Buprenorphine in Clinical Practice: Medication Assisted Treatment or Pain Management

Kathleen Broglio, DNP, ANP-BC, ACPHN, CPE, FPCN
Nurse Practitioner Section of Palliative Care
Assistant Professor of Medicine
Dartmouth Hitchcock Medical Center
Lebanon, NH
Kathleen.broglio@Hitchcock.org

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Disclosures

- Up To Date – Royalties
- TASA – Legal
- Emmi Solutions – patient education reviews

Objectives

- Describe the unique properties of buprenorphine which make it a viable option for both opioid use disorder and pain management.
- Discuss the incorporation of buprenorphine for medication assisted treatment into clinical practice
- Utilizing a case based approach, discuss the use of transdermal and buccal buprenorphine for pain management

Case 1

- 50 y.o. woman with chronic low back pain secondary to work injury 10 years ago
- Back pain treated with multiple modalities which were ineffective and has been on chronic opioid therapy for 8 years with morphine equivalent daily dose greater than 100 mg
- Opioid use has been escalating and she often runs out of medications early due to overuse during pain flares

Case 1 continued

- In last office visit she reports she is ‘worried’ about her use of opioids as they are escalating and she feels she is getting out of control with their use and is often not fulfilling home obligations
- Denies any other substance use, but does report a remote history of experimenting with illicit drugs, currently smoking 1 PPD cigarettes
- Family history positive for chronic pain, ETOH abuse

Scope of the Problem

- About 42,000 of the more than 63,000 overdose deaths in 2016 involved opioids
- 115 Americans die daily of an opioid overdose
- In 2015 – 91 million took a prescription pain medication
  - 11.5 million adults misused prescription pain relievers
- Non-medical use of pain relievers (opioids) second most commonly used class of drugs – 4.3 million

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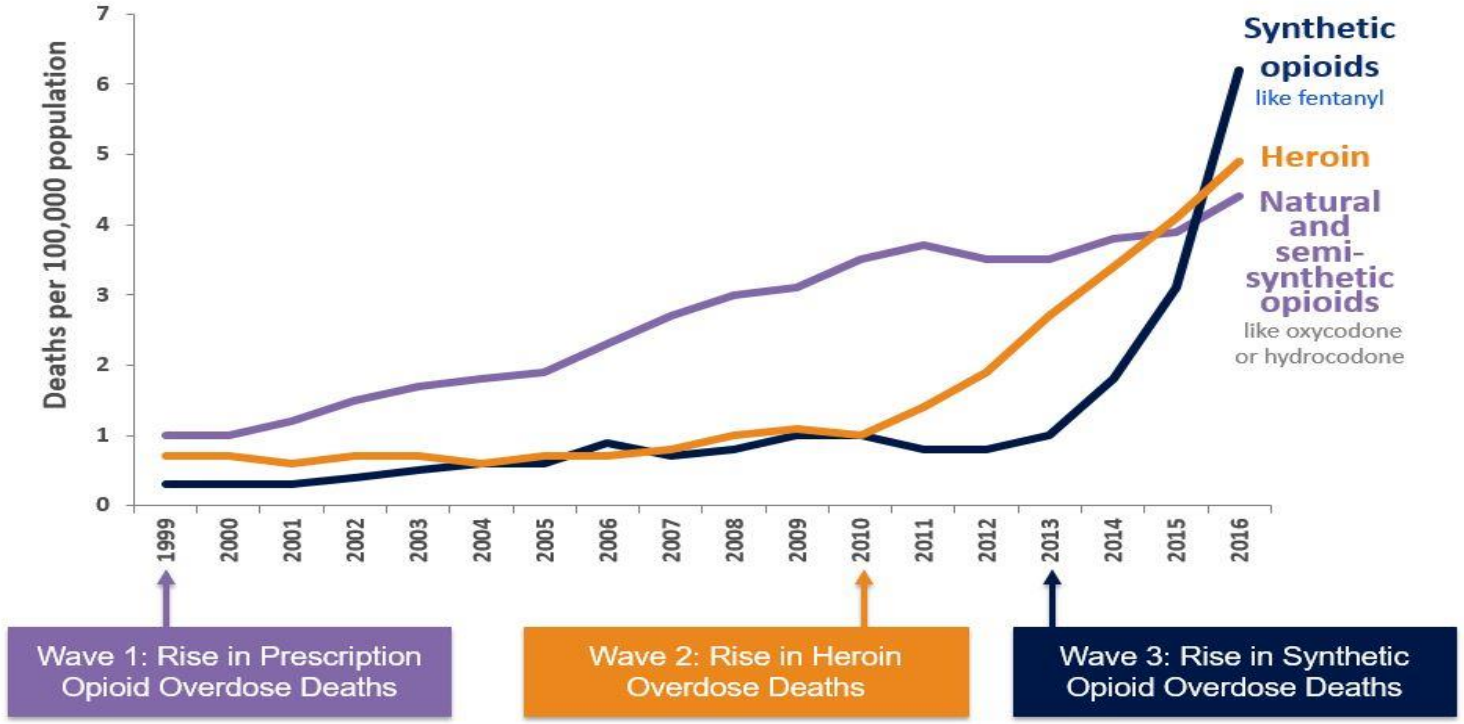
https://www.samhsa.gov/data/sites/default/files/report_3210/ShortReport-3210.html; July 2017
https://www.cdc.gov/drugoverdose/epidemic/index.html; Updated August 2017

3 Waves of the Rise in Opioid Overdose Deaths



SOURCE: National Vital Statistics System Mortality File.

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https://www.cdc.gov/drugoverdose/epidemic/index.html; Updated August 2017

Opioid Use Disorder
Substance Use Disorder

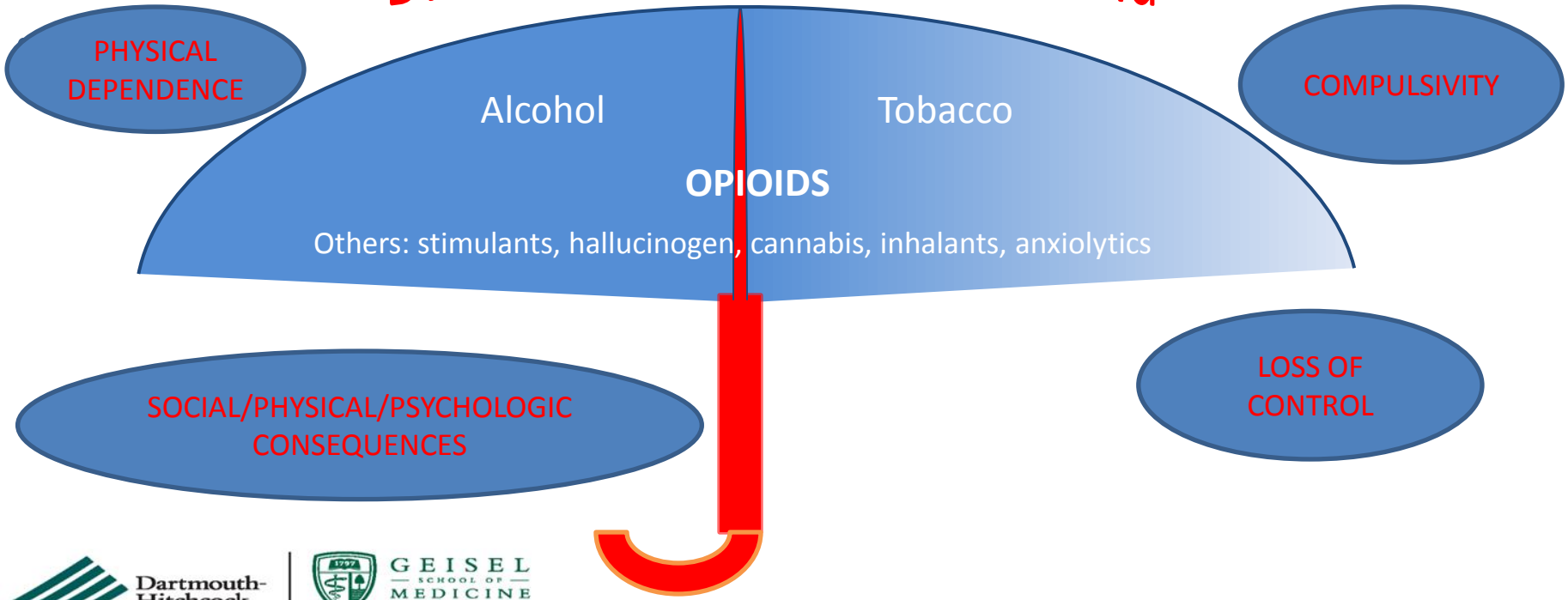
- In 2016, more than 1 million individuals sought treatment for opioid dependence
- Per SAMHSA 2016 report more than 350,000 people received methadone in opioid treatment programs (OTPs) **and more than 60,000 individuals were treated with buprenorphine**
- Utilization of **buprenorphine for opioid use disorder (OUD) expected to increase with passage of Comprehensive Addiction and Recovery Act (CARA)**
  - Nurse Practitioners and Physician Assistants can be waivered to treat OUD with buprenorphine as of 2017

http://www.drugwarfacts.org/node/1578
The Comprehensive Addiction and Recovery Act, 2016
http://www.cadca.org/comprehensive-addiction-and-recovery-act-cara

Substance Use Disorder

~~Addiction~~

Disorders have similar criteria



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Opioid Use Disorder

A problematic pattern of opioid use leading to clinically significant impairment or distress- ≥ 2

- Taken in larger amounts for longer than expected
- Unsuccessful attempts to cut down or control use
- Craving or strong desire or urge to use opioids

- Great time spent in activities to obtain, use, recover from effects
- Use in situations which are hazardous
- Continued use despite recognition of social/interpersonal problems related to use

- Failure to fulfill major role obligations
- Important social, occupation or recreational activities given up due to use
- Use despite knowledge of physical/psychological problems

- Tolerance (not applicable when taken as medically indicated)
- Withdrawal (not applicable when taken as medically indicated)

Mild = 2-3
Moderate= 4-5
Severe ≥ 6

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https://pcssnow.org/wp-content/uploads/2014/02/5B-DSM-5-Opioid-Use-Disorder-Diagnostic-Criteria.pdf

Medication Assisted Treatment

Medication	Action	Dose	Where is it obtained?	Comments
Methadone	Full mu-opioid agonist – can reduce craving for 24 hours	60-120 mg PO once daily – patient goes to opioid treatment program clinic daily for observed dosing May graduate to take doses home on weekends or have weekly pick-ups	Must be administered through a federal Opioid Treatment Program	Provides analgesia for 6-12 hrs.; more than once daily dosing necessary for pain management; Many drug/drug interactions; can cause QTc prolongation
Buprenorphine/ naloxone Buprenorphine (pregnancy) Buprenorphine implants	Partial mu-agonist-occupies mu receptors reduces craving	8-24 mg sublingual/transmucosal daily 80 mg implant q6mo Weekly/monthly injection	Prescribed by physicians, nurse practitioners and physician assistants in ambulatory office setting who have waiver Consider obtaining waiver!	May provide analgesia if given in split doses (every 8 or 12 hours); if mu opioids administered need higher doses; Implants can be removed prior to six months; less drug/drug interactions than methadone
Naltrexone	Full mu-receptor antagonist	50 mg orally daily 380 mg monthly intramuscular depot injection	Injection administered by any clinician who is prescriber	Also used for Alcohol Use Disorder. Will block the effects of opioids

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Source document for information in table Kampman & Jarvis. *Journal of Addiction Medicine,* 2015; *9,* 358-367

BUPRENORPHINE

Buprenorphine

- Partial mu agonist, kappa antagonist
- Blocks full mu effect and prevents effect from other mu agonists, **but only** partially activates the receptor
- Schedule III
- Analgesia at lower doses
- Ceiling effect at higher doses (reported to be > 32mg/d)
- Poor GI bioavailability, fair sublingual
- Some drug/drug interactions due to CYP450 - 3A4

Kampman & Jarvis. *J of Addict Med,* 2015; *9,* 358-367

Buprenorphine

- Formulations for treatment of OUD
  - Sublingual tablet
  - Buccal film
  - Sublingual film
  - usually combined with naloxone (except in pregnancy)
    - Naloxone minimizes risk of overdose if misused by injection
  - Doses generally 8-24 mg daily
  - Six month implant delivering about 8 mg daily buprenorphine
  - Weekly/monthly injections (FDA approved 2017)

Bryson, *Curr Opin Anesthes*, 2014; *27*(3), 359-364.; Nasser et al. *Clin Pharmacokinet;* 2014; *53*, 813-824.

Medication Assisted Treatment
Buprenorphine- Nuts & Bolts

- Obtain EDUCATION, support and mentorship
  - Provider's Clinical Support System for Medication Assisted treatment http://pcssmat.org/
- Obtain waiver
  - 24 hour training can be conducted online
  - Submit training certificate – wait about 6 weeks
  - Issued additional DEA number – starts with X
  - Can manage maximum 30 patients in first year

Medication Assisted Treatment
Buprenorphine- Nuts & Bolts

- Screening patients
  - Motivated for recovery
  - If could be effectively treated with less than 60- 80 mg methadone daily
  - Willingness to engage in psychologic counseling/treatment related activities
- Utilize guidelines for treatment – personalize for clinic setting
  - Treatment agreement
  - Urine drug screening
  - Outline frequency of visit
  - Support system (nurses, nursing or medical assistants, availability psychologic counseling)

Medication Assisted Treatment
Buprenorphine- Nuts & Bolts

- Induction
  - Office versus home induction
  - Patient must be in mild opioid withdrawal otherwise buprenorphine can precipitate withdrawal
- Stabilization
- Mentorship

- **Have a plan for back-up provider**
- **Mentorship very helpful**

Don't start with the most difficult complex patients if you are doing this on your own in a clinic practice WITHOUT support of others more experienced in this practice

Case continued

- Screening
  - Determined to meet criteria for ‘moderate’ Opioid Use Disorder
  - Motivated to initiate medication assisted treatment and meet with counselor in clinic
  - Started buprenorphine/naloxone and titrated to 8mg/2mg twice daily
    - Twice daily dosing provided excellent pain management

- Four months into treatment was in a serious motor vehicle accident as a passenger and sustained multiple fractures requiring surgery

Buprenorphine – The Challenges

- Mu opioid receptors occupied but not activated
- If patient requires opioids for pain – WILL REQUIRE much higher doses to overcome occupied mu receptors
- If buprenorphine discontinued takes about 72 hours to disassociate from mu receptors
- If patient admitted on buprenorphine with pain crisis/trauma –

What is your course of action?

Buprenorphine and Elective Admission

- Option 1
  - Wean by 2 mg every three days and stop 72 hours prior to surgery –
  - If pain/intolerable withdrawal, use methadone 30mg daily prior to admission
  - Utilize multimodal analgesia
  - If pain resolves during hospitalization allow for mild withdrawal and then resume buprenorphine

OR

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Bryson, *Current Opinion in Anesthesiology*, 2014; *27*(3), 359-364

Buprenorphine/Pain/Unplanned Admission

- Continue buprenorphine therapy and consider divided doses every 6-8h and can increase dose to maximum of 32 mg daily
- Utilize multimodal analgesia
- Treat acute pain with mu-opioid agonists such as fentanyl, hydromorphone or morphine or sublingual or intravenous buprenorphine if available

OR

Bryson, *Cur Opin Anaesthesiology,* 2014:*27,* 359-364

Buprenorphine/Pain/Unplanned Admission

- Discontinue buprenorphine
- Utilize multimodal analgesia
- Treat acute pain with mu-opioid agonists such as fentanyl, hydromorphone, or morphine
- Anticipate higher doses needed for 72 hours until buprenorphine (disassociates from mu receptor) and is cleared from system
- Consider monitored setting as may have increased risk for respiratory depression once buprenorphine cleared from system
- Once pain decreases will have to discontinue opioids, allow patient to be in mild withdrawal and then restart buprenorphine

Bryson, *Cur Opin Anaesthesiology,* 2014:*27,* 359-364

Buprenorphine and Acute Care Admission for Pain

- NO one right way to do things
- Multiple protocols
- Must plan for pain management during hospitalization and maintenance of patient in recovery after discharge

Buprenorphine Implant for OUD

- Approved May 2016 – 80 mg subdermal implants for 6 month treatment
- Possible benefits
  - Increased adherence
  - Decreased risk of diversion
  - Accidental pediatric ingestion

Chavoustie et al. *Exp Rev Clin Pharm*. 2017 doi.org/10.1080/18512433.2017.1336434

Buprenorphine Implant for OUD

- Candidates for use
  - Stable on 8 mg or less of sublingual buprenorphine daily
  - Stable in recovery – no recent illicit substance use
  - Available practitioner to implant subdermally

Chavoustie et al. *Exp Rev Clin Pharm*. 2017 doi.org/10.1080/18512433.2017.1336434

Buprenorphine Implant
Nuts & Bolts

- Practitioner must
  - have experience in last 3 months performing aseptic surgical procedure
  - have waiver to prescribe buprenorphine
  - attend live Risk Evaluation and Mitigation Strategy (REMS) training for insertion/removal

Chavoustie et al. *Exp Rev Clin Pharm*. 2017 doi.org/10.1080/18512433.2017.1336434

Buprenorphine Injection

- FDA approved 2017
- For use after stabilized for at least one week on sublingual buprenorphine
- 300 mg injections delivered subcutaneously in abdomen monthly for 2 months followed by 100 mg monthly
- Only can be dispensed by pharmacy who has completed REMS and provider who has completed the REMS

https://www.sublocade.com/?gclid=Cj0KCQjwrLXXBRCXARIsAIttmRPcfoLqEU9Aqf8MD8jaBVcEYsPL_vtfaxJjaNYo4Nd5rp2dJVy0jBEaAvjQEALw_wcB

BUPRENORPHINE FOR PAIN MANAGEMENT

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Case 2

- 81 y.o. man with metastatic prostate cancer with bone metastases
- Developed pain in lumbar spine due to metastatic disease
- Acetaminophen was not effective
- Unable to take NSAIDs due to chronic kidney disease – and age
- Taking tramadol 50 mg 4 times daily, now without adequate effect
- “AFRAID” of opioids due to central nervous system effect and constipation

Buprenorphine Transdermal Patch Option for Pain Management

- Who may be a good candidate?
  - Opioid naïve
  - Chronic pain not relieved with non-opioid options and requires around the clock opioid therapy
  - Concern about pill burden- applied once weekly
  - Requires less than 80 mg morphine equivalent dosing of opioid for pain relief

Math Refresher

1 mg = 1000 mcg

20 mcg/hr = 480 mcg/day (max dose daily) = .48 mg

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Plosker & Lyseng-Williamson, *CNS Drugs,* 2012; 26(4); 367-373

Equianalgesia Buprenorphine
NO good answer

- Variable citations from:
  - 1 mg buprenorphine = 10 mg morphine
  - 1 mg buprenorphine = 30 mg morphine
- Equianalgesic charts indicate 0.4 mg IV morphine = 10 mg IV morphine
- Some sources say 5 mcg/hr patch = between 10-12 mg oral morphine daily

Who knows?

https://opioidcalculator.practicalpainmanagement.com/methods.php

Potential Benefit of Buprenorphine Transdermal

- Once weekly application
  - Consider patients in assisted living or nursing home situations who may have difficulty with pill burden
- Patients with swallowing difficulty who may not be candidate for higher dose opioid such as fentanyl transdermal patch
- Ceiling effect for respiratory depression **(UNLESS utilized with other CNS depressants)**
- Schedule III opioid so refills may be possible in many states

Plosker & Lyseng-Williamson, *CNS Drugs,* 2012; 26(4); 367-373

Limitations of Transdermal Buprenorphine

- Opioid side effects similar to full mu opioid agonists
- More difficult to titrate than oral medications
- May not be effective for those persons requiring more than 80 mg morphine equivalent daily – can not utilize more than 20 mcg/hr patch in the U.S.
- Doses greater than 20 mcg/hr shown to prolong QTc

Plosker & Lyseng-Williamson, *CNS Drugs,* 2012; 26(4); 367-373

Initiating Buprenorphine Transdermal

- Utilize opioid risk assessment tools, treatment agreement
- Opioid naïve patient
  - Start buprenorphine 5 mcg/hr patch
- Opioid experienced patient on morphine equivalent between 30-80 mg daily
  - Start buprenorphine 10 mcg/hr patch
- Refer to product insert or website for more guidance

BUTRANS prescribing information https://www.butrans.com/resources/opioid-conversion-tool.html

Case continued

- Patient was started on buprenorphine 5 mcg/hr patch which provided adequate pain relief
  - Rarely took tramadol or acetaminophen for breakthrough pain
- Buprenorphine patch titrated to 7.5 mcg/hr and then to 10 mcg/hr
  - Started oxycodone 2.5-5 mg 3 times daily for breakthrough pain

Because buprenorphine dose SO low mu-agonist opioids can override and provide benefit and can be used

- Transitioned to home hospice and remained on buprenorphine patch until death

Potential Reasons to Utilize Transdermal Buprenorphine

- May be effective for those patients requiring low dose opioids
- May have decreased risk for respiratory depression due to partial agonist (ceiling dose effect)
- May cause less side effects such as constipation (no first pass effect)
- Ease of use – once weekly dosing
- May be able to refill without seeing patient monthly

BUPRENORPHINE BUCCAL FOR PAIN MANAGEMENT

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Case 3

- 45 y.o. man with history of HIV and now with esophageal cancer s/p chemoradiation with persistent pain
- Has gastrostomy tube for feeding
- Minimal tolerance of oral food or medications
- Utilizing morphine solution 15 mg three times daily for pain
- Tried buprenorphine and fentanyl patches which caused skin irritation
- Multiple medications interact with methadone

Buccal Buprenorphine for Pain Management

- **NOT** the same as buccal buprenorphine for opioid use disorder
  - Formulations 75 **mcg** – 900 **mcg** doses utilized every 12 hours
  - For opioid use disorder 2 **mg** -24 **mg** daily

Math Refresher

1 mg = 1000 mcg

1800 mcg (max dose daily) = 1.8 mg

Why Consider Use Buccal Buprenorphine?

- Requires around the clock opioids for severe pain
- Pain control able to be achieved on less than 160 mg morphine equivalent daily
- May be initiated in opioid naïve patient (75 mcg q12h)
- May have less risk of respiratory depression due to partial agonist effect
- May have less risk of constipation
- ? Anti-hyperalgesic

Rauck et al. *Postgrad Med.,* 2016; 138:1; 1-11

Initiating Treatment with Buccal Buprenorphine

- Utilize opioid risk screening, treatment agreements
- For opioid naïve patient start at 75 mcg daily and if tolerated increase to every 12 hours
  - Titrate at the minimum every 4 days
- For those on chronic opioid therapy may need to taper down to less than 30 mg morphine equivalent daily due to risk of inducing 'withdrawal'
  - Results recent trial – switch over after 8-12 hours of opioid at 50% morphine equivalent dose did not precipitate withdrawal[1]

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Belbuca prescribing information
https://s3.amazonaws.com/belbuca/website/pdfs/belbuca-prescribing-info.pdf

Initiating Treatment with Buccal Buprenorphine

- Opioid tolerant patients
  - Wean to 30 mg ,orphine equivalent daily (concern about withdrawal with buprenorphine)
- For patients previously taking

  30-89 mg morphine equivalent daily – start 150 mcg every 12 hours

  90-160 mg morphine equivalent daily – start 300 mcg every 12 hours

  ➢ 160 mg morphine daily – may not be effective
- Doses greater than 300 mcg are **NOT starting doses – should be titrated to these dose**
- May need to continue immediate release opioids until pain controlled
- Titration should not be sooner than every 4 days - no more than 150 mcg at each titration

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Belbuca prescribing information
https://s3.amazonaws.com/belbuca/website/pdfs/belbuca-prescribing-info.pdf

What about Risks for Opioid Withdrawal

- For those on chronic opioid therapy need to taper down to less than 30 mg morphine equivalent daily due to risk of inducing 'withdrawal' per prescribing information
- However results recent trial – switch over after 8-12 hours of opioid at 50% morphine equivalent dose did not precipitate withdrawal[1]

[1]Webster et al. *Pain Med.*2016; 17: 899-907

Case continued

- Started on buccal buprenorphine 75 mcg every 12 hours
- Still required morphine 15 mg about 2 times daily
- Titrated to 450 mcg every 12 hours with adequate relief and rare use of breakthrough opioids

Limitations for Use Buccal Buprenorphine Pain Management

- May not effectively treat pain requiring more than 160 mg morphine equivalent daily (ex- progressive disease cancer
- Probable need for prior authorization
- Potential costs of co-pays

Consider patient population, benefits vs. limitations

Off-Label Use Sublingual Buprenorphine/Naloxone Pain Management

- Observational study pain center
  - Efficacious- especially for those on morphine equivalent 100-199 mg daily
  - May be anti-hyperalgesic
  - Potentially less long-term side effects
  - May decrease risks of abuse/diversion

Daitch et al., *Pain Physician;* 2012;15:ES59-ES66

Caveats for ‘off-label’ Use

- Lack of randomized control trials
- Risk for increased scrutiny ?
- Prior authorizations for medication due to ‘off-label’ use
- Patient concern about stigmatization

Take Home Messages

- Buprenorphine as a partial agonist may confer some benefits not seen with pure mu opioid agonists
- Treatment of opioid use disorder with buprenorphine now an option for nurse practitioners in clinic based setting
- Buprenorphine may be viable option for pain management as well with the FDA approved formulations transdermal and buccal