THE DOUBLE LIVES OF MAT: METHADONE, BUPRENORPHINE AND NALTREXONE

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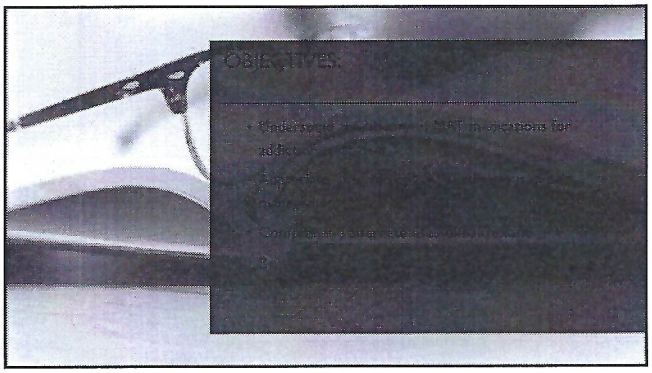


WHAT IS MAT?

- MAT: Medication Assisted Treatment
- Treatment for OUD, SUD, addiction
- These three medications are methadone, buprenorphine, and naltrexone
- Naloxone is not used for MAT, but for opioid overdoses

SAMHSA's center for substance abuse and treatment manages federal regulations of MAT

CURRENT STATISTICS USA
(NCDAS, 2023)

OPIOID ABUSE

- 2.7 million > 12 y have OUD
- 7.4% also abuse heroin
- 51.3% obtain pain meds from friends
- Hydrocodone is #1 with 5.1 million abusers

ILLICIT DRUG ABUSE

- 13.5% > 12 y have used illicits within the last 30 days
- 50% > 12 y have used illicit drugs in their lifetime
- 138.522 million > 12 y drink alcohol
- Of those, 20.4% have alcohol use disorder

CDC STATISTICS 2022

- More deaths from synthetic opioids (fentanyl) under age 50 than homicide, suicide, heart disease, cancer or accidents
- The potential for another individual to intervene in these overdose deaths was 46%

METHADONE

- Created in 1939 by German scientists at IG Farben Lab
- Morphine was scarce during WW2 and Hitler wanted an alternative for his soldiers, and to be independent from the rest of the world
- The US Dept of Commerce brought methadone to the US in 1947, and was FDA approved for **pain management**
- Brand name Dolophine

HOW DID METHADONE BECOME THE TREATMENT FOR OPIOID ABUSE?

- Morphine was being used in the to treat the upswing in heroin abuse of the early 1960s
- Dr Vincent Dole and Dr Marie Nyswander, and Rockefeller University's Mary Jane Kreek, researcher, began interviewing hundreds of heroin abusers in NYC and hypothesized that drug addiction was a metabolic disorder of the brain
- With morphine failing, they began clinical trials with methadone, and their landmark results were published in 1966
- The FDA approved methadone for heroin and opiate treatment in 1973
- The algorithm created for heroin abuse is still the same algorithm used today

METHADONE

When used for addiction/opioid use disorder (OUD) therapy

- Higher doses given once a day
- **Will not** appear on NYS Prescription Monitoring Program (iStop)
- Can only be prescribed by a licensed Methadone Maintenance Program

When used for pain

- Lower doses given more than once a day
- **Will** appear on NYS Prescription Monitoring Program (iStop)
- Can be prescribed by any provider

METHADONE

- Synthetic long-acting full Mu receptor agonist
- Schedule II drug
- Renal safe
- Pain effects last 8 to 12 hours
- 3x stronger than morphine
- Half life 36-72 hours
- Lipophilic and many routes: PO, IV, IM, SQ, PR (epidural and intrathecal off label)
- Metabolized by the liver, no active metabolites, and 80% bioavailability

INPATIENTS ON METHADONE

- Continue home doses – taken for pain or addiction - while in hospital and plan to add immediate release (IR) opioids for acute pain management.
- May require higher doses of IR secondary to tolerance, dependance, and opioid receptor occupation by methadone.
- If the patient is on methadone for addiction, must call the methadone clinic to verify the dose.

METHADONE CAUTION!

Can prolong QTc!

- Need baseline EKG
- Check liver function
- Check labs K+ and Mg++
- Structural heart disease?
- Family history of prolonged QT?
- On other meds that prolong QTc?

QTC PARAMETERS

Normal QTc Interval - Criteria

QTc (msec)	Male	Female
Normal	<430	<450
Borderline	431-450	451-470
Prolonged	>450	>470

BUPRENORPHINE

- Created in 1966 by English chemist John Lewis
- FDA approved for pain management in the USA in 1981
- FDA approved for OUD in 2002
- Derived from the poppy flower - thebaine

BUPRENORPHINE

FOR OPIOID ABUSE/ ADDICTION

- Buprenorphine/Naloxone SL Film - Suboxone
- Buprenorphine/Naloxone SL Tablets - Zubsolv
- Buprenorphine/Naloxone Buccal Film - Bunavail
- Buprenorphine Implants – Probuphine (currently off market)
- Buprenorphine ER Injection - Sublocade (2017) monthly
- Buprenorphine ER Injection – Brixadi (2023) weekly/ monthly

FOR CHRONIC PAIN MANAGEMENT

- Buprenorphine SL Tablets - Subutex
- Buprenorphine Transdermal – Butrans (weekly)

BUPRENORPHINE

- Synthetic short acting partial Mu opioid receptor agonist
- Schedule III drug
- Considered renal safe
- Slow dissociation from mu receptors - allows the clinical effects of buprenorphine to last significantly longer than would be expected based solely on its elimination half-life, can remain in system up to 2 weeks and effects can last up to 3 days
- Half-life 25 - 70 hours
- Lipophilic, and many routes PO, SL, subdermal, transdermal, IV
- Metabolized by liver approx. 80%, has active metabolites, and 35 – 50 % bioavailability

BUPRENORPHINE

Has very high affinity and low intrinsic activity at the mu receptor

- High affinity - will displace morphine, methadone, and other full opioid agonists from the receptor
- Low intrinsic activity – partial agonist - can produce effects such as euphoria or respiratory depression at low to moderate doses but are weaker than full opioid agonists
- Has a ceiling effect - increased safety in overdose (respiratory depression)
- Lower abuse potential

BUPRENORPHINE
MU OPIOID RECEPTOR OCCUPATION

The higher the dose, the more the Mu receptor is occupied

- 2 mg Buprenorphine – approx. 60 % mu-opioid receptors available
- 16 mg Buprenorphine – approx. 20 % mu-opioid receptors available
- 32 mg Buprenorphine – approx. 4 % mu-opioid receptors available

INPATIENTS ON BUPRENORPHINE

- Continue home doses – taken for pain or OUD- while in hospital and plan to add immediate release (IR) opioids for acute pain management.
- May require higher doses of IR secondary to tolerance, dependance, and opioid receptor occupation by buprenorphine.
- Verify dose via NYS PMP, which will also verify buprenorphine vs buprenorphine with naloxone.
- The American Society of Addiction Medicine updated their buprenorphine recommendations in 2020 – **we no longer stop buprenorphine prior to surgery.**

The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder – 2020 Focused Update

BUPRENORPHINE CAUTION

- With hepatic issues, use buprenorphine without naloxone
- Higher abuse potential with buprenorphine than with naloxone combination – naloxone is poorly metabolized PO with low bioavailability, but will have a high bioavailability if crushed and injected or snorted.
- **An X-Waiver is no longer needed to prescribe buprenorphine/ naloxone, and was never needed for prescribing buprenorphine.**

NALTREXONE

- Created in 1966 by Endo Labs
- Developed to treat opioid addiction
- FDA approved for OUD in 1984
- Was originally a schedule II drug

NALTREXONE (FDA APPROVED USES)

FOR SUD/ AUD

Vivitrol (2010)

- Injectable monthly
- 380 mg

Revia (1994)

- Start with 25 mg PO
- 50 mg QD, 100 mg QOD, 150 mg Q 3 days

FOR WEIGHT LOSS

Contrave (bupropion/ naltrexone) (2014)

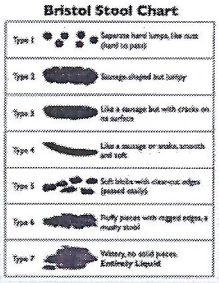
- Dose is 8/90
- Increase weekly 1 AM; 1 AM and 1 PM; 2 AM and 1 PM; then 2 AM and 2 PM
- Weight loss at higher doses; 16 weeks; lose up to 8% of body weight

FOR OIC:

BLOCK THE MU RECEPTORS IN THE GI TRACT

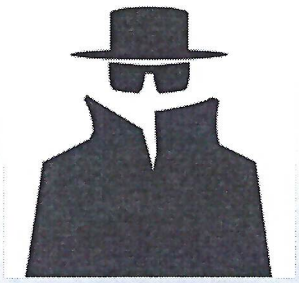
Methylnaltrexone (Relistor)

- 8-12 mg SQ QD (weight based)
- 450 mg PO QAM



NALTREXONE

- Full Mu receptor antagonist
- Not a scheduled substance
- Significant hepatic metabolism, active metabolite 6 beta naltrexol
- Mostly renal excretion
- Fast dissociation from Mu- may make receptor very sensitive
- PO bioavailability 5 – 40%
- Two isomers: L isomer blocks the Mu receptor and D isomer binds to immune cells



NALTREXONE'S OFF LABEL USES:

- Chronic pain
- Chronic fatigue syndrome
- Fibromyalgia
- IBD
- OCD
- MDD
- Autism
- Immunocompromised- CA, HIV/AIDS
- Pruritis

NALTREXONE'S OFF LABEL USES

Autism

- Double-blind placebo-controlled crossover study of 13 children with autism
- Ages 3 – 8 years
- Observed in school, home and outpatient settings
- 8 of 13 children improved in behavior and communication in at least 2 settings

Koleman, et al, LAACAP, 1995

NALTREXONE'S OFF LABEL USES

Chronic Fatigue Syndrome

- Profound fatigue and post exertional malaise
- 4-12 mg per day
- Article based on three case studies

Bolton et al, BMJ, 2020

NALTREXONE'S OFF LABEL USES

Severe pruritis in geriatrics

- Severe pruritis from various skin conditions
- 18 patients over age 65 who failed other treatments
- 50 mg daily
- 16 of 18 had symptomatic improvement; 13 of 18 were "much improved"; 6 of 18 had complete resolution

Lee et al, AD, 2016

NALTREXONE'S OFF LABEL USES

Obsessive compulsive disorder

- Repetitive behaviors in response to reduce stress
- Thought to be dopamine dysregulation
- 56 y male with schizophrenia and dementia with PICA behavior- 100 mg daily
- 3 y male with developmental delays and self injurious behavior- 37.5 mg day

Tillery, MHC, 2015

NALTREXONE'S OFF LABEL USES

Multiple Sclerosis

- Patients on LDN reported increase in function (Norway 2013)

Crohn's Disease

- Pediatric study 25% achieving remission and 67% only showed mild disease activity after 8 weeks

Fibromyalgia

- Several studies of women on LDN with decrease in pain, increased mood and physical function

Chiang et al, JUCM, 2023

NALTREXONE'S OFF LABEL USES

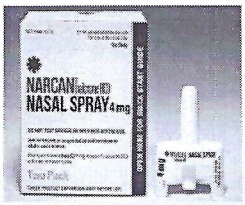
Fibromyalgia

- 99 female fibromyalgia participants followed at the Pain Center of Odense University Hospital in Denmark with minimal NPRS of 4/10
- 49 in the control group (naltrexone 6 mg daily), and 50 in the placebo group
- Followed for 12 weeks
- Change in NPRS was 1.3 in the control group and 0.9 in the placebo group
- Not statistically significant

(Lancet Rheumatology 2023)

NALTREXONE CAUTION

- Is not utilized for opiate overdose
- Highly metabolized by liver, caution with hepatic patients
- Parent drug and metabolite high renal excretion, caution with renal patients
- Start naltrexone with a "naloxone challenge" approx. 3-7 days after last opioid (0.2 mg IV and observe, then 0.6 mg IV
- **Discontinue oral 72 hours prior to surgery; injectable one month prior to surgery**



WHAT ABOUT NALOXONE? PLEASE DO NOT CONFUSE ME WITH NALTREXONE!

- Created in 1961 by Dr Jack Fishman and Dr Mozes Lewenstein for Sankyo Labs
- FDA approved in 1971
- Was originally a schedule II drug, now unscheduled
- Available injection only until nasal spray was FDA approved in 2015

NYS LEGISLATION S2966 EFFECTIVE JUNE 2022

Naloxone co-prescribing is required with **high-risk** opioid prescriptions in the ambulatory setting or upon discharge from acute care.

Should be done annually with the first prescription of the year.

High risk:

- **High dose opiates**
- **H/O OUD/ SUD**
- **Concomitant benzodiazepines**
- **Concomitant sedative hypnotics**

RECENT FDA APPROVALS

Naloxone was FDA approved for over the counter sales Summer 2023 (no Rx)

- RiVive 3 mg nasal spray, Summer 2023
- Generic 4 mg nasal spray from Amneal Pharmaceuticals, Spring 2024

Naloxone was FDA approved as a higher prescription dose in Spring 2023

- Kloxxado 8 mg nasal spray

Nalmefene (opioid antagonist) was FDA approved as a prescription opioid antagonist in Spring 2023. Has been available in the US since 1995.

- Opvee 2.7 mg nasal spray

OVERDOSE AND NALOXONE EDUCATION

NALOXONE

If naloxone is delivered in the community, patient is sent to the hospital for observation 6 - 12 hours.

- Mentally alert, GCS 15
- No further doses of naloxone required
- O2 sat of at least 92%
- RR > 10
- B/P at least 110 - 140/90
- Tolerating liquids PO
- Able to ambulate
- Need a ride home from the hospital

FOR OIC:

BLOCK THE MU RECEPTORS IN THE GI TRACT

Naloxogel (Movantik)

- 12.5 or 25 mg QAM

Also…

Naldemedine (Symproic)

- 0.2 mg PO QAM

NALOXONE'S OFF LABEL USES

Charles Louy, MD, PhD (Cedars Sinai, CA)

- 800 postop patients with pruritis- low dose IV decreased pruritis and nausea without increased pain score
- 97 postop ortho patients with postop urinary retention- low dose IV increased void and decreased catheterizations
- 72 postop colorectal surgery patients- ultra low dose IV added to remifentanil with quicker return of bowel function and decreased LOS

(reported at Pain Week, Sept 2023)

NALOXONE CAUTION

- Will reverse prescription opiates and illicit opiates (heroin, fentanyl); will not reverse xylazine, cocaine, captagon, kratom, khat, ketamine
- Can administer intranasally to pulseless/ breathless patient
- Patient will wake up fast and furious, followed by s/s opioid withdrawal
- No contraindications except known hypersensitivity

THANK YOU!
QUESTIONS?