Buprenorphine in Opioid use Disorder and Pain

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Disclosure

No conflicts of interest

Objectives

- Understand main differences between regular opioids and buprenorphine
- Learn principles of buprenorphine use
- Be familiar with basics of pharmacology and pharmacogenomics of buprenorphine
- Develop insight into buprenorphine application to Opioid Use Disorder

Buprenorphine Myths

- Buprenorphine does not control pain
- It is illegal to prescribe buprenorphine for pain without a special license
- Buprenorphine is less potent ("weaker") than morphine
- Buprenorphine cannot be combined with full mu agonist

- Arbuck D, Buprenorphine: A Promising Yet Overlooked Tool for the Pain Practitioner's Armamentarium. Pract Pain Manag April/May 2019: 33-38

Buprenorphine Myths

- Buprenorphine is safe and cannot cause respiratory depression
- Buprenorphine/naloxone combination has minimal risk of abuse
- Naloxone in combination with buprenorphine blocks pain control

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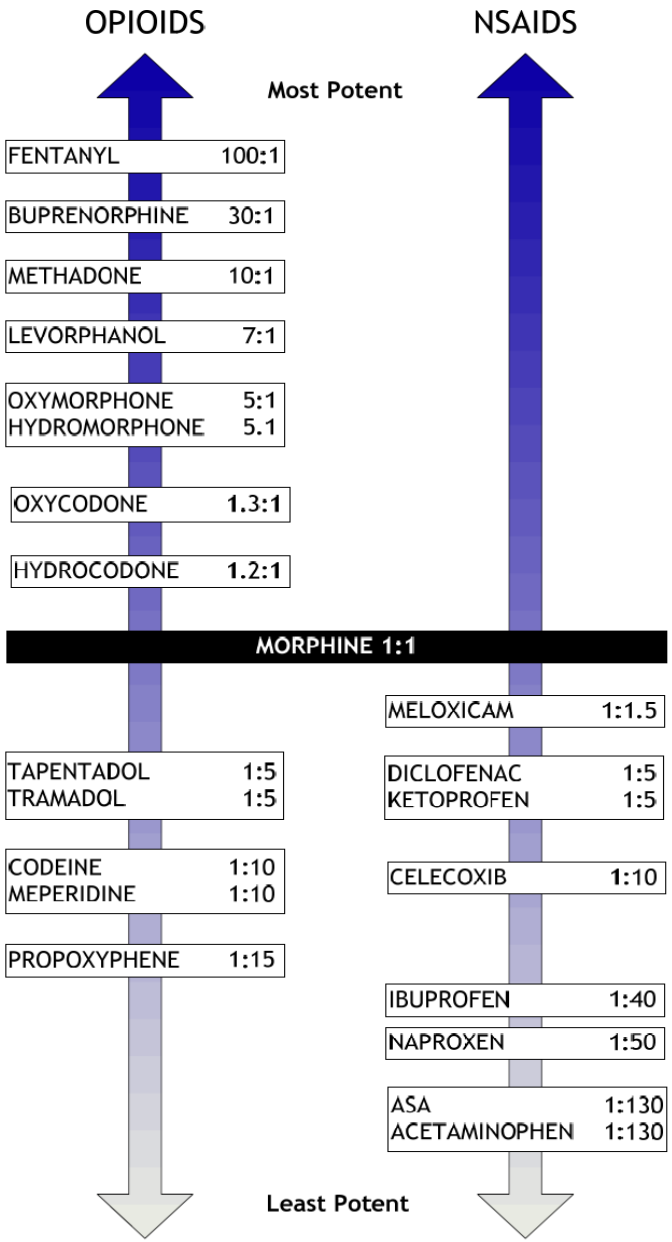
EQUIVALENCY CHART IN RELATIONSHIP TO MORPHINE



Buprenorphine

- Unveiled in 1971, on GB market since 1978. In the US liquid form was in use since 1980s and from 2002 – sublingual
- Patch form for pain in Europe since 2001: 35, 52.5 and 70mcg
- Administration: IV, SL, transdermal, intrathecal in India
- Metabolized by P-450 3A4

1. Huang P., Kehner GB, Cowan A, Liu-Chen LY (2001). "Comparison of pharmacological activities of buprenorphine and norbuprenorphine: norbuprenorphine is a potent opioid agonist". *J. Pharmacol. Exp. Ther.* 297 (2): 688–95.

2. Modified from Pain Physician 2011; 14:E343-360

Buprenorphine

- Partial Mu agonist, kappa antagonist
- Antagonizes nociceptin opioid peptide receptor (NOP), also known as the nociceptin/orphanin FQ (N/OFQ) receptor or kappa-type 3 opioid receptor, is a protein that in humans is encoded by the OPRL1 (opioid receptor-like 1) gene
- Lesser euphoria
- Poorly antagonized by naloxone
- Lesser abuse potential
- Mood improvement

1. Huang P., Kehner GB, Cowan A, Liu-Chen LY (2001). "Comparison of pharmacological activities of buprenorphine and norbuprenorphine: norbuprenorphine is a potent opioid agonist". *J. Pharmacol. Exp. Ther.* 297 (2): 688–95.

2. Calo' G, Guerrini R, et al. "Pharmacology of nociceptin and its receptor: a novel therapeutic target". British Journal of Pharmacology. April 2000;129 (7): 1261–83.

3. Webster L, Gudin J, Understanding Buprenorphine for Use in Chronic Pain: Expert Opinion. Pain Med. 2020 Apr 1;21(4):714-723

Buprenorphine

- 30-50 times potency of MS
- Suppresses hyperalgesia
- Up regulates mu receptors (1)
- Facilitates mu receptors migration to cell membranes (2)
- Significantly alleviates more pain types than fentanyl (3)
- Pronounced antihyperalgesic effect because of kappa antagonism (4)
- Not as immunosuppressive as morphine (5)

Davis M: Buprenorphine in cancer pain. *Support Care Cancer*. 2005;13:878-887

Thomas JM, Hoffman BB: Buprenorphine prevents and reverses the expression of chronic endorphine-induced sensitization of adenylyl cyclase in SK-N-SH human neuroblastoma cells. *J Pharmacol Exp Ther*. 1993;264(1);368-374

Andersen T, Upton RN et al. Pharmacokinetic/pharmacodynamic relationships of transdermal buprenorphine and fentanyl in experimental human pain models. *Basic Clin Pharmacol Toxicol*. 2011; 108(4):274-284

Ciccozzi A, Angeletti C. et al. High dose of buprenorphine in terminally ill patient with liver failure *J Opioid Manag,* 2012; 8(4):253-259

Still R: Transdermal buprenorphine in cancer pain and palliative care. *Palliat Med*. 2006; 20 Suppl 1: s25-s30

Brand preparations of buprenorphine currently approved in the US

Buprenorphine (pain indication)	Buprenorphine/Naloxone (opioid dependence substitution indication)	Buprenorphine long-acting (opioid dependence substitution indication)
Belbuca® 75, 150, 300, 450, 600, 750, 900mcg	Suboxone® 2/0.5, 4/1, 8/2, 12/3mg	Sublocade® injection 100, 300mg (1 mo)
Butrans® 5, 7.5, 10, 15, 20 mcg/h 7days patch	Zubsolv® 0.7/0.18, 1.4/036, 2.9/071, 5.7/1.4, 8.6/2.1, 11.4/2.9 mg	Probuphine® implant 74.2mg (6 mo)
Buprenex® 300mcg/ml for IM or IV use	Bunavail® 2.1/0.3, 4.2/0.7, 6.3/1mg	Brixadi® injection Weekly 8,16,24 and 32 mg Monthly 64, 96 and 128 mg

Approximate absorption rates and dose equivalency

Preparation	Absorption rate/ Bioavailability (from corresponding medication package inserts)	Amount taken	Amount absorbed
Suboxone	25%	4mg	1mg
Zubsolv	35%	2.9mg	1mg
Bunavail	50%	2.1mg	1mg
Belbuca	55%	1.8mg	1mg
Butrans patch	15%	20mg is contained in a patch	20mcg/h (0.48mg/d)
Buprenex	100%	1mg	1mg

Receptor	Events	Association
Mu	Analgesia Euphoria Respiratory depression Sedation Suppression of hypthalamo-pituitary-adrenal axis Dopamine and acetylcholine release	Dependence Abuse
Kappa	Analgesia Dysphoria Decrease in GI motility Appetite suppression Psychotic symptoms Insomnia Diuresis Orthostatic hypotension	Anti-depressive Minimal respiratory inhibition Dependence Abuse
Delta	Hormonal changes Appetite suppression Dopamine release	Minimal potential for dependence May counteract respiratory depression and constipation

Binding affinity

Opioids	Range of Ki Value
Buprenorphine	0.21- 1.5
Naltrexone	0.4-0.6 (antagonist effects)*
Fentanyl	0.7-1.9
Methadone	0.72-5.6
Naloxone	1.0-3.0 (antagonist effects)*
Morphine	1.02-4

Fudin J, Chu R, Ciani A, Raouf M. Opioid Agonists, Partial Agonists, Antagonists: Oh My! Pharmacy Times. January 6, 2018

Buprenorphine overdose

Buprenorphine is bound to the MOR tighter than naloxone or naltrexone and, as such, it is poorly antagonized by opioid antagonists. This presents a challenge in treating a buprenorphine overdose as it sometimes responds insufficiently to antidotes.

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Would combination with full mu agonists cause withdrawal symptoms?

Opioids	Range of Ki Value	
	No withdrawal symptoms present when fentanyl added	Withdrawal symptoms present when fentanyl added
Buprenorphine	0.21	1.5
Fentanyl	1.9	0.7

Buprenorphine properties

- Excreted minimally unchanged with bile, feces (68%) and urine (27%)
- Swallowing buprenorphine diminishes its efficacy due to the first bypass
- Exhibits a long half-life of 20 to 44 hours.

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Buprenorphine properties

- Metabolized by the P-450 3A4 enzyme system primarily in the liver, as well as the UGT 1A1 and 2B7
- Only up to 30% of buprenorphine metabolism is mediated by cytochrome (CYP) 3A4 , not predicted to cause clinically important drug interactions with other drugs

Kobayashi K, Yamamoto T, Chiba K, et al. Human buprenorphine N-dealkylation is catalyzed by cytochrome P450 3A4. Drug Metab Dispos. 1998;26:818–821.

Buprenorphine in pain

Buprenorphine is an excellent first line opioid medication, especially in neuropathic pain.

1. BoehmeK,LikarR.Efficacy and tolerability of a new opioid analgesic formulation, buprenorphine transdermal therapeutic system (TDS), in the treatment of patients with chronic pain. A randomized, double-blind, placebo-controlled study. Pain Clinic. 2003;15:193–202. 125.
2. Poulain P, Denier W, Seremet M, Kober A, Sopata M. Analgesic efficacy and safety of transdermal buprenophine 70 mg/h in patients with severe, chronic cancer pain. A randomized, multicentre, placebo-controlled, double-blind study. Proceedings of the 4th Research Forum of the European Association for Palliative Care. Venice. 2006.
3. Sittl R, Griessinger N, Likar R. Analgesic efficacy and tolerability of transdermal buprenorphine in patients with inadequately controlled chronic pain related to cancer and other disorders: a multicenter, randomized, double-blind, placebo-controlled trial. Clin Ther. 2003;25:150–168.
4. Sorge J, Sittl R. Transdermal buprenorphine in the treatment of chronic pain: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. Clin Ther. 2004;26:1808–1820

Buprenorphine in perioperative pain

No difference in opioid requirements noted between patients who perioperatively stopped SL-BUP versus those who continued SL-BUP

1. Fishman MA, Kim PS. Buprenorphine for Chronic Pain: a Systemic Review. Curr Pain Headache Rep. 2018 Oct 5;22(12):83
2. Ehrlich AT1, Darcq E. Recommending buprenorphine for pain management. Pain Manag. 2019 Jan 1;9(1):13-16.
3. Martin YN1, Deljou A. Perioperative opioid requirements of patients receiving sublingual buprenorphine-naloxone: a case series. BMC Anesthesiol. 2019 May 8;19(1):68.

Buprenorphine and drug screens

- Transdermal buprenorphine itself is not expected to cause significant alteration of other drugs' metabolism because of the low plasma concentrations reached after transdermal application

- This low concentration also explains the frequent false negative urine drug screens for patients on transdermal buprenorphine. False negatives are seen in confirmatory gas chromatography/mass spectrometry testing as well, falling below the threshold of equipment calibration.

Kobayashi K, Yamamoto T, Chiba K, et al. Human buprenorphine N-dealkylation is catalyzed by cytochrome P450 3A4. Drug Metab Dispos. 1998;26:818–821.

Doe, Jane
DOB: 10/24/1956
Order Number: 616888
Report Date: 6/19/2017
Clinician: Dmitry Michael Arbuck MD
Reference:

Questions? Customer Service

OPIOIDS

USE AS DIRECTED	MODERATE GENE-DRUG INTERACTION		SIGNIFICANT GENE-DRUG INTERACTION	
buprenorphine (Butrans®)	**codeine** (Codeine Contin®)	4	**meperidine** (Demerol®)	1,4,6
buprenorphine/naloxone (Suboxone®)	**fentanyl** (Duragesic®)	4	**methadone** (Dolophine®)	1,4,6
naltrexone (Revia®, Vivitrol®)	**hydrocodone** (Vicodin®)	4		
tapentadol (Nucynta®)	**hydromorphone** (Dilaudid®)	4		
	morphine (Avinza®)	4		
	oxycodone (Oxycontin®)	4		
	oxymorphone (Opana®)	4		
	tramadol (Ultram®)	1,4		

NON-OPIOIDS

USE AS DIRECTED	MODERATE GENE-DRUG INTERACTION	SIGNIFICANT GENE-DRUG INTERACTION
carisoprodol (Soma®)		
celecoxib (Celebrex®)		
cyclobenzaprine (Flexeril®)		
diclofenac (Voltaren®)		
ibuprofen (Advil®, Motrin®)		
ketorolac (Toradol®)		
meloxicam (Mobic®)		
naproxen (Aleve®, Naprosyn®)		

CLINICAL CONSIDERATIONS

1: Serum level of the active compound may be too high, lower doses may be required.
4: Genotype may impact drug mechanism of action and result in reduced efficacy.
6: Use of this drug may increase risk of side effects.

All analgesic medications require clinical monitoring.
This report is not intended to imply that the drugs listed are approved for the same indications or that they are comparable in safety or efficacy. The brand name is shown for illustrative

Buprenorphine Policy

Stanford University Medical Center policy released in 2017, based on findings that patients who had discontinued buprenorphine before surgery "consumed significantly greater amounts of opioid in the immediate postoperative period, yet the pain scores for the two groups were not at all that different.

Aggarwal A. American Academy of Pain Medicine Annual Meeting. March 1519, 2017, Orlando, FL.

University of Kentucky Health Care System's protocol

Given the increased mortality rate immediately after discontinuing buprenorphine-naloxone, we strongly recommend continuing buprenorphine-naloxone preoperatively to ensure overall patient stability and prevent relapse from stopping and restarting the medication

Ward EN, Quaye AN-A, Wilens TE. Opioid use disorders: perioperative management of a special population. Anesth Analg. 2018;127:539-547.

Consensus

For pregnant patients on buprenorphine, there is consensus that treatment should be maintained to prevent withdrawal during delivery

Pure buprenorphine vs. buprenorphine/naloxone is recommended

1. Nguyen L et al. Treating women with opioid use disorder during pregnancy in Appalachia: Initial neonatal outcomes following buprenorphine + naloxone exposure. Am J Addict. (2018)

2. Mullins N et al. Buprenorphine and Naloxone Versus Buprenorphine for Opioid Use Disorder in Pregnancy: A Cohort Study.
J Addict Med. (2019)

3. Wiegand SL et al. Buprenorphine and naloxone compared with methadone treatment in pregnancy. Obstet Gynecol. (2015)

Adverse effects

- The most common adverse effects of buprenorphine are nausea and vomiting
- Constipation
- Urinary retention
- Headaches
- Lower leg edema
- Itching
- Intractable insomnia
- Sensation of shortness of breath
- Withdrawal

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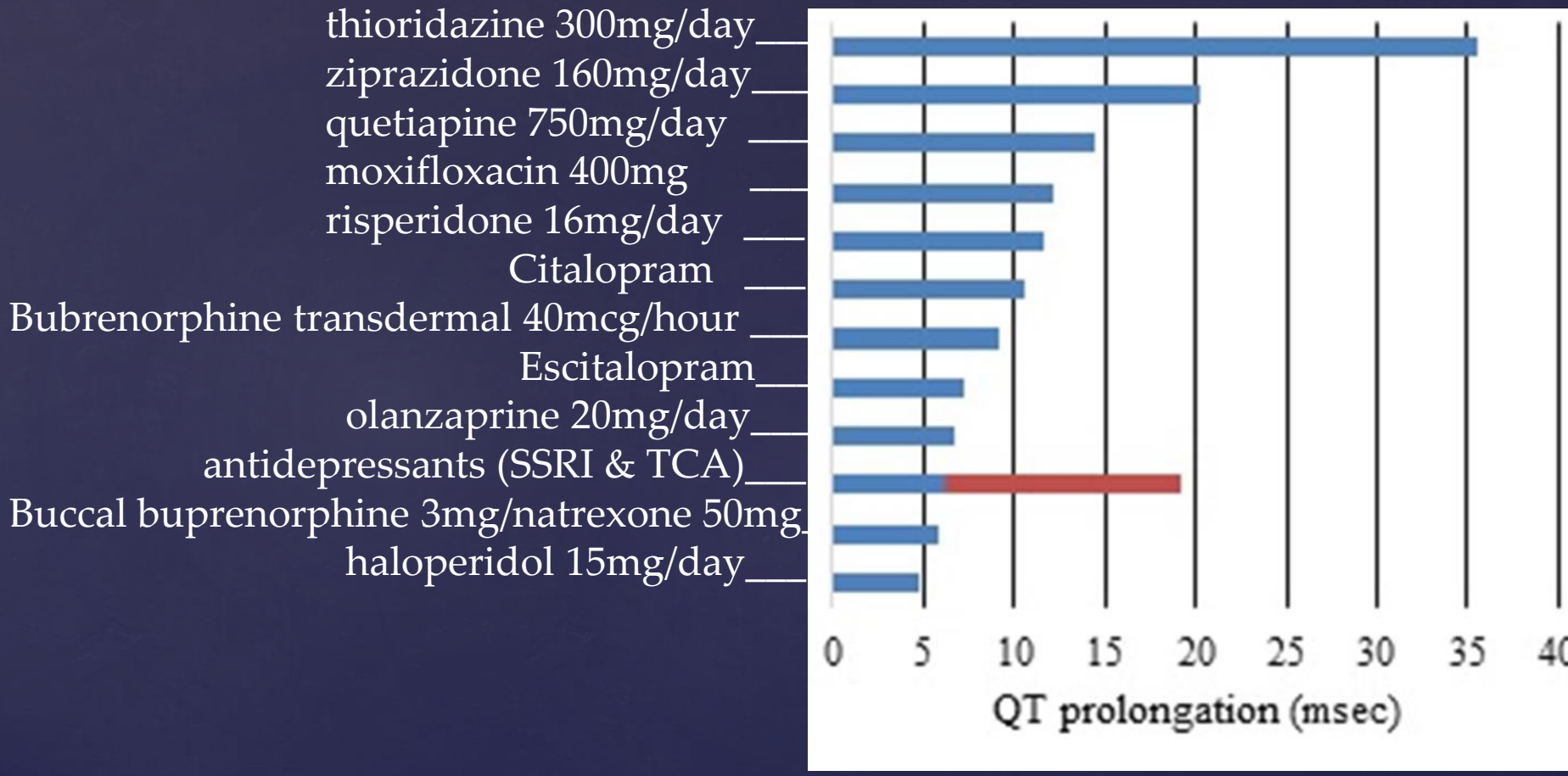
Adverse effects

Black Box Warnings[A]	Contraindications	Warnings/Precautions
• Addiction, abuse, and misuse • Life-threatening respiratory depression • Accidental exposure • Neonatal opioid withdrawal syndrome	• Significant respiratory depression • Acute or severe asthma • Known or suspected GI obstruction	• Adrenal insufficiency • CNS depression • Hepatic events • Hypersensitivity reactions • Hypotension • Respiratory depression • QTc prolongation

QT Prolongation of Various Medications



Fudin J, Cleary J, Gottwald J. A Brief Review of Buprenorphine Products. Pharmacy Times. March 22, 2016.

Limitation and safety

- Ceiling effect on analgesia and CO2 accumulation
- Combining buprenorphine with alcohol, benzodiazepines or other CNS depressants can result in respiratory depression and death

Buprenorphine in OUD

- In the USA, the Drug Addiction Treatment Act of 2000 made buprenorphine the only opioid medication for opioid addiction that can be prescribed in an office-based setting.
- Owing to its high affinity for the μ-receptor, buprenorphine inhibits the reinforcing effect of exogenous opioids.
- The ceiling effect of buprenorphine's μ-agonist activity reduces the potential for drug overdose and confers low toxicity even at high doses.

Ling W, Mooney L. Buprenorphine for opioid addiction. Pain Manag. 2012 Jul; 2(4): 345–350.

Buprenorphine in OUD

Development of buprenorphine as an addiction treatment was spearheaded in the USA by the National Institute on Drug Abuse (NIDA), which supported extensive clinical research on its usefulness.

Preceding FDA approval in 2002, buprenorphine had been extensively examined in clinical research

1. Doran C, Shanahan M, Mattick R, Ali R, White J, Bell J. Buprenorphine versus methadone maintenance: a cost–effectiveness analysis. Drug Alcohol Depend. 2003;71(3):295–302.
2. West S, Keri K, O'Neal K, Graham C. A meta-analysis comparing the effectiveness of buprenorphine and methadone. J. Subst. Abuse. 2000;12(4):405–414

Duration of buprenorphine pharmacotherapy

- The package insert did not originally refer to 'maintenance' but reissuance of the insert now does
- Initial use in detoxification
- Short-term use in this manner is often followed by relapse
- Duration of buprenorphine pharmacotherapy should be tailored to the needs of the patient

Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. Arch. Gen. Psychiatry. 2011;68(12):1238–1246.

Is buprenorphine treatment just trading one addiction for another?

No- with successful buprenorphine treatment, the compulsive behavior, the loss of control of drug use, the constant cravings, and all of the other hallmarks of addiction vanish. When all signs and symptoms of the disease of addiction vanish, we call that remission, not switching addictions.

The American Academy of Pain Medicine (AAPM), American Pain Society (APS), American Society of Addiction Medicine (ASAM)

Questions