The Latest on Buprenorphine – Pharmacology, Formulations and Misconceptions

Mark Greenwald, Ph.D.

Gertrude Levin Endowed Chair in Addiction and Pain Biology
Professor, Associate Chair, and Director of Substance Abuse Research Division
Dept. of Psychiatry and Behavioral Neurosciences; and Dept. of Pharmacy Practice
Wayne State University, Detroit, MI, USA
mgreen@med.wayne.edu

Pain & Addiction Common Threads

Disclosure information 1

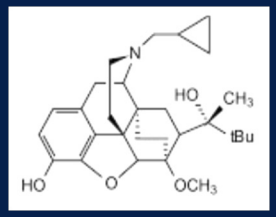
- Indivior
  - Compensated: consultant/speaker re: BUP-XR for treatment of OUD and neurobiology of addiction
  - Not compensated: collaborator/coauthor on several projects and manuscripts (published and ongoing)
- NIH-funded clinical research projects related to OUD
  - R01 DA015462, R21/R33 DA044946, F30 DA052118, U01 HL050551 (HEAL) and R34 DA053758
- Peter F. McManus Charitable Trust
  - Grant (PI): rTMS investigation of stress reactivity in OUD
- NET Recovery Corp.
  - Contract (PI): Clinical trials of neuromodulation (medical device) treatment of OUD

Disclosure information 2

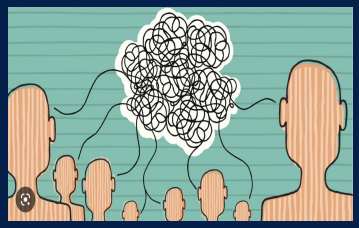
- Park Therapeutics
  - Pending NIH grant application (Co-PI): Development of *mu*-opioid/nociceptin receptor agonist for treatment of OUD
- MI CARES
  - Grant subcontract (Co-investigator): Online program to educate U.S. physicians, medical students and advanced practice professionals in addiction medicine
- Arborsense, Inc.
  - Paid consultant for novel drug detection methodology

Learning objectives

- Improve understanding of the pharmacology of BUP relating to its safety and efficacy in treating opioid use disorder (OUD)



- Identify and clear up common misconceptions and unanswered questions surrounding BUP induction and maintenance



- Improve clinician confidence in BUP dosing practices for management of OUD and co-occurring pain

Buprenorphine selectively activates *mu*-opioid receptors (μORs) at physiologically relevant concentrations

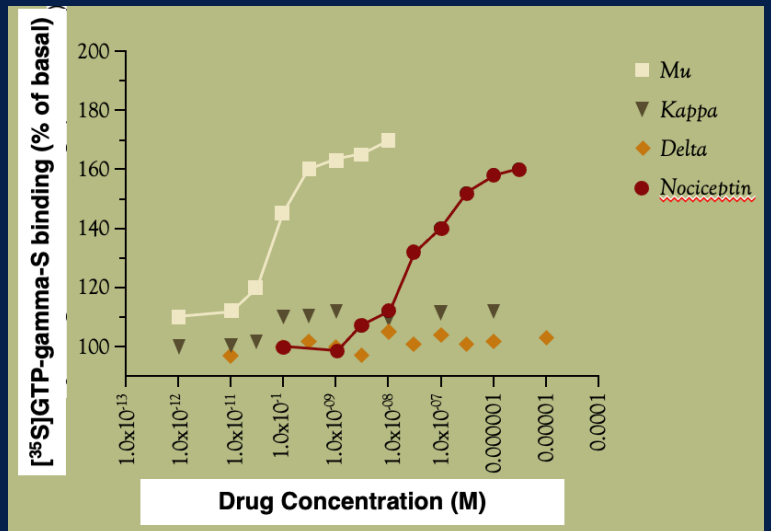
"Partial agonist" misconception: μOR partial agonism does not mean BUP clinical effects are universally limited. Rather, partial agonism refers to limited activation of GPCR machinery (figure). Clinical effects – which are mediated downstream via different intracellular signaling pathways – can differ in their *intrinsic activity*. This means there is not a ceiling effect for every outcome measure.

> "A drug, acting at a single receptor subtype, can have multiple intrinsic efficacies that differ depending on which of the multiple responses coupled to a receptor is measured." (Berg and Clarke, 2018)

Kappa/delta receptor involvement? No convincing evidence yet in animals or humans that BUP antagonism at *kappa* or *delta* receptors mediates its clinical efficacy for treating OUD.

"Nociception misconception": BUP-induced GPCR activation is ≈1000x more potent at μORs than nociceptin receptors, therefore, nociceptin receptors are not mediating BUP effects at *clinically relevant doses*.

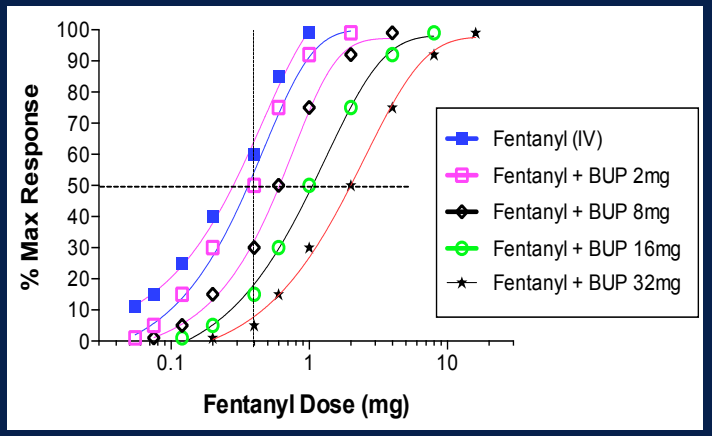
Occam's razor: BUP effects are – based on current knowledge – selectively attributable to its partial agonist effects at the μOR.



Adapted from Huang P, Kehner GB, Cowan A, Liu-Chen L-Y (2001) Comparison of pharmacological activities of buprenorphine and norbuprenorphine: norbuprenorphine is a potent opioid agonist. JPET 297(2): 688-695. PMID: 11303059

Addressing some misconceptions

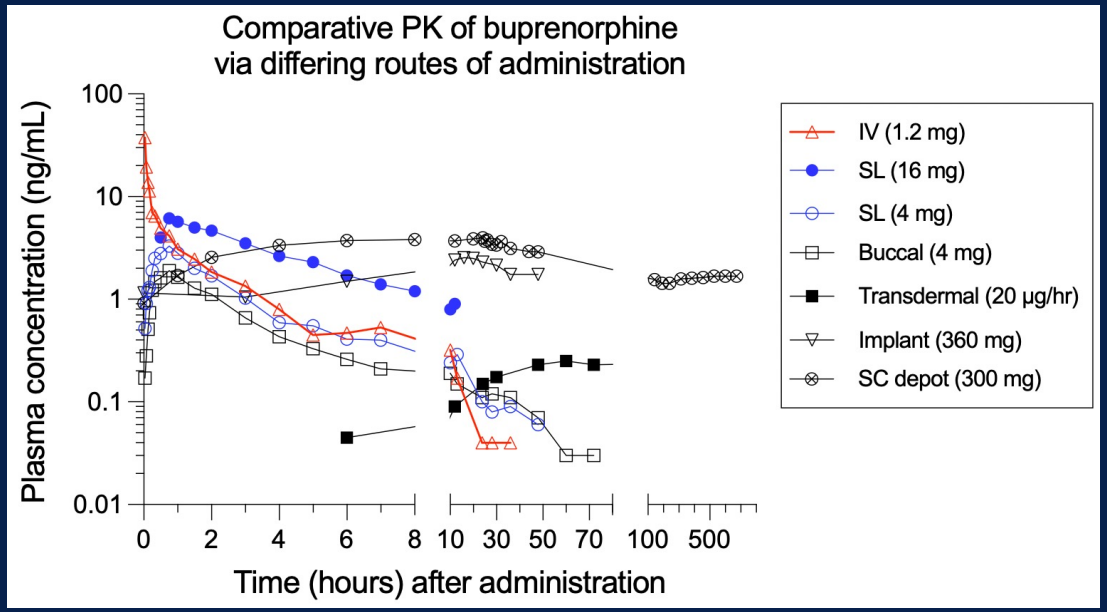
- Opioid blockade: What is it and how is it achieved?
  - Efficacy of BUP to attenuate certain effects of an opioid (e.g. fentanyl, hydromorphone), so that the opioid's effects – typically liking (abuse potential), or toxicity such as respiratory depression – are comparable to placebo challenge (Greenwald et al. 2014; adopted by FDA for phase II studies).
  - Figure: Mechanism is likely cross-tolerance, leading to a rightward shift (reduction in potency) of the illicit opioid. A formerly lethal dose is no longer lethal.
  - Misconception: Naloxone co-formulated with BUP is <u>not</u> the agent producing opioid blockade, nor was that ever the intent.



- BUP is a weak/ineffective analgesic in OUD (*Incorrect, although there are limits, as will be discussed*)
  - Confusion arises because of its dual indication for OUD and pain, and addressing both issues when there is comorbid pain and OUD, e.g. what formulation(s) and dose(s) to use?

BUP routes/formulations and pharmacokinetics (PK)

- Routes/formulations that are FDA-approved for OUD and analgesia
  - Injection (IV, IM and SC depot)
  - Transmucosal (SL tablet or buccal film)
  - Transdermal (patch)
  - Implant (surgical) – no longer marketed in USA



Data references:

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

Kuhlman JJ, et al. (1996) Human pharmacokinetics of intravenous, sublingual, and buccal buprenorphine. J Anal Toxicol 20: 369-378.

Laffont CM, et al. (2016) Population pharmacokinetic modeling after repeated administrations of RBP-6000, a new, subcutaneously injectable, long-acting, sustained-release formulation of buprenorphine, for the treatment of opioid use disorder. J Clin Pharmacol 56: 806-815. {Data provided by the study sponsor.}

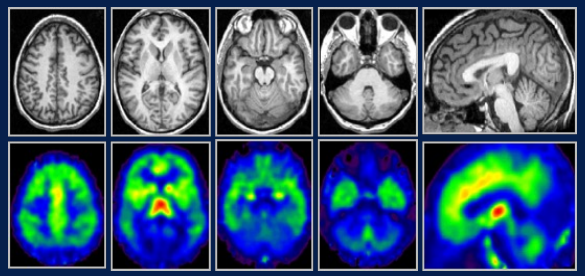
McAleer SD, et al. (2003) Pharmacokinetics of high-dose buprenorphine following single administration of sublingual tablet formulations in opioid naïve healthy male volunteers under a naltrexone block. Drug and Alcohol Dependence 72: 75-83.

White J, et al. (2009) Open-label dose-finding trial of buprenorphine implants (Probuphine®) for treatment of heroin dependence. Drug Alcohol Depend 103: 37-43.

Neuropharmacological rationale: Application of receptor theory to MOUDs

Target for treating OUD is *mu*-opioid receptor (μOR), implicated in reinforcing and physical dependence related effects of opioids

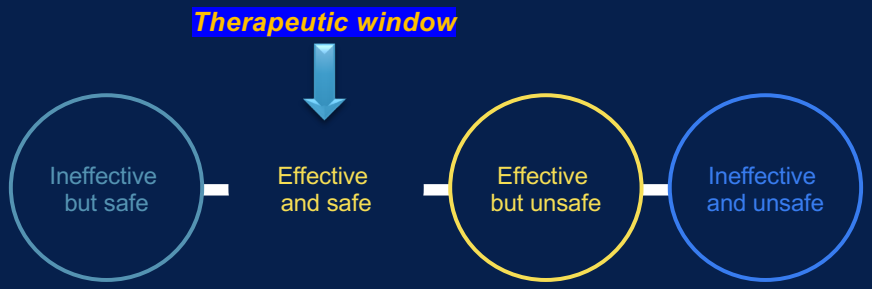
Mu-opioid receptors (human)



Greenwald MK, et al. (2003) Effects of buprenorphine maintenance dose on *mu*-opioid receptor binding potential, plasma concentration, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology* 28: 2000-2009.

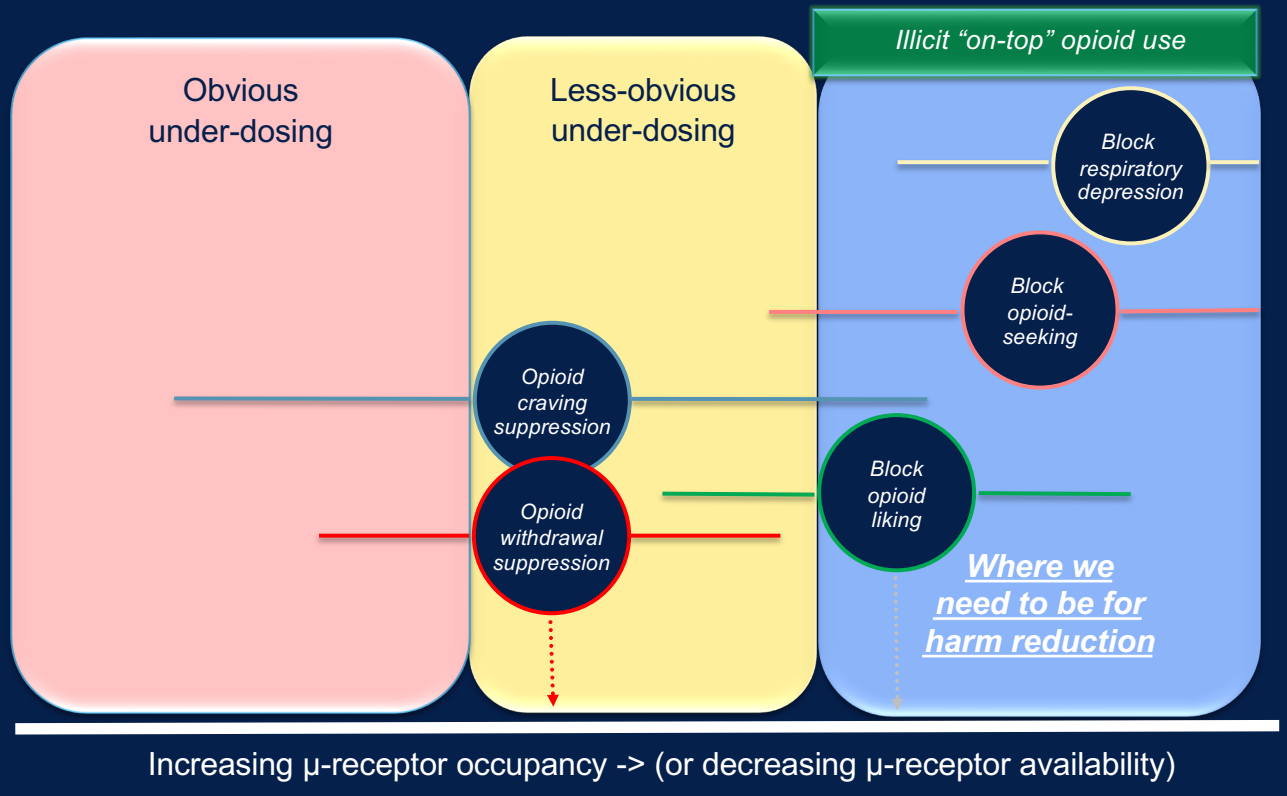
With addiction medicines, we're trying to maximize efficacy & minimize side effects within a therapeutic window along a continuum (mediated by μOR occupancy)

But we need to be clear: ***which*** efficacy measures?



Increasing receptor occupancy (or plasma concentration)

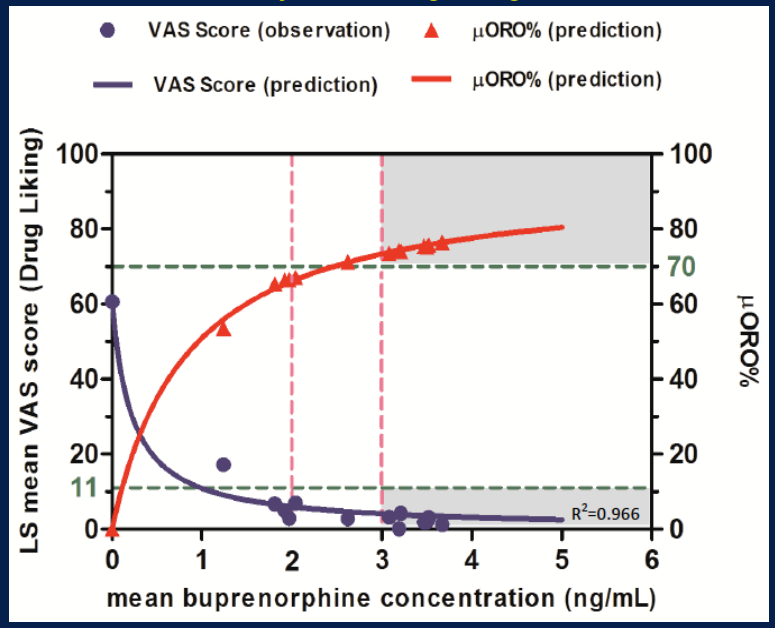
Estimated ordering and variability of μOR occupancy requirements for differing therapeutic thresholds in persons with OUD



Higher BUP plasma concentrations and μOR occupancy block opioid liking and reduce opioid-seeking behavior

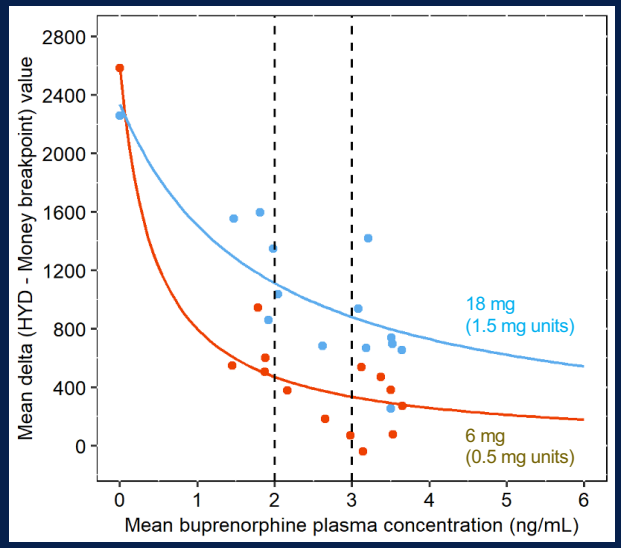
Morning: Challenge with hydromorphone (18 mg)

Subjective drug liking



Afternoon: Work for units of total morning hydromorphone dose vs. money on 12-trial choice, progressive ratio schedule

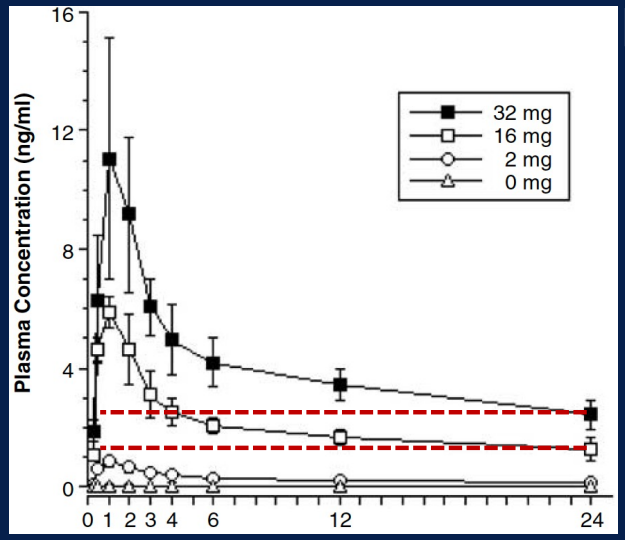
Drug-seeking behavior



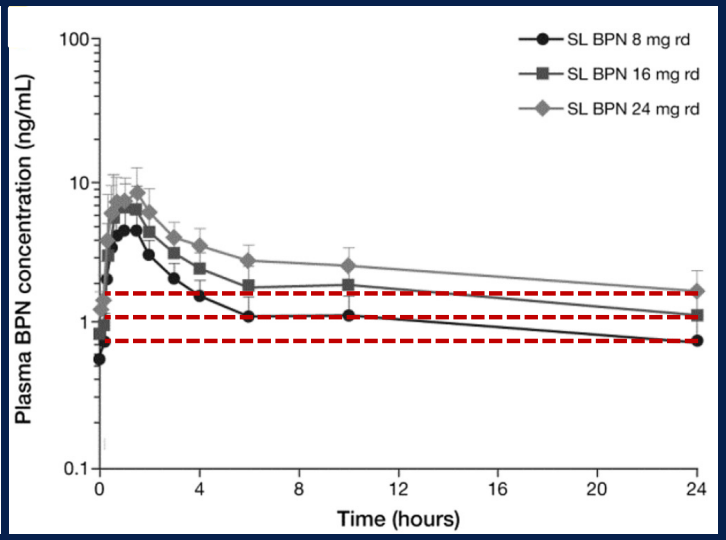
Nasser AF, Greenwald MK, et al. (2016) Sustained-release buprenorphine (RBP-6000) blocks the effects of opioid challenge with hydromorphone in subjects with opioid use disorder. *J Clin Psychopharmacol* 36: 18-26.

Unpublished analysis, based on Nasser et al. (2016)

Misconception: For maintenance dosing, don't focus on C_{max}; instead, aim for C_{min} (think: harm reduction)

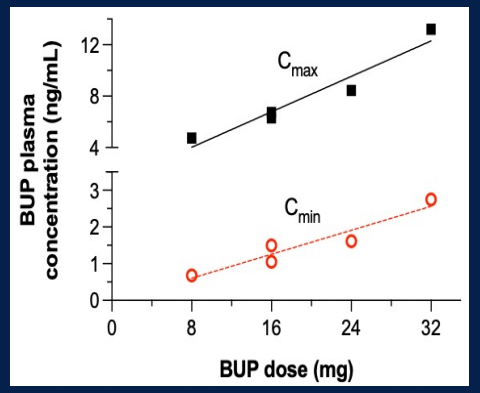


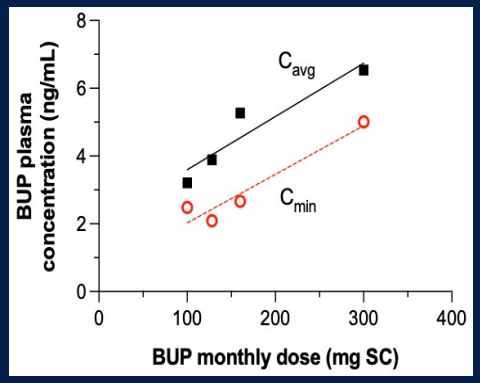
Greenwald MK et al. (2003) Effects of buprenorphine maintenance dose on *mu*-opioid receptor binding potential, plasma concentration, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology* 28: 2000-2009.



Albayaty M, et al. (2017) Pharmacokinetic evaluation of once-weekly and once-monthly buprenorphine subcutaneous injection depots (CAM2038) versus intravenous and sublingual buprenorphine in healthy volunteers under naltrexone blockade: an open-label phase 1 study. *Adv Ther* 34: 560-575.

Dose-linear relationship between BUP daily dose and C_{max} & C_{min}

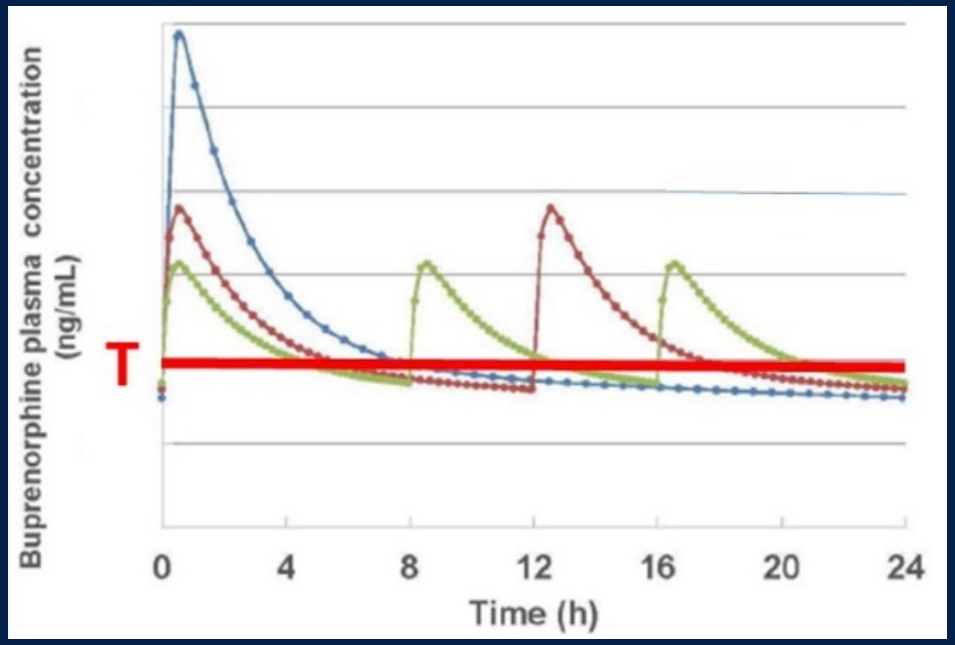




Adapted from: Coe MA, et al. (2019) Buprenorphine pharmacology review: update on transmucosal and long-acting formulations. *J Addict Med* 13: 93-103.

Divided dosing in BUP treatment of individuals who experience chronic pain, are pregnant, or are “fast metabolizers”

- Simulated plasma concentrations of buprenorphine utilizing physiologically based pharmacokinetic modeling of nonpregnant subjects.
- Thick red line (“T”) represents the threshold for clinically relevant opioid withdrawal symptoms.
  - Again, think C_{min}!
- Three times daily dosing (green line) results in a steadier plasma level and less time below withdrawal threshold compared to twice daily (red-purple) or once daily (blue) dosing (10.8, 14.4 and 16.3 hours, respectively).



Caritis SN, et al. (2017) An evidence-based recommendation to increase the dosing frequency of buprenorphine during pregnancy. Am J Obstet Gynecol. 217: 459.e1-459.e6

Addressing more misconceptions

- Precipitated opioid withdrawal (POW): What is it, and when does it occur?
  - Produced by an opioid partial agonist (e.g. BUP) or antagonist (e.g. NAL) with relatively high affinity and at sufficient concentrations in the presence of moderate to higher concentrations of a full agonist (e.g. fentanyl), especially when that agonist has been taken chronically (leading to neuroadaptations).
  - *Abrupt net reduction in agonist activity* at spare functional *mu*-opioid receptors; this dynamic shift (Δ) in receptor complexes between BUP and the prior opioid agonist (related to BUP K_{on} vs. opioid K_{off} and slow rate of BUP penetration into central compartment) leads to rapid onset in expression of withdrawal signs/symptoms
  - Misconception: Challenging with an opioid agonist on top of BUP does not lead to POW!
  - Misconception: POW is sometimes described clinically as on/off phenomenon ('flipping a switch'), but it can be measured along a continuum of severity
- Cumulative BUP dosing: If BUP leads to POW, then additional BUP doses will *not* always cause more withdrawal
  - After initial BUP dose that leads to POW, follow-on higher BUP doses typically suppress withdrawal
  - *Implication*: Long induction periods unnecessary

BUP induction hurdle: Premises of working model

1) Acute outcome of BUP induction (agonist – withdrawal balance, *Y-axis*) is a function of pre-initiation opioid balance, defined as symptom state or μOR occupancy (*dual X-axes and inset*).

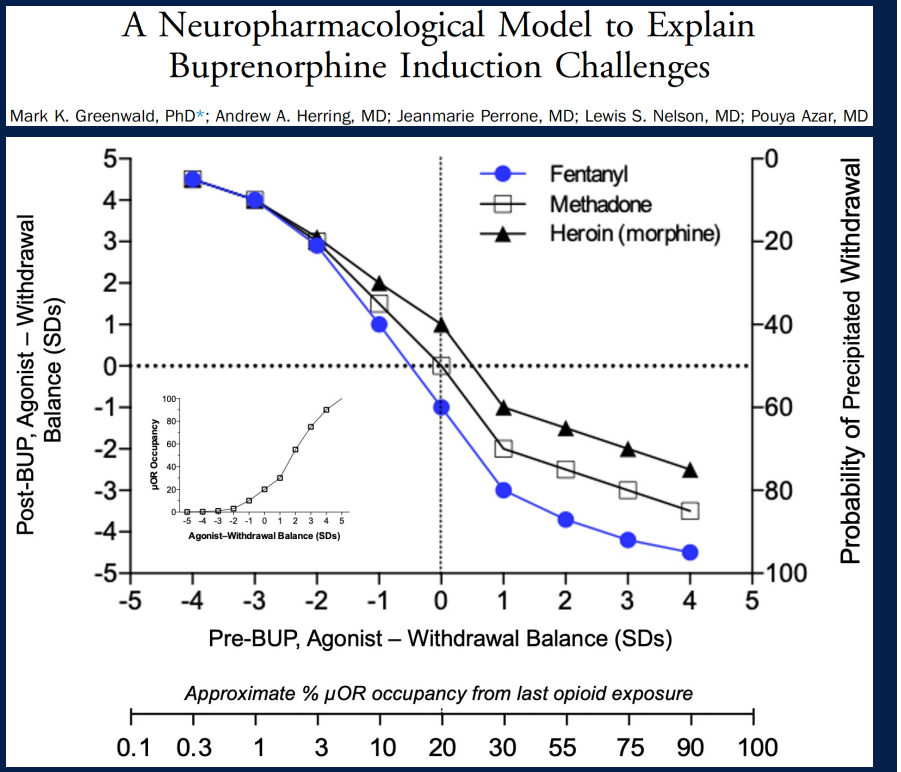
   a. Negative balance (withdrawal and lower % μOR occupancy) before initial BUP dose is associated with greater post-BUP agonist balance (*upper left quadrant*).

   b. Positive balance (agonist effect from residual opioid and higher % μOR occupancy) is associated with greater likelihood and severity of POW by initial BUP dose (*lower right quadrant*).

2) BUP induction outcome will differ by pre-exposure to opioids with high ALE values (affinity * lipophilicity * intrinsic efficacy).

   a. Pre-exposure to fentanyl (higher ALE value, and longer time to re-sensitize μORs) leads to more difficult BUP induction, whereas heroin/morphine (lower ALE value) leads to easier BUP induction.

   b. Extended exposure to fentanyl (dependence) increases the probability and severity of POW, because underlying μOR desensitization may not be fully reversed.



Greenwald MK, et al. (2022) A neuropharmacological model to explain buprenorphine induction challenges. *Annal Emerg Med*. 80(6): 509-524.

Avoiding POW and maximizing agonist effects during BUP induction

When there is residual agonist effect from prior opioid exposure, intermediate BUP starting doses (approx. 1-12 mg) increase risk of POW (shaded area, informally termed “the donut hole”)

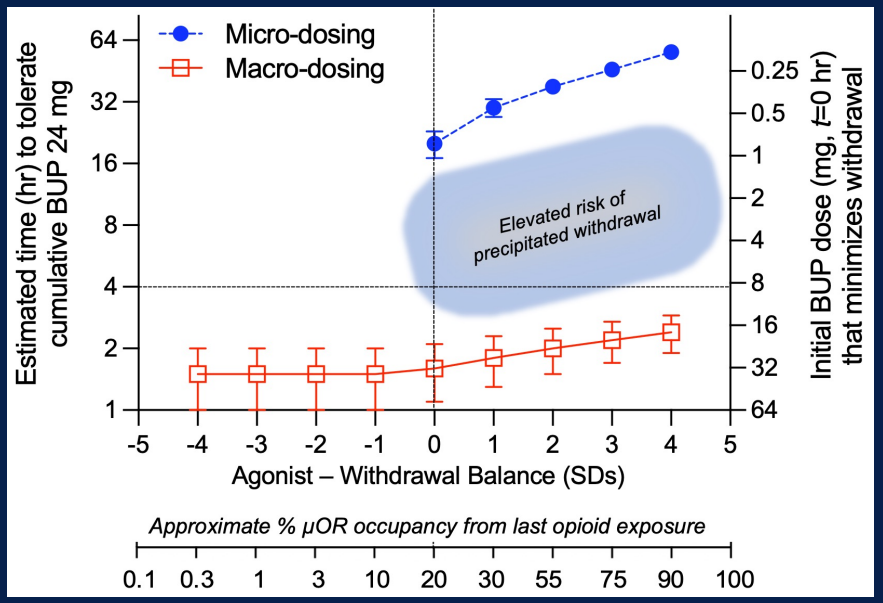
Why? Intermediate BUP doses displace enough residual agonist to POW, but insufficient to maximally stimulate spare functional μORs.

In contrast, “macro-dosing” (i.e. starting doses >16 mg SL) or “micro-dosing (i.e. starting doses of <0.5 mg SL) will be better tolerated with less chance of POW.

When baseline withdrawal is present (low μOR occupancy),

- Macro-dosing should result in a positive agonist balance, whereas
- Micro-dosing is unlikely to sufficiently replace the residual agonist and abstinence withdrawal will persist (i.e. micro-dosing is counter-productive when there is baseline withdrawal).

These curves may shift depending on the ALE value of the last opioid used.



Greenwald MK, et al. (2022) A neuropharmacological model to explain buprenorphine induction challenges. *Annal Emerg Med*. 80(6): 509-524.

Working model of BUP induction: Clinical application

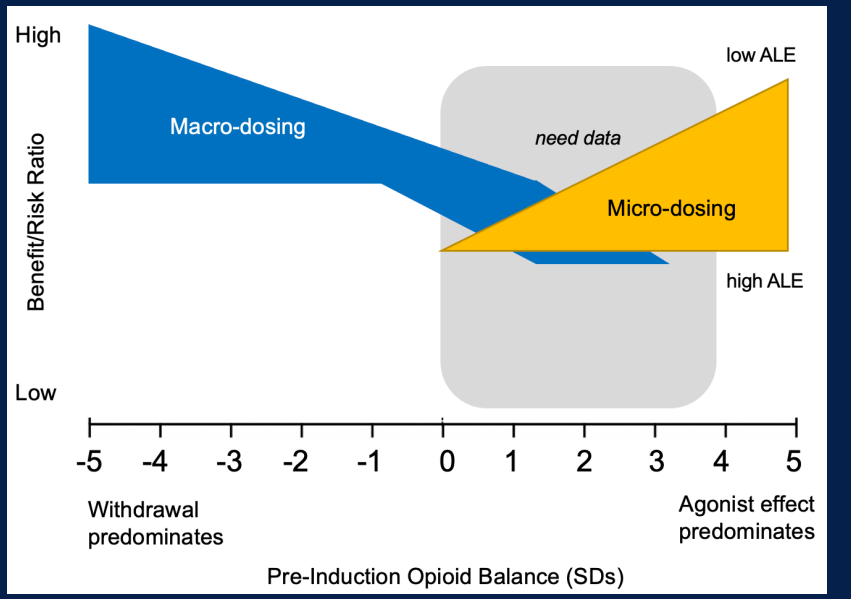
Macro-dosing (high/fast approach) is most effective and safe under conditions of baseline withdrawal (minimal μOR occupancy from prior opioid exposure

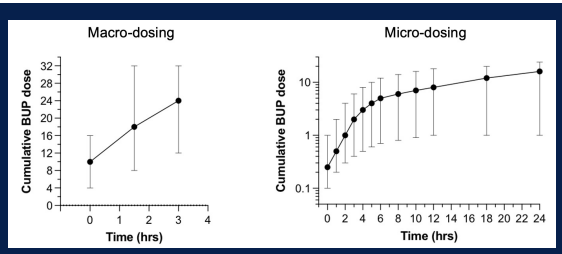
> *Reason*: μORs are likely to have undergone restorative processes (e.g. de-phosphorylation, re-sensitization) from the prior opioid, such that BUP can occupy functional μORs and produce its agonist effects

Micro-dosing (low/slow approach) can be effective and safe under conditions of baseline agonist activity (higher % μOR occupancy from prior opioid exposure)

> *Reason*: μORs remain partly occupied and desensitized from prior opioid exposure, so lower BUP doses can gradually re-occupy and re-sensitize μORs without POW

More empirical data are needed in situations where agonist baseline conditions prevail, to better understand tradeoffs between macro- and micro-dosing.

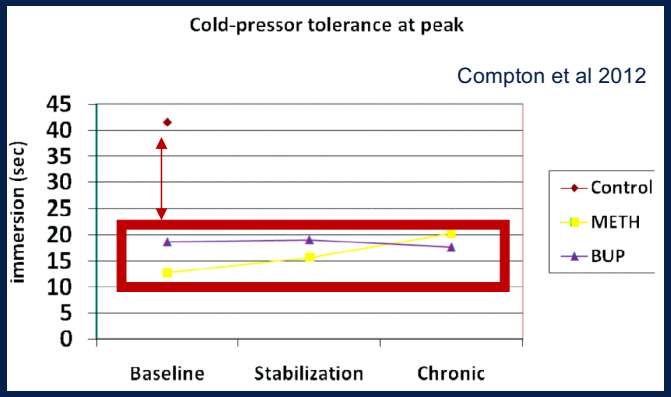




Greenwald MK, et al. (2022) A neuropharmacological model to explain buprenorphine induction challenges. *Annal Emerg Med*. 80(6): 509-524.

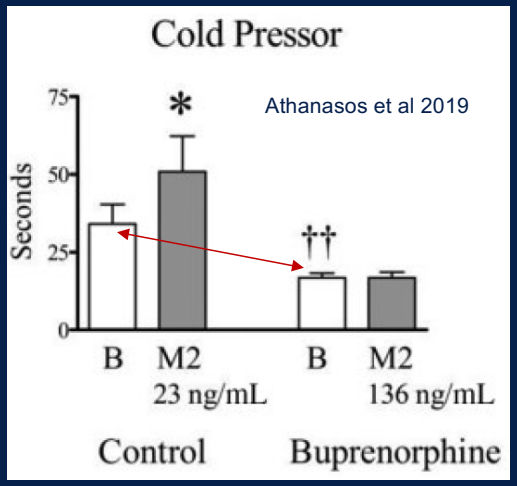
What is the role of BUP maintenance in hyperalgesia?

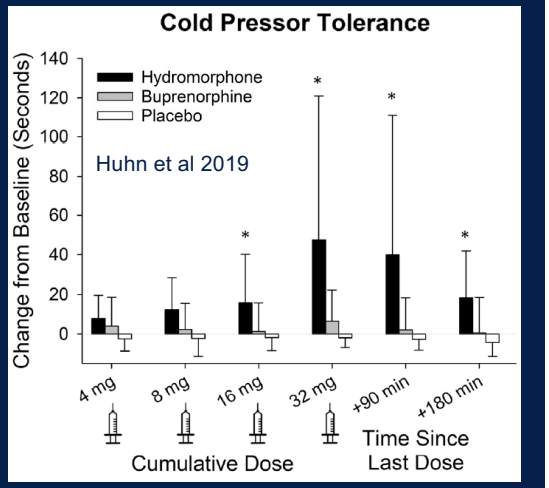
- Overall, few controlled clinical studies
- Experimental acute pain studies (Compton et al. 2012; Athanasos et al. 2019; Huhn et al. 2019) have found greatest sensitivity with cold pressor tolerance (time [sec] to remove arm from ice water):
  - Chronic opioid users are hyperalgesic (remove arm from cold water quicker than healthy controls)
  - BUP or MTD maintenance does not worsen or reverse this hyperalgesia
  - During BUP maintenance (12-16 mg/day SL), high-dose IV hydromorphone (16-32 mg) produced time-dependent reversal of hyperalgesia whereas high IV doses of BUP and morphine did not



Compton P, et al. (2012) Hyperalgesia in heroin dependent patients and the effects of opioid substitution therapy. *J Pain* 13: 401-409.

Huhn AS, et al (2019) Analgesic effects of hydromorphone versus buprenorphine in buprenorphine-maintained individuals. *Anesthesiology* 130: 131-141.

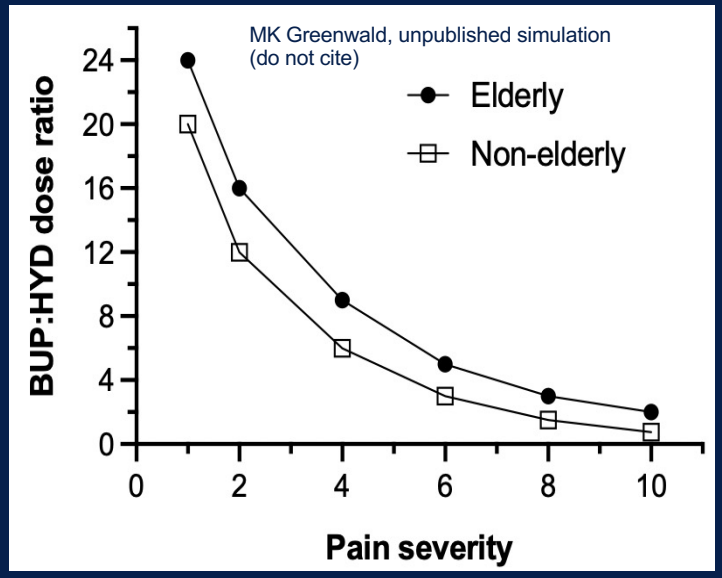




Athanasos P, et al. (2019) Buprenorphine maintenance subjects are hyperalgesic and have no antinociceptive response to a very high morphine dose. *Pain Med* 20: 119-128.

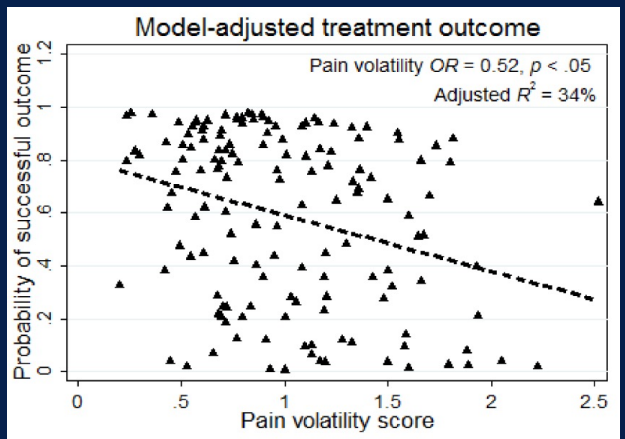
Pain intensity and BUP vs. ‘on-top’ agonist dosing: a proposal

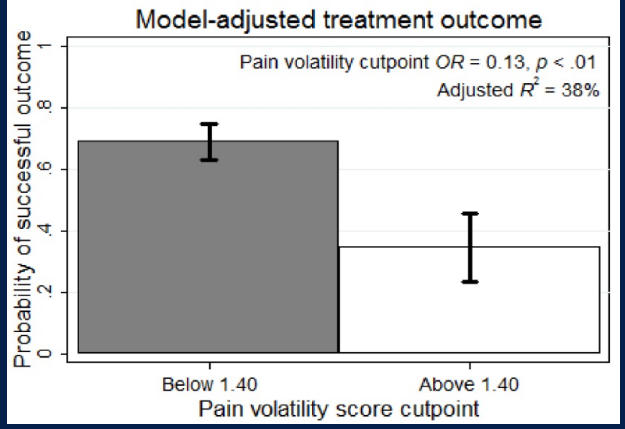
- Misconception and debate (esp. among anesthesiologists and surgeons) re: use of BUP and/or ‘on-top’ opioid agonist (or adjunctive analgesic) dosing for chronic pain and perioperative pain.
- Algorithm is partly a function of the severity of ongoing pain (chronic) or anticipated pain (perioperative).
- To balance BUP agonist effects with the need to treat breakthrough pain, a potentially useful concept is to consider the ratio of BUP (total daily dose) to ‘on-top’ agonist dosing (hydromorphone [HYD] units, reflecting use of more potent opioids than morphine in this context).
- Figure shows proposed form of the function. BUP:HYD ratios need to be empirically determined, and may differ due to individual differences such as age (e.g. BUP more favorable analgesic for the elderly)
  - At low pain severity, higher BUP:HYD ratio is feasible, i.e. continue BUP dosing, minimal need for additional agonist.
  - At higher pain severities, BUP:HYD ratio would decrease, e.g. increase on-top dosing to overcome cross-tolerance, and/or reduce BUP, based on clinical judgment.
  - Usually, not necessary to discontinue BUP for acute pain (Veazie et al. 2020). As pain severity decreases, BUP dose (if tapered) can be restored as needed for OUD.



Pain volatility predicts worse treatment (BUP + counseling or medical management) outcome

- Most studies have focused on pain severity, whereas pain *volatility* (within-subject variability across time) could be more informative or predictive of clinical outcomes
- Worley et al. (2015) conducted secondary analysis of POATS study, which had not demonstrated different opioid abstinence outcomes by chronic pain status (Weiss et al. 2011)
- *Pain volatility* = deviation of each patient's pain scores around their own pain trajectory across 12 study weeks, controlling for intercept, slope and covariates (mean absolute residual)
- Higher pain volatility – expressed as a continuous score (*upper panel*) or group (*lower panel*) – was associated with significantly less opioid abstinence
- Worley et al. (2017) extended this finding to the 4-week BUP dose taper period





Worley MJ, et al. (2015) Pain volatility and prescription opioid addiction treatment outcomes in patients with chronic pain. *Exp Clin Psychopharmacol 23*: 428-435.

Worley MJ, et al. (2017) Volatility and change in chronic pain severity predict outcomes of treatment for prescription opioid addiction. *Addiction* 112: 1202-1209.

Final Takeaways

- Numerous misconceptions and questions
  - Partial agonism at μORs (not other receptors), ceiling effects, POW, opioid blockade, on-top analgesia, hyperalgesia, C_{min} vs. C_{max}, divided daily dosing
  - Although not covered in this talk … When/for whom to start XR formulations and duration of BUP treatment should be determined by patient benefit
- Induction
  - Opioid-preexposure (including ALE value) critical in avoiding POW and maximizing agonist effects during transition (slow vs. rapid BUP induction dosing)
- Maintenance
  - While acknowledging that doses should be titrated using clinical judgment, higher doses (higher C_{min}) offer *more certain benefit* for a *higher proportion of patients* for treating OUD (e.g. withdrawal suppression, opioid blockade, preventing respiratory depression)
  - But for patients with chronic pain (esp. volatile pain) or perioperative pain, high BUP doses should be balanced against benefits of potent full agonists for on-top analgesia (BUP:HYD ratio)
- Tapering
  - Untreated pain volatility seems to predict relapse risk

References. 1

Albayaty M, et al. (2017) Pharmacokinetic evaluation of once-weekly and once-monthly buprenorphine subcutaneous injection depots (CAM2038) versus intravenous and sublingual buprenorphine in healthy volunteers under naltrexone blockade: an open-label phase 1 study. *Adv Ther* 34: 560-575.

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

Athanasos P, et al. (2019) Buprenorphine maintenance subjects are hyperalgesic and have no antinociceptive response to a very high morphine dose. *Pain Med* 20: 119-128.

Berg KA, Clarke WP (2018) Making sense of pharmacology: inverse agonism and functional selectivity. Int J Neuropsychopharmacology 21: 962-977.

Buresh M, et al. (2020) Treating perioperative and acute pain in patients on buprenorphine: narrative literature review and practice recommendations. *J Gen Intern Med* 35: 3635-3643.

Caritis SN, et al. (2017) An evidence-based recommendation to increase the dosing frequency of buprenorphine during pregnancy. *Am J Obstet Gynecol*. 217: 459.e1-459.e6

Coe MA, et al. (2019) Buprenorphine pharmacology review: update on transmucosal and long-acting formulations. *J Addict Med* 13: 93-103.

Compton P, et al. (2012) Hyperalgesia in heroin dependent patients and the effects of opioid substitution therapy. *J Pain* 13: 401-409.

Goel A, et al. (2019) Perioperative pain and addiction interdisciplinary network (PAIN) clinical practice advisory for perioperative management of buprenorphine: results of a modified Delphi process. *Br J Anaesth* 123: e333-e342.

Greenwald MK et al. (2003) Effects of buprenorphine maintenance dose on *mu*-opioid receptor binding potential, plasma concentration, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology* 28: 2000-2009.

Greenwald MK, Johanson CE, Bueller J, Chang Y, Moody DE, Kilbourn MR, Koeppe RA, Zubieta JK (2007) Buprenorphine duration of action: Mu-opioid receptor availability, pharmacokinetic and behavioral indices. *Biol Psychiatry* 61: 101-110.

References. 2

Greenwald MK, Comer SD, Fiellin DA (2014) Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. *Drug Alcohol Depend* 144: 1-11.

Greenwald MK, et al. (2022) A neuropharmacological model to explain buprenorphine induction challenges. *Annal Emerg Med*. 80: 509-524.

Huhn AS, et al (2019) Analgesic effects of hydromorphone versus buprenorphine in buprenorphine-maintained individuals. *Anesthesiology* 130: 131-141.

Huang P, et al. (2001) Comparison of pharmacological activities of buprenorphine and norbuprenorphine: norbuprenorphine is a potent opioid agonist. *JPET* 297: 688-695.

Kuhlman JJ, et al. (1996) Human pharmacokinetics of intravenous, sublingual, and buccal buprenorphine. *J Anal Toxicol* 20: 369-378.

Laffont CM, et al. (2016) Population pharmacokinetic modeling after repeated administrations of RBP-6000, a new, subcutaneously injectable, long-acting, sustained-release formulation of buprenorphine, for the treatment of opioid use disorder. *J Clin Pharmacol* 56: 806-815.

McAleer SD, et al. (2003) Pharmacokinetics of high-dose buprenorphine following single administration of sublingual tablet formulations in opioid naïve healthy male volunteers under a naltrexone block. *Drug Alcohol Depend* 72: 75-83 .

Nasser AF, Greenwald MK, et al. (2016) Sustained-release buprenorphine (RBP-6000) blocks the effects of opioid challenge with hydromorphone in subjects with opioid use disorder. *J Clin Psychopharmacol* 36: 18-26.

Reimer J, et al. (2020) Impact of buprenorphine dosage on the occurrence of relapses in patients with opioid dependence. *Eur Addict Res* 26: 77-84.

Veazie S, et al. (2020) Managing acute pain in patients taking medication for opioid use disorder: a rapid review. *J Gen Intern Med* 35(Suppl 3): S945-S953.

White J, et al. (2009) Open-label dose-finding trial of buprenorphine implants (Probuphine®) for treatment of heroin dependence. *Drug Alcohol Depend* 103: 37-43.

Worley MJ, et al. (2015) Pain volatility and prescription opioid addiction treatment outcomes in patients with chronic pain. *Exp Clin Psychopharmacol* 23: 428-435.

Worley MJ, et al. (2017) Volatility and change in chronic pain severity predict outcomes of treatment for prescription opioid addiction. *Addiction* 112: 1202-1209.