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Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

BUPRENORPHINE-NALXONE 101

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UNIVERSITY OF WASHINGTON

UW Medicine
UW SCHOOL OF MEDICINE

Integrated Care Training Program
UW Psychiatry & Behavioral Sciences

project ECHO

GENERAL DISCLOSURES

The University of Washington School of Medicine also gratefully acknowledges receipt of educational grant support for this activity from the Washington State Legislature through the Safety-Net Hospital Assessment, working to expand access to psychiatric services throughout Washington State.

SPEAKER DISCLOSURES

- ✓ Any conflicts of interest-none

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OBJECTIVES

1. To describe why one would consider using Buprenorphine-Naloxone to treat OUDs
2. To understand the pharmacology behind Buprenorphine-Naloxone
3. Be enhance your knowledge about using Buprenorphine-Naloxone in your practice

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DATA 2000 WAIVER

- DATA 2000 Waiver NEEDED
- Providers' Clinical Support System
  - PCSSMAT.org webinar for waiver

- ASAM
  - http://www.asam.org/education/live-online-cme/buprenorphine-course

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THE GROUND RULES

- Initial limits: 30 patient
  - 100
    - May request increase after 1 year
  - 275
    - Need waiver treating 100 patients x 1 year
    - 1 or 2 qualifications
      - Additional credential i.e. board certififed ASAM, ABAM, ABMS
      - Qualified practice setting

http://www.samhsa.gov/sites/default/files/programs_campaigns/medication_assisted/understanding-patient-limit275.pdf

WHICH OF THE FOLLOWING IS TRUE?

- There were 42,249 deaths related to opioids in 2016 in the US.
- There were 41,070 deaths related to breast cancer in the US last year.
- There were 44,193 deaths by suicide in 2015.
- 2.1 million people had an opioid use disorder in 2016.
- Overdoses are the leading cause of death of Americans under 50.

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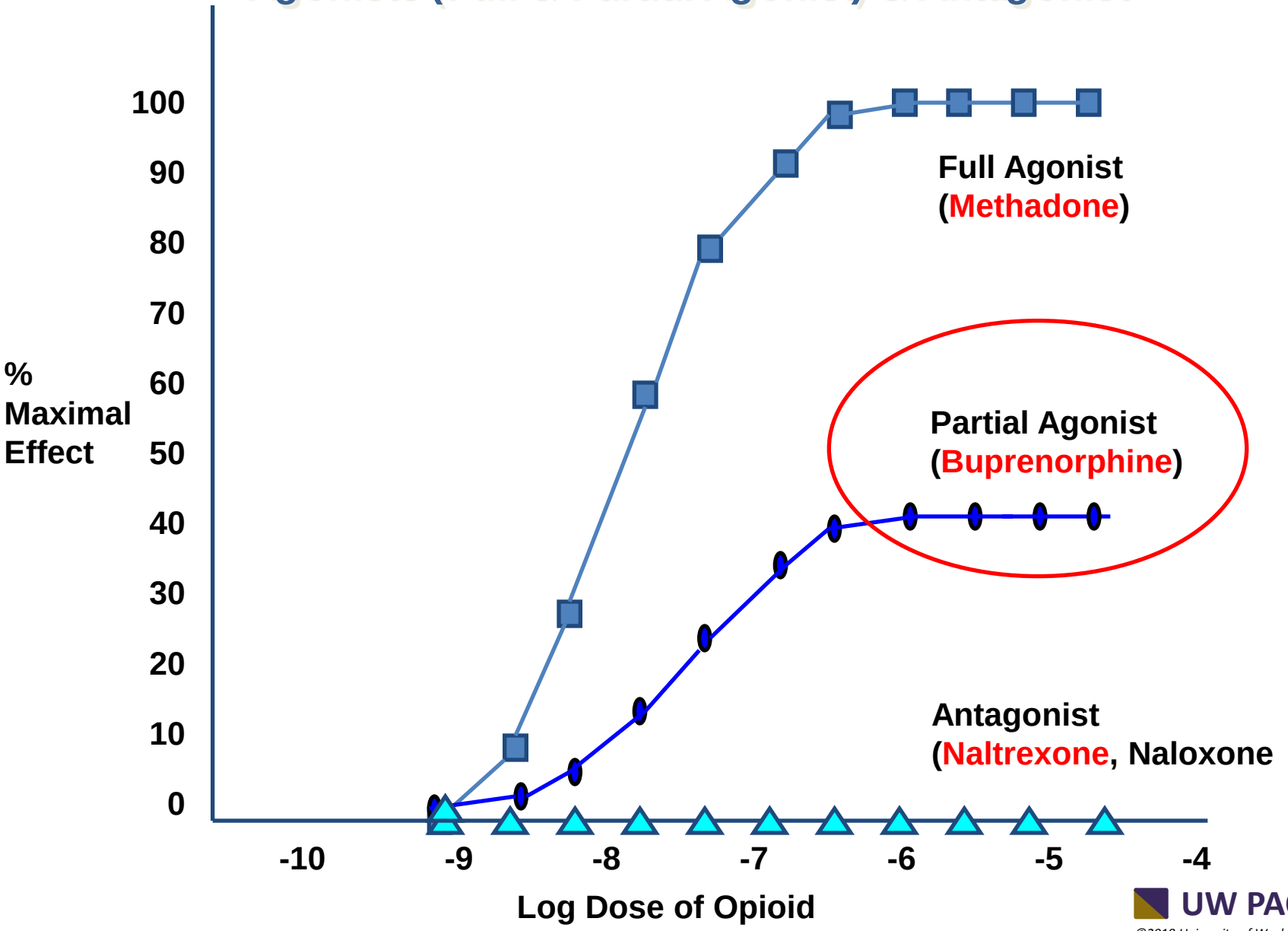
29YO F TO M TRANSGENDER PATIENT WITH A HISTORY OF CONGENITAL ADRENAL HYPERPLASIA, AND REGULAR ED VISITS FOR ADRENAL CRISIS, TRIGGERED BY A CYCLIC VOMITING SYNDROME. USES CANNABIS DAILY, BUT WOULD LIKE TO REDUCE HIS USE. HE HAS BEEN COMING TO THE CLINIC FOR THE PAST 10 YEARS. HE HAS BEEN ON LORAZEPAM PRN FROM HIS OUTSIDE PSYCHIATRIST. DAILY CANNABIS USE. HIS OPIOID USE DISORDER STARTED 6 YEARS AGO WITH PRESCRIPTION OPIOIDS WHICH HE STARTED TAKING DUE TO PAIN. EVENTUALLY TRANSITIONED TO METHADONE WHICH HE WAS GETTING FROM A PAIN DOCTOR. AFTER HIS DOCTOR CLOSED HIS PRACTICE AND LEFT THE COUNTRY HE WENT THROUGH WITHDRAWAL AND STOPPED USING. RETURNED TO DAILY HEROIN USE DUE TO CHRONIC PAIN AFTER 3 YEARS SOBER WITHOUT TREATMENT. HE IS ON DISABILITY AND LIVES AT HOME WITH HIS MOTHER WHO KNOWS ABOUT HIS RETURN TO OPIOIDS AND IS VERY SUPPORTIVE OF HIM GETTING TREATMENT. SHE IS ACCOMPANYING HIM ON HIS VISIT TODAY AND THE PATIENT IS IN OPIOID WITHDRAWAL TODAY. HE WOULD LIKE TO START TREATMENT FOR HIS OPIOID USE DISORDER.

29YO F TO M TRANSGENDER PATIENT WITH A HISTORY OF CONGENITAL ADRENAL HYPERPLASIA, WITH A RECURRENT OUD. DAILY CANNABIS, SPORADIC PRESCRIBED LORAZEPAM. HE WOULD LIKE TO START TREATMENT FOR HIS OPIOID USE DISORDER.

- What treatment would you recommend next?
  - Narcotics Anonymous
  - Buprenorphine-Naloxone
  - Methadone
  - Sublocade
  - EX IM Naltrexone
  - Inpatient Treatment
  - Naloxone Rescue Kit

Medication-assisted Treatment (MAT) Options:

Agonists (Full & Partial Agonist) & Antagonist



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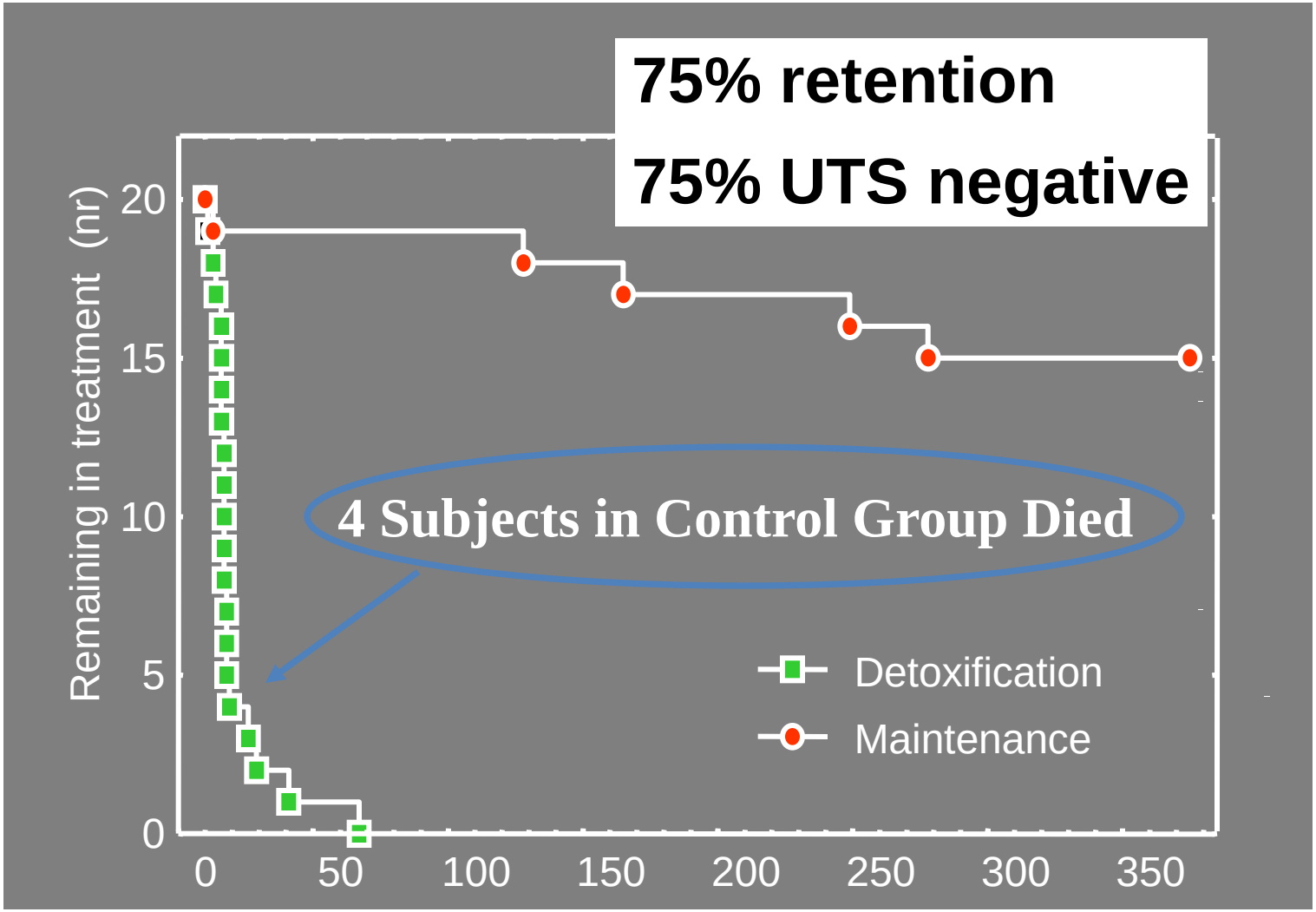
BUPRENORPHINE VS. PLACEBO FOR HEROIN

KAKKO, LANCET



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THE BUPRENORPHINE EFFECT

- Retains patients in treatment
- Reduces illicit opioid use
- Reduces overdose-related deaths
- Reduces medical complications
  - HIV

SAMSHSA TIP 63

BUPRENORPHINE: HOW IT WORKS

- Partial agonist
  - Partially stimulates the opioid receptors in the brain
  - Binds to receptor very tightly!
    - Bup Ki: 0.21 to 1.5
    - Morphine Ki: 1.02 to 4
  - No significant high

- Results
  - *Possible Precipitated withdrawal*
  - Blunts or blocks effects of other opioids
  - Reduces/eliminates cravings
  - *Ceiling effect around respiratory depression*

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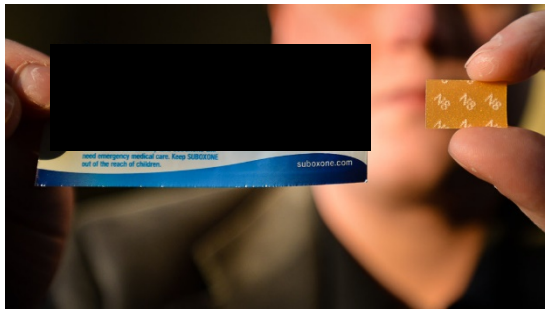
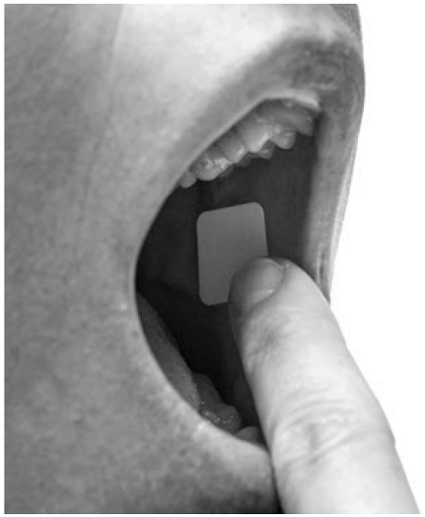
BUPRENORPHINE FORMS

Films (now generic)

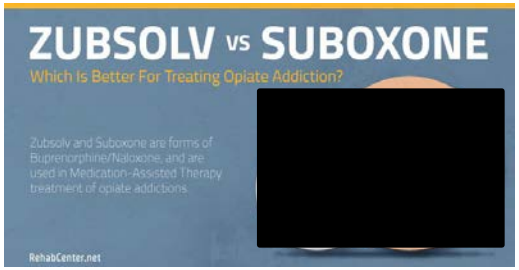


Probuphine Implant

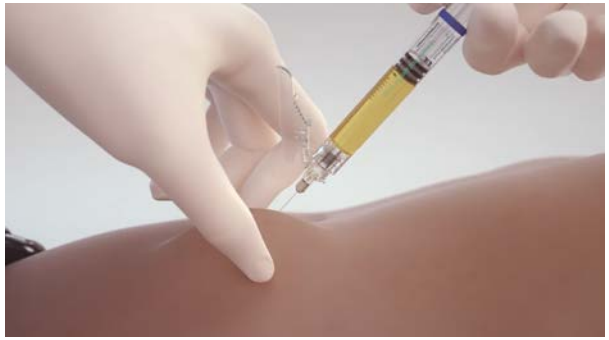
Bunavail Buccal



Tablets



Sublocade depot injection



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BUPRENORPHINE: DETAILS

- Oral Products not well absorbed in the gut
- Max plasma concentration 40min-3.5 hours
- Long duration (24-42 hours)
  - But can start fast due to no effect on breathing
- Metabolized by CYP450 3A4
- Can contribute to serotonin syndrome
- High affinity for μ receptor

Ki Value Range	
Buprenorphine 0.21-1.5	Naltrexone 0.4-0.6
Morphine 1.02-4	Naloxone 1-3
Fentanyl 0.7-1.9	Codeine 65-135

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BUPRENORPHINE-NALOXONE

AKA “Suboxone”

- Naloxone
  - Short-acting opioid blocker added to Buprenorphine
  - Reduces potential for misuse
    - Not absorbed orally or in the gut
    - Will block effects of buprenorphine if injected
  - Allergies are extremely uncommon to Naloxone

BUPRENORPHINE: PATIENT EXPERIENCE

- AE: Oral numbness, constipation, vomiting, decreased attention, insomnia, sweating, headaches, sexual dysfunction, blurred vision, sedation
- No risk of overdose by itself
  - BUT... OD possible if also taking Benzodiazepines, Alcohol, Barbiturates
- "worst withdrawal ever"?
- Less restrictive, but still restrictive

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BUPRENORPHINE: FYI

- Can take once a day, but ok to take multiple times a day
- Emergency pain control may be an issue
- Has some antidepressant and antianxiety effects

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BUPRENORPHINE: PATIENT SELECTION

- 1st Line Treatment
  - Most accessible
  - Solid evidence
  - Pretty easy to start
  - Fairly safe
- *Should be offered to (most) everyone as first option*

- No evidence to predict who will do well
  - If patient has not done well on buprenorphine in the past, you may want to consider other options

- Co-occurring drug use does not rule people out

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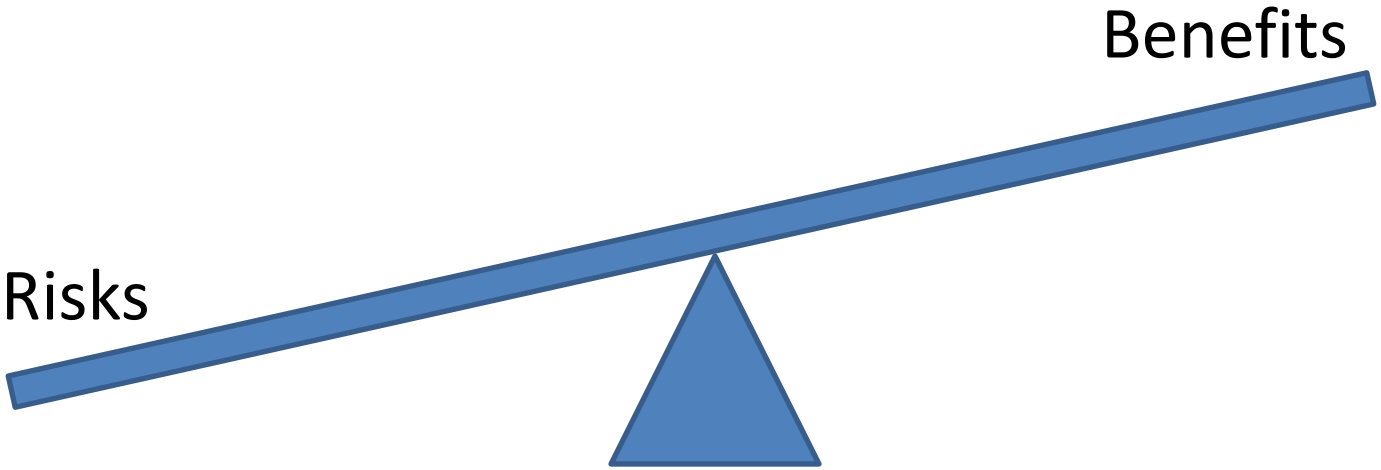
54YO F WITH HISTORY OF CHRONIC PAIN WHO HAD BEEN ON LONG-TERM OPIOID TREATMENT. MULTIPLE MEDICAL PROBLEMS OVER THE YEARS, BUT RECENTLY SOME OF THOSE DIAGNOSES HAVE COME INTO QUESTION, OR SHE HAS GOTTEN BETTER (GASTRIC BYPASS→WT LOSS→NO LONGER NEEDS INSULIN). MEDS INCLUDED: TRANSDERMAL BUP, OXYCONTIN PRN FOR HA'S, PHENOBARB FOR MIGRAINES.

HAD BEEN "STABLE" FOR YEARS. PSYCHOSOCIAL STRESSOR→UTOX NEGATIVE FOR BUP, BUT POSITIVE FOR OTHER DRUGS INCLUDING METHAMPHETAMINE. D/C FROM PAIN CONTRACT, WENT TO PAIN CLINIC DOWN THE ROAD AND SUBSEQUENTLY DISCHARGED FOR METHAMPHETAMINE USE.

REPRESENTED BACK TO PCP WEARING A TRANSDERMAL BUP PATCH IN A CONSPICUOUS AREA ASKING TO BE PUT BACK ON HER PAIN CONTRACT. UTOX: NEG FOR BUP, POSITIVE FOR MORPHINE, FENTANYL, ALCOHOL, OXYCODONE.

- Anything else you would like to know?
- Q: Should the PCP start this patient on Buprenorphine-Naloxone for your OUD?

SHOULD I START TREATMENT FOR AN OPIOID USE DISORDER IN THIS PATIENT?



- No and Yes-her OUD needs to be treated, but you may not be the best setting to do it.
- Recommendation: refer to mental health/addiction treatment center

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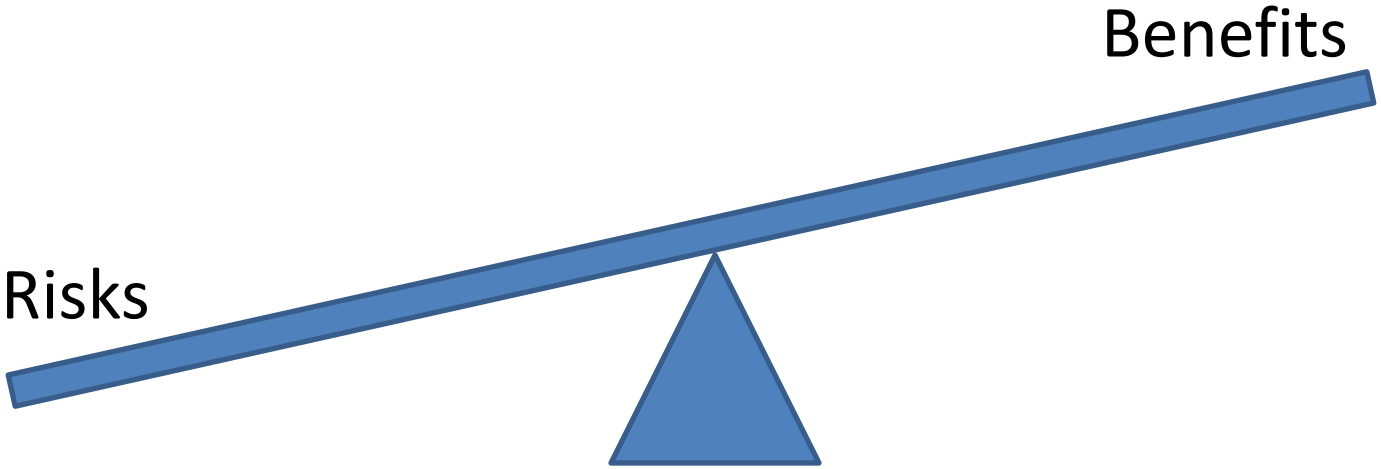
32YO F DISCHARGED FROM METHADONE CLINIC DUE TO MISSING TOO MANY APPOINTMENTS/DOSES AND NOT GOING TO GROUPS. HAD BEEN ON 55MG QDAY. HISTORY OF PTSD, DEPRESSION, AND ANXIETY.

NOW USING OXYCODONE AND HEROIN. HISTORY OF IVDU AND POLYSUBSTANCE USE. ASKS HER PCP IF SHE CAN START BUP-NAL.

- Anything else you would like to know?
- Q: Should the PCP start this patient on Buprenorphine-Naloxone for your OUD?

SHOULD I START TREATMENT FOR AN OPIOID USE DISORDER IN THIS PATIENT?



- Yes.
- Recommendation: offer Bup-Nal treatment. Trouble-shoot transportation issues, leverage family support. Follow-up on mental health issues.

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CONTRAINDICATIONS

- Allergic to medication
- Compromised Respiratory Function
- Hepatic Impairment
  - HCV and its treatment is NOT a contraindication
  - Moderate impairment (Child-Pugh score of 7-9) consider using mono product to avoid precipitating withdrawal
  - Severe impairment (Child-Pugh score 10-15) use mono product

MONITORING OF LIVER FUNCTION TESTS AND HEPATITIS IN PATIENTS RECEIVING BUPRENORPHINE (WITH OR WITHOUT NALOXONE)

- http://pcssnow.org/wp-content/uploads/2014/03/PCSS-MATGuidanceMonitoringLiverFunctionTests-and-HepatitisInBupPatients.Saxon_.pdf

PCSS MAT TRAINING
PROVIDERS' CLINICAL SUPPORT SYSTEM
For Medication Assisted Treatment

PCSS Guidance

Topic: Monitoring of Liver Function Tests and Hepatitis in Patients Receiving Buprenorphine (With or Without Naloxone)

Original Author: Andrew J. Saxon, M.D.

Last Updated: 02/26/2014 (Adam Bisaga M.D.)

Guideline Coverage:
This topic is also partially addressed in Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction (TIP 40), pages 33-34. http://buprenorphine.samhsa.gov/Bup%20Guidelines.pdf

Clinical Questions:
1. How should I monitor liver function tests in patients with or without underlying chronic hepatitis who are receiving buprenorphine for the treatment of opioid dependence?
2. What should I do if a patient receiving buprenorphine does develop evidence of acute hepatitis or worsening chronic hepatitis?

Background:
Early reports of adverse events related to buprenorphine treatment raised concerns about possible hepatotoxicity as some participants showed increases in serum aminotransferase levels (Berson et al., 2001b; Lange et al., 1990). A retrospective study found that patients with a history of hepatitis (but not those without such a history) exhibited statistically significant (but not necessarily clinically meaningful) increases in ALT (median increase=8.5 IU) and AST (median increase=9.5 IU (Petry et al., 2000). In this study, higher buprenorphine doses were associated with greater odds of an increase in AST. Several case reports describe patients with Hepatitis C (HCV) who developed severe, acute hepatitis while injecting buprenorphine or taking it sublingually (Berson et al., 2001b; Herve et al., 2004; Zuin et al., 2009). Some of these patients remained on lower dose buprenorphine or were re-challenged with it without further evidence of liver injury. Based on preclinical studies a mechanism of buprenorphine hepatotoxicity was proposed involving disruption of mitochondrial respiration via proton donation (Berson et al., 2001a).

A recent multi-center study prospectively examined hepatic safety of buprenorphine in 740 opioid dependent individuals who were at high risk for liver disease (Saxon et al., 2013). Median dose was 24 mg and participants were monitored for 24 weeks. While relatively low rates of serious exacerbation of liver injury indices was found a small number of participants (2.1%) had extreme elevations were more likely to have hepatitis seroconversion during the study and were using illicit drugs during the first 8 weeks of treatment suggesting that factors other than exposure to buprenorphine were responsible for observed hepatotoxicity.

In a study in adolescents (14-21yo) treated with buprenorphine for 2 or 12 weeks, liver function tests were collected at baseline and monthly afterwards (Bogenschutz et al., 2010). This study did not find evidence for hepatotoxic effects of buprenorphine. The vast majority of abnormalities seen were mild elevations (<5 upper limit of normal) and elevated values were associated with HCV. Interestingly, in this study rates of elevated transaminases and elevated values were much lower in those maintained on buprenorphine for 12 weeks than in those who received detoxification suggesting that buprenorphine may protect against liver toxicity related to illicit opioids use.

Hepatic safety of buprenorphine was assessed prospectively for 12 months in 303 patients with HIV maintained on antiretroviral medication (Vergara-Rodriguez et al., 2011). In this population of patients at high risk for liver problems, hepatotoxicity attributable to buprenorphine/naloxone was rare at most and limited to patients with concurrent HCV infection. Moreover, no clinically significant interactions with

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BUPRENORPHINE FORMS

Tablets

Suboxone (Generic) • Bup-Nal combo	Zubsolv (Not Generic) • Bup-Nal combo	Subutex (Generic) • Bup only
• Big tab, orange-tasting • Slowly dissolving (several minutes) • Limited (2) dosing options	• Smaller tab, menthol taste • Higher bioavailability • Dissolves faster vs Suboxone Tab • More (5) dosing forms available (0.7mg-11.4) Webster L, 2016	• Reserved for treatment during pregnancy. • Associated with higher rates of injection and diversion Larance B, 2016
"Good Enough"	**"Clinically Equivalent & More Expensive"**	**"Reserved for pregnancy and decreased liver function"**

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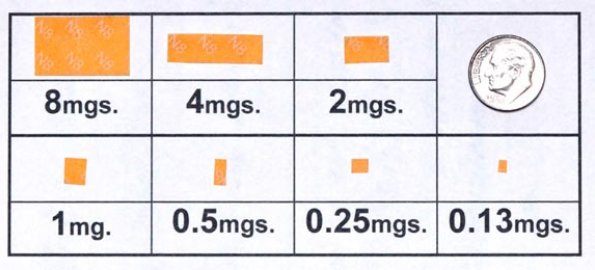
BUPRENORPHINE FORMS

Suboxone Films (FDA approved 1st generic in June 2018)

- Dissolve faster (1min faster)
- Rapid adherence to oral mucosa (good for observed dosing)
- More favorable taste
- Individually wrapped doses-more child resistant and more portable
- Same levels of diversion and misuse as tablets

Larance B, 2016



****"Patient Preferred"****

Bunavail Buccal (not generic)

- Unidirectional absorption of film→limits dose in saliva being swallowed
- Higher bioavailability
- Completely dissolves
- 3 doses available 2.1mg, 4.2mg, 6.3mg (eq to 12mg of oral bup)
- Drug company sponsored studies→effective pain management
- Drug company sponsored→reduced Bup prescriptions and saved money

Alyer R, 2018; Rauck RL, 2015; Sullivan JG, 2015; package insert

"Effective-but not clinically different"

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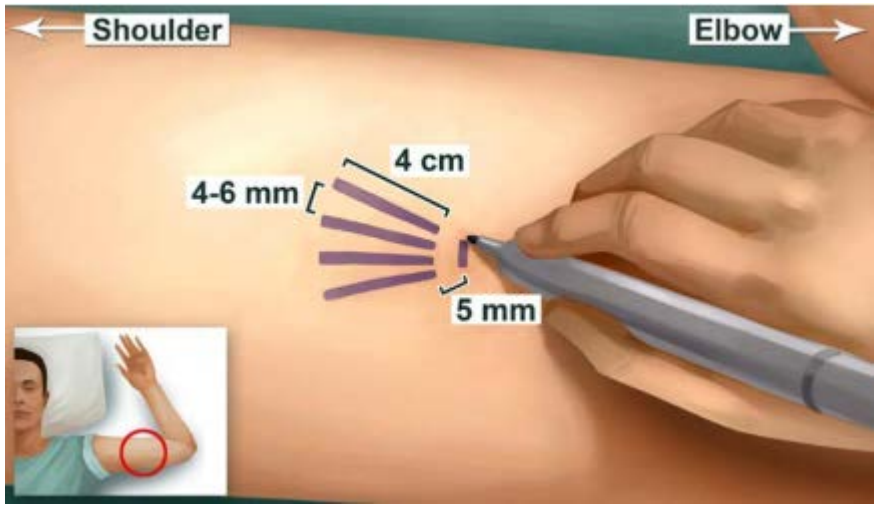
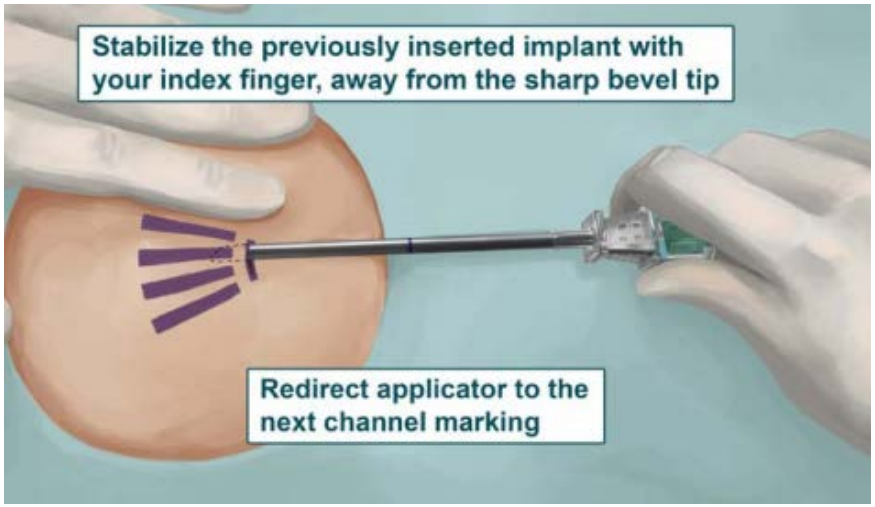
BUPRENORPHINE FORMS

Probuphine
(buprenorphine) implant





Summary:

- No evidence to say its use is better then oral forms
- Cumbersome to use
- Limited duration of treatment

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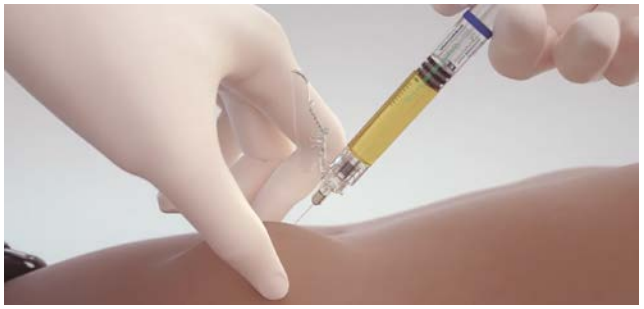
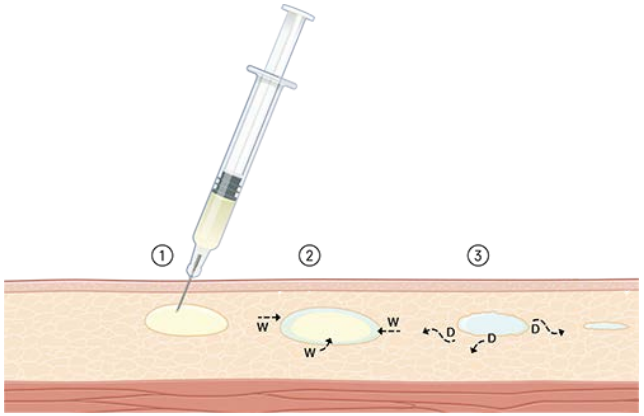
BUPRENORPHINE FORMS

Sublocade
(buprenorphine extended-release)





Summary:

- Drug company sponsored study: Injection vs Bup-Nal SL tablet
  - Not inferior in retention in treatment and negative urine tests
  - Increase reduction in illicit opioid use over the course of the study vs Tablet
- Must be on oral x 7 days
- At steady state (4-6 months) dose (100mg) is about 10% higher than 24mg of oral SL dose
- To use: Need to sign up for Sublocade Risk Evaluation and Mitigation Strategy

Lofwall, MR, 2018; Medical Letter, 2018

PATIENT ASSESSMENT

- Check PMP
- Confirm pt has an opioid use disorder
- Review past OUD treatment
- Other substance use
- Focused physical exam
- Check utox
- Pregnancy test
- Liver function check
- Check for HCV and HIV

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OBTAIN CONSENT

- Their diagnosis
- Risks and benefits
  - They will be dependent on this medication
- Treatment expectations

Treatment agreements can be helpful prompts.

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29YO F TO M TRANSGENDER PATIENT WITH A HISTORY OF CONGENITAL ADRENAL HYPERPLASIA, WITH A RECURRENT OUD. HE WOULD LIKE TO START TREATMENT FOR HIS OPIOID USE DISORDER. HE HAS A SUPPORTIVE MOTHER WHO HAS COME TO HIS APPOINTMENTS AND IS WILLING TO HELP. HIS PCP IS WILLING TO PRESCRIBE HIS BUPRENORPHINE-NALOXONE.

- Would you offer home induction or office induction onto Buprenorphine-Naloxone?
  - Type your answer into the chat feature?

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HOME INDUCTIONS-*OK TO DO THEM*

- Safe and effective
- More comfortable for patient
- Easier for clinic
- Higher risk patients can be seen more frequently
- It is not candy!

Lee, JD, 2014

Lee JD et al, 2009

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WHEN SHOULD I START TREATING?

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Wait as long as possible from your last opioid use before starting Buprenorphine-Naloxone to avoid triggering a severe opioid withdrawal reaction from the medication.

Around 12 hours from your last use of heroin, Oxycontin, Percocet, Vicodin, Oxycodone

Around 24 hours from your last dose of Oxycodone (36 hours for Methadone)

IMPORTANT: You should have at least several of the following *opioid withdrawal symptoms*: enlarged pupils, loss of appetite, bone aches, bad chills, goose pimples, restlessness, runny nose/tearfulness, heavy yawning. If you are having diarrhea, you waited too long.

If you are unsure if you should start, wait longer.

Day 1

Take ½ tablet or film (4mg).

Around 2-3 hours later, if you are still having withdrawal symptoms take an additional ½ tablet/film (4mg). If no withdrawal symptoms. Do not take any more medication for the day after this.

Total Amount Taken on Day 1 _____

****If at any time you think you are having precipitated or triggered withdrawal, call your doctor.****

Day 2

Take the total amount of medication you took on day 1. Either ½ or 1 full tablet/film.

Wait 2-3 hours. If you have withdrawal symptoms take an additional ½ tablet/film (4mg).

Wait another 2-3 hours. If you still have withdrawal symptoms take ½ tablet/film (4mg).

Do not take more than 2 tablets/films (16mg) on day 2.

Total Amount Taken on Day 2 _____

Days 3-7

Take total amount of medication you took on Day 2 until you are seen by your provider.

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INDUCTION IN CONTEXT OF LONG ACTING OPIOIDS

- i.e. methadone
- Should wait 36 hours from the last dose (maybe longer)
- May need additional medications
  - Clonidine
  - Ondansetron
  - Gabapentin
  - Trazodone

PRECIPITATED WITHDRAWAL

- When opioid withdrawal symptoms worsen after the first dose.
  - Often within 1-3 hours

- To consider:
  - Give another dose of Buprenorphine
  - Provide symptomatic treatment

WHAT ARE KEY ELEMENTS TO RETAINING PATIENTS IN TREATMENT?

A. Pre-screening patients for an appropriate level of care
B. Dose of Buprenorphine
C. PHQ9<5
D. Using cannabis daily
E. Unstructured time to make it to all of their appointments

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BUPRENORPHINE DOSE AND STABILITY

Cochrane 2014

- >2mg
  - Increased retention in treatment
- >16mg
  - Reduces illicit opioid use

Comer S, et al, 2001; Fareed A, et al, 2012, Hser Y, et al, 2014

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OPIOIDS: BUPRENORPHINE DOSE AND STABILITY

The START Trial: N=1,267

- > 16mg
  - Less illicit use
  - Increased retention in treatment
    - Hazard Ratio 3.09 for drop out at < 16mg of Buprenorephine

Key Point: People seem to do better at higher doses

Comer S, et al, 2001; Fareed A, et al, 2012, Hser Y, et al, 2014

BUPRENORPHINE GUIDELINES TARGET DOSE

- VA SUD: 12-16mg qday (up to 32mg)
- ASAM: ≥ 8mg
- SAMSHA TIP 63: 16mg
- Australian National Guidelines: evidence 8-16mg, most patients will require 12-24mg (up to 32mg)

OPIOIDS: EARLY STABILITY

The START Trial: N=1,267

- 25% of Bup patients dropped out before 1 mo

- Early regular engagement
  - Weekly check-ins
  - Additional social support
  - "the risk of unstructured time"
    - Clonidine?
  - Be nice!

Kowalczyk, WJ 2017; Hser Y, et al, 2014

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ONGOING TREATMENT AND STABILITY

- Relapse rates off Buprenorphine: 50-90%
  - Maintenance treatment should be continued

- Caution: Patient vs Provider view of treatment success→can lead to premature termination
  - Patient's want to remain in treatment

Bentzley BS et al, 2015

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MONITORING TREATMENT

- Weekly visits at the start
- Regular review of the PMP
- Urine Drug Screens
  - Diversion monitoring
  - Other drugs
  - No set approach
- Pill counts

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MEDICATION MANAGEMENT VISIT

- Elements
  - Review substance use since the last visit
  - Review adherence
  - Advises abstinence
  - Addresses non-abstinence to treatment if indicated
  - Asks about NA or other self-help group and lifestyle issues
  - Asks about pain
  - Makes referrals and asks about previous referrals if indicated
  - Dispenses Buprenorphine

http://ctndisseminationlibrary.org/protocols/0030.pdf

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A CHRONIC DISEASE

- There will be relapses
- Provider clinical support→UW PACC!
- Are they on an adequate dose
- Co-occurring issues?
- Allow for some flexibility

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WA STATE HCA-CLINICAL GUIDELINES

- For Apple Health
- No PA needed for tabs and films
  - Up to 32mg qday (16years and older)
  - Except for Buprenorphine monotherapy
- No limits on duration but...
  - Fill out form 13-333 every 12 months (could be requested)

- https://www.hca.wa.gov/assets/billers-and-providers/Clinical-guidelines-coverage-limitations.pdf

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WA STATE HCA-CLINICAL GUIDELINES

- Must follow these guidelines
  - Need waiver
  - Address mental health and social needs
  - If unable to reduce use and improve function pt should be referred to addiction medicine professional
  - PMP should be reviewed at time of induction, q3 months in first 6 months, and then q6 months
  - Document medical, substance, and psychiatric history
  - Do appropriate level of physical exam
  - No more then 7 day supply at time of induction
  - Urine drug screens should be performed in 1st month of treatment
  - Comanage with addiction or mental health specialist as needed
  - See pt weekly in the first month
  - Obtain at least 2 urine drug screens documenting pt is taking Buprenorphine
  - Prescribed amount varies based in duration in treatment
  - Screen for depression and anxiety twice a year (unless being treated)
  - And there are many others...

- https://www.hca.wa.gov/assets/billers-and-providers/Clinical-guidelines-coverage-limitations.pdf

29YO TRANSGENDER M PATIENT CASE FOLLOW-UP: VOTE ON COURSE OF ILLNESS

a) Stabilized on Buprenorphine 24mg-6mg films. Pain under control but now getting scheduled clonazepam, and has appointment at OHSU for evaluation around transition surgery.

b) Stopped the Buprenorphine, and returned to illicit opioid use because pain was uncontrollable. Cannabis use continued and he eventually dropped out of treatment. No longer living at home.

c) Stabilized on Buprenorphine 24mg-6mg films. Lost tip of 4th digit on R hand in the timing belt of his car, but pain was managed well with nerve block, NSAIDs, and Acetaminophen. Living with mother still.

d) Still on buprenorphine and has stopped using opioids. Benzo use is sporadic and he continues to use cannabis daily. He is now managing an apartment complex with his supportive mother.

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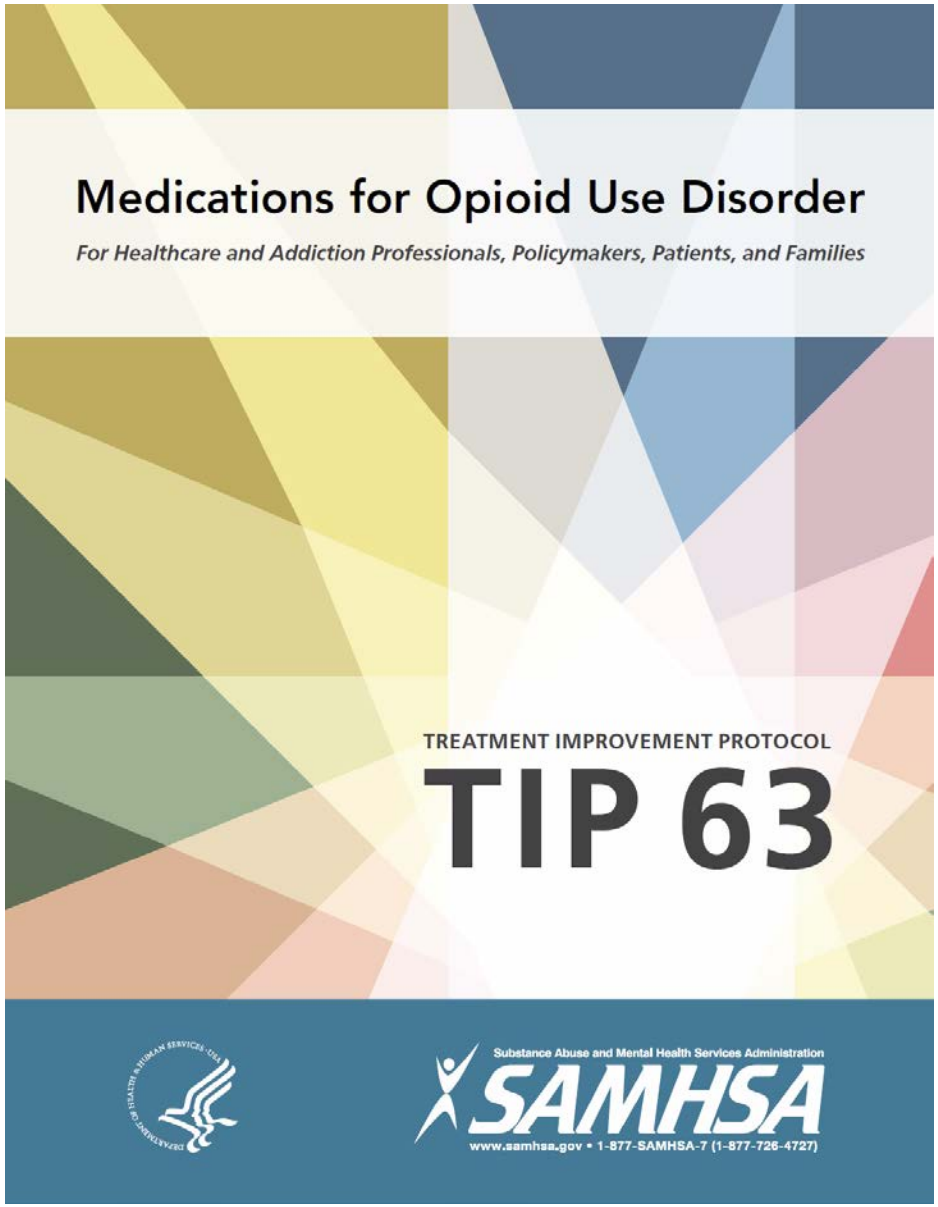
RESOURCES

https://store.samhsa.gov/product/TIP-63-Medications-for-Opioid-Use-Disorder-Full-Document-Including-Executive-Summary-and-Parts-1-5-/SMA18-5063FULLDOC



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RESOURCES

- Treatment Improvement Protocol 40
  - Clinical Guidelines for the Use of Buprenophine in the Treatment of Opioid Addiction
    - http://www.store.samhsa.gov/product/TIP-40-Clinical-Guidelines-for-the-Use-of-Buprenorphine-in-the-Treatment-of-Opioid-Addiction/SMA07-3939
- ASAM Practice Guidelines
  - http://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf
- VA/DOD Treatment Guidelines
  - http://www.healthquality.va.gov/guidelines/MH/sud/