

PALLIATIVE PEARLS

BY ENCLARA PHARMACIA

Substance Abuse and Pain October 2017

Patient Case

JB is a 67 year old female with lung cancer with suspected bone metastases and comorbidities of depression and chronic back pain from a work-related injury 10 years ago. She has a past history of substance use disorder (tobacco, prescription oxycodone and heroin) and no known drug allergies. JB quit smoking and has not used drugs or alcohol for the past 4 years.

JB's depression is managed with Bupropion SR 150mg twice daily and is prescribed Butrans® 15mcg/hr transdermal patch weekly for opioid dependence. When admitted to hospice 1 month ago, her scheduled naproxen 500mg BID regimen for back pain was replaced with Dexamethasone to help manage dyspnea in addition to bone pain attributed to cancer. Despite titrating her Dexamethasone to 8mg BID the prior week, she is experiencing only moderate relief of her discomfort. JB and her caregiver are concerned that her pain will worsen and are hesitant to initiate opioids. Based on the typical trajectory of metastatic lung cancer, the interdisciplinary team agrees that the use of opioids will be inevitable to adequately manage her symptoms.

WHAT IS SUBSTANCE ABUSE AND HOW DOES IT RELATE TO OPIOID USE DISORDER?

Substance abuse is defined as taking a substance to “modify or control mood or state of mind in a manner that is illegal or harmful to oneself or others.”¹ Substance abuse pertaining to opioids can lead to **opioid use disorder**, a manifestation of at least two of the following within 12 months:^{2,3}

- Opioids taken in larger quantity or longer durations than originally planned
- Continuing desire to cut back, or failed efforts to cut back
- Significant time spent obtaining or using the opioid, or recovering from its effects
- Craving, or strong desire or urge to use
- Use interferes with obligations
- Use continues despite knowledge of having persistent or recurrent physical or psychological problem likely caused or worsened by the opioid
- Important social, work or recreational activities are abandoned or reduced due to opioid use
- Opioids are used in situations where use is physically hazardous
- Tolerance to opioids, defined by the need for markedly increased amounts to achieve intoxication or desired effect OR markedly diminished effect with continues use of the same amount

-Note: This criterion is not considered to be met for patients taking opioids solely under the appropriate medical supervision.

PALLIATIVE PEARLS

BY ENCLARA PHARMACIA

- Withdrawal, as manifested by anxiety, restlessness, rhinorrhea, lacrimation, dilated pupils, nausea, vomiting, diarrhea and abdominal cramps OR opioids are taken to relieve or avoid withdrawal symptoms

-Note: This criterion may not be considered indicative of abuse in all patients but rather a sign of physical dependence and may not be met for patients taking opioids solely under the appropriate medical supervision.

The United States is in the midst of a serious public health epidemic of opioid use disorder. The 2015 National Survey on Drug Use and Health estimate that 3.8 million Americans use opioid for non-medical reasons every month. Drug overdoses are now the number one cause of unintentional death. In 2015, 63.1% of drug overdose deaths involved an opioid.

Managing pain in patients with a current or past history of an opioid use disorder (OUD) is challenging. Patients in remission are often fearful of using opioids, even when experiencing severe pain near the end-of-life. On the other hand, patients actively abusing opioids are difficult to assess properly and may misuse prescribed opioids or other medications. Patients with active OUD should be referred to a formal addiction treatment clinic. It is not recommended to start opioid therapy in a patient that is actively using drugs to maintain a OUD except for those with a limited prognosis or with an acute pain issue (i.e., broken bone).^{4,5}

WHICH MEDICATIONS ARE APPROVED FOR OPIOID USE DISORDER AND HOW DO THEY COMPARE?^{2,6}

Patient JB's medication, Butrans[®], contains buprenorphine, a mixed agonist-antagonist narcotic. This medication, when combined with naloxone, a narcotic antagonist, is prescribed for patients with a history of substance abuse to deter addiction and opioid use disorder. It should be emphasized that products containing narcotic antagonists, like naloxone, are NOT indicated for pain. Buprenorphine by itself is indicated for both opioid agonist dependence AND pain. Unlike full opioid agonists (i.e., methadone, morphine, oxycodone) buprenorphine's partial activity at the opioid receptors projects a ceiling to its pharmacological effects – this means that the danger of overdose, abuse and toxicity from buprenorphine is less compared to full opioid agonists (a good thing for opioid dependence) but it is not useful for severe levels of pain requiring > 80mg of oral morphine equivalent to relieve.

Buprenorphine:

- **Indication 1:** Pain - Transdermal (TD) patch (Butrans[®]), transmucosal (Belbuca[®]), IM/IV (Buprenex[®])
- **Indication 2:** Opioid agonist dependence - TD patch, subdural implant (Probuphine[®]), sublingual tablet (Subutex[®])
- **How it works:** Mixed opioid agonist-antagonist
- **Advantage(s):** Easier to titrate and taper than methadone; Safer in pregnancy compared to combination buprenorphine-naloxone

PALLIATIVE PEARLS

BY ENCLARA PHARMACIA

- **Disadvantage(s):** Can precipitate withdrawal; More abuse potential compared to combination buprenorphine-naloxone
- **Converting *From* OME To Buprenorphine transdermal patch (Butrans®):**

A buprenorphine to OME (in mg) conversion ratio of 1:75 has been suggested by expert opinion however in recent years, literature has supported ranges from 1:70 to 1:100.⁷ Utilizing a conversion ratio should not replace clinical judgment. Note that the TD patch is in “mcg/hr” and the ratio is in “mg/day”.

See [Butrans® prescribing information](#) for recommendations^{8,18}

- **Converting *From* OME To Buprenorphine buccal film (Belbuca®):**

See [Belbuca® prescribing information](#) for recommendations^{8,19}

-

- **Converting *From* OME To Buprenorphine sublingual tablet (Subutex®):**

Off-label use as this dosage form is not formally indicated for pain and data is limited on this indication.⁹ A buprenorphine to OME (in mg) conversion ratio of 0.4:30 has been suggested by expert opinion in the literature however should not replace clinical judgment⁷

There is no literature on a transition *From* SL buprenorphine *To* another opioid. Attempting to convert SL buprenorphine to another opioid using the ratio above is NOT supported as it often yields a larger than expected opioid dose/day.^{9,10,11}

Methadone (Dolophine®, Methadose®):

- **Indication(s):** (1) Pain (2) Opioid agonist dependence
- **How it works:** Opioid agonist; blunts opioid euphoric effect due to slow onset and long duration of action; suppresses withdrawal and craving³
- **Advantage(s):** Most affordable; drug of choice in pregnancy
- **Disadvantage(s):** Higher risk of CNS and respiratory depression and QTC prolongation; Abuse potential; Drug interactions
- **Conversion between oral morphine equivalents (OME):** Conversion ratio *From* OME *To* methadone is variable and dependent on a number of factors based on the chosen method/model for conversion and indication for use.⁷

Buprenorphine-naloxone (Suboxone®, Zubsolv®, Bunavail®):²

- **Indication(s):** Opioid agonist dependence
- **How it works:** Buprenorphine is a mixed opioid agonist-antagonist; Naloxone is an opioid antagonist

PALLIATIVE PEARLS

BY ENCLARA PHARMACIA

- **Advantage(s):** Easier to titrate and taper than methadone; When used sublingually or buccally, naloxone effect is minimal due to very low absorption; If misused by injection, naloxone may block the effects of buprenorphine which increases the likelihood for withdrawal
- **Disadvantage(s):** Can precipitate withdrawal; Concerns that naloxone may cause withdrawal in fetus for pregnant patients; NOT indicated for pain
- **Conversion between oral morphine equivalents (OME):** N/A

Naltrexone (ReVia®, Vivitrol®):

- **Indication(s):** Opioid agonist dependence
- **How it works:** Opioid antagonist
- **Advantage(s):** Cannot be abused; good choice for highly motivated patients
- **Disadvantage(s):** Can precipitate withdrawal in patients who have not been abstinent from short acting opioids for at least 7 days and at least 10 days from long acting opioids; NOT indicated for pain
- **Conversion between oral morphine equivalents (OME):** N/A

WHAT ARE SOME COMMON MISCONCEPTIONS FOR PATIENTS WITH PAIN AND OPIOID USE DISORDER?^{2,12,13}

- **FALLACY:** The maintenance opioid agonist (methadone or buprenorphine) is providing analgesia
FACT: For patients being treated solely for opioid use disorder, medications are prescribed at low doses to only suppress withdrawal, not for analgesia
- **FALLACY:** Use of opioids for analgesia may result in addiction relapse
FACT: There is currently no evidence to suggest that exposure to opioid analgesic for acute pain increases the rate of relapse. On the contrary, theories suggest that stress associated with unrelieved pain is more likely to trigger relapse.
- **FALLACY:** The additive effects of opioid analgesics and medication for opioid use disorder may cause severe CNS and respiratory depression
FACT: For patients being treated for opioid use disorder on a maintenance dose, tolerance to CNS and respiratory effects for the maintenance dose has already occurred. The use of short term opioid analgesics under medical supervision (in addition to the maintenance dose) have never been clinically demonstrated to cause severe drug toxicity
- **FALLACY:** The pain complaint is drug-seeking behavior
FACT: Pain is highly subjective. A careful clinical assessment of objective evidence for pain will be required to assess the difference between pain and drug-seeking behavior.

HOW SHOULD PAIN BE TREATED IN PATIENTS USING BUPRENORPHINE FOR OPIOID USE DISORDER?

Pain Assessment:

PALLIATIVE PEARLS

BY ENCLARA PHARMACIA

- Perform a history of past and present, including quantity used, of tobacco, alcohol, prescription and recreational drug abuse AND use a validated screening tool to assess risk of opioid misuse (i.e., [Screener and Opioid Assessment for Pain Patients \(SOAPP\)](#) and the [Opioid Risk Tool \(ORT\)](#) ^{14,15,16}
- Differentiate active substance use, at-risk behaviors, recovery, and enrollment in a treatment program.
- Evaluate for depression and anxiety, or other potential treatable psychiatric disorder, which are common both in chronic pain and those with SUDs
- Assess for current use of sedatives (like muscle relaxants and benzodiazepines)⁵

Initial Management:

- Describe treatment expectations
- Refer to an addiction specialist/clinic when possible to provide a multi-disciplinary approach. If patient is already under the care of a specialist practice, consult the team to care plan
- Continue with opioid use disorder treatment dose or dose equivalent to minimize withdrawal
- Utilize a written opioid agreement that includes safe practices and consequences. This may give motivated individuals a sense of control over their SUD. Components of an opioid agreement include: establishing a single opioid prescriber, using a single pharmacy, employing pill counts and periodic urine drug testing
- Consider checking your state's prescription drug monitoring program to ensure that the patient is not obtaining prescriptions from other prescribers
- Consider non-pharmacologic and non-opioid therapies (i.e., physical therapy, acupuncture, topical remedies, NSAIDS) first

Treatment Options:¹²

1. Continue buprenorphine maintenance therapy AND titrate a short-acting opioid analgesic to effect
2. For buprenorphine regimens administered daily or BID, consider dividing the daily dose of buprenorphine and administer it every 6 to 8 hours to take advantage of its analgesic properties.
3. Discontinue buprenorphine therapy and treat the patient with full scheduled opioid agonist analgesics by titrating to effect to avoid withdrawal and then to achieve analgesia.
 - When discontinuing buprenorphine therapy, it is suggested to choose a conservative dose and regimen of the new opioid and titrate based on patient response.
 - When adding short-acting opioids for pain control, keep in mind that cross tolerance is likely which may require higher doses for adequate pain relief
 - Short-acting opioids are recommended on a scheduled basis (not as needed), especially for patients with anxiety about pain
4. If the patient is hospitalized with acute pain, his or her baseline opioid requirement can be managed and opioid withdrawal can be prevented by converting buprenorphine to methadone at 30 to 40 mg/day. If opioid withdrawal persists, subsequent daily methadone doses can be increased in 5 to

PALLIATIVE PEARLS

BY ENCLARA PHARMACIA

10mg increments. This method allows titration of the opioid analgesic for pain control in the absence of opioid withdrawal.

Monitoring: ^{2,5}

- For patients with substance abuse disorder **in remission**, the goal (as with any other patient in pain) is to provide adequate pain relief, but also to focus on preventing relapse. Relapse is attributed to both intrapersonal and interpersonal stressors (i.e., pain-related diminished quality of life, untreated depression, emotional and social distress) and the inability to utilize an effective coping response.
- **Regularly ask about other substances** or using their pain medication to get high or cope with stressors – remind them that these are questions asked of all patients
- **Frequent contact and/or visits** allow for close patient observation and prescription of **limited quantities of opioids**
- **Readdress opioid agreement**
- To identify relapse, screening tools such as urine drug screenings and prescription monitoring programs can be utilized. If relapse is identified and opioid detoxification is attempted, slowly taper opioid dose (usually no more than 20-25% every 2 days) to minimize withdrawal symptoms and then discontinue. It is critical to continue to support efforts towards recovery and maintain control over opioid access. Relapse should not be considered a treatment failure, but is a part of the process of recovery from an addictive disease to successful pain management.
- Recognize that addiction is a chronic, relapsing illness – and respond with increasing structure and compassion

ASSESSMENT & MANAGEMENT - PATIENT CASE:

Assessment of JB using the Opioid Risk Tool shows that current risk of misuse is low. JB was screened for anxiety and depression upon admission and is managed well on bupropion and currently is not prescribed anxiolytics or muscle-relaxants. Non-opioid pain therapies have been trialed including naproxen, and now dexamethasone, but are not fully relieving “old” chronic back pain, “new” bone pain nor dyspnea.

The hospice discusses with JB and her caregiver that opioid therapy seems the best option to relieve both her old and new symptoms. The Butrans 15mcg/hr patch is limited for the pain she is experiencing and pain may worsen, further limiting its use. JB agrees to opioid therapy. Expectations of JB and her caregiver are then reviewed, as well as instructions on proper disposal of unwanted medications. A patient-provider agreement on opioid safe practices and consequences is implemented. Medication instructions are as follows:

Day 1: Decrease Butrans to 10mcg/hr with initiation of Morphine (Roxanol) 20mg/mL oral concentrate at a dose of 0.25mL (5mg) PO every 4 hours as needed for pain.

PALLIATIVE PEARLS

BY ENCLARA PHARMACIA

Around Days 4-7: Decrease Butrans to 5mcg/hr and assess use of breakthrough morphine and adjust dose/regimen accordingly.

Day 8 or later: Remove Butrans patch and begin scheduled use of Morphine. At this time, consideration can be made for beginning methadone scheduled therapy for pain or another long-acting opioid.

Methadone is preferred as it manages mixed types of pain, is associated with less abuse potential compared to other opioids and JB is not at risk for drug-disease interactions. Bupropion poses a moderate drug-drug interaction causing increased levels of methadone, however a methadone dose adjustment can be made to account for this interaction at the time of dose conversion.

References:

1. Chang Y, Compton P. Management of chronic pain with chronic opioid therapy in patients with substance use disorders. *Addiction Science & Clinical Practice*. 2013; 8:21.
2. PL Detail-Document, Management of Opioid Dependence. Pharmacist's Letter/Prescriber's Letter. August 2015.
3. Opioid use disorder: Diagnostic criteria. American Psychiatric Association. Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, 2013. [PDF link](#)
4. Reisfield GM, Paulian GD, Wilson GR. Fast Facts and Concepts #127: Substance abuse disorders and the palliative care patient. 2015 July. [Article link](#)
5. Kennedy AJ, Arnold RM, Childers JW. Facts and Concepts #311: Opioids for chronic pain in patients with history of substance use disorders part 1: Assessment and initiation. 2016 Feb. [Article link](#)
6. Clinical Pharmacology [database online]. Tampa, FL: Elsevier/Gold Standard, Inc.; 2017. Accessed 2017 Sep 8.
7. McPherson ML. 2011 Update In: Demystifying opioid conversion calculations: A guide for effective dosing. ASHP, Inc, Bethesda; 2011: 15-31.
8. PL Detail-Document, Equianalgesic Dosing of Opioids for Pain Management. Pharmacist's Letter/Prescriber's Letter. July 2015.
9. PL Detail-Document, FAQs About Buprenorphine for Chronic Pain. Pharmacist's Letter/Prescriber's Letter. February 2016.
10. Daitch J, Frey M, Silver D, et al. Conversion of chronic pain patients from full-opioid agonists to sublingual buprenorphine. *Pain Physician* 2012;15:ES59-66.
11. Foster B, Twycross R, Mihalyo M, Wilcock A. Buprenorphine. *J Pain Symptom Manage* 2013;45:939-49.
12. Alford D, Compton P, Samet J, et al. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. *Ann Intern Med*. 2006 January 17; 144(2): 127-134.
13. Volkow ND, McLellan AT. Opioid abuse in chronic pain - misconceptions and mitigation strategies. *N Engl J Med* 2016;374:1253-63. [PDF link](#)
14. Claxton R, Arnold RM. Facts and Concepts #244: Screening for opioid misuse and abuse. 2015 Aug. [Article link](#)
15. Course-in-a-box: The Screener and Opioid Assessment for Patients with Pain (SOAPP) in Clinical Practice. PainEDU.2017 Aug 1. Accessed 2017 Oct 9. [Site link](#)

PALLIATIVE PEARLS

BY ENCLARA PHARMACIA

16. Webster L. Opioid Risk Tool (ORT). OpioidRisk.com. 2005. Accessed 2017 Oct 9. [PDF link](#)
17. Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction. U.S. Department of Health and Human Services: Substance Abuse and Mental Health Services Administration (SAMHSA) – Center for Substance Abuse Treatment
18. Butrans® prescribing information. Accessed 2017 Sep. Available from: <https://butrans.com/>
19. Belbuca® prescribing information. Accessed 2017 Sep. Available from: <https://www.belbuca.com/hcp/>