Buprenorphine for Pain

Why and How?

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Buprenorphine, the History

- Discovered in 1966 in England, looking for alternative tx's for addiction through antagonists or partial agonists.
- Late 1990 with 1-2 million needing opioid addiction tx and only 150,000 able to receive methadone tx.
  - Needing office based tx
- Trials in USA for addiction, in 2000 -2002 successful
- FDA approval in 2002 for opioid addiction, office based
  - 8 hrs or training for MD Waiver
- Limits of 30 patients initially, then to 100 and now to 275 per provider in 2016
- PA/NP approval in 2018,
  - 24 hrs of training required for Waiver

Buprenorphine

- Partial agonist at Mu
  - high affinity with slow dissociation
- Strong antagonist at Kappa
- 25-100x more potent than morphine
- Sublingual and transdermal (highly lipophilic)
- Bioavailable (relative to IV)
  - 70% IM, 55% buccal, 30%SL, 15% TD
- Half life in hours
  - 2.2-3 IV, 27.6 buccal, 37 SL, 26 TD (depot effect)
- QT prolongation
  - X4 less than methadone

Khanna 2015, McNicholas 2004

Buprenorphine, Just Remember!!

1. **Very high affinity for Mu**
   - Will dominate at the receptor
2. **Partial Agonist**
   - Will activate receptor only partially

1+2 = Precipitated withdrawal
   - But only if already on other opioids
   - Is etiology to any w/d, not naloxone

- Long Half life 28-37 hrs (SL)
- Incomplete reversal by naloxone

Buprenorphine: FDA Approvals

- Addiction
  - With Naloxone
    - Suboxone
    - Bunavail
    - Zubsolv
  - Without Naloxone
    - Subutex
      - (least expensive)
  - Parenteral
    - Sublocade (implant)
    - Probuphine (implant)
    - Buprenex (IV)
- Pain
  - Butrans (TD)
  - Belbuca (buccal)

Benefits of Buprenorphine

Reduced Risk Of	Benefits
Respiratory failure Constipation Renal failure ◦ Stable blood levels Cognitive impact Immunosuppression Hormone suppression QTc ◦ Less than methadone	Pain management ◦ 25/26 trials positive ◦ Not partial analgesic Neuropathic pain Antihyperalgesic Antidepressant

Buprenorphine On-Label in Pain

FDA approved for pain

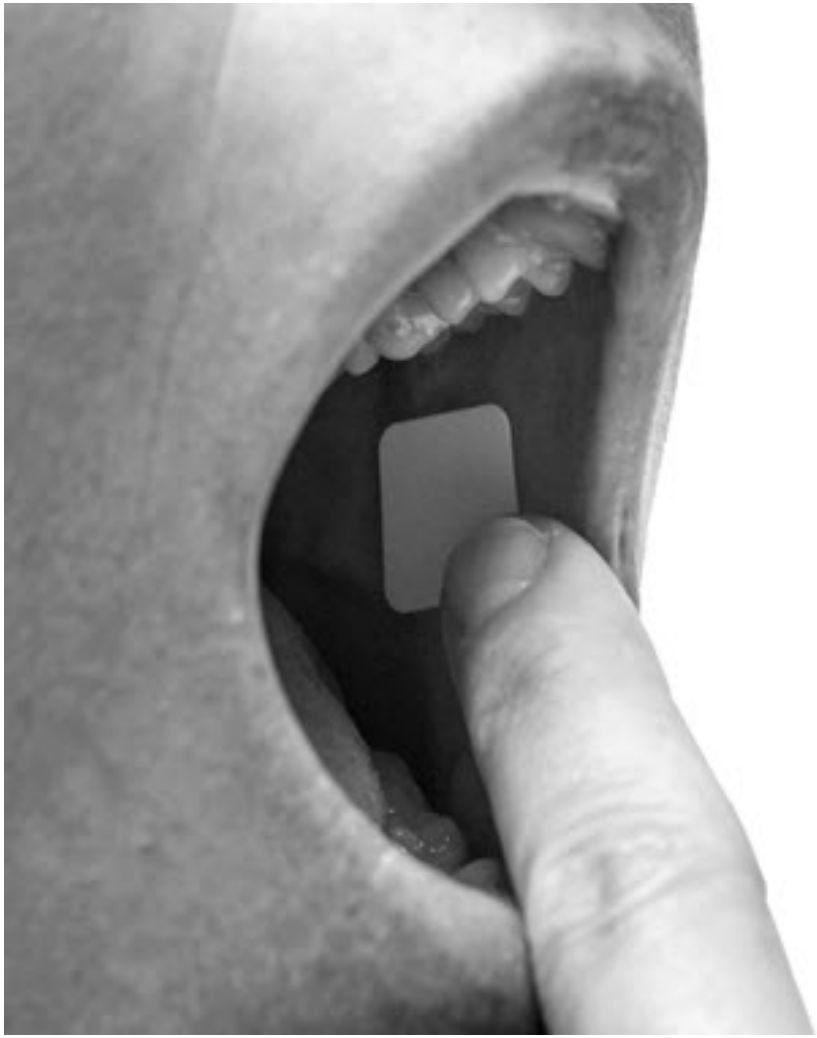
- Butrans
  - FDA approve in 2013
  - Patch technology
    - 5, 7.5, 10, 15 and 20 mcg/hr
    - 7 day patch
- Belbuca
  - FDA approved 10/2015
  - Buccal patch, dissolving
  - 75 to 900 mcg patches

Butrans

- Transdermal patch
- Mcg/hr doses of 5, 7.5, 10, 15, 20
- Starting dose:
  - 5 mcg
    - if <30mg MEQ previous
  - 10mcg
    - if 30-80 MEQ previous

Belbuca

- Buprenorphine buccal film
- MCG doses of 75, 150, 300, 450, 600, 750, 900
- For bid dosing
- Starting dose depends on previous MME



Belbuca Dosing

MSE dose prior to tapering to 30 mg

- Less than 30 mg oral MSE
- 30–89 mg oral MSE
- 90–160 mg oral MSE
- Greater than 160 mg oral MSE

Starting dose

- 75 mcg every 12 hrs
- 150 mcg every 12 hrs
- 300 mcg every 12 hrs
- Consider alternative tx

Buprenorphine Off-Label in Pain

- Clinical application
  - First line opioid pain tx
  - Pain medication misuse
  - Comorbid medication use (benzo, etc)
  - MRJ and ETOH use
  - Previous potential SUD
  - Active SUD
- Death rate low
  - Cultural safety
- Mono vs dual product
- Buprenorphine cost on Good Rx

USDHHS 2019

Buprenorphine Off-Label in Pain

No waiver needed, for "disease of pain" when using Suboxone/Subutex off label

- Educate about "precipitated withdrawal"
  - Not naloxone effect
  - Not reversible
  - Consider test dose
- Start when COWS score mild to moderate (10-13)
  - If on other opioids
- Suggest 1-2mg bid start if opioid naïve

TABLE 7

COWS

Symptoms	*Scores*	*Examples*
Resting pulse rate	0-4	0=80 or less; 1= 81-100; 2=101-120; 4=120 or greater
Sweating	0-4	0=none; 4=sweat streaming from face
Restlessness	0-5	0=sits still; 5=unable to sit still (even for a few seconds)
Pupil size	0-5	0=normal; 5=dilated (only iris rim visible)
Bone or joint aches	0-4	0=none; 4=severe discomfort
Runny nose or tearing	0-4	0=none; 4=constant
GI upset	0-5	0=none; 5=multiple episodes of vomiting or diarrhea
Tremor	0-4	0=none; 4=gross tremor
Yawning	0-4	0=none; 4=yawning several times/minute
Anxiety & Irritibility	0-4	0=none; 4=severe, precluding participation
Gooseflesh skin	0-5	0=smooth; 5=prominent piloerection

COWS=Clinical Opiate Withdrawal Scale; GI=gastrointestinal.

Score: 5-12 mild; 13-24=moderate; 25-36=severe.

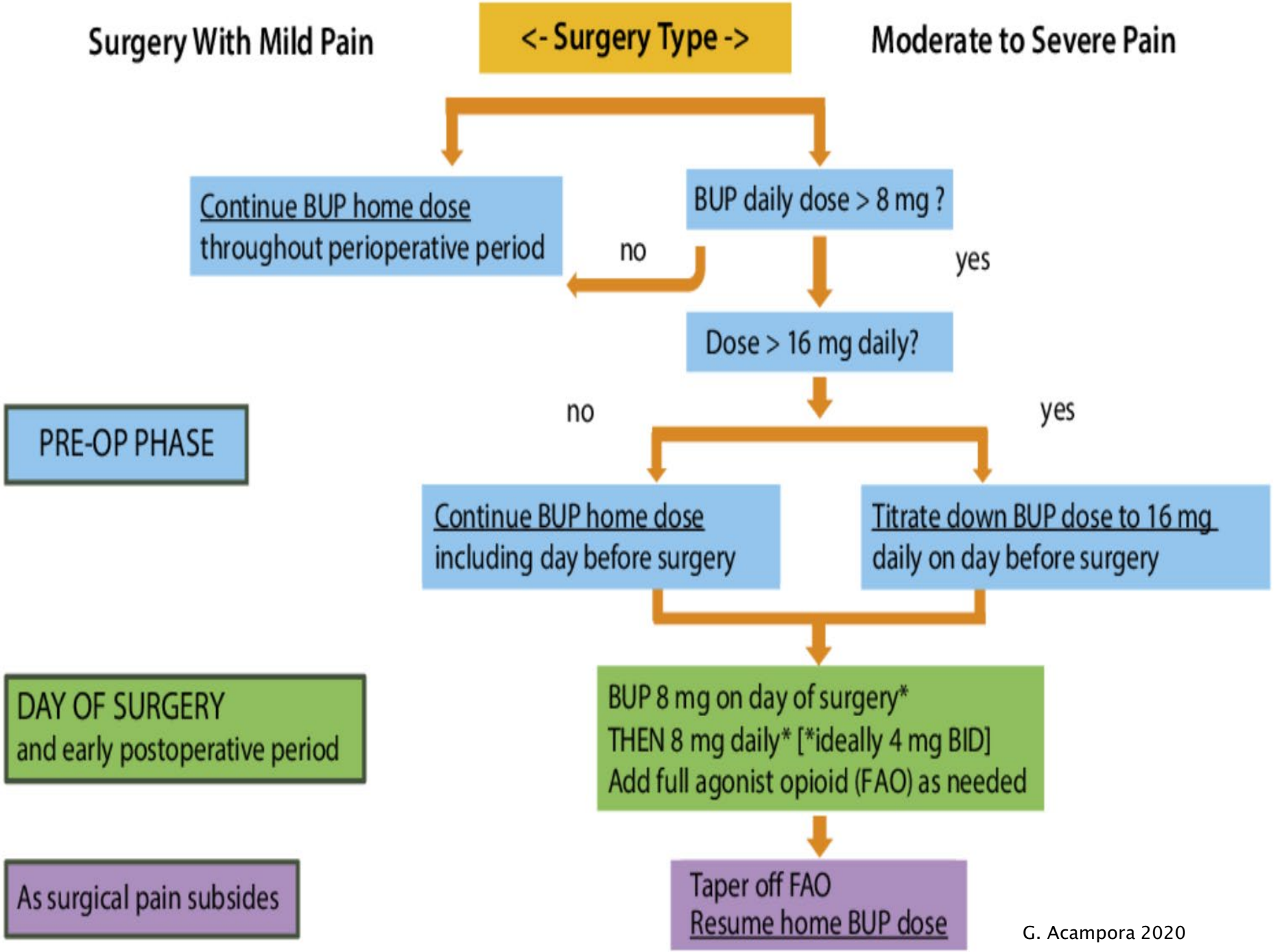
Baron D, Garbely J, Boyd RL. *Primary Psychiatry.* Vol 16, No 9. 2009.

Buprenorphine Induction

- Induction for Suboxone or Subutex
  - STOP full agonist, wait for COWS of >10, then….

Find dose that reverses withdrawal (the* only *initial target)

  - Day 1…. 4mg initial dose,
    - IF NEED, may dose every 2 hrs at 2-4mg
    - Total max of 12 mg if need
  - Day 2…. Give dose that reversed w/d (if found)
    - That is now the daily dose, may split it if need
    - If w/d not reversed on 12mg day 1, then start with 12mg day 2
    - Add 4mg in 2 hrs
    - Total max dose of 16mg day 2-5
  - Common first day dose is 8mg
  - 16mg most common SUD tx dose
  - 32mg max effective dose


Surgery With Mild Pain
<- Surgery Type ->
Moderate to Severe Pain
Continue BUP home dose
throughout perioperative period
BUP daily dose > 8 mg ?
no
yes
Dose > 16 mg daily?
PRE-OP PHASE
no
yes
Continue BUP home dose
including day before surgery
Titrate down BUP dose to 16 mg
daily on day before surgery
DAY OF SURGERY
and early postoperative period
BUP 8 mg on day of surgery*
THEN 8 mg daily* [*ideally 4 mg BID]
Add full agonist opioid (FAO) as needed
As surgical pain subsides
Taper off FAO
Resume home BUP dose
G. Acampora 2020

Buprenorphine News

- Micro-Induction of Buprenorphine
  - Low dose (.5mg or less) with ongoing opioid
  - W/D to start induction not needed
    - Micro dose does not cause w/d
  - Helps with higher MME transitions
- Macro-Induction of Buprenorphine
  - High first dose start, 12-28mg
  - Study in ED for OUD
    - Dosing 12-28mg
    - No respiratory or sedation issues
    - Precip w/d in 5/391 cases
    - N/V in 2-6%

Buprenorphine Microinduction

- Controversial and minimal data
- Avoids precipitated withdrawal
- No clear ‘best protocol’ yet
- Starting dose .2-.5mg most common
  - Daily, bid to qid
- Full agonist continues
  - Hydromorphone bridge
  - SL or TD bup products
- Inductions complete in 3-10 days mostly

Microinduction Buprenorphine

- Review 2020
  - 18 papers, 63 patients
  - Initial dose .2-.5mg buprenorphine
  - Final dose 8-16 mg
  - Transition over 4-8 days most common
    - Range 3-112 days
  - Variety of opioids, no significant w/d sx's
  - Cross taper vs dropping opioid

Ahmed 2020

Buprenorphine Microinduction

- Becker and Frank (Becker et al., 2020) reporting on 6 inpatient cases of microdosing induction from full agonists various types. No withdrawal sx's during transition

- 5-day microdosing
  - 0.5mg bid day 1
  - 1mg bid mg on day 2
  - 1mg tid mg on day 3
  - 3mg bid on day 4
  - 3mg qid on day 5 and DC full agonist

University of Minnesota

Outpatient

- Day 1 .5mg
- Day 2 .5mg bid
- Day 3 1mg bid
- Day 4 2mg bid
- Day 5 4mg bid
- Day 6 8mg bid

Inpatient w/ Pain

- Day 1 75mcg qid
- Day 2 150mcg qid
- Day 3 450mcg qid
- Day 4 1mg qid
- Day 5 4mg bid
- Day 6 8mg bid
  - taper or DC other opioid

Microinduction Example

Day	Buprenorphine-Naloxone (Only Buprenorphine Dosage Listed)	Controlled-Release Oxycodone Dosage
1	0.5 mg twice daily*	80 mg 3 times daily
2	1 mg twice daily†	80 mg 3 times daily
3	1 mg 3 times daily†	80 mg 3 times daily
4	2 mg 3 times daily	80 mg twice daily
5	4 mg 3 times daily	None
≥6	Adjust dose to symptoms	None

Hämmig et al., 2016; Payler, 2016; Caulfield et al., 2020; Crane et al., 2020; Rozylo et al., 2020).

UNC; Macro vs Micro Induction

Outpatient

- Day 1("in lot of w/d")
  - 16mg
  - 8mg repeat 1 hr
    - If needed
- Day 2
  - 24mg
- Day 3 or 4
  - 16mg

Inpatient

- Day 1 .5mg
- Day 2 .5mg bid
- Day 3 1mg bid
- Day 4 2mg bid
- Day 5 4mg bid
- Day 6 8mg bid

Robyn Jordan 2022 unpublished

Macroinduction in the ED

- High-Dose Buprenorphine in ED for OUD
  - Dosing 12-28mg
  - No respiratory or sedation issues
  - Precip w/d in 5/391 cases
  - N/V in 2-6%

- Effective tx of W/D in the ED
  - Post OD tx
  - Decreases OD risk for 1-2 days due to kinetics

Edwards 2020

Do I use Bup Now?

Thinking Through

Difficult Cases

Buprenorphine in Chronic Pain

- Clinical application
  - Use any time you feel med behaviors are truly dangerous
  - First line opioid pain tx
  - Higher risk medication use
    - Opioid misuse
    - Comorbid medication use (benzo, etc)
    - Impulsivity
    - Dysfunctional medication effects
  - Illicit substance use
    - MRJ and ETOH use
    - Previous potential SUD
    - Active SUD
- Death rate low
  - Cultural safety
- Mono vs dual product
- Buprenorphine cost on Good Rx

USDHHS 2019

Difficult Conversations

Relate everything to safety (self or culture) or function

- Never about you, Med Board, CDC, etc.
  - "We have new data now"
- Includes…….
  - UDS failures
    - Substances or additional medication
  - When limiting/stopping meds
    - Cultural or patient safety
  - Asking for too aggressive of treatment
    - Realistic expectations
    - "More" can be dangerous

Helpful Clinical Approach

- Curious, not authoritarian
  - Normalize misuse behaviors
    - Directions on bottle is not reality of CNCP
  - Let them teach you
  - Don't play 'gotcha'
- Collaborative
  - Shared decision-making
  - Safety may dictate unilateral tx
    - Cultural and personal
- Clear limits
  - Football field analogy
- Bilateral transparency
  - Intentions and goals clear and mutual
  - "Don't teach me that you aren't truthful"

Opioid MISUSE

- Rate in last year for 2020, SAMHSA
  - 3.3% (9.3mil)
    - 1.1% drop from 2017
  - **<u>80% say misuse is for pain, tension, sleep, or mood</u>**
    - 12% say they use to "get high or feel good," 2.3% "hooked"
    - 64% pain
- Rate in Pain and Primary Care (review of 38 studies)
  - 21-29% with misuse

2017 NSDUH Report, Vowles 2015

- Misuse is not SUD

Substance Related Disorders

- Pharmacological indicators
  - Tolerance
  - withdrawal
- Impaired control
  - Greater amount and longer use
  - Unable to quit
  - Time to obtain extensive
  - Craving
- Social impairment
  - Role failure
  - Use with known social harm
  - Social loss due to use
- Risky use
  - Use in spite of physical danger
  - Use with continued psych/social harm

Severity score

-Mild (2-3)

-Moderate (4-5)

-Severe (6 and more)

Opioid Misuse

- Substance Use Disorder? (SUD/OUD)
  - Can be very difficult to differentiate from misuse
  - SUD in chronic pain
    - 8-12% in CNCP and 7-8% gen population
  - Return to criteria for SUD dx
- Misuse is not SUD
  - 80% for pain or other sx's we would tx
- Be CURIOUS as to reason for misuse
  - When, why, hoped for what outcome?
    - Use questions not statements
  - Let them teach you why they are doing this
    - Normalize the behavior
    - Atypical med reactions common
  - Authoritarian intervention usually not therapeutic

Impulsivity

- Common clinical problem
  - Most common etiology in med misuse
- Found in many disorders (state sx)
  - Mood, anxiety, SUD, ADHD, chronic pain, etc
- Personality most common factor (trait sx)
  - Cluster A, B, C
  - Emotional decision making
    - Not trying to trick you
  - Stable, like personality
  - Predictable thus treatable

Dysfunctional Medication Responses

- Atypical medication reactions
  - Expect sedation, get stimulation
    - Opioids, topiramate, pregabalin, benzodiazepines, etc.
  - Expect stimulation, get sedation
    - Stimulants, NE agents, etc.
- Typical med reactions causing dysfunction
  - Gabapentin, pregabalin, benzo, muscle relax, opioids
- Cognitive impact opioids vs pain
  - Cognitive dysfunction high w/ pain alone
  - Memory, fatigue, etc
- Generic medications

CPOD
Complex Persistent Opioid Dependence

Ballantyne MD in 2012, Washington State

- Opioid tapering, patients manifesting
  - Pain increase
    - With aberrant behaviors
  - Declining function
  - Psychiatric instability
    - Depression, anxiety, insomnia, anhedonia
- Arising slowly after LTOT
- Not responsive to usual treatments
  - Buprenorphine as tx
- Not addiction (OUD)
  - Does not meet criteria, in context of pain

Opioid Misuse Scenarios; “Short”

Patient short on medication, again!

- Curious as to why, when, how much, etc.
- Potential reasons (decreasing order)
  - Pain control
  - Impulsivity
  - Poor memory
  - OUD
  - Selling
- Intervention
  - 3 bottle system
  - Reduced availability
    - Partner holding, shorter scripts
  - Fully random UDS/pill count

3 Bottle System

- Bottle #1
  - Stock Bottle
  - From the pharmacy
  - Touch once per day to fill bottle #2 (daily), put away
- Bottle #2
  - Daily Bottle
  - Filled only with daily amount as per script
  - Keep on your person, safely
- Bottle #3
  - OMG Bottle
  - Filled with any pills leftover in #2
  - Keep with stock bottle
  - Can use ONLY from here if prn higher need
    - But only if pills present
    - Encourages ‘paying self forward’ for prn need

Opioid Misuse Scenarios; UDS With Additional Meds

UDS with meds not currently prescribed

- Curious as to reason
- Common reasons
  - Misuse, then to previous slide (pain, mood, etc)
  - Impulsivity
  - "Have to have"
    - SUD vs misuse of other medication
  - Other prescriber
- Intervention
  - Clarification of med list or prescribing roles
  - Limitation of current meds if dangerous
  - Medication destruction of old scripts
    - House sweeps by others

Opioid Misuse; What to do?

Use as cue to Functional Need!
May be the reason the taper is failing

- Opioid stim
  - Treating depression or ADHD?
  - Helping them function?
  - (Careful with sleep aides if opioids stim)
- Opioid sedation
  - Treating anxiety?
  - Sleeping aide?
- Misuse as cue about what they feel is needed
  - So, replace it
  - Likely not SUD

Opioid Misuse Scenarios; UDS With Illicit Substance

- Curious as to reason
  - What, why, when, quantity, hx of, etc
- Common reasons
  - Long hx of use, intermittent
  - Potential SUD
  - Impulsivity
  - “Have to have”
    - SUD vs misuse
- Intervention
  - MRJ and ETOH
    - Have clinic protocol
    - CBD vs THC in UDS
  - Cocaine, fentanyl, MS
    - Rare social use vs SUD
  - Bup in parallel
  - Cultural safety maintained

Opioid Misuse: Pearls

- Morphine and/or fentanyl = heroin
  - Fentanyl in many illicit products now
- Metabolites not present in UDS confirmation
  - Just took pill
  - Dipped pill
  - Not tested for
  - P450 issue
- Pill count accuracy suspect
  - Pills available for count, street contract

Difficult Case; Potential Solutions

- Atypical opioid
  - **Buprenorphine**, mico vs macro induction
  - Tramadol, tapentadol
  - May be mandated for safety
- Medication dispensing
  - Weekly, biweekly, family member
  - 3 bottle system
- Collateral information
  - May be mandated before obtaining ongoing scripts
- Psychotherapy
  - May be mandated in some situations

Misuse? Abuse? Not Sure?

- Send for SUD evaluation
  - They will apply criteria
  - Best if it is someone that understands both pain and opioids
- Choose safer opioid
  - Tramadol
  - Tapentadol
  - Buprenorphine

CONTACT INFORMATION

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- Accepting patients currently
- Telehealth available across North Carolina
- If interested in ongoing case conference, please contact me

THANK YOU