De-escalation of Opioids and Long-Term Management.

Theresa Davis, NP
Brenna McCarty, NP
Anita Kuzhiyil, MD

Disclosures

- None to report

MASSEY COMPREHENSIVE CANCER CENTER VCU

Objectives

1. Explore the pharmacologic properties of buprenorphine and its use in cancer-related pain
2. Define appropriate criteria for buprenorphine use in patients with cancer related pain and concomitant opioid use disorder
3. Explore methods to initiate and transition to buprenorphine in clinical care
4. Determine when opioid de-escalation is clinically indicated in oncology patients
5. Explore a few de-escalation protocols and taper strategies.

MASSEY COMPREHENSIVE CANCER CENTER VCU

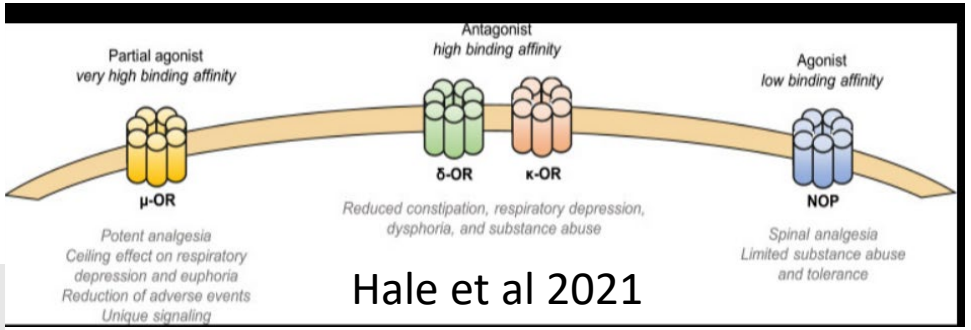
Buprenorphine

- Schedule III semisynthetic opioid
- Partial agonist to μ receptor with strong affinity to μ opioid receptor
  - Displaces other μ -agonists
- Slow association and dissociation from u opioid receptor -> longer duration of action long analgesic half life.
- Chaperone ligand: induces μ opioid receptor expression
- Highly lipophilic, limited PO bioavailability -> well absorbed in oral mucosa, skin

Boas et al 1985,
Gudin et al 2020

Buprenorphine Mechanism of Action

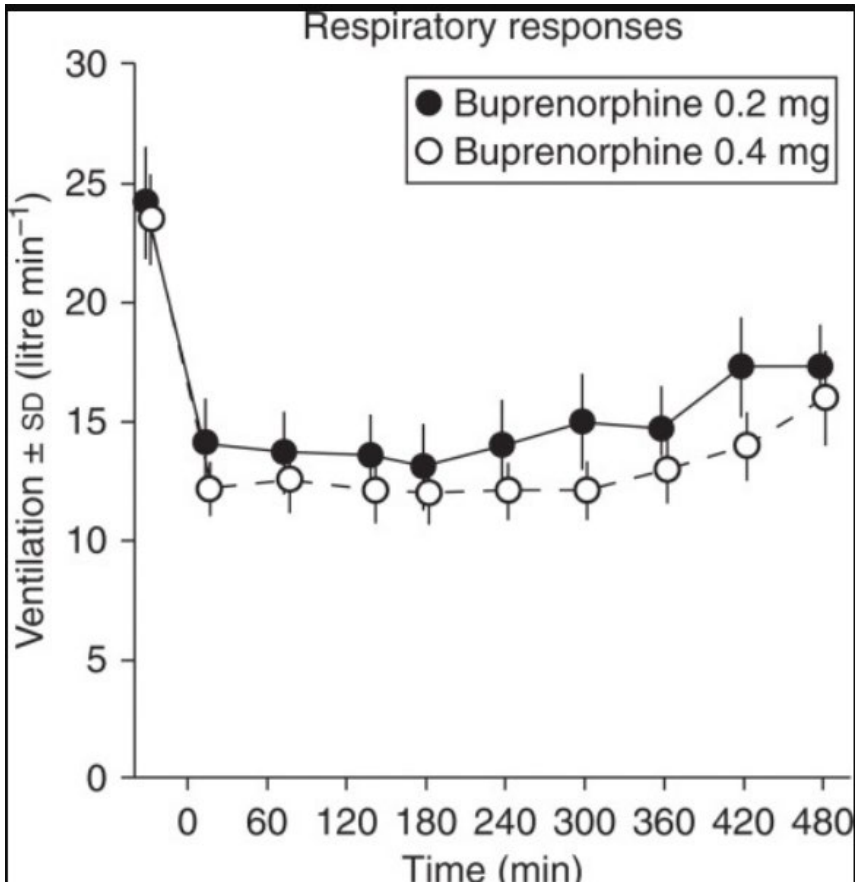
Receptor	Activity	Clinical effect
μ-opioid (MOR)	**Partial agonist** High potency and slow dissociation	Analgesia, Reduced resp dep Limited impact on GI motility Reduced risk overdose
κ-Opioid (KOR)	Antagonist	Mood effects: reduce dysphoria, depression, anxiety (may improve mood) Blocks central sensitization/reduced hyperalgesia
δ opioid (DOR)	Antagonist	Modulates mood Limited impact on GI motility
ORL-1/NOP	Full agonist	Supraspinal analgesia, anxiolysis Dampen brain reward system, implying less tolerance and reward

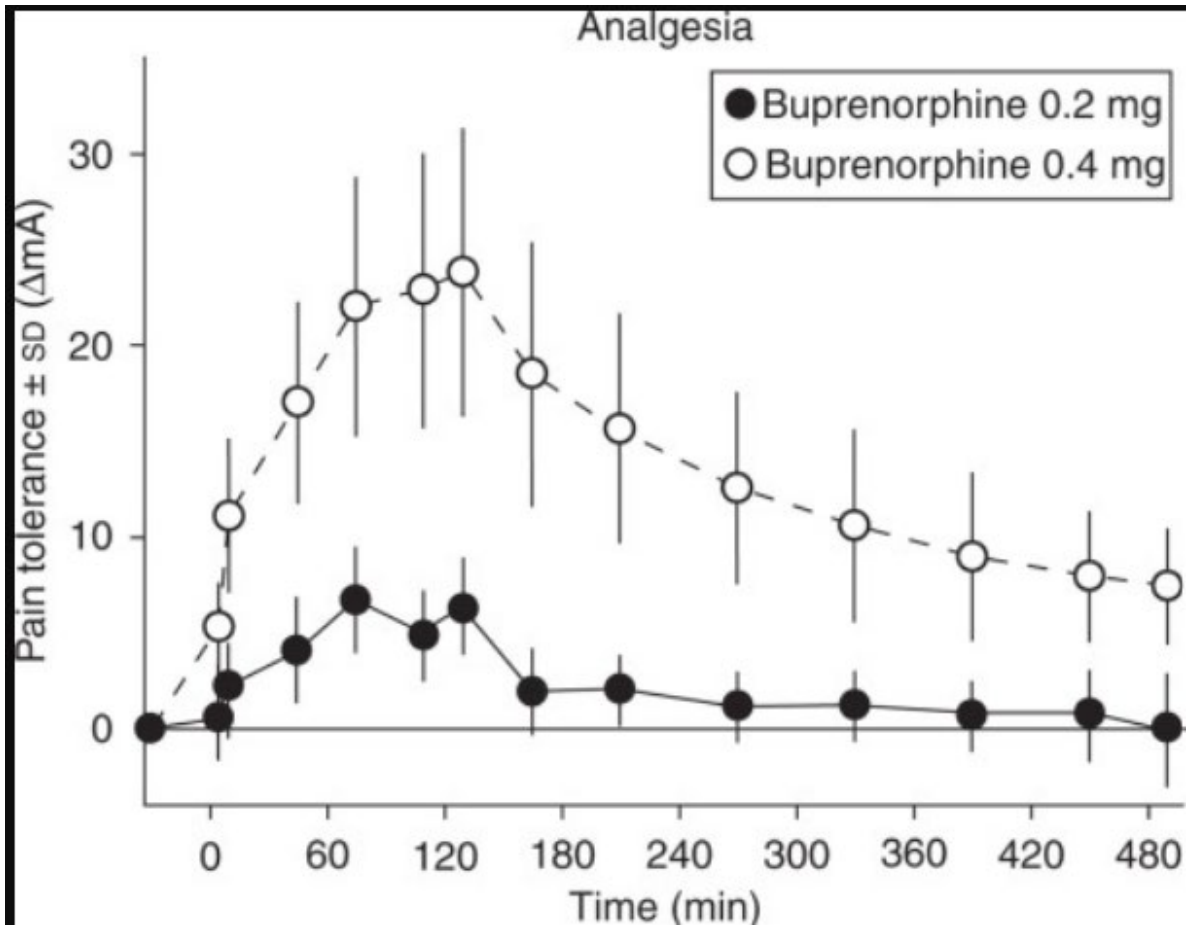


Hale et al 2021

Gudin et al 2020

Ceiling effect on resp depression not analgesia

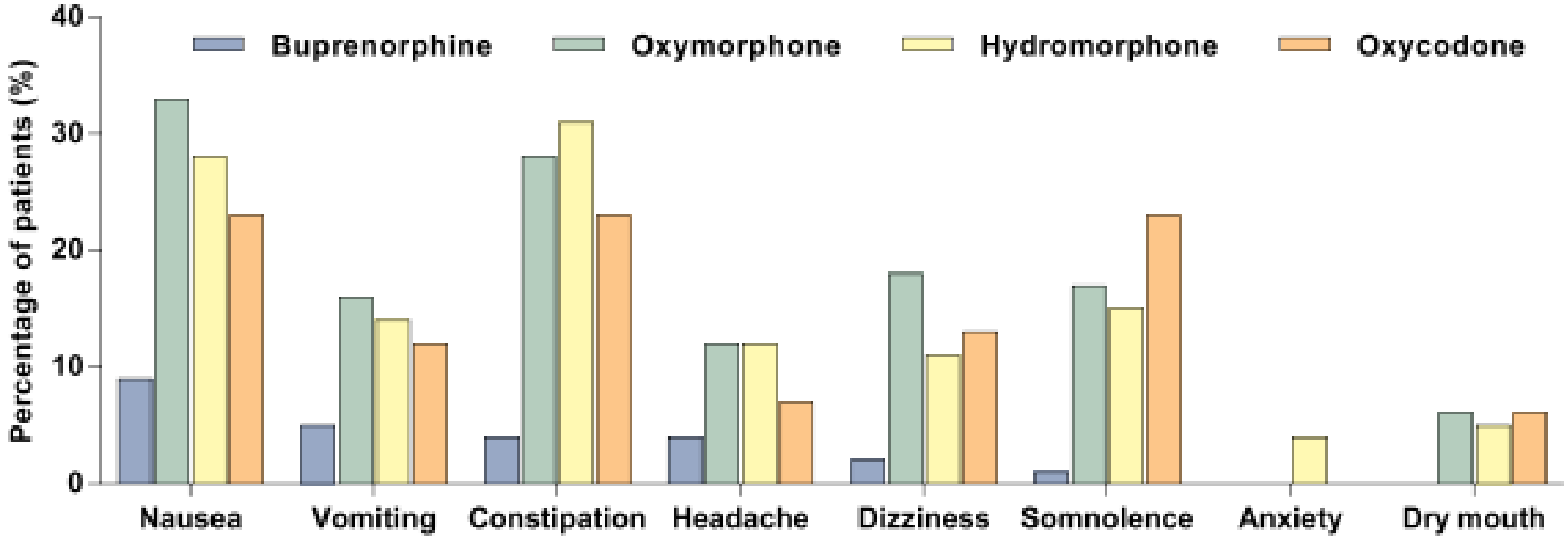




Dahan et all 2006

MASSEY COMPREHENSIVE CANCER CENTER VCU

Adverse events – Bupe vs conventional opioids



Pergolizzi et al 2019,
Hale et al 2021

MASSEY COMPREHENSIVE CANCER CENTER VCU

Indications

- Active disease
  - Elderly/frail, cannot tolerate MOR d/t side effects, renal failure – with stable pain
  - Cancer related pain **– stable pain/ neuropathic pain.**
  - Hx or active OUD/SUD + cancer related pain – mOUD
- Cancer survivors
  - Chronic pain
  - Hx or active OUD - mOUD
  - Taper off full agonists
- Aberrant use; non-medical opioid use – sharing/selling/diversion
- Chronic persistent opioid use disorder
- Risky behavior/ substance use

Mattick et al
2014

MASSEY COMPREHENSIVE CANCER CENTER VCU

Common misconceptions

- X waiver no longer required – can be prescribed by anyone with a DEA for chronic pain/ OUD
- Powell et al 2021 – systematic review
  - Incidence of **precipitated withdrawal** is rare (27, 36) – esp with newer techniques of bupe initiation.
  - **Improved analgesia** observed after rotation (27, 35, 36, 37)
  - **Improvement in function** observed after rotation (35, 37)
- Overdose on buprenorphine can happen – typically involves con-ingestion of benzodiazepine / High dose opioids/ other CNS depressants;
- Naloxone component in Suboxone (bup+naloxone) – abuse deterrent
- Adding short acting full agonists on top of bupe can help manage breakthrough/acute pain – it can still have analgesic effects.

MASSEY COMPREHENSIVE CANCER CENTER VCU

Side effects and special considerations

- Respiratory depression
  - Ceiling effect on respiratory depression
  - When compared fentanyl 13 fold safety
- QT prolongation – however ↑Qtc not shown to result in clinical meaningful outcomes likely drug induced arrhythmias (eg. torsades) in the absence of other risk factors (123, 124)
  - Torsade de pointes and sudden cardiac death -> 4x more likely with methadone than buprenorphine
- Safe in renal failure – excreted through bile
- Safe in liver failure
  - Avoid naloxone except decompensated liver failure/Childs pugh C – so can use bupe mono-product

Formulations & Dosing in Cancer Pain

Transdermal (Butrans®) $$

Every 7 days

Doses: 5, 7.5, 10, 15, 20 mcg/hr
Preferred for stable chronic cancer pain; avoid in fever/diaphoresis; not for opioid-naive only

Sublingual (Subutex®/generic) $ and Suboxone

Q6–12h

Doses: 0.2–2 mg
Widest dose range; useful when other routes unavailable; off-label for pain

Buccal Film (Belbuca®) $$$

Q12h

Doses: 75–900 mcg
Rapid titration; useful for breakthrough or rotation; good for mucositis if placed carefully

IV/IM (Buprenex®)

Q6–8h

Doses: 0.3 mg/dose
Inpatient use; acute pain or post-op; can dose-stack with caution

Equianalgesic note: Buprenorphine 0.3 mg IV ≈ morphine 10 mg IV; TD 20 mcg/hr ≈ oral morphine 30–45 mg/day | Davis MP, Ann Palliat Med 2012; NCCN Guidelines 2023

To initiate opioid-experienced patients on BELBUCA[1]:

STEP 1		STEP 2	STEP 3: Titrate in increments of 150 mcg					
IDENTIFY CURRENT DAILY MME	TAPER OPIOID-EXPERIENCED PATIENTS	BELBUCA STARTING DOSE†	TITRATE BELBUCA TO OPTIMAL DOSE‡					
			1	2	3	4	5	6
<30-mg oral MME	Taper opioid-experienced patients current opioid dose to ≤30-mg MME daily	75 mcg QD or q12h	150 mcg	300 mcg	450 mcg	600 mcg	750 mcg	900 mcg
30–89-mg oral MME		150 mcg q12h	300 mcg	450 mcg	600 mcg	750 mcg	900 mcg	
90–160-mg oral MME		300 mcg q12h	450 mcg	600 mcg	750 mcg	900 mcg		

To reach optimal dose, BELBUCA can be titrated every 4 days[1]

Optimal dose was defined as a dose satisfactory for both analgesia and tolerability[2]:
- without the need for rescue medication, OR
- with no more than 2 tablets of HC/APAP per day

Scan for MME Conversion Calculator
or locate at belbuca.com/hcp

†For opioid-naive and opioid-intolerant patients, begin at 75 mcg QD or q12h. Only doses up to 450 mcg q12h were studied in opioid-naive patients.
‡**To mitigate the risk of QTc interval prolongation, do not exceed the maximum dose of 900 mcg every 12 hours.** If pain is not managed at this maximum dose, or for patients previously taking >160-mg MME, consider an alternate analgesic.

MASSEY COMPREHENSIVE CANCER CENTER VCU

Adding Buprenorphine with other opioids

- Adding Buprenorphine can be successfully accomplished in the outpatient setting with close monitoring

Day #	Buprenorphine/naloxone (mg)	
• 1	0.5 mg/0.125 mg (1/4 of a 2 mg film)	
• 2	0.5 mg/0.125 mg (1/4 of a 2 mg film)	
• 3	1 mg/0.25 mg (1/2 of a 2 mg film)	
• 4	2 mg/0.5 mg (One 2 mg film)	BID
• 5	4 mg/1 mg (One 4 mg film)	BID
• 6	8 mg/2 mg (One 8 mg film)	BID

- **CONTINUE Full Agonist** Day 1 – Day 5; discontinue Day 6/transition to breakthrough pain

Combining with other pain medication

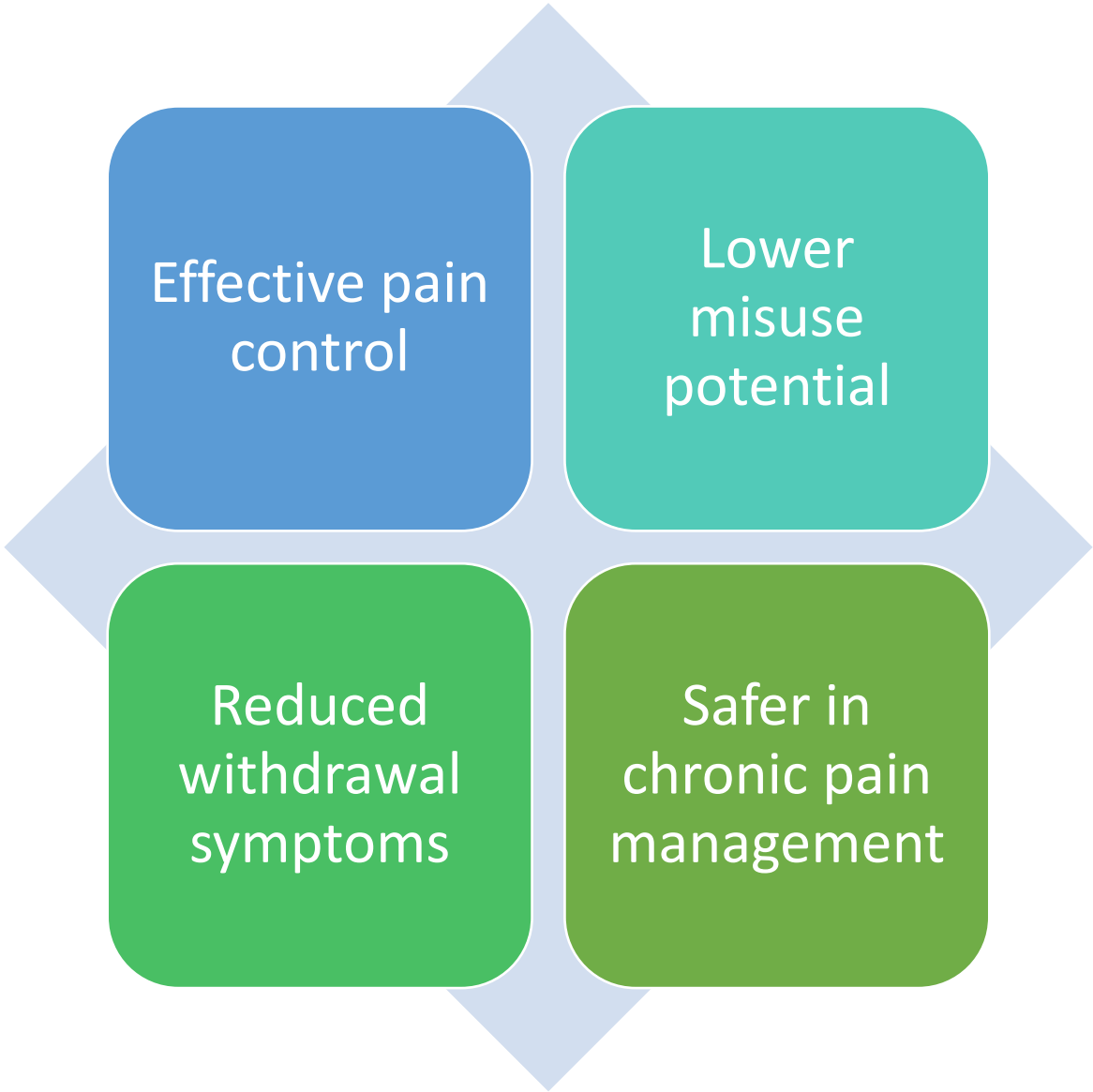
Often paired with non-opioid pain medications

May be used alongside certain full opioid agonists under careful monitoring

Helps reduce overall opioid requirements

MASSEY COMPREHENSIVE CANCER CENTER VCU

Benefits



MASSEY COMPREHENSIVE CANCER CENTER VCU

Risks and precautions

- Sedation
- Possible interaction with other opioids
- Requires constant medical oversight
- Risk increases for sedation and resp depression when combined with alcohol, benzodiazepines, CNS depressants, skeletal muscle relaxants (1)

MASSEY COMPREHENSIVE CANCER CENTER VCU

Key takeaways

Buprenorphine can safely complement pain medication

Help manage pain while minimizing opioid risks

MASSEY COMPREHENSIVE CANCER CENTER VCU

Opioid De-escalation: Rationale & When to Consider

De-escalation: Planned reduction in opioid dose, potency, or frequency — in patients with improved pain control, remission, or opioid-related adverse effects — without compromising analgesia.

When to De-escalate

- Remission or significant response to oncologic therapy
- Nerve block, ablation, or interventional pain procedures
- Resolution of acute pain episode (post-surgical, pathologic fracture healed)
- Evidence of Opioid induced Hyperalgesia or dose-escalation without clinical benefit
- Patient preference / functional improvement
- Harms outweigh benefits, consider tapering opioids to lower dose or taper and discontinue (VA)

Common Barriers

- Fear of undertreated pain (patient & provider)
- Opioid dependence (physiologic) vs. addiction conflation
- Lack of standardized protocols in oncology
- Prognostic uncertainty in advanced cancer
- Patient anxiety about dose reduction
- Stigma & medicolegal concerns

J Pain Symptom Manage 2017; Koyyalagunta D et al., Pain Physician 2013

When to consider opioids tapering/de-escalation

- No pain reduction, no improvement in fxn or pt request to discontinue therapy
- Severe unmanageable adverse effects (e.g. drowsiness, constipation, cog impairment)
- Dosage indicates high risk of adverse events (eg 90 MEDD or higher)

- Non-Adherence to treatment plan or unsafe behaviors (early refills, lost/stolen prescription, buying or borrowing opioids, failure to obtain or aberrant UDT)
- Concerns related to an increased risk of SUD
- Overdose event involving opioids

- Medical comorbidities that can increase risk (lung disease, sleep apnea, liver disease, renal disease, fall, risk, advanced age)
- Concomitant use of medications that increase risk
- Mental health comorbidities that can worsen w/ opioid therapy (PTSD, Depression, Anxiety)

MASSEY COMPREHENSIVE CANCER CENTER VCU

US Dept of VA – Pain management opioid taper decision tool

De-escalation Protocol & Decision Framework

Assess Pain Control
(NRS ≤3/10 × ≥2 weeks)

Confirm No Active Disease Progression

Set De-escalation Goal
(Target OME reduction)

Slow Taper

10–20% OME decrease

American Pain Society 2009: 10% reduction weekly (Chou et al 2009)
Canadian national Opioid use Guideline Group 2010 : Taper 10% total daily dose every 1-2 weeks (Kahan et al 2011)
ASIPP 2012 Agency Medical Directors Group 2010: Taper by 10% of original dose per week. (Va 2010, WAMDG 2010))
VA 2010 : 5%-20% every 4 weeks.

Monitor DAILY pain scores
Maintain rescue access

Moderate Reduction

25–50% OME decrease

Veterans Affair 2010: taper 20-50% weekly (VA/dod 2010)

Scheduled pain reassessment
Interdisciplinary input

Discontinuation Path

>50% or full taper

American Pain society/American Academy of Pain med 2009: Rapid 25-50% reduction every few days.
VA 2010: Decrease by 20-50% daily until 30mg daily (13)
Canadian National Opioid use Guideline group: Taper by 10% of total daily dose every day; once 1/3 of original dose is reached reduce rate of taper by atleast 50%; consider rotation to Morphine. (14)

≥4–8 weeks minimum
Palliative care co-mgmt
Psychological support PRN

Monitoring: NRS q24–48h, withdrawal symptoms (COWS scale), functional status, sleep quality

VA/DoD 2010, Kahan 2011,

Case 1

- 55 y/o with hx of triple neg Breast CA s/p b/l mastectomy and chemoradiation; now NED initially presented to our clinic on Fentanyl 12mcg/hr TD Q72H, and Oxy-Ace (10-325) Q4H PRN; has been on this regimen for about 2-3 years
- Discussed plan to de-escalate, involvement of multidisciplinary team, routine assessment of pain and pain experience.
- Significant psychosocial distress – death in the family, close family diagnosed with end stage cancer
- UDS showed aberrant behavior – neg for one of the prescribed opioid, and positive for cocaine and transitioned to Suboxone (Slow induction); with continued taper of oxycodone-acetaminophen from Q4H dosing to stopping PRNs

- End result: Tapered over the course of ~ 2 years tapered off Fentanyl patch, and oxy-acet 10/325 Q4HPRN; and is now just on Suboxone 8/2 BID.
  - Referred to PT, pain psychology, addiction med for intermittent cocaine use

MASSEY COMPREHENSIVE CANCER CENTER VCU

Factors to consider

- **Physical pain – Chronic**
  - Characteristics – Sharp stabbing pain in pelvic/lower abdomen; non radiating; not worse with food/other factors.
  - Chronic back pain; DJD
  - Imaging no cancer; MRI of pelvis/spine – mild degenerative changes to spine and hips; no suspicions osseous lesions.
- **Psychosocial factors**
  - Death of close family members; family members diagnosed with end stage cancer
  - Car accident
- **Behavioral patterns**
  - Cocaine metabolites positive
  - UDS neg for Fentanyl patch which was prescribed.
- **Prognosis**
  - NED; Great prognosis
- **Performance status**
  - PPS 80

MASSEY COMPREHENSIVE CANCER CENTER VCU

Case 2

- 66 y/o with hx of recurrent ovarian cancer
- Home regimen: Oxycodone IR 10mg Q6H PRN (was previously on Fentanyl patch, Oxycontin 15mg Q12H)
- CT A/P: Stable for the past 6 months; 2mm lesion in ovary without any significant change in size.
- Presents to clinic for pain management

Case 2 contd.

- Opioid regimen: Oxycodone IR 10mg every 6 hours PRN
  - MEDD ~ 60
  - Given hx of illicit substance use; supplementing with Oxycodone that she isn't being prescribed.
  - Butrans patch 15mcg/hr – with Norco 7.5/325mg Q8H PRN

Table 1. Initial Buprenorphine Transdermal Patch Dose Recommendations

Previous Total Daily Opioid Dosage[a]	Initial Transdermal Dosage
Opioid-naïve	5 mcg/h
<30 mg	5 mcg/h
30-80 mg	10 mcg/h (must taper previous opioid for up to 7 days to no more than 30 mg of oral morphine [or its equivalent] per day prior to initiating patch)
>80 mg	Consider an alternative analgesic

[a] *In oral morphine-equivalents. Source: Reference 1.*

Factors to consider – Case 2

- **Physical pain – chronic/cancer related**
  - Characteristics – Sharp stabbing pain in pelvic/lower abdomen; non radiating; not worse with food/other factors.
  - Chronic back pain; hx of falls - DJD
  - Imaging - Good treatment response; stable tumour size
- **Psychosocial factors**
  - Childhood trauma, Hx of sexual abuse, Complicated grief (loss of a child and her mother),
  - Food insecurity
  - Insurance issues with psychiatrist
- **Behavioral patterns**
  - NMOU - Oxycodone use, Cocaine metabolites positive intermittently
- **Prognosis**
  - Great treatment response; prognosis ~years.
- **Performance status**
  - PPS 80

MASSEY COMPREHENSIVE CANCER CENTER VCU

Key Takeaways

- Buprenorphine has a unique and favorable pharmacologic profile, and can be used in cancer related pain
- Buprenorphine has a ceiling effect on respiratory depression but not on Analgesia
- Buprenorphine Induction/micro-induction strategies help reduce chances of precipitated of withdrawal
- Opioid de-escalation is feasible and appropriate in selected cancer patients
- Shared decision making, functional goals, and patient anxiety/psychosocial management are critical non-pharmacologic component of de-escalation.

MASSEY COMPREHENSIVE CANCER CENTER VCU

Questions

References

Boas RA, Villiger JW. Clinical actions of fentanyl and buprenorphine. The significance of receptor binding. Br J Anaesth. 1985;57(2):192-196.

Dahan A, Yassen A, Romberg R, et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. Br J Anaesth. 2006;96(5):627-632. doi:10.1093/bja/ael051

Dahan A, Yassen A, Bijl H, et al. Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. Br J Anaesth. 2005;94:825-834.

Davis MP. Buprenorphine in cancer pain. Support Care Cancer. 2012. [Referenced multiple times as Davis MP J Supp Onco 2012 and Davis MP Ann Palliat Med 2012]

Dupouy J, Palmaro A, Fatséas M, et al. Mortality associated with time in and out of buprenorphine treatment in French office-based general practice: a 7-year cohort study. Ann Fam Med. 2017;15(4):355-358. doi:10.1370/afm.2098

Gudin, Jeffrey, and Jeffrey Fudin. "A narrative pharmacological review of buprenorphine: a unique opioid for the treatment of chronic pain." *Pain and therapy* 9.1 (2020): 41-54.

Hale M, Garofoli M, Raffa RB. Benefit-risk analysis of buprenorphine for pain management. J Pain Res. 2021;14:1359-1369. doi:10.2147/JPR.S305146.

Harris SC, Morganroth J, Ripa SR, et al. Effects of buprenorphine on QT intervals in healthy subjects: results of 2 randomized positive- and placebo-controlled trials. Postgrad Med. 2017;129:69-80.

Kahan M, Wilson L, Mailis-Gagnon A, Srivastava A; National Opioid Use Guideline Group. Canadian guideline for safe and effective use of opioids for chronic noncancer pain: clinical summary for family physicians. Part 2: special populations. Can Fam Physician. 2011;57(11):1269-76, e419-28.

Koppert W, Ihmsen H, Korber N, et al. Different profiles of buprenorphine-induced analgesia and antihyperalgesia in a human pain model. Pain. 2005;118(1):15-22. doi:10.1016/j.pain.2005.06.030

Koyyalagunta D, et al. De-escalation of opioid therapy. Pain Physician. 2013.

Kress HG. Clinical update on the pharmacology, efficacy and safety of transdermal buprenorphine. Eur J Pain. 2009;13(3):219-230. doi:10.1016/j.ejpain.2008.04.011

Mattick RP, et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2014.

NCCN Clinical Practice Guidelines in Oncology: Adult Cancer Pain. Version 2025. National Comprehensive Cancer Network.

Pergolizzi J, Böger RH, Budd K, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an international expert panel. Pain Pract. 2008;8(4):287-313. doi:10.1111/j.1533-2500.2008.00204.x

Pergolizzi JV Jr, Raffa RB. Safety and efficacy of the unique opioid buprenorphine for the treatment of chronic pain. J Pain Res. 2019;12:3299-3317.

Portenoy RK, et al. Chronic use of opioid analgesics in non-malignant pain. Pain. 1990.

MASSEY COMPREHENSIVE CANCER CENTER VCU

Powell VD, Kullgren J, Anwar S, et al. Evaluation of buprenorphine rotation in patients receiving long-term opioids for chronic pain: a systematic review. JAMA Network Open.2021;4(9):e2124152. doi:10.1001/jamanetworkopen.2021.24152

Blondell RD, Ashrafioun L, Dambra CM, et al. A clinical trial comparing tapering doses of buprenorphine with steady doses for chronic pain and coexistent opioid addiction. J Addict Med.2010;4(3):140-146.

Roux P, Sullivan MA, Cohen J, et al. Buprenorphine/naloxone as a promising therapeutic option for opioid abusing patients with chronic pain. Pain. 2013;154(8):1442-1448.

Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2014 Feb 6;2014(2):CD002207.

Neumann AM, Blondell RD, Hoopsick RA, Homish GG. Randomized clinical trial comparing buprenorphine/naloxone and methadone for the treatment of patients with failed back[syndrome].

Smith TJ, et al. Opioid de-escalation in oncology. J Clin Oncol. 2012.

Tran PN, Sheng J, Randolph AL, et al. Mechanisms of QT prolongation by buprenorphine cannot be explained by direct hERG channel block. PLoS One. 2020;15:e0241362.

VHA Pharmacy Benefits Management Services. Pain Management Opioid Taper Decision Tool. U.S. Department of Veterans Affairs. Available at: https://www.pbm.va.gov/PBM/AcademicDetailingService/Documents/Pain_Opioid_Taper_Tool_IB_10_939_P96820.pdf

VA/DoD Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain. Washington, DC: Veterans Administration; 2010. Available at: http://www.va.gov/PAINMANAGEMENT/docs/CPG_opioidtherapy_fulltext.pdf

Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine:ceiling effects at high doses. Clin Pharmacol Ther. 1994;55(5):569-580.

Washington Agency Medical Directors Group. Interagency guideline on opioid dosing for chronicnoncancer pain. Olympia: Washington Agency Medical Directors Group; 2010. Available at:http://www.agencymeddirectors.wa.gov/Files/OpioidGdline.pdf

Webster L, Gruener D, Kirby T, et al. Evaluation of the tolerability of switching patients on chronic full mu-opioid agonist therapy to buccal buprenorphine. Pain Med. 2016;17(5):899-907.

Wilson SH, Hellman KM, James D, Adler AC, Chandrakantan A. Mechanisms, diagnosis,prevention and management of perioperative opioid-induced hyperalgesia. Pain Manag.2021;11(4):405-417.

Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009;10(2):113-30.

Bobb BT, et al. Opioid de-escalation. J Pain Symptom Manage. 2017.

Butrans (buprenorphine transdermal system) [package insert]. Stamford, CT: Purdue Pharma LP; June 2014.

MASSEY COMPREHENSIVE CANCER CENTER VCU