Outpatient cross-titration to buprenorphine for chronic pain

KATHERIN PEPERZAK, MD
Medical Director, Center for Pain Relief at UWMC-Roosevelt

Department of Anesthesiology & Pain Medicine

AUGUST 5, 2024

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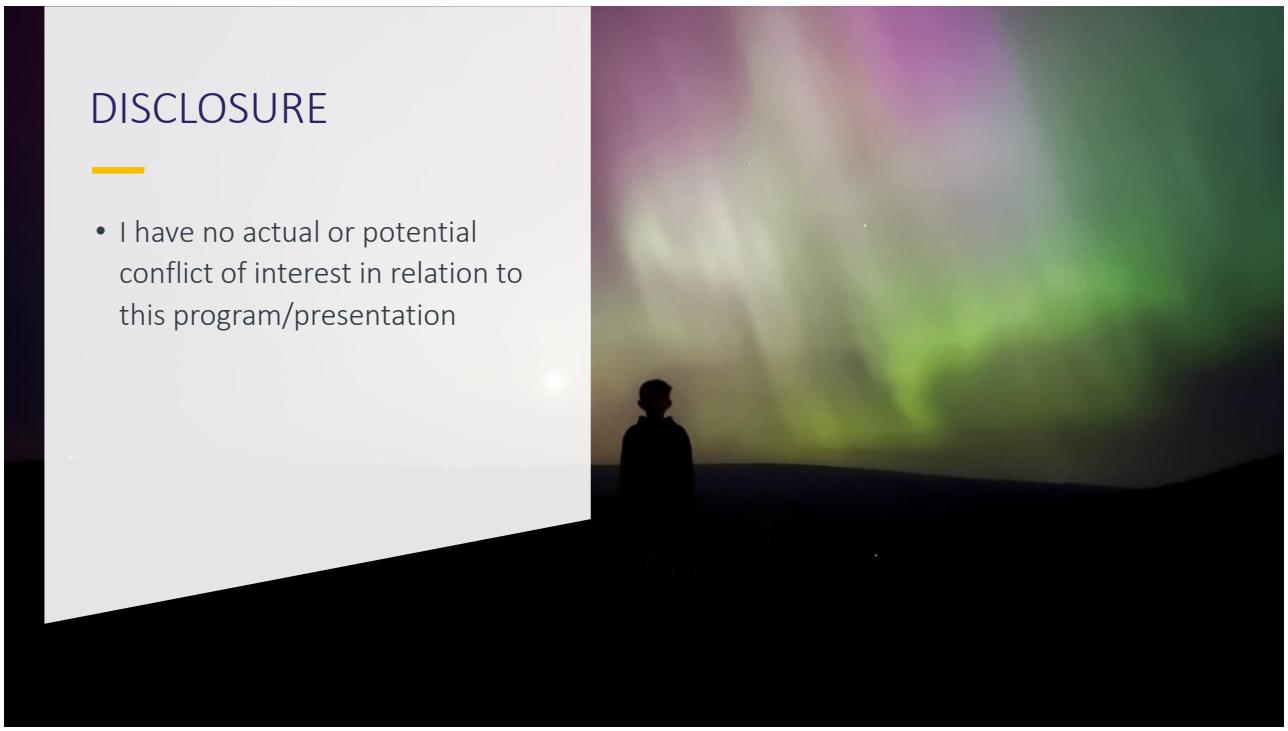
DISCLOSURE

- I have no actual or potential conflict of interest in relation to this program/presentation



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Objectives

- Recommend an approximate goal dosage of buprenorphine based on prior MME for chronic pain
- Be aware of factors that may contribute to extending the duration of cross-titration or increase goal dosage
- Determine which formulation of buprenorphine may be most appropriate based upon starting MME of full agonist opioids

Outpatient cross-titration to buprenorphine for chronic pain: A retrospective analysis

Satoru Ito, PharmD, BCPS; Mackenzie Welsh, PharmD; Christina Bockman, PharmD; Rebecca Dale, DO; David Pilkington, DO; Katherin Peperzak, MD

Journal of Opioid Management, vol. 19, no. 6, Dec. 2023, pp. 543-54, doi:10.5055/jom.0839.

Why Cross-Titrate to Buprenorphine?

- The opioid epidemic is well known
- Buprenorphine has lower risk of adverse effects including constipation, cognitive impairment, falls, respiratory depression compared to full μ–agonists
- Transition can be challenging with previous guidance to give buprenorphine when patient is showing signs of withdrawal or MEDD less than 30mg in cases of buccal films or TD patches[1,2]
- The OUD literature has growing support for microdosing or cross-titration induction
- The same pharmacology applies to the chronic pain population

1. BioDelivery Sciences International, Inc.: Belbuca (Buprenorphine) [Prescribing Information]. Raleigh, NC: BioDelivery Sciences International, Inc., 2021.
2. Purdue Pharma LP: Butrans (Buprenorphine) [Prescribing Information]. Stamford, CT: Purdue Pharma LP, 202

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The UW Experience

- Clinicians have been performing ad-hoc cross-titrations from full agonist opioids to buprenorphine in the outpatient pain clinic for ~10 years
- Further experience was obtained performing micro-inductions for patients with OUD in the inpatient setting
- In 2020, the wealth of clinical experience was aggregated into a written protocol to encourage more consistency in practice
- Sought to evaluate the safety and efficacy of our protocol, hypothesizing >=50% of patients would be successful with transition after 4 weeks

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Inclusions/exclusions

- Evaluated patients prescribed buprenorphine 9/2020-12/2021

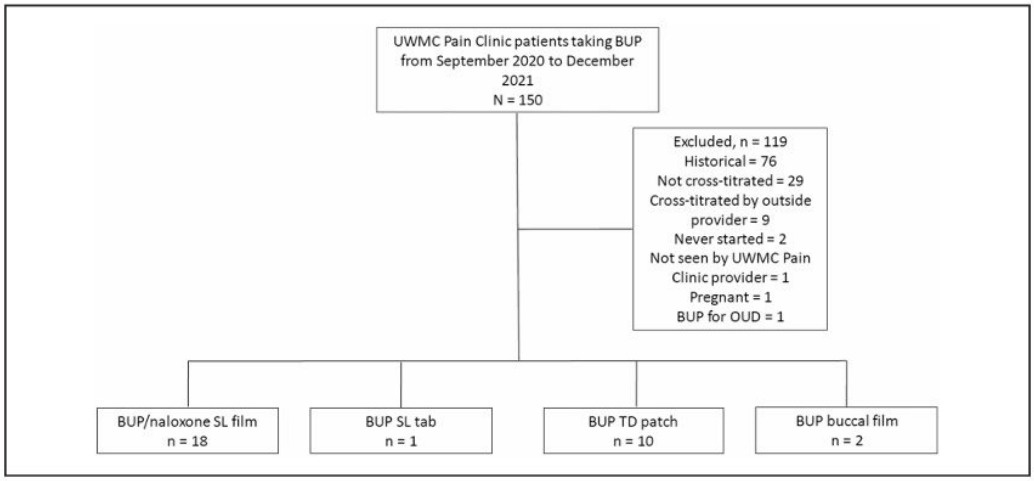

Figure 1. Flow diagram of included patients.

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Origin of pain	Chronic back pain, 18 (58.1 percent) Chronic lower extremity pain, 10 (32.2 percent) Neuropathy, 9 (29 percent) Chronic abdominal pain, 4 (12.9 percent) Fibromyalgia, 3 (9.7 percent) Rheumatoid arthritis, 2 (6.5 percent) Trigeminal neuralgia, 2 (6.5 percent) Chronic flank pain, 1 (3.2 percent) Sickle cell disease, 1 (3.2 percent) CRPS, 1 (3.2 percent) Chronic hip pain, 1 (3.2 percent) Multiple sclerosis, 1 (3.2 percent)	
Prior full μ-opioids	*Long-acting opioids*	*Short-acting opioids*
	Fentanyl patch, 3 (9.7 percent) Hydromorphone ER, 1 (3.2 percent) Methadone, 4 (12.9 percent) Morphine ER, 5 (16.1 percent)	Hydrocodone, 9 (29 percent) Hydromorphone, 3 (9.7 percent) Oxycodone, 9 (29 percent) Morphine, 3 (9.7 percent) Tramadol, 3 (9.7 percent)
Prior MEDD	≤30, 13 (41.9 percent) 31-60, 5 (16.1 percent) 61-90, 4 (12.9 percent) 91-120, 1 (3.2 percent) >120, 8 (25.8 percent)	Median (IQR), 56 (30-116.5)
Highest MEDD in last 2 years	≤30, 7 (22.6 percent) 31-60, 7 (22.6 percent) 61-90, 8 (25.8 percent) 91-120, 0 (0 percent) >120, 9 (29 percent)	Median (IQR), 75 (40-129)

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Indications for cross-titration

- Inadequate pain control with current opioid regimen
- Concern for adverse effects from opioids
  - Constipation
  - Fatigue
  - Respiratory depression (or risk of)

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Key Decisions

- Formulation of buprenorphine
- Goal dose of buprenorphine
- Duration
  - Standard 4-5 weeks
    - Patient preference
    - Patient requires encouragement/continued motivation
  - Rapid 7-10 days
    - Highly motivated
    - Safety concerns

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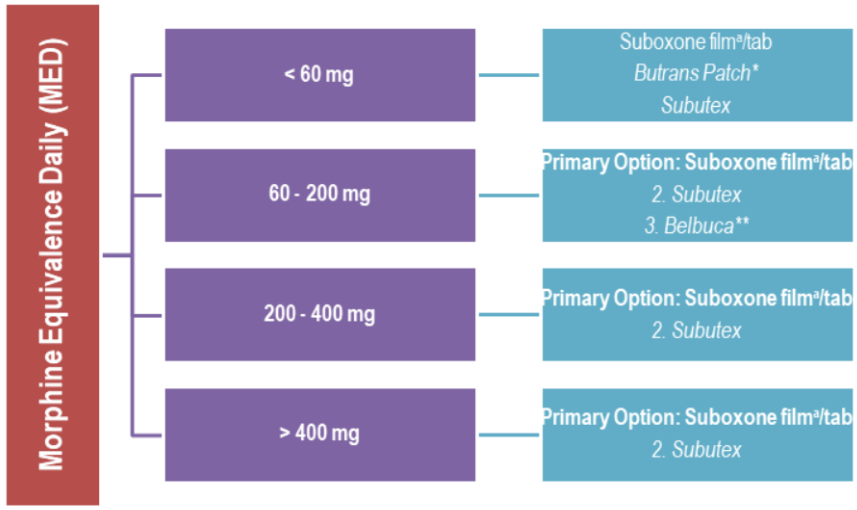

[a]Suboxone films may be more easily divided into ¼ pieces compared to tablets, and may be preferred for initial titration
*Butrans not eligible for rapid titration due to weekly patch changes (Appendix D)
**Belbuca not to be used for MED > 160 mg or rapid titration (Appendix E)
Insurance may prefer one Suboxone formulation (tablet vs film) over another – either formulation is considered first line.

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Dosing

Table 1. Buprenorphine product selection and target doses

MEDD	Product	Target dose
<60 mg	Buprenorphine/naloxone SL film/tablet*	2-4 mg/day
	Buprenorphine SL tablet	2-4 mg/day
	Buprenorphine TD patch†	Up to 20 mcg/hr
60-200 mg	Buprenorphine/naloxone SL film/tablet*	2-4 mg/day
	Buprenorphine SL tablet	2-4 mg/day
	Buprenorphine buccal film‡	Up to 900 mcg BID
200-400 mg	Buprenorphine/naloxone SL film/tablet*	4-6 mg/day
	Buprenorphine SL tablet	4-6 mg/day
>400 mg	Buprenorphine/naloxone SL film/tablet*	6-8 mg/day
	Buprenorphine SL tablet	6-8 mg/day

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Table 2. Buprenorphine cross-titration schedule guide				
Buprenorphine/naloxone 2 mg/0.5 mg film				
Timeline	**MEDD < 200 mg**	**MEDD 200-400 mg**	**MEDD > 400 mg**	**Full μ-opioid**
Week 1	1/4 film BID (1 mg/day)	1/4 film TID (1.5 mg/day)	1/4 film TID (1.5 mg/day)	Continue current regimen (option to trial reduction)
Week 2	1/4 film TID (1.5 mg/day)	1/2 film TID (3 mg/day)	1/2 film TID (3 mg/day)	Reduce regimen by 20-30 percent
Week 3	1/2 film TID (3 mg/day)	Days 15-18: 1 film AM, 1/2 film noon, 1/2 film HS (4 mg/day)	Days 15-18: 1 film AM, 1/2 film noon, 1/2 film HS (4 mg/day)	Reduce regimen by 20-30 percent
		Days 19-21: 1 film AM and noon, 1/2 film HS (5 mg/day)	Days 19-21: 1 film AM and noon, 1/2 film HS (5 mg/day)	
Week 4	1 film BID (4 mg/day)	1 film TID (6 mg/day)	1 film TID (6 mg/day)	Reduce regimen by 20-30 percent or discontinue
Week 5	If inadequate pain control, consult provider		2 film AM, 1 film noon and HS (8 mg/day)	Discontinue
Week 6			If inadequate pain control, consult provider	
BID: twice daily; TID: three times daily; HS: night.				

Buprenorphine transdermal patch		
Timeline	**Buprenorphine patch dose**	**Full μ-opioid agonist**
Week 1	5 mcg/h	Continue current regimen (option to trial reduction)
Week 2	5 mcg/h	Reduce regimen by 20-30 percent
Week 3	10 mcg/h (stop here if MEDD <30)	Reduce regimen by 20-30 percent (suggest reducing 48 h after increase in patch)
Week 4	15 mcg/h	Reduce regimen by 20-30 percent (suggest reducing 48 h after increase in patch)
Week 5	20 mcg/h*	Discontinue
*Note: Only for MEDD < 60 mg; doses >20 mcg/h have been used in Europe with effective pain control, for doses >20 mcg/h should be discussed with a physician.		

Results

- 15 of 31 patients successfully completed transition to buprenorphine, without use of full agonist opioids 4 weeks after completion
- Median duration of successful transition was 29 days
  - 7 required > 4 weeks
- Average dose for those successfully transitioned
  - 7.9 ± 5.7 mg/day for those on buprenorphine/naloxone films
  - 11.9 ± 4.8 mcg/h for buprenorphine patches
- Patients on >120 MEDD prior to cross-titration stabilized on 8-16mg/day
- All patients taking <30 MEDD transitioned to buprenorphine patch
  - 7 required > 4 weeks

Table 4. Characteristics of patients with successful transition to failed transition to buprenorphine

	Successfully transitioned (N = 15)	Failed transition (N = 16)
Buprenorphine formulation	Buprenorphine/naloxone SL films, 8 Buprenorphine TD patches, 5 Buprenorphine buccal films, 2 (both switched to buprenorphine/naloxone SL films during cross-titration)	Buprenorphine/naloxone SL films, 10 Buprenorphine TD patches, 5 Buprenorphine buccal films, 0 Buprenorphine SL tablets, 1
Prior long-acting opioid	Fentanyl patch, 1 Hydromorphone ER, 1 Methadone, 3 Morphine ER, 3	Fentanyl patch, 2 Methadone, 1 Morphine ER, 2
Prior short-acting opioid	Hydrocodone, 5 Hydromorphone, 1 Oxycodone, 8 Tramadol, 1	Hydrocodone, 4 Oxycodone, 6 Morphine, 3 Tramadol, 2
Prior MEDD	Median (IQR), 31.3 (22.5-105) ≤30, 7 31-60, 2 61-90, 2 91-120, 1 >120, 3	Median (IQR), 60 (30-133.8) ≤30, 6 31-60, 3 61-90, 2 91-120, 0 >120, 5

Reasons for failure

- Inadequate pain control (8)
- Intolerable adverse effects (4)
  - Rash
  - Cognitive impairment
- Lost to follow-up (1)
- Fall (1)
- Insurance concern (1)

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Side Effects

- Nausea (22.6%)
- Headache (19.4%)
- Opioid Withdrawal symptoms (12.9%)
  - Prior MEDD of these patients: 105mg, 350mg, 420mg, 456 mg
    - Resolved with slowing titration and all completed titration
  - No patients transitioned to buprenorphine patch experienced withdrawal

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Precipitated Withdrawal-Binding Affinity

WEAK	
Drug	Ki (nM)
Tramadol	12486
Codeine	734.2
Meperidine	450.1

MODERATE	
Drug	Ki (nM)
Hydrocodone	41.58
Oxycodone	25.87
Methadone	3.378
Nalbuphine	2.118
Fentanyl	1.346
Morphine	1.168

STRONG	
Drug	Ki (nM)
Oxymorphone	0.405
Hydromorphone	0.365
Buprenorphine	0.215
Sufentanil	0.138

Volpe DA, Tobin GA, Mellon RD, et al. Uniform assessment and ranking of opioid Mu receptor binding constants for selected opioid drugs. Regulatory Toxicology and Pharmacology. 2011;59:385-390.

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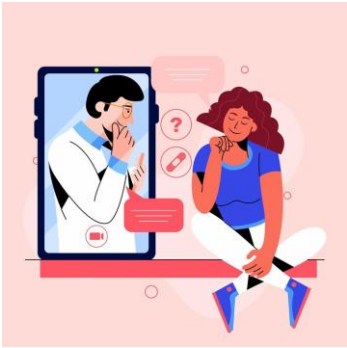
Possible Contributors to Success

- More frequent follow up with pharmacists or physician
- Specific diagnoses?
  - Neuropathic pain
  - Fibromyalgia
- Extension of transition
  - 5 patients were extended an additional 2 weeks



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Possible contributors to failure or dose adjustment

- Co-morbid mental health diagnoses
  - Over half of the patients in the study had diagnosis of depression
  - Over half of the patients in the study had diagnosis of anxiety
- Prior high MEDD?
  - Our study did not find statistical significance
- Poorly controlled pain prior to transition (14/31 in this study)
- Reason for transition
  - Provider or patient driven?
- COVID-19 Pandemic

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Next steps

- Continue to use our Cross-Titration Protocol as a starting point
  - Did demonstrate safety and efficacy for those who completed transition
- Re-evaluate data with greater sample size
- Consider dose adjustment to protocol depending on findings

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QUESTIONS?

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