ACCEPT
Addiction & Co-morbid Conditions: Enhancing Prevention & Therapeutics

Agenda

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For attendance, purposes please text the following code: RUHQED to 608-260-7097

Session Date: Friday, January 15, 2021

Didactic Topic and Presenter:
Buprenorphine for Pain Management

Michael Miller, MD, DFASAM, DLFAPA
Board-certified General and Addiction Psychiatrist
Past President, Amer Society of Addiction Medicine (ASAM)
Former Director, Amer Board of Addiction Medicine (ABAM)
Former Director, Amer College of Academic Addiction Medicine (ACAAM)

Content Experts:
Ritu Bhatnagar, MD; Lindsey Peterson, MS, CRC; Sheila M. Weix, MSN, RN, CARN

- 12:15 PM: Attendance text-in – Introductions
- 12:25 PM: Case Presentation
  - Presenter: Robert Freidel, MD
- 1 PM: Didactic Presentation
  - Presenter: Michael Miller, MD, DFASAM, DLFAPA
- 1:15 PM: End of Session

CONTINUING EDUCATION INFORMATION:

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Interprofessional Continuing Education Partnership
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School of Medicine and Public Health
School of Nursing
School of Pharmacy

Project ECHO
University of Wisconsin

ACCEPT
Addiction & Co-morbid Conditions: Enhancing Prevention & Therapeutics
2020-2022

Buprenorphine for Pain Management
Friday, January 15, 2021
Michael M. Miller, MD, DFASAM, DLFAPA – Didactic Presenter
Robert Freidel, MD – Case Presenter

Provided by the University of Wisconsin–Madison Interprofessional Continuing Education Partnership (ICEP)

Intended Audience:
Nurses, Nurse Practitioners, Pharmacists, Physicians, Physician Assistants, Pharmacy Technicians, Psychologists, Social Workers, Patient/Caregivers, Students

Objectives:
As a result of this educational regularly scheduled series, learners will be able to:

1. Implement appropriate opioid prescribing and monitoring practices.
2. Effectively participate in office-based, collaborative management of substance use disorders.
3. Consistently provide in overdose prevention education to appropriate patients.
4. Identify the role of medication assisted therapies, such as methadone, naltrexone, and buprenorphine, and contributions of different members of the healthcare team to the management of substance use disorders.

Policy on Disclosure
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Name/Role	Financial Relationship Disclosures	Discussion of Unlabeled/Unapproved uses of drugs/devices in presentation?	COI completion date
Randall Brown, RSS Chair	No relevant financial relationships to disclose	Yes	4/8/2020
Briana Kleinfeldt, RSS Coordinator	No relevant financial relationships to disclose	No	4/8/2020
Kathleen Maher, RSS Coordinator	No relevant financial relationships to disclose	No	4/18/2020
Nada Rashid, RSS Coordinator	No relevant financial relationships to disclose	No	7/1/2020
Ritu Bhatnagar, Planner	No relevant financial relationships to disclose	Yes	4/15/2020
Richard Crawford, Planner	No relevant financial relationships to disclose	No	4/9/2020
Paul Hutson, Planner	No relevant financial relationships to disclose	No	4/9/2020
Susan Mindock, Planner	No relevant financial relationships to disclose	No	4/6/2020
Lindsey Peterson,	No relevant financial relationships to disclose	No	4/6/202

Planner			
Alyssa Tilhou, Planner	No relevant financial relationships to disclose	No	4/13/2020
Sheila Weix, Planner	No relevant financial relationships to disclose	No	4/6/2020
Michael M. Miller, Speaker/Author	Advancing a Healthier Wisconsin Endowment (Contractor) AmmonLabs (Consultant) Alkermes (Speakers Bureau) AMITA Health (Honorarium – Conference Keynote) Aware Healthcare (Contractor) Childrens Community Health Plan (Consultant) JBS International (Contractor) US WorldMeds, LLC (Physician Advisory Board) Waypoint Health Innovations (Contractor) SixDegrees Health Care Consulting, Inc. (Contractor) Wisconsin Veterinary Medical Association (Contractor)	Yes	1/12/21
Robert Freidel, Speaker/Author	No relevant financial relationships to disclose	No	1/7/21

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ACCEPT

Addiction & Co-morbid Conditions: Enhancing Prevention & Therapeutics

Patient Case Presentation

***Please do not attach any patient-specific files or include any Protected Health Information.**

1. Date: 1/15/2021
2. Presenter Name: Bob Freidel, MD
3. Presenter Organization: University of Wisconsin-Madison School of Medicine and Public Health; UW Department of Family Medicine and Community Health
4. ECHO ID: 7771
5. Have you presented this patient during this teleECHO clinic before? ☐ Yes ☒ No
6. Please state your main question for this case: How can buprenorphine be used for pain management?

Patient Demographic Information:

7. Age: 46
8. Sex: Male
9. Education/Literacy:
    a. Did not finish high school
10. Income source:
    a. Early on, dealt cocaine and heroin. Now, intermittent construction jobs, frequent unemployment.
11. Social Factors/History:
    a. Mother w/ AUD. Hx abuse.
    b. Two sons. Girlfriend actively using.
    c. On disability due to visual impairment, was shot by bb gun legally blind in left eye.
    d. Lives alone in a house, arranged by a counseling and human services group. Previously, housing insecurity.
    e. Mother, brother, and cousin all passed away in 2018-2019, which was difficult for him.
12. **Substance Use History**:
    a. Nicotine since high school
    b. Alcohol since high school, mixed binge and maintenance periods, now 1 L/day, largely related to pain
    c. Frequent marijuana to treat anxiety, pain since HS
    d. Cocaine since early 20s, started as nasal, then moved to crack-cocaine, then IV use age 44 year ago
    e. After a motorcycle accident that broke his pelvis in his 30s, his pain was managed with opioids, which became a chronic opioid pain plan. On a UDS, fentanyl was found in his urine and his plan was discontinued. To manage pain, he started using nasal heroin regularly and moved to IV around age 44, up to 1 gram/day.
    f. Illicit benzos occasionally
    g. Used to be on Adderall for ADHD, now denies amphetamines
    h. Has tried LSD and psilocybin; not regularly using

13. Consequences of Substance Use:

- Social/occupational/educational:
    - Disconnected with his kids due to use (failure to meet roles)
    - Conflicts with girlfriend, bosses, and prior providers related to use
    - Several legal issues, including several OWIs; driver's license revoked
- Physical (including evidence of tolerance/withdrawal):
    - Has used heroin in "dirty" situations. Does not always clean before injecting.
    - Will spent "100s of dollars" and lots of time obtaining doses
    - Overdosed twice, received narcan with improvement
    - Self-reports tolerance and withdrawal symptoms for heroin and alcohol.

14. Interventions that have been tried:

a. Methadone OTP for OUD and pain
b. Inpatient psych
c. Rehab facility

15.

Current Addiction and Mental Health-related Medications:	Medical/Behavioral Health Diagnosis:
• Buprenorphine/naloxone 18-4.5 mg BID ○ Uses 12-3 mg films, one and a half strips 2 times daily • Clonidine prn • Naloxone nasal spray • Bupropion 150 mg qday • Hydroxyzine 25 mg TID prn • Tizanidine 2 mg TID • Zolpidem 10 mg qhs • Pregabalin 150 mg BID	• TBI • PTSD • HTN • Major depressive disorder • Anxiety • Insomnia • ADHD • Chronic pelvic pain s/p pelvic fracture • Chronic midline low back pain w/o sciatica • Opioid use disorder, severe • Alcohol use disorder, severe • Cocaine use disorder • Marijuana use • Tobacco use

16.

Patient Strengths/protective factors:	Risk factors:
• Established w/ a counseling and human services group • Housing	• Chronic pain • Mental health • Financial and housing instability • Mother w/ AUD • Girlfriend actively using

17. Labs (as indicated), include summary of urine testing or last urine drug screen results:

- Last CMP 7/2020 normal except:
    - Cr 1.34, at baseline

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- 2020 UDS results (14 tests):
    - Buprenorphine, norbuprenorphine: always appropriate
    - Amphetamine, methamphetamine: 7/2020:
    - Fentanyl: 3/2020, 6/2020, 7/2020
    - Morphine: 6/2020
    - Cocaine or benzoylecgonine: nearly constantly +
    - Marijuana constantly

18. Patient Goals/Motivations for Treatment:

- Stop withdrawal
- No IVDU
- Reduce pain
- Be a better dad
- Housing security

19. Proposed Diagnoses:

a. Opioid use disorder, currently in remission
b. Cocaine use disorder, active
c. Chronic pelvic pain
d. Chronic low back pain with sciatica
e. Major Depressive Disorder

20. Proposed Treatment Plan:

a. Reduce to 30 mg (2.5 strips of 12 mg each)
b. Regular UDS
c. F/u 2 weeks

By initialing here __RF__ you have acknowledged that Project ECHO case consultations do not create or otherwise establish a provider-patient relationship between any ECHO clinician and any patient whose case is being presented in a teleECHO clinic.

DSM 5 Criteria for Substance Use Disorder

A use disorder is characterized by maladaptive use resulting in repetitive consequences over the previous 12 months. A minimum of 2-3 criteria is required for a mild substance use disorder diagnosis, while 4-5 is moderate, and 6-7 is severe (American Psychiatric Association 2013)

1. Taking the substance in larger amounts and for longer than intended
2. Wanting to cut down or quit but not being able to do it
3. Spending a lot of time obtaining the substance
4. Craving or a strong desire to use
5. Repeatedly unable to carry out major obligations at work, school, or home due to use

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6. Continued use despite persistent or recurring social or interpersonal problems caused or made worse by use
7. Stopping or reducing important social, occupational, or recreational activities due to opioid use
8. Recurrent use in physically hazardous situations
9. Consistent use despite acknowledgment of persistent or recurrent physical or psychological difficulties from using
10. *Tolerance as defined by either a need for markedly increased amounts to achieve intoxication or desired effect or markedly diminished effect with continued use of the same amount. (Does not apply for diminished effect when used appropriately under medical supervision)
11. *Withdrawal manifesting as either characteristic syndrome or the substance is used to avoid withdrawal (Does not apply when used appropriately under medical supervision)

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"Buprenorphine for Pain Management"

UW ACCEPT Project ECHO Didactic

Dept. of Family Medicine and Community Health
Univ. of Wisc. School of Medicine and Public Health
January 15, 2021

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Project ECHO® University of Wisconsin

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Project ECHO University of Wisconsin

Disclosures

I disclose the following relevant relationships with commercial interests:

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AMITA Health (Honorarium – Conference Keynote)
AmmonLabs (Consultant)
Aware Heatlhcare (Contractor),
Children's Community Health Plan (Consultant)
JBS International (Contractor)
SixDegrees Health Care Consulting (Consultant)
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Waypoint Health Innovations (Contractor)
Wisconsin Veterinary Medical Association (Webinar)

Historical Relationships (>12 months)

- Physician Advisory Board for Probuphine® (Braeburn Pharmaceuticals)
- Physician Advisory Board for Bunavail® (US WorldMeds)
- Curry Rockefeller Group re: physician and patient education and marketing materials for Bunavail® (consultant)

Buprenorphine:

- Approved by FDA 2003 as a Sched. III sublingual product for the treatment of opioid dependence and opioid withdrawal
  - Suboxone® bup-nlx combo product SL film
  - Subutex® bup mono product SL film (no longer made)
  - Zubsolv® bup-nlx combo product SL tablet
  - Bunavail® bup-nlx combo product buccal file (no longer made)
  - Buprenorphine-naloxone generic combo product SL film
  - Buprenorphine HCl generic mono product SL film
  - Probuphine® bup implant (6 months) sub cut (usually biceps)
  - Sublocade® long-acting injectable (30 days) sub cut (usually administered in the abdominal wall)
  - Brixadi® long-acting injectable (7 days or 30 days) sub cut

Buprenorphine Pharmacology

At the μ-Opioid receptor (MOR): Partial agonist. Binds with high affinity, but only partially activates the receptor (ceiling effect). Also has slow dissociation. The combination of high MOR affinity and slow MOR dissociation results in buprenorphine effectively displacing other MOR agonists, which can lead to precipitated withdrawal. In maintenance treatment, buprenorphine blocks the MOR (though not as well for fentanyl and analogs)

Buprenorphine Pharmacology

- At the κ-Opioid receptor (KOR): Antagonist.
- At the δ-Opioid receptor (DOR): Antagonist.
- Nociceptin receptor (NOP, ORL-1): Weak affinity. Very weak partial agonist. However, the antagonism via the ORL-1 receptor contribute to the ceiling effect ("mixed agonist-antagonist") [nociceptin is also known as orphanin; the new name for the ORL-1 receptor is the nociceptin opioid peptide receptor, NOP]

Kress (2009)

- Buprenorphine, unlike fentanyl, shows a ceiling effect for respiratory depression, but not for analgesia.
- Despite past misconceptions concerning its analgesic potency, buprenorphine, in fact, has been shown to have a dose-linear response curve, with no analgesic 'ceiling effect' observed within the therapeutic analgesic dose range in man.

Webster et al. (Consensus Panel)

"Buprenorphine appears to have a ceiling effect on respiratory depression."

[referencing US Dept of HHS Pain Management Best Practices Inter-Agency Task Force Report, 2019]

"As a caveat, respiratory depression is still a concern, especially when bup is used in combination with nonopioid sedatives/anticonvulsants such as benzodiazepines and gabapentin, carisoprodol and other muscle relaxants, amitriptyline, and Z-drugs."

Kress (2009)

"As the metabolism of certain benzodiazepines also involves CYP 314, excessive CNS depression due to the combination of buprenorphine and benzodiazepines may occur in patients with impaired liver function."

Raffa et al. (2014)

The fact that buprenorphine appears to be a true partial agonist on the endpoint of respiratory depression, with a ceiling effect, cannot be generalized to analgesia.

In the same *in vitro* assays in which bup produces <100% effect, morphine likewise produces <100% effect (a fact perhaps not widely known).

Buprenorphine Pharmacology

Although other opioids act as agonists of the kappa opioid receptor, thereby increasing the production of dynorphin, an endogenous opioid peptide known to contribute to hyperalgesia and antinociceptive tolerance, buprenorphine is the lone opioid that acts as an antagonist at the kappa opioid receptor. Therefore, buprenorphine use can counter one of the key mechanisms thought to be responsible for hyperalgesia and tolerance (Rudolf 2020).

Buprenorphine Pharmacology

- The inverse agonist activity at the kappa receptor may explain buprenorphine-associated antihyperalgesic activity, as hyperalgesia is likely the result of dynorphin upregulation (Davis et al., 2018).
- Kappa receptor antagonism is associated with antidepressant activity, which may be one reason why bup has been found to reduce depression and suicide ideation (Davis et al.)

Webster et al. (Consensus Panel)

Citing Serafini G et al., *Int J Mol Sci.* 19:2410 (2018)

"The Efficacy of Buprenorphine in Major Depression, Treatment-Resistant Depression and Suicidal Behavior: A Systematic Review"

Buprenorphine has been shown to effectively reduce depressive symptoms and suicidal ideation in patients unresponsive to conventional antidepressant medications.

Webster et al. (Consensus Panel)

- "The in vitro classification of buprenorphine as a "partial agonist" at the μ-opioid receptor may lead to the misconception that it is less effective as an analgesic than a reference opioid that is considered a full μ-opioid receptor agonist."
- Buprenorphine has lower intrinsic activity than full μ-OR agonists (potentially limiting negative effects) but enough activity to be an effective analgesic
- Bup is an antagonist at the δ- and κ-opioid receptors which lessen constipation, dysphoria and abuse potential and helps reduce mental depression

Rudolf (2020)

- Although a ceiling effect does exist with respect to buprenorphine's low potential for respiratory depression relative to other opioids, rendering it safer in clinical use, the analgesic activity of bup is dose-dependent without such a ceiling effect.
- Buprenorphine has a much greater likelihood of producing analgesia relative to risk of respiratory depression, whereas the opposite is true of fentanyl.

Kress 2009

- Very nice summaries of the literature on buprenorphine and respiratory depression, opioid-induced hyperalgesia, and immune system suppression.

Buprenorphine Pharmacology

- Buprenorphine provides a primarily spinal site of mu opioid receptor agonist activity rather than direct activity at mu opioid receptors in the brain. (Rudolf 2020, citing Ding Z and Raffa R, *British J of Pharmacology* 157:831-42, 2009).
- Buprenorphine analgesia is largely medicated through mu receptors in the dorsal horn (Davis et al., 2018).

Buprenorphine Pharmacology (Davis et al., 2018)

- Time to analgesia from the time of parenteral injection ranges between 10 and 30 minutes, with an average duration of analgesia ranging from 6 to 8 hours
- Clearance from the CNS is slower than plasma clearance, which accounts for the difference between plasma half-life of the drug and duration of analgesia.

Buprenorphine Pharmacology (Davis et al., 2018)

- Similar to methadone, craving can be checked by a single or twice-daily dose, whereas analgesia will require multiple daily doses.

[Miller commentary: for a patient stable on bup maintenance (SL) for addiction who develops pain, the first intervention should be do divide the bup dose]

Buprenorphine Pharmacology

- Elimination is primarily via stool, although 10% to 30% is excreted in urine as conjugated forms of buprenorphine and its metabolite norbuprenorphine (approx. 10%) (Rudolf 2020).
- Oxidative metabolism is via the CYP 3A4 enzyme.
- Buprenorphine has less drug-drug interactions than tramadol as the rate-limiting metabolizing enzymes are conjugases and not mixed-function oxydases (cytochromes) (Davis et al., 2018).

Buprenorphine Pharmacology

- Clearance is independent of renal function and is not removed by dialysis, making it a preferred analgesic in renal failure (Davis et al., 2018).
- Clearance is also not influenced by mild to moderate liver failure (Davis et al., 2018).

http://accurateclinic.com/accurate-education-pain-medications-buprenorphine/

Synthetic opioids such as tramadol, tapentadol (Nucynta®), methadone, meperidine (Demerol®), levorphanol (and dextromethorphan) block serotonin and norepinephrine reuptake. These opioids may be associated with the serotonin syndrome when combined with antidepressants. Fentanyl and oxycodone are also associated with the serotonin syndrome, likely by a mechanism independent of serotonin and NE reuptake inhibition. Buprenorphine does not block serotonin and norepinephrine reuptake nor is it associated with the serotonin syndrome. (almost verbatim from Davis et al., 2018)

Buprenorphine Products

- For Addiction
  - Suboxone® et al.
- For Pain
  - Buprenex®
  - Butrans®
  - Belbuca®

Buprenorphine Products:

- Approved by FDA 1981 (Buprenex®) as a Sched. II injectable product for the treatment of acute pain (almost always inpatient use); based on the Harrison Act (1914), it was not approved for the treatment of opioid dependence (OUD) or opioid withdrawal
- Approved by FDA 2010 (Butrans®) as a Sched. III transdermal product for the treatment of chronic pain; based on the Harrison Act (1914), it was not approved for the treatment of opioid dependence (OUD) or opioid withdrawal
- In USA, Butrans strengths: 5, 7.5, 10, 15 and 20 µg/hr
  (7.5 and 15 µg/hr are newer)
- In Europe, BTDS strengths: 35, 52.5 and 70 µg/hr

Bup products

- Butrans BTDS approved in 2010 in US
- Strengths: 5, 7.5, 10, 15 and 20 µg/h over 7 d
- Wait a minimum of 3 days between dosage titrations (it takes 72 h to reach steady state)
- BTDS shares the common side effects of opioid therapy, such as nausea, headache, dizziness, constipation, and somnolence (maybe < fentanyl patch; see Davis et al.)
- Application site reactions (pruritis, erythema, rash) in 25%

Cote and Montgomery

- Butrans: max dose is 20 µg/h
- According to the manufacturer's prescribing information, this dose may not provide adequate analgesia for patients requiring more than 80 mg per day of oral morphine

Using BTDS

- The recommended initial dose selection is based on the MEDD that the patient is currently receiving, as those receiving less than 30 mg, and 30 to 80 mg of MEDD should be initiated on the 5µg/h and the 10 µg/h patch, respectively (Rudolf 2020).
- Maximum of 20 µg/h in the US: doses above this have been shown to cause QT prolongation.
- In the UK, the current dosage limit is 140 µg/h (Transtec® is the product name in Europe)

Using BTDS

- CAVEAT from Davis et al. – QTc intervals are prolonged when buprenorphine is combined with certain antiretroviral medications (delavirdine and ritonavir)

Buccal Film Buprenorphine:

- Approved by FDA 2015 (Belbuca®) as a Sched. III buccal product for the treatment of chronic pain; based on the Harrison Act (1914), it was not approved for the treatment of opioid dependence (OUD) or opioid withdrawal
- In USA, Belbuca strengths: between 75 and 900 µg BID (150-1800/d or about 6-72 µg/h), even with much greater bioavailability than the BTDS (75, 150, 300, 450, 600, 750, 900)

Bunavail

uniquely engineered drug delivery system, BEMA, now used in Belbuca®

- Disclosure: I was formerly on a Physician Advisory Board for Probuphine® (Braeburn Pharmaceuticals) and a Physician Advisory Board for Bunavail® (US WorldMeds) and a consultant to Curry Rockefeller Group re: physician and patient education and marketing materials for Bunavail®

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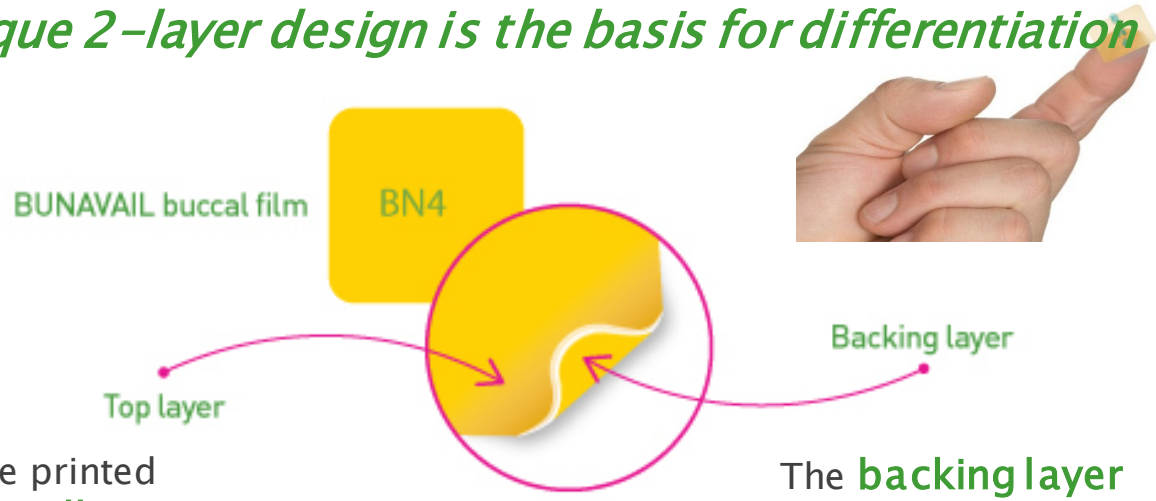

The printed **mucoadhesive layer** with active drug goes on the inside of the cheek

The **backing layer** was specifically designed to facilitate unidirectional flow of medicine

BEMA Potential Advantages

ADHERES → **DELIVERS** → **DISSOLVES**

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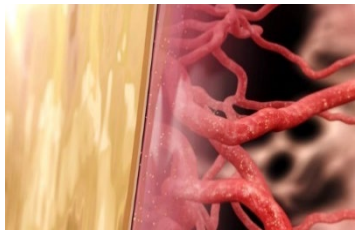
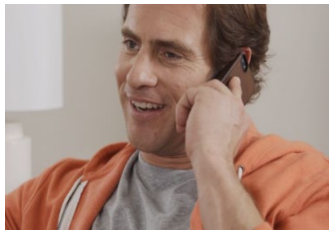
- Mucoadhesive layer adheres to oral mucosa upon contact



- Backing layer facilitates unidirectional flow across the oral mucosa, resulting in high bioavailability
- Drug absorbed within minutes



- Patient is free to talk while the film completely dissolves
- Pleasant taste

Webster et al. (2020)

- Buprenorphine buccal film (Belbuca) and the buprenorphine transdermal system (Butrans) are formulations indicated for the management of pain severe enough to warrant daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate.

Tom Kosten (2021)

- Bioavailability of bup via BTDS is less than bioavailability of bup via the SL film, which is less than bioavailability of bup via SL tablets
- Walter Ling found bio-avail of film = 60% that of tablets

Does bup work for pain?

Raffa et al. (2014)

Buprenorphine has a multimechanistic pharmacology, and thus partial agonist at a specific receptor is not particularly relevant to its overall analgesic action

Examined 24 controlled clinical trials and two other studies, to address “the issue of whether bup produces the same or different clinical analgesic efficacy as analgesics considered full agonists”

Findings: in 25 of 26 studies, there was full clinical analgesic effect

Raffa et al. (2014)

- IM bup 0.6 mg vs IM MSO4 15 mg after C-section
- IM bup 0.3 mg vs IM MSO4 10 mg after upper abd surg
- SL bup vs PCA MSO4 after prostatectomy
- IV bup vs IV MSO4 after elective abd surg, after coronary bypass surg, and after unilateral thoracotomy in children
- PCA bup vs PCA fentanyl after unilateral thoracotomy
- Bup patch vs fentanyl patch, oral morphine, oral oxycodone in cancer pain
- Also: Webster et al. (2020:) SL bup was as effective as IV morphine in managing acute renal colic pain (citing a group from Tehran)
- Also: Same group (Jalili et al.) reported that SL bup 0.4 mg is as effective and safe as IV morphine 5 mg for acute bone fractures in the ED

Rudolf (2020)

- The transdermal formulation was studied over periods of 3.4 years in patients with cancer pain and 5.75 years in patients with noncancer pain and was found to be subjectively effective for pain in 90% of all subjects (Likar et al., *Clin Ther* 28:943-52, 2006)
- In a German study that surveyed 9489 patients with noncancer pain who were treated with transdermal bup, 80% reported their pain as good or very good at final assessment, compared with 6% at initial assessment (Poulain et al., *Journal of Pain Symptom Management* 36:117-25, 2008)

Davis et al. (2018)

- Analgesia is equivalent to other opioids, but with a dose-related ceiling effect on respiratory depression, less constipation, and less hypogonadism, thus having a better therapeutic index than other potent opioids.
- Advantages include a ceiling on the euphoriant effects and on respiratory depression, but not on analgesia.
- Bup is not associated with fall risks and is not an immunosuppressant (unlike morphine and fentanyl, adds Kress 2009)

Webster et al. (Consensus Panel)

"The panel agreed that for buprenorphine the term *partial agonist* should not be translated as "partial efficacy."

Webster et al. (Consensus Panel)

"The prescribing information for the bup buccal film and the BTDS suggests that opioid-experienced patients be tapered down from their current daily opioid dose to ≤30 mg of oral MME before initiating therapy."

Do full opioid agonists work in the presence of bup?

Webster et al. (Consensus Panel)

"In most patients receiving transdermal or buccal buprenorphine who are undergoing a surgical procedure or who have sustained traumatic injuries, bup should be continued in the perioperative/trauma period. In these scenarios, a short-acting full μ-opioid receptor agonist with high binding affinity, such as fentanyl, hydromorphone, or sufentanyl, or IV buprenorphine, can be used in the short term in addition to the previously established buprenorphine regimen."

Clinical consensus:

- For patients on SL or other bup formulations for addiction, or for patients on BTDS or Belbuca for pain, who suddenly (emergency surgery, acute major trauma) need better pain relief, use fentanyl or hydromorphone (or Buprenex®)
- Why fentanyl?

Tom Kosten (2021)

- Why use fentanyl for pain control in a buprenorphine-maintenance patient? While bup works on the cAMP part of the G-protein linked MOR, fentanyl works at the β-arrestin part of the MOR

Kress (2009)

- In contrast to previous concerns based on preclinical animal data, a number of clinical and post-marketing surveillance studies have clearly shown that buprenorphine can be safely and effectively combined with full μ-agonists thereby providing **an addictive analgesic effect.**
- At clinically relevant doses, buprenorphine acts like a full μ-opioid receptor agonist.

Webster et al. (Consensus Panel)

"There is a misconception that bup will prevent the binding of and compromise the efficacy of concomitantly administered full μ-opioid receptor agonists in the perioperative period.

"Discontinuation of bup in a patient receiving stable therapy should be avoided, as discontinuing therapy may confer medical risk…. Patients who continue their usual bup dose perioperatively may also benefit by requiring less patient-controlled analgesia (PCA)."

Silverman, Raffa et al. (2017)

- (Because) bup may potentially displace or prevent the binding of competing MOR agonists, including immediate-release opioids, health care professionals may assume that the use of IR opioids for supplemental analgesia during BTDS therapy is not acceptable.
- Conclusion: Patients who were prescribed IR opioids (supplemental to transdermal buprenorphine) reported lower scores for pain intensity via the Brief Pain Inventory (BPI), without greater adverse events

Webster et al. (Consensus Panel)

"Upon discharge, patients may continue to require a full μ-opioid receptor agonist until their moderate to severe pain subsides, at which point the full μ-opioid receptor agonist can be weaned. A gradual return to baseline analgesic levels through dose titration may help to avoid withdrawal symptoms."

Rudolf (2020)

- Continuing use of buprenorphine as a baseline agent combined with another opioid after surgery or for treatment of acute pain of any cause has been shown in a multitude of studies to be safe and effective for analgesia.
- Because therapeutic doses of buprenorphine do not occupy 100% of available opioid receptors, unoccupied receptor availability can allow patients to achieve pain relief in varying degrees of a full opioid agonist is added to buprenorphine.

Heit and Gourlay (2008)

- Effective analgesia is achieved at a relatively low receptor occupancy of 5% to 10%.

Off-label Use of SL bup for pain

Best summaries: Cote and Montgomery (2014) and Kress (2009)

In UK, it's not off-label (different regulatory system; introduced to UK market in 2007)

Off-label Use of SL bup for pain

"Although it has been shown to be effective in the treatment of acute and chronic pain and has been indicated for the management of moderate-to-severe pain, sublingual buprenorphine was not used much in clinical practice, mainly owing to a widespread underestimation of its analgesic potency and some safety concerns based on the misinterpretation of experimental animal data." (Kress 2009)

Off-label Use of SL bup for pain

- The DEA at first said "don't do it" even though the DEA "has no opinion on the practice of medicine." (see Heit Gourlay "Open Letter to DEA")
- The Controlled Substances Act of 1970 mandates the Drug Enforcement Administration to provide a "closed system" for legitimate manufacturers, distributors, and dispensers of scheduled drugs. Such a closed system helps to reduce the diversion of these drugs from legitimate channels into the illicit market.
- DEA = diversion control

- Off-label use has not been uncommon, and is well documented in the medical literature
- Off-label prescribing is when a physician gives you a drug that the U.S. Food and Drug Administration (FDA) has approved to treat a condition different than your condition. This practice is legal and common. In fact, one in five prescriptions written today are for off-label use. https://www.ahrq.gov/patients-consumers/patient-involvement/off-label-drug-usage.html
- FDA = the practice of medicine, using products proven safe and effective at a given dosage range for a specific condition

Cote and Montgomery

- The risks of standard opioid therapy for chronic pain are well-known: tolerance, dependence and addiction, hyperalgesia, hypogonadism, and immunosuppression are among the most significant. Unlike full MOR agonists, buprenorphine may have a wider safety profile, especially with respect to respiratory depression, and kappa antagonism has been associated with less risk of dysphoria and other psychotomimetic effects.

Cote and Montgomery (2014)

- Ten trials involving 1190 patients were included
- All studies reported that sublingual buprenorphine demonstrated some effectiveness as a chronic pain analgesic. One study: less nausea, dizziness and vomiting with the patch compared to sublingual tablets
- The majority of studies were observational and of low quality.
- Low-dose sublingual buprenorphine tablets (200 µg) have been available in Europe since 1982 as a strong analgesic for the relieve of severe pain (e.g., following surgery or injuries, in myocardial infarctions, and in cancer).

SL bup for pain (Rudolf 2020)

- The FDA permits the use of sublingual buprenorphine as an off-label analgesic, despite common perception otherwise.
- Onset of effect is 30 to 60 minutes following dosing, with a peak at 1 to 4 hours.
- Its pronounced antihyperalgesic effect is a compelling pharmacologic attribute that make it particularly attractive as an option for patients habituated to long-term, high-dose opioids who may be experiencing hyperalgesia.

Cote and Montgomery (2014)

- As the equianalgesic dose of buprenorphine has been debated and not fully established, caution is recommended during opioid rotation
- [Kress 2009 says 25-100x more potent than morphine]
- Current guidelines for the use of buprenorphine in opioid dependence suggest stopping all previous opioids and allowing withdrawal symptoms to manifest prior to initiating bup/nal. The available published clinical experience using sublingual bup for chronic pain has reported a similar method.

Daitch et al. (2012)

- Retrospective study of 104 patient converted from full MOR agonists to SL bup
- Using a 10-point visual analog scale of pain intensity, those who stayed on SL bup 6 months reported a drop in paid scores of 2.3
- Largest reductions in pain scores (2.7)were among those on 100-199 MMED vs 200-399 or 400+ MMED
- Largest reductions in pain scores were among those converted from morphine, oxycodone and fentanyl
- But these patients did not have increase in QoL scores

How to prescribe the SL product for pain

- Buprenorphine formulations for maintenance therapy can be used off-label for analgesia but must be clearly marked on the prescription that the intent is analgesia (Davis et al., 2020).

Miller commentary: write “for pain” in instructions. But realize that some pharmacies won’t fill it without the prescriber having an X number, and some pharmacy benefit plans won’t cover the DATA 2000 drugs for the indication of pain (PA requires ICD 10 code for OUD)

Thank you!

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Bibliography

"Buprenorphine for Pain Management"
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Sublingual Buprenorphine as an Analgesic in Chronic Pain: A Systematic Review. Cote J, Montgomery L. *Pain Medicine.* 151171-78 (2014).

The Clinical Analgesic Efficacy of Buprenorphine. Raffa RB et al. *Journal of Clinical Pharmacy and Therapeutics.* 39:577-83 (2014).

Treating Chronic Pain: An Overview of Clinical Studies Centered on the Buprenorphine Option. Davis MP, Paternak G, Behm B. *Drugs* 78:1211-28 (2018).

Buprenorphine in the Treatment of Chronic Pain. Rudolf GD. *Phys Med Rehabil Clinics North Amer.* 31:195-204 (2020).

Sublingual Buprenorphine is Effective in the Treatment of Chronic Pain Syndrome. Malinoff HL, Barkin RL, Wilson G. *Amer Journal of Therapeutics.* 12:379-84 (2005).

Understanding Buprenorphine for Use in Chronic Pain: Expert Opinion. Webster L et al. *Pain Medicine.* 21:714-23 (2020).

Dear DEA (Open Letter). Heit HA, Covington E, Good PM. *Pain Medicine.* 5:303-08 (2004).

Conversion of Chronic Pain Patients from Full-Opioid Agonists to Sublingual Buprenorphine. Daitch J et al. *Pain Physician.* 15:ES59-ES66. (2012).

Use of Immediate-Release Opioids as Supplemental Analgesia during Management of Moderate-to-Severe Chronic Pain with Buprenorphine. Silverman S, Raffa R. et al. *Journal of Pain Research.* 10:1255-63 (2017).

Medication-Assisted Therapies for Opioid Use Disorders in Patients with Chronic Pain. Oesterle T et al. *Journal of the Neurological Sciences*. 411:116728 (2020). (online prior to print).