UNDERUTILIZED DRUG THERAPIES IN PAIN MANAGEMENT

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Disclosures

- I have no financial relationships to disclose related to any content within this presentation.
- Content includes discussion of off-label medication use

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Learning Objectives

- Describe the unique pharmacology of buprenorphine
- Explain the role of ketamine in pain management, especially in regards to opioid tolerance
- Identify patients on chronic opioid therapy who may benefit from transitioning to alternative therapies

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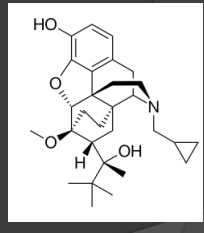
Buprenorphine

- Indications and formulations
- Pharmacology
  - Implications of unique receptor activity
- Common misconceptions
- Equianalgesic conversions



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What is Buprenorphine?

- Opioid medication used for:
  - Acute Pain
  - Chronic Pain
  - Opioid Use Disorder
- Formulated as:
  - Sublingual film*
  - Sublingual tablet*
    - With or without added naloxone
  - Transdermal patch
  - Buccal film
  - Injectable solution*

Labeled Indication	Formulation Product
Treatment of Opioid Dependence	Sublingual Film Sublingual Tablet
Pain Management	Transdermal Patch Buccal Film Injectable Solution

*Generic available. Note that all generically available formulations relevant to outpatient setting are not labeled for pain management

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Buprenorphine Pharmacology Overview

- Mu opioid receptor
  - Partial agonist
  - High binding affinity
- Kappa opioid receptor
  - Antagonist
- Nociceptin receptor
  - Agonist (weak)
- Plasma elimination half-life
  - SL/buccal: 26-37 hours
    - Depot effect
  - Clinically, duration of analgesia typically 6-12 hours
- CYP3A4 metabolism to weakly active metabolite
  - Reduce initial dose by 50% in severe hepatic impairment
  - No dose adjustment for renal impairment

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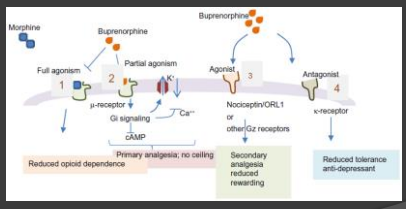
Receptor Activity



Pillarisetti SKhanna I. Buprenorphine: an attractive opioid with underutilized potential in treatment of chronic pain. *Journal of Pain Research*. 2015:859

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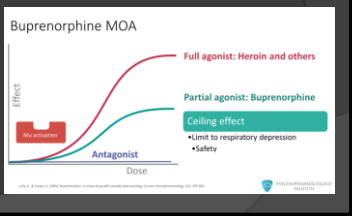
Mu Receptor Partial Agonism

- Does not imply buprenorphine is less effective than full agonist therapy for pain management

- What about the "ceiling effect"?
  - Varies by physiologic effect
    - Demonstrated for respiratory depression and euphoria
    - Does not appear to be a clinically relevant issue for analgesia



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Analgesic Ceiling Effect

- Has not been demonstrated clinically
- In 2007 study by Mercadante et al., 10 cancer patients with uncontrolled pain on 70mcg/hr buprenorphine patch were titrated to a possible maximum of 140mcg/hr (equivalent to ~300mg oral morphine)
  - 6/10 patients achieved adequate pain control
    - 4/10 did not achieve pain control; all were rotated to full agonist opioids and required the equivalent of 400-600mg oral morphine
- Further case reports

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Precipitated Withdrawal

- Sudden onset of withdrawal symptoms after administration of buprenorphine to an opioid dependent patient
  - Potentially explained by high binding affinity resulting in displacement of existing ligands
- Rationale for waiting until onset of opioid withdrawal symptoms prior to first dose of buprenorphine
  - May be overstated in pain management contexts

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Kappa Receptor Antagonism

- Potential reversal of hyperalgesia
  - Dynorphin: endogenous kappa agonist implicated in pain sensitization
- May be significant driver of improved pain control seen after rotation to buprenorphine
- Anti-depressant effects
- More evidence needed to determine role conclusively

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Nociceptin Receptor Agonism

- Reduced reward pathway activation
- Analgesic effects
- Only currently approved drug for human use with known nociceptin activity
  - Poor bioavailability has prevented development of marketable pure nociceptin agonists
  - Unclear if buprenorphine is sufficiently active at this receptor to meaningfully contribute to clinical effects

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Pharmacology Take-Home/Recap

- Summary of receptor activity
  - 1) Partial mu agonism
    - Improved safety profile without impacting analgesic efficacy
  - 2) Kappa antagonism
    - Hyperalgesia reversal
  - 3) Weak nociceptin agonism
    - May inhibit reward pathway activation
    - May add to analgesic effect

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Opioid "Blockade"

- Buprenorphine use does not preclude the use of full agonist opioids for breakthrough pain
  - However: account for high opioid tolerance and dose proportionally
- 2006 study by Mercadante et al. demonstrated effectiveness of IV morphine for breakthrough pain in 29 cancer patients maintained on transdermal buprenorphine for basal pain control
  - Breakthrough dosing proportional to baseline opioid regimen
    - 20% of baseline regimen given as IV morphine per breakthrough pain event
    - Patients were maintained on patch strengths up to 70mcg/hr
  - 92% of breakthrough events were successfully treated with IV morphine

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Lipophilicity

- Lipophilic opioid options are limited
  - Fentanyl
  - Methadone
  - Buprenorphine
- Why do we care? ⇒ Sublingual absorption!
  - Immensely useful when oral administration is not reliable
    - Small bowel obstruction
    - NG tube to suction
    - Extent of GI function is unclear
  - When long-acting opioid desirable in patients who are g-tube dependent

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Buprenorphine Limitations

- Dose limitations of buprenorphine in patients with very high opioid requirements
  - Practically speaking, daily doses above 32mg become problematic due to pill burden
    - Successfully transitioning from extreme doses of opioids would also be impractical beyond ~400mg oral morphine equivalents
  - The 'ceiling effect' may also arise as a real issue for analgesia at extreme doses
- Not every patient responds well to every opioid for unclear reasons

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Equianalgesic Conversions

- Controversial
  - Not typically listed in standard equianalgesic tables
- Best evidence from transdermal patch studies
  - 70-115mg:1mg ratio of TD buprenorphine to oral morphine

Product	Dose	24-hour dose total	Oral Morphine Equivalents/24 hours
Transdermal Patch	20µg/hr	480µg (~0.5mg)	35-55mg

  - Extrapolated to other formulations based on bioavailability:

Product	Dose	Bioavailability	Approximate systemically available dose	**Extrapolated** Oral Morphine Equivalents
Sublingual Tablet	8mg	15-25%	1200-2000µg	85-230mg
Buccal Film	150µg	46-65%	70-100µg	Very limited data (5mg-25mg)

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Equianalgesic Tables

- Oversimplification of significant interpatient variability
  - Extent of absorption
  - Differences in metabolism
    - Genetic (including 2D6)
    - Drug or food interactions
- Variance among tables
  - Difference in opinion about where to draw the line to create a useful table

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Buprenorphine

- Questions?

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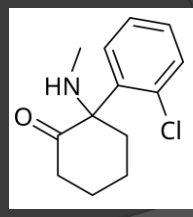
Ketamine

- Approved for use as anesthetic agent
- Sometimes used off-label at low doses for pain management
  - Most commonly administered as continuous IV infusion
  - Active in PO form, however no commercially available PO formulations



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Ketamine Pharmacology

- Potent N-methyl-D-aspartate (NMDA) receptor antagonist
- Hepatically metabolized with significant first-pass effect
  - Parent drug has low oral bioavailability
  - Limited and indirect evidence regarding analgesic activity of ketamine metabolite **norketamine**
    - Appears to contribute to analgesic activity
    - 1/3 **anesthetic** potency compared to ketamine
  - Evidence for auto-induction of metabolism with chronic use
    - Uncertain clinic relevance

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Ketamine Pharmacology

- Renal excretion (primarily as conjugates)
- Parent drug and metabolites remain detectable in urine for up to 2 weeks
- Short plasma half-life (~15 minutes)
  - Does not seem to correspond with clinical effects
- Overall, clinical effects appear to occur independently from pharmacokinetic parameters
  - May be more appropriate to view ketamine as a discrete treatment course

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Low-Dose Ketamine for Pain Management

- Guidelines primarily driven by larger number of IV infusion studies
  - Very few studies evaluated PO use, so evidence is limited
- May also stand alone as an analgesic
- IV infusion, PO, SL
- Most common side effects are hallucinations or dysphoria
  - Treated with PRN antipsychotic or benzodiazepine
- Case reports of hypertension

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Low-Dose Ketamine for Pain Management

- Dosing
  - IV: 0.1-1mg/kg/hr
    - In practice, lower end of range (0.1-0.3mg/kg/hr) most commonly used
  - PO/SL: 0.25-1mg/kg/dose
    - Again, most commonly dosed at lower end of range (0.25-0.5mg/kg/dose)
    - Typically dosed 3-4 times daily
  - Loading doses not recommended

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Low-Dose Ketamine for Pain Management

- Typically reduces opioid requirement ~40%
  - Significant interpatient variability seen in practice
  - Reduction persists beyond discontinuation of ketamine (at least 1 month)
- Relative Contraindications
  - Derived from side effects seen with anesthetic doses
  - **Psychiatric conditions**, severe cardiovascular disease, elevated intraocular or intracranial pressure, hepatic dysfunction

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Patient Selection

- History of chronic opioid use, especially at high doses
  - Typically used for short time period (1-7 days) until satisfactory reduction in opioid requirement seen, then discontinued
- Pain refractory to opioids (in select cases)
  - In addition to PO/SL/infusion regimens, has been administered via patient controlled analgesia (PCA) device
    - Downsides to this approach given lack of commercial product

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Ketamine

- Questions?

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Chronic Opioid Therapy in Context

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Chronic Opioid Therapy

- Treatment of pain lasting longer than 3 months or beyond normal tissue healing time
- 2016 CDC Guideline for Prescribing Opioids for Chronic Pain
  - Intended for primary care clinicians in outpatient settings
- Not to be confused with opioid therapy for acute pain
  - E.g. trauma or post-surgical pain management

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Chronic Opioid Therapy – CDC Guidelines

- Efficacy: No high-quality evidence regarding efficacy of opioid analgesics when used for >1 year
  - Does not mean evidence suggests opioids **aren't** useful for some chronic pain patients
- Potential Harms
  - Accidental overdose fatalities
  - Chronic constipation
  - Endocrine disruption, increased fracture risk, delayed wound healing, and reduced immune function in some studies

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Difficult Conversations in Pain Management

- Common Scenario: Pain is always a 10/10, even after significant opioid doses
  - **Opioids aren't working**
    - Does not mean the patient is lying or you don't believe they're in pain
    - Caveat for acute pain: Be mindful that a 'significant' opioid dose will be different in patients with varying levels of tolerance due to chronic use. Highly opioid tolerant patients require customized dosing
- Stark contrast vs stable opioid dose with clear functional benefit

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Chronic Opioid Therapy – Risk Thresholds

- We do have more evidence regarding overdose potential with chronic opioid therapy
- When compared to opioid dosages <20 MME/day:
  - 20-49 MME/day: 1.3-1.9x increase in overdose risk
  - 50-99 MME/day: 1.9-4.6x increase in overdose risk
  - **100+MME/day: 2.0-8.9x increase in overdose risk**
- However, causative factors are not as well-established

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Chronic Opioid Therapy – Continue, Taper, or Transition?

- Not all patients on chronic opioid therapy must be tapered
  - Multifactorial decision including patient benefits, risk factors, and adherence to treatment and monitoring plan
- If decision is made to taper off opioid therapy, there are many potential strategies
  - Fast taper, slow taper, opioid rotation, non-opioid medication assisted tapers
- While tapering may work well for some patients, this is often a long and painful process
  - Transition to buprenorphine may be more successful

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Patient Case

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Patient Case

ED is a 58 y/o male new to your practice after his previous physician retired. He has a PMH notable for bilateral knee OA, and morbid obesity (BMI 52). He complains primarily of pain in his knees, but also endorses generalized pain in "all my other joints and just about everywhere else". He has been taking opioids as part of his pain regimen for >5 years, but finds they now "only take the edge off".

His orthopedic surgeon does not consider him a knee replacement candidate due to his weight.

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Current Analgesic Regimen

- Oxycodone ER 40mg PO Q8H
- Acetaminophen 1000mg PO Q8H
- Oxycodone IR 15mg PO Q4H PRN breakthrough pain
  - Averages 6 tablets per day
- Duloxetine 30mg PO daily
- Meloxicam 15mg PO daily
- No Known Drug Allergies

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Current Issues

- Uncontrolled pain
  - Implications for weight management
- Opioid regimen concerns
  - Not effective despite taking ~315mg oral morphine equivalents (OME)
    - Pain management mantra: "Opioids aren't working"
  - Possible hyperalgesia
  - Safety

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Options

- Add another pain medication or optimize existing agents
- Taper opioid therapy
  - Advantages: Improves safety and eventually addresses hyperalgesia
  - Disadvantages: Worsen pain in short run, likely to be a long process
- Transition to buprenorphine
  - Advantages: Improves safety, addresses hyperalgesia, may improve pain
  - Disadvantages: Insurance coverage, stigma, withdrawal period (if used)

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Buprenorphine Transition

- Based on current opioid use of ~315mg OME, anticipate patient may need up to 8mg SL buprenorphine TID
  - Will typically start at lower dose and titrate to response
- In-office buprenorphine induction
  - Stop oxycodone products 24 hours prior to appointment
  - Patient typically arrives with mild to moderate withdrawal symptoms
    - Give 4mg SL x1, reassess after 45mins – 1 hr. May repeat dose x1 based on response
- Direct transition without withdrawal period?

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Patient Case

- Discussion/Questions/Other Approaches

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Final Questions?

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