinic with a chief complaint of “non-stop pain”. She tells you “it’s my fibromyalgia - nothing helps!”

- Tried SNRIs, opioid analgesics, and gabapentin in the past with no relief
- Experienced CHF exacerbation with use of NSAIDs
- Reports taking acetaminophen (APAP) “like candy”

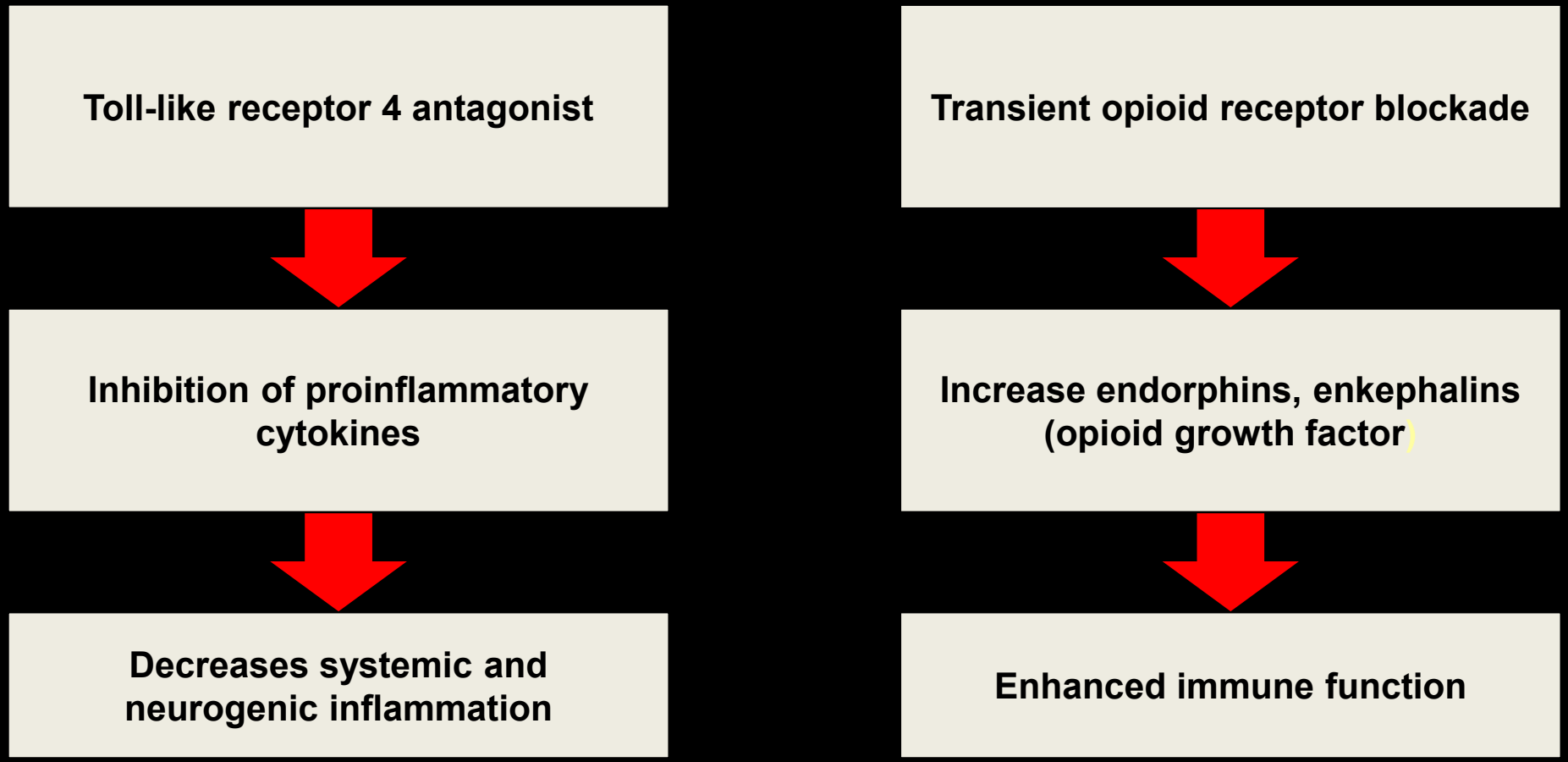
- Current medications include:
  - Acetaminophen 500 mg, sig. 2 tablets QID
  - Amitriptyline 100 mg, sig. 1 tablet QHS for depression
  - Furosemide 20 mg, sig. 1 tablet daily
  - Pregabalin 150 mg, sig. 1 capsule TID

Treating Pain With A Paradox

Background

- Naltrexone was developed in 1963 as an orally active opioid receptor antagonist
- It is FDA approved for medical-assisted treatment of alcoholism and opioid use disorder at doses of 50-100 mg daily
- At lower doses, naltrexone has been reported to exhibit a paradoxical analgesic effect and anti-inflammatory properties
- Low dose naltrexone (LDN) has been used off-label for many diseases
  - Autoimmune diseases
  - Chronic pain conditions

Low-Dose Naltrexone Mechanism of Action



Hatfield E., et al. JADA. 2020;151(12):891-902.

Dose-Dependent Mechanism of Action and Clinical Use

Dose Range	Dose Specific Mechanism of Action	Clinical Use
Standard (50-100 mg)	Opioid receptor antagonism	Alcohol and opioid abuse
Low-dose (1-5 mg)	Toll-like receptor 4 antagonism, opioid growth factor antagonism	Fibromyalgia, Multiple Sclerosis, Crohn's disease, cancer, Hailey-Hailey disease, complex regional pain syndrome (CRPS)
Very low dose (0.001-1 mg)	Same as low-dose	Add-on to methadone detoxification taper
Ultra low-dose (<0.001 mg)	Binding to high affinity filamin-A (FLNA) site and reducing mu-opioid receptor associated Gs-coupling	Potentiating opioid analgesia

Toljan K., et al. Medical Sciences. 2018;6(4):82.

Low-Dose Naltrexone As A Coanalgesic

- LDN for off-label use is based off of clinical evidence
- Dosing
  - Ranging between 1-5 mg per day
  - Titration is not straightforward
  - Must be compounded by specialty pharmacy
- No known abuse potential
- Adverse events may include vivid dreams, fatigue, headache, nausea

Is There Evidence?

Evidence for Low-Dose Naltrexone in CRPS

- 3 case reports published in the literature on use of LDN
  - Doses of 1.5 mg and 4.5 mg
  - Outcomes:
    - Alleviated pain
    - Reduced CRPS flares
    - Reduced other symptoms of CRPS, including dystonic spasms, energy/fatigue, sleep disturbances, and improved mood
  - Time to alleviation of symptoms
    - 2 days to <2 months
  - No adverse events reported

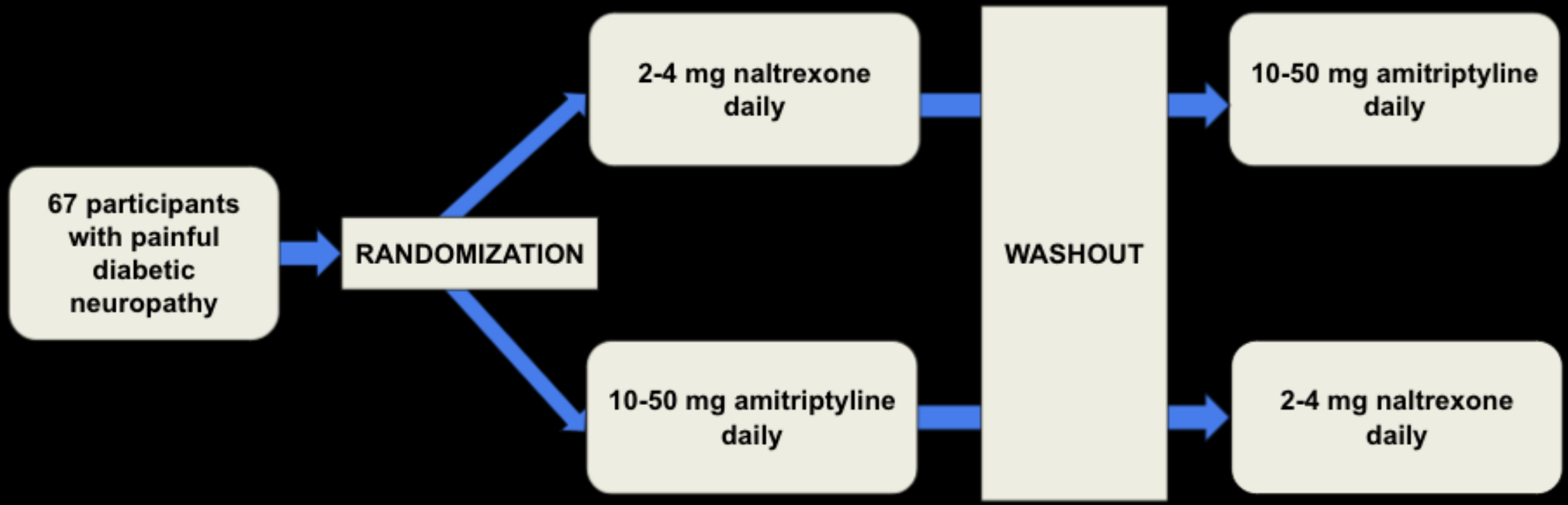
Soin A., et al. Pain Physician. 2021;24(4):E393-E406

Evidence for Low-Dose Naltrexone in Fibromyalgia

- Small studies looked at the use of LDN vs placebo
  - Daily doses of 2.5 to 4.5 mg
  - Outcomes:
    - Reduced self-reported fibromyalgia symptoms, pain severity, fatigue
    - Increased pain tolerance
    - Improved life satisfaction and mood
    - Reduced inflammatory plasma markers
  - Well tolerated
  - Reported adverse events included vivid dreams, nausea, insomnia, and headache

Hatfield E., et al. JADA. 2020;151(12):891-902.

Efficacy and Safety of LDN in Painful Diabetic Neuropathy: A Randomized, Crossover Trial



Srinivasan A., et al. Journal of Diabetes. 2021. 1-9.

Efficacy and Safety of LDN in Painful Diabetic Neuropathy: A Randomized, Crossover Trial Cont...

Measurement	Naltrexone group*	Amitriptyline group*	Difference between groups*
VAS	26.7 (24.8-28.5) p-value <.001	25.0 (23.2-26.8) p-value = <.001	1.6 (-0.9-4.2) p-value = .21

**Results reported as change in scores from baseline*

- Most common adverse events were mild diarrhea with naltrexone (n=3, p-value = .24) and somnolence with amitriptyline (n=18, p-value = <.001)
- Authors conclusions:
  - "Low-dose naltrexone exhibited similar efficacy and a superior safety profile compared with amitriptyline in painful diabetic neuropathy"

Srinivasan A., et al. Journal of Diabetes. 2021. 1-9.

Potential Benefits to Using Low Dose Naltrexone

- ✔ Low cost
- ✔ Minimal reported adverse events
- ✔ No known abuse potential
- ✔ Suggested to be beneficial for pain reduction and improving quality of life in patients experiencing chronic pain

Low-Dose Naltrexone Pearls

- Naltrexone is reported to exhibit dose-dependent properties, including analgesic and anti-inflammatory characteristics at low doses
- Low-dose naltrexone has shown promise and may provide benefit for managing challenging pain syndromes
- There is no “one size fits all approach” to dosing low-dose naltrexone
- Further studies are needed to establish full therapeutic utility of low-dose naltrexone in pain management

Back to Mrs. Payne

- Low-dose naltrexone capsules were initiated, as follows:

  Week 1: 1.5 mg by mouth once daily

  Week 2: 3 mg by mouth once daily

  Week 3-4: 4.5 mg by mouth once daily

- By week 4, she reported reported significant reductions in level of pain and ability to complete daily activities
- Patient was able to reduce use of APAP to ‘as needed’

Key Take Aways

- Low-dose analgesics have a role in complex pain and symptom management
- Micro-dosing of buprenorphine can be used to initiate buprenorphine for treatment of pain without the need to taper full agonists prior to initiation
- Low-dose methadone can improve analgesia when patients are stabilized on other opioids and is generally well tolerated
- Low dose naltrexone offers promise for the treatment of refractory chronic pain syndromes
- All of these approaches are not a one-size fits all approach
- Pay special attention to drug interactions, complexity of the regimen, and patient and clinician education

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Questions