A Neuropharmacological Model to Explain Buprenorphine Induction Challenges

Mark K. Greenwald, PhD*; Andrew A. Herring, MD; Jeanmarie Perrone, MD; Lewis S. Nelson, MD; Pouya Azar, MD

*Corresponding Author. E-mail: mgreen@med.wayne.edu.

Buprenorphine induction for treating opioid use disorder is being implemented in emergency care. During this era of high-potency synthetic opioid use, novel and divergent algorithms for buprenorphine induction are emerging to optimize induction experience, facilitating continued treatment. Specifically, in patients with chronic fentanyl or other drug exposures, some clinicians are using alternative buprenorphine induction strategies, such as quickly maximizing buprenorphine agonist effects (eg, macrodosing) or, conversely, giving smaller initial doses and slowing the rate of buprenorphine dosing to avoid antagonist/withdrawal effects (eg, microdosing). However, there is a lack of foundational theory and empirical data to guide clinicians in evaluating such novel induction strategies. We present data from clinical studies of buprenorphine induction and propose a neuropharmacologic working model, which posits that acute clinical success of buprenorphine induction (achieving a positive agonist-to-withdrawal balance) is a nonlinear outcome of the opioid balance at the time of initial buprenorphine dose and mu-opioid–receptor affinity, lipophilicity, and mu-opioid–receptor intrinsic efficacy (the "ALE value") of the prior opioid. We discuss the rationale for administering smaller or larger doses of buprenorphine to optimize the patient induction experience during common clinical situations. [Ann Emerg Med. 2022;80:509-524.]

INTRODUCTION

Access to opioid use disorder treatment is limited by structural barriers, including stigma, underinsurance, too few trained health care providers, and disparities in access to care.[1] However, some clinical approaches reduce barriers to opioid use disorder treatment (eg, telemedicine, interim dosing, rapid-access clinics, and bridge programs).[2-9] Notably, the emergency department has become a pivotal treatment entry node because it is a health care safety net and a clinical cauldron for implementing and monitoring overdose rescue and opioid use disorder treatment induction and bridging strategies.

Buprenorphine is a long-acting, high-affinity, high-potency partial agonist (ie, intermediate intrinsic efficacy) at mu-opioid receptors. Various buprenorphine formulations, including transmucosal (buccal or sublingual ± naloxone), injectable, and implantable, have received regulatory agency approvals for opioid use disorder treatment. Buprenorphine is indicated for maintenance therapy and assisting illicit opioid discontinuation in patients with opioid use disorder. However, because of buprenorphine's pharmacologic profile, there are also challenges to induction that may be addressed through a high dose, microdose, or some combination (micro macro) of the two.

This review introduces a working model based on neuropharmacologic principles and data to provide a scientific foundation for improving clinical understanding and practice and leverages this information to optimize buprenorphine induction, particularly as it relates to challenges of synthetic opioid use.

BUPRENORPHINE INDUCTION

Induction onto buprenorphine or buprenorphine/ naloxone (hereafter, "buprenorphine" refers to either formulation) for opioid use disorder treatment is being studied in outpatient, hospital, and emergency department (ED) settings.[7,10-19] Current clinical guidelines suggest the following: (1) buprenorphine induction should be carefully monitored, (2) prior to initial dosing, patients should manifest at least mild opioid withdrawal severity, and (3) a stepwise dosing approach should be used.[18,19] Under these conditions, the clinician typically administers an initial buprenorphine dose of 2 to 4 mg; waits 1 to 2 hours for the absence of withdrawal effects; and, if well tolerated, administers additional doses of $\leq$16 mg on day 1, monitors safety, and (if ED or inpatient) discharges with linkage to outpatient follow-up care. The Substance Abuse and Mental Health Services Administration recommends a similar induction strategy but one which is limited to $\leq$8-mg sublingual in the first 24 hours.[20]

For the present review, clinical studies were identified through December 2021 using systematic PubMed literature search terms "buprenorphine" AND ("induction" or "initiation") AND ("opioid use" OR "opiate use"), with additional reference searching within identified articles. In contrast to standard buprenorphine induction, one emerging alternative involves macrodose (rapid high dose) induction, in which patients are administered up to 32-mg sublingual buprenorphine within the first few hours.[21] The effectiveness of macrodose buprenorphine induction has been investigated in case reports and retrospective studies (Table 1).[22-31] Reviews, position statements, and guidelines have also been published.[32-38] Using this strategy, patients experiencing opioid withdrawal are administered ≥16 mg buprenorphine doses; additional doses can be administered until withdrawal abates.[19]

In contrast to rapid high-dose buprenorphine induction, a slower approach called "microdosing" has been described.[39,40] Table 2 summarizes microdosing studies (review by Moe et al[37]), in which the buprenorphine dose was gradually uptitrated while the patient continues their nonmedical opioid use or medical opioid (eg, methadone during agonist treatment). There are 2 approaches—both involve buprenorphine uptitration but differ by the following: (1) tapering the prior opioid agonist throughout uptitration or (2) abruptly discontinuing the prior opioid upon reaching the buprenorphine therapeutic dose. This method was first described for chronic pain patients using medically prescribed opioids but was recently extended to patients who were administered methadone and patients using illicit opioids such as fentanyl.[41]

When conducted under medical supervision, both macrodosing and microdosing techniques can be described as pharmacologic crossover protocols with the goal of agonist substitution. The figure in Appendix E1 (available at http://www.annemergmed.com) illustrates typical doses (estimated median and range) of macrodosing and microdosing protocols on the basis of the studies described in Tables 1 and 2, which can provide general guidance for clinicians.

FOUNDATION: PRINCIPLES AND DATA

Because of buprenorphine's high mu-opioid–receptor affinity and partial agonism, its acute effects depend on the baseline pharmacologic conditions, along an agonist-to-withdrawal continuum, and individual differences. In addition, clinicians often do not know the patient's recent drug exposure or unique vulnerability to buprenorphine's antagonist effects, making it difficult to predict whether buprenorphine induction will be successful. Our working model and analysis are focused on this gap in understanding.

We first defined the buprenorphine induction process broadly through several parameters: initial dose, follow-on dosing frequency (interdose interval), and cumulation rate (dose-escalation at these intervals), allowing for T_{max} (≈ 0.5 to 1.5 hours for sublingual buprenorphine tablet).[42,43] Taken together, one can quantify the induction rate as an area-under-the-curve (AUC) buprenorphine dose (or plasma or brain concentration) representing the total exposure within a specified time frame or the time to reach a cumulative dose/concentration target.

Furthermore, we accounted for buprenorphine bioavailability. Unless noted, we refer to sublingual dosing, although buprenorphine could be administered intramuscularly, intravenously, or by extended-release subcutaneous injection, which would generate dose-adjusted, higher-than-sublingual AUC values because of greater bioavailability and different pharmacokinetics. Thus, we alternatively defined buprenorphine exposure in terms of concentration (plasma levels in nanograms per milliliter or mu-opioid–receptor occupancy) and dose. Making distinctions along this exposure continuum is arbitrary; however, for convenience, we refer to "macrodose" regimens where acute cumulative AUC_{6-hr} buprenorphine sublingual exposure is ≥ 16 mg, to "intermediate-dose" regimens with AUC_{6-hr} from 2-15 mg, and to "microdose" regimens with $AUC_{6-hr} < 2$ mg.

We conceptualize that the probability and magnitude of buprenorphine-precipitated withdrawal effects is a product of several pharmacokinetic and pharmacodynamic factors: initial dose of buprenorphine; mu-opioid–receptor affinity, lipophilicity, and mu-opioid–receptor intrinsic efficacy of buprenorphine relative to that of the last used opioid; and elimination pharmacokinetics of the last opioid (including active metabolites). Importantly, "precipitated withdrawal" is not invariably severe but occurs along a continuum from minimal to robust, has a plausible neuropharmacologic basis, and can be treated. What matters is not the incidence of precipitated withdrawal but the withdrawal AUC and how well it can be managed (such that the patient completes the induction).

Furthermore, induction outcomes could differ on the basis of a patient's level of opioid physical dependence, genetics, comorbidities, or prior buprenorphine experience—but we lack evidence for the impacts of these factors. Pharmacologic characteristics of various opioids (eg, fentanyl, heroin, and oxycodone), and polysubstance use or withdrawal (eg, alcohol, sedatives, psychostimulants, and xylazine) may alter buprenorphine induction response

Table 1. ED-based studies of buprenorphine starting dosing protocols for treatment of opioid use disorder.

Study Authors, Year	N	Type of Study	Pre-ED Opioid(s)	Other Drugs (If Known)	Baseline Opioid Withdrawal	Naloxone? (If So, the Total Dose Given)	BUP Dosing (Sublingual Unless Otherwise Noted)	Clinical Outcome
Zamani and Hassanian-Moghaddam,[101] 2017	1	Case report	MTD 150 mg	Fluoxetine 200 mg, clonazepam 20 mg	Initially mild (after first NLX), then 2.5 hr later COWS=14	0.4 mg prior to BUP (given by EMS)	0.6 mg IV	COWS decreased from 14 to 3 after BUP, and the patient was clinically stable for 24 hr, but respiratory depression re-emerged (treated with NLX infusion)
Herring et al,[23] 2019	3	Case report series	Heroin (all 3 cases) + fentanyl (cases #1, 2)	Methamph. (case #3)	Overdose (no WD) before NLX, with subsequent NLX precipitated withdrawal (mild)	0.4 mg IV (cases #1, 2); 2 mg IN then 0.3 mg IV (case #3)	8 mg then 8 mg ca. 90 min later (cases #1, 2) and 4 mg (followed shortly by 0.3 mg IV), 8 mg, 8 mg at 90-120 min intervals (case #3)	BUP induction following naloxone overdose reversal was well tolerated in all cases. Length of stay < 6.5 hr in all cases
Phillips et al,[24] 2019	1	Case report; deliberate naloxone-precipitated withdrawal	Heroin IV		No withdrawal (COWS=0)	0.5 mg IV (at 5-min post, COWS=17)	4 mg (with 8 mg IV ondansetron); 75 min later, 4 mg	At 105 min after NLX, the patient felt well (observed until 3hr 15 min post). At discharge, the patient was prescribed 8 mg/2 mg BUP/NLX.
Antoine et al,[26] 2021	4	Case report series	Fentanyl only (n=1) or fentanyl + heroin (n=3)	Cocaine + UDS in 2 of 4 cases; benzo + UDS in 1 case	Patients were opioid abstinent 20-48 hr and presented with (COWS ≥9)	No	4 mg (n=3) or 2 mg (n=1) initial dose, followed at varying intervals	Precipitated withdrawal in cases #1 and #2 (COWS=9 and first dose = 4 mg); better outcomes in cases #3 and #4, waited until COWS =13 & given 4 repeated 2 mg doses q. 60-90 min
Edwards et al,[25] 2020	53	Prospective observational	Heroin (57%), oral semisynthetic opioid (18%), BUP (16%), MTD (8%)		To qualify for induction: COWS ≥5 and no heroin or fentanyl past 12 hr, no hydrocodone or oxycodone past 24 hr, no long-acting opioid past 48 hr, no MTD past 5 days	No	Usual initial dose of 4 mg.	Average length of stay 3 hr 18 min. Nineteen of 53 patients returned to ED for BUP dosing under the DEA 72-hr rule (average length of stay for a return visit, 1 hr 33 min).
Berg et al,[27] 2007	88	Retrospective chart review	Data not reported		Group frequencies of individual symptoms reported	No	Initial dose of 0.3-0.9 mg IM or IV. Maximum dose not reported.	No precipitated withdrawal was observed. No clear advantage of BUP over other symptomatic treatments.
LeSaint et al,[31] 2020	77	Retrospective chart review	Heroin (74%), BUP (8%), MTD (5%), oxycodone (5%), fentanyl 1%, other/unknown (8%)		SOWS ≥10 (first protocol) or COWS ≥8 (second protocol). 43% presented without withdrawal	No	8 mg initial dose (if SOWS ≥10 [n=17] or COWS ≥8 [n=38]), followed by 4-8 mg at provider's discretion	Median length of stay 6.1 hr; 30% followed up at OUD clinic within 1- week after ED.

BUP, buprenorphine; DEA, Drug Enforcement Administration; EMS, emergency medical services; IM, intramuscular; IN, intranasal; IV, intravenous; MTD, methadone; NLX, naloxone; OUD, opioid use disorder; SOWS, Subjective Opiate Withdrawal Scale; UDS, urine drug screen; WD, withdrawal.

Table 2. Studies of buprenorphine microdosing induction for opioid use disorder.

Reference	N	Type of Study	Opioid(s) Prior to Cross-Taper	Other Drugs (If Known)	Baseline Opioid Withdrawal	BUP Dosing (Sublingual Unless Otherwise Noted)	Clinical Outcome
Azar et al,[41] 2018	1	Inpatient case report (54-year–old man)	IV heroin use ($30/d) while on MTD (30 mg/d), UDS confirmed	None detected by UDS	COWS=0	5-day transdermal fentanyl (25 µg/hr) bridge to BUP/NLX. Removed transdermal fentanyl (COWS=0), and 3 hr later initiated BUP (1+1+2+2+2 mg) over 5 hr)	Cumulative BUP/NLX (8 mg/ 2 mg) on cross-taper day did not increase COWS scores, and patient remained on this daily dose after discharge from hospital.
Klaire et al,[11] 2019	2	Inpatient case reports (case 1: 33-year–old woman; case 2: 40-year–old man)	Case 1: IV heroin Case 2: intranasal heroin	None reported	Case 1: COWS= 2 Case 2: COWS= 0	Case 1: IV HYD bridge (days 0-4; total daily doses were 3, 11, 15, 15 and 4 mg, respectively), while cross-tapering BUP/NLX doses (days 1-5; initial dose 0.25 mg; total daily doses were 1, 2.5, 5, 8 and 16, respectively) Case 2: oral HYD bridge (days 0-2; total daily doses were 24, 26, and 24 mg, respectively), while cross-tapering BUP/NLX doses (days 1-3; initial dose 0.5 mg; total daily doses were 2.5, 8 and 12 mg, respectively)	No precipitated withdrawal in either case. COWS ≤ 2 for case 1, and COWS = 0 throughout for case 2.
Raheemullah and Lembke,[93] 2019	15	Inpatient case report series	n=9 heroin; primary opioid not identified for other 6 patients. MME range 30-341 mg prior to cross-taper (day 0).			Days 1-2: BUP transdermal 20 µg/hr bridge (microdosing for 48 hr) while tapering prior opioids. Day 2: BUP SL 2 mg test dose, then 2-4 mg BUP q. 2-4 hr PRN (max daily dose = 8 mg) while tapering prior opioids. Day 3: Administer day 2 total dose, then 2-4 mg BUP q. 2-4 hr PRN (max daily dose = 16 mg) while tapering prior opioids. Day 4: discontinue prior opioids.	COWS scores remained low (≤8) for all patients throughout the cross-taper. Patients rated the transition as more comfortable than traditional BUP induction.
Rozylo et al,[91] 2019	1	Inpatient/outpatient case report (55-year–old man)	Daily IV heroin. The patient told to slowly decrease use while cross-tapering	IV methamph. q. 3 days	Not reported	Day 1: 0.25 mg; day 2: 0.25 mg BID; day 3: 0.5 mg BID; day 4: 1 mg BID; day 5: 2 mg BID; day 6: 4 mg BID; day 7: 12 mg; day 8: 16 mg	Successful induction (no precipitated withdrawal) but subsequent prescription error (resulting in a 3-day medication gap) led to relapse. Patient later readmitted for second induction, which was again well tolerated (mild craving only)
Terasaki et al,[13] 2019	3	Inpatient case report series	MTD (2 patients on 40 mg/d, and 1 patient on 100 mg/d); full dose given on days 1-7, then abruptly stopped on day 8	Oxycodone only on initial days for 2 patients	Minimal to none	day 1: 0.5 mg qd; day 2: 0.5 mg bid; day 3: 1 mg bid; day 4: 2 mg bid; day 5: 4 mg bid; Day 6: 8 mg qd; day 7: 8 mg then 4 mg; day 8: 12 mg	All 3 patients successfully transitioned from MTD to BUP with minimal withdrawal
Azar et al,[82] 2020	1	Inpatient case report (16-year–old girl)	IV fentanyl 4 hr before admission. UDS+ for opioids and fentanyl	IV methamph. 4 hr before admission. UDS+ for amphet.	COWS range from 2-6 on days 1-2	Oral hydromorphone bridge (days 1-2), while increasing BUP/NLX doses on day 1 (0.5 mg q. 3hr; total= 3 mg); day 2 (1 mg q. 3 hr; total=7 mg); day 3 (8 mg single dose); day 4 (300 mg extended-release–BUP injection)	Adjunctive medications on day 1 (clonazepam, dimenhydrinate, clonidine) and day 4 (ibuprofen). COWS ≤6 across all cross-taper days. No precipitated withdrawal. Induction onto XR-BUP successful, but patient did not return for second monthly dose and relapsed.

Study	N	Type	Baseline opioid	Other substances	Withdrawal	Induction protocol	Outcome
Brar et al,[102] 2020	7	Outpatient case report	MTD (n=1), slow-release oral morphine (n=3), illicit fentanyl (n=3)	UDS+ for fentanyl, other opioids, and stimulants for all 7 patients	Not reported (but presumably minimal or absent)	Day 1: 0.5 mg qd; day 2: 0.5 mg bid; day 3: 1 mg BID; day 4: 2 mg BID; day 5: 3 mg BID; Day 6: 4 mg BID; day 7: 12 mg; with subsequent titration to 12 to 32 mg	Successful induction (no precipitated withdrawal)
Callan et al,[66] 2020	1	Inpatient case report (38-year–old woman with pain and MRSA treated with antibiotics)	MTD: day 0: 70 mg (25/25/20 mg); day 1: 50 mg (25/25 mg); day 2: 30 mg; days 3-7: none		None	Oral HYD bridge: days 0-1: 4 mg q. 4 hr PRN; days 2-3: 8 mg q. 4 hr PRN; day 4: 8 mg twice, 6 mg twice; days 5-7: none BUP: days 0-3: none; day 4: 2 mg, 4 mg, and 8 mg given 2.5 hr apart (14 mg total); day 5: 8 mg BID (16 mg total); day 6: 8 mg TID (24 mg total); day 7: 12 mg BID (24 mg total) Adjunctive meds: ibuprofen 600 mg qid, acetaminophen 1000 mg tid, lidocaine 5% patch/day, gabapentin 500 mg tid, clonidine 0.1 mg tid, clonazepam 1.5 mg tid PRN	"Experienced withdrawal" after last HYD dose, just before being administered the initial BUP dose (day 4). "Throughout the transition, the patient reported persistent mild withdrawal symptoms" (page e275)
Hamata et al,[92] 2020	1	Inpatient case report (29-year–old woman with infective endocarditis and septic shock)	≈1 gram IV heroin daily. UDS+ for opioids and fentanyl	IV methamph. every other day. UDS+ for amphet.	"Mild" withdrawal	Fentanyl infusion 200 mcg/min (total daily doses-day 1: 2 mg; day 2: 4 mg; day 3: 8 mg; day 4 down-taper: 19 mg) with oral HYD 1-4 mg q. 3 hr PRN because of pain and opioid withdrawal and adjunctive meds (clonidine 0.1 mg q. 8 hr, gabapentin 100 mg q. 8 hr, methotrimeprazine 10 mg q. 4 hr). Cross-taper with BUP (day 1: 0.25 mg q. 3 hr; day 2: 0.5 mg q. 3 hr; day 3: 1 mg q. 3 hr; day 4: 12 mg + 1 mg q. 3 hr PRN)	Successful induction (no precipitated withdrawal) in this complex case (patient had been intubated prior to starting cross-taper)
Oretti,[103] 2015	7	Retrospective	MTD (last dose the day before initial BUP)		Patients reached COWS>10 before initial BUP	4 mg (BUP or BUP/NLX) was administered when COWS>10, with additional BUP up to 24 mg (BUP/NLX) or 32 mg (BUP) over 24 hr	6 of 7 patients succeeded in transfer. Additional medications used with BUP used to manage withdrawal symptoms
Moe et al,[37] 2021	57	Systematic review of 20 studies				Median initial dose 0.5 mg (range, 0.03–1.0 mg). 26 of 57 patients had prescribed overlapping opioid agonists (9 MTD, 5 fentanyl, 5 HYD, 3 morphine, 4 multiple), whereas 31 not prescribed an overlapping opioid but used illicit opioids during cross-taper	Only 6 of 20 studies used a standardized withdrawal measurement approach (5 COWS, 1 SOWS). No precipitated withdrawal in 54 of the 57 cases. In those cases, the cross-taper opioid varied (column to the left), and median starting BUP dose was 0.5 mg, median duration of cross-taper 6 d, and median rate of BUP dose change to reach 8 mg was 1.36 mg/d (SD 0.41) Precipitated withdrawal occurred in 3 of 57 cases; in those cases, MTD was the cross-taper opioid (∼20-30 mg on days 1-3), median starting BUP dose 0.4 mg, median duration of cross-taper 6 d, and median rate of BUP dose change to reach 8 mg was 1.17 mg/d (SD 0.11)

Table 2. Continued.

Reference	N	Type of Study	Opioid(s) Prior to Cross-Taper	Other Drugs (If Known)	Baseline Opioid Withdrawal	BUP Dosing (Sublingual Unless Otherwise Noted)	Clinical Outcome
Thakrar et al,[104] 2021	2	Inpatient case reports	Case 1: MTD 65 mg (preadmit), 40 mg (day 0), 20 mg (days 1-3). IV HYD 1-2 mg q. 4 hr (day 1), 2 mg q. 4 hr (days 2-4). Case 2: oral oxycodone 20 mg q. 4 hr + oral HYD (8 mg q. 4 hr) + IV HYD (1 mg q. 4 hr) + oral tramadol (50 mg q. 4 hr) on day 0. Oral HYD (6-8 mg q. 4 hr) + oral tramadol (50 mg q. 4 hr) on day 1. Oral HYD (8 mg q. 4 hr) on days 2-3. Oral HYD (4-8 mg q. 4 hr) on day 4. Oral HYD 2-4 mg q. 4 hr tapered over 3 weeks at d/c	Case 1: no other drugs. Case 2: acetaminophen, ibuprofen, pregabalin	Not documented with COWS	IV BUP: 0.15 mg q. 6 hr (day 1), 0.3 mg q. 6 hr (day 2), and 0.6 mg q. 6 hr (day 3). Transition to SL BUP: 4-8 mg q. 4-6 hr PRN (day 4) and 8-12 mg BID (day 5) (days 4 and 5 BUP unit doses differed for the 2 patients)	Both patients successfully transitioned to BUP, and denied withdrawal symptoms throughout transition.

BID, twice daily; *COWS*, Clinical Opiate Withdrawal Scale; *HYD*, hydromorphone; *mME*, milligram morphine equivalent dose; *MTD*, methadone; *PRN*, as needed; *SL*, sublingual; *TID*, thrice daily; *mg qd*, mg every day, *d/c*, discharge; *methamph*, methamphetamine; *XR-BUP*, extended release buprenorphine; *MRSA*, methicillin-resistant Staphylococcus aureus.

through pharmacokinetic and/or pharmacodynamic interactions. To operationalize these concepts, we propose a neuropharmacologic framework that collapses salient pharmacokinetic and pharmacodynamic factors into a single independent variable, "opioid balance," defined as the opioid agonist effect minus opioid withdrawal effect (standardized difference score). This opioid balance metric can be used to assess preinduction clinical status and examine dose/exposure-response relationships during buprenorphine induction.

ASSUMPTIONS OF THE WORKING MODEL
Assumption 1

On the basis of clinical observations and research literature surrounding induction onto buprenorphine (Tables 1 and 2), we hypothesize that the acute outcome of buprenorphine initial dosing (postbuprenorphine agonist minus withdrawal symptoms) depends on the following: (1) prebuprenorphine opioid balance and (2) the residual agonist's "affinity × lipophilicity × intrinsic efficacy (ALE) value," which is the mathematical product of mu-opioid–receptor binding affinity (K_i value, nM), lipophilicity (logP or n-octanol: water partitioning coefficient at physiologic levels [pH=7.4]), and mu-opioid–receptor intrinsic efficacy (percent maximum G-protein activation) of the residual agonist (and active metabolites). We defined an opioid's affinity, lipophilicity, and intrinsic efficacy value as 1/affinity (inverse of its mu-opioid–receptor binding affinity because lower K_i values reflect higher affinity) × lipophilicity × intrinsic efficacy. The ALE value integrates well-established pharmacologic knowledge, which states that opioid agonist actions at mu-opioid receptors are enhanced by the following: (1) higher lipophilicity (central nervous system partitioning), which increases rapidity of onset and extends elimination half-life; (2) higher binding affinity (increased percent of a time period in which the ligand interacts with mu-opioid receptors); and (3) higher intrinsic efficacy (more G-protein activation, which increases mu-opioid–receptor intracellular signaling). These parameter values have been computed for clinically used opioids in standardized in vitro studies, which we employed here (the table in Appendix E1).[44-46] Herein, this ALE value equally weights its components (affinity, lipophilicity, and intrinsic efficacy); however, further research might revise whether one parameter should be weighted more heavily. For instance, fentanyl and hydromorphone have similar ALE values (3.61 and 3.71, respectively); however, hydromorphone has a higher mu-opioid–receptor affinity than fentanyl (K_i=0.37 versus 1.35 nM), whereas fentanyl

has higher lipophilicity than hydromorphone (logP=4.28 versus 1.46).[44,45] Thus, if buprenorphine inductions are empirically more difficult following fentanyl than following hydromorphone, one could reweigh the components of the ALE values or include alternative parameters (assumption 2) in this working model. Other unique pharmacologic aspects of fentanyl may contribute to difficult buprenorphine induction.[47]

Assumption 2

We hypothesize that more extensive opioid agonist pre-exposure alters baseline mu-opioid–receptor functional status—which correlates with the degree of opioid tolerance or dependence–prior to initial buprenorphine dosing. Presently, we lack objective data on the magnitude of this baseline shift because different μ-opioid agonists vary widely in their propensities to phosphorylate the carboxy-terminal tail of mu-opioid receptor; recruit β-arrestin binding to the phosphorylated receptor, thus decoupling mu-opioid receptors from G-protein signaling so they become desensitized (ie, functionally less active or inactive), which occurs within several minutes; internalize mu-opioid receptors into endosomes, where they are dephosphorylated, the first step in receptor recovery, which occurs in $\approx$ 30 min; and recycle reactivated mu-opioid receptors to the cell membrane, which may take $\approx$ 1 hour but can be several hours following chronic opioid exposure.[48-65]

Despite this complexity, mu-opioid–receptor agonists with higher ALE values (eg, hydromorphone, fentanyl) and methadone (intermediate ALE value [1.67]) generally stimulate this chain of effects (phosphorylation->desensitization->internalization) more than μ-agonists with lower ALE values, such as hydrocodone (0.04) and oxycodone (0.03). Although ALE values do not directly reflect these intracellular events, they offer a reasonable proxy. We propose that greater pre-exposure to opioids with high ALE values will increase the likelihood of mu-opioid–receptor desensitization and internalization, leading to an increased risk of withdrawal symptoms during buprenorphine induction. As a partial agonist, a sufficient quantity of sensitized and available mu-opioid receptors is required for buprenorphine signaling to restore opioid balance in a patient. The observed effectiveness of buprenorphine is a product of the concentration of buprenorphine and sensitized mu-opioid–receptor availability. Thus, in a desensitized/internalized mu-opioid–receptor state, greater central nervous system concentrations of buprenorphine are predicted to be needed to achieve opioid balance versus

in the less tolerant/sensitized state. Clinically, it was observed that as abstinence and withdrawal progress (and tolerance is reversed), a given dose of buprenorphine will have increased agonist efficacy. Similarly, patients who might require a large buprenorphine dose on the first day of induction will stabilize on normal doses after receptor resensitization has occurred (days 2 to 3).

In individuals who chronically use opioids, the likelihood of buprenorphine-induced withdrawal will depend on the proportion of functional spare mu-opioid receptors (which should inversely correlate with "opioid balance"). Two critical factors are the rate of resensitization of mu-opioid receptors (ie, functional receptors) and the proportion of these mu-opioid receptors that are unbound (ie, spare). If there are few functional spare mu-opioid receptors (ie, higher baseline positive opioid balance), then a slower rate of buprenorphine exposure (microdosing) could sometimes be advantageous to avoid withdrawal symptoms; however, if there are more functional, spare mu-opioid receptors (leading to neutral to negative opioid balance), the rate of buprenorphine induction should be faster (macrodosing) to maximize opioid signaling and to match the complete agonist deficit. This could explain several phenomena. First, the low intrinsic efficacy of buprenorphine requires its widespread mu-opioid receptor availability and a higher ratio of bound versus unbound buprenorphine at functional mu-opioid receptors to produce its clinical effects. Thus, microdosing can be effective for buprenorphine induction in the presence of agonists with high ALE values because there are few functional spare mu-opioid receptors (resensitization is slower, and those mu-opioid receptors are occupied by the agonist with high ALE values) that require gradual, cumulative buprenorphine dosing.[11,26,41,66] Second, it has been shown in vitro that buprenorphine can reverse desensitization produced by full μ-opioid agonists.[67] This could explain why microdosing could sometimes proceed more rapidly (ie, not require multiday induction protocols) if simultaneously the high-ALE agonist is dissociating from mu-opioid receptors. Third, this could explain why, once competitive displacement of the agonist with high ALE has begun, macrodosing can be effective by maximizing mu-opioid receptor–bound buprenorphine, thereby accelerating resensitization and increasing agonist signaling. Fourth, this could explain why administering naloxone, which reverses opioid overdose and rapidly resensitizes mu-opioid receptors, could be immediately followed by buprenorphine macrodoses.[68] Finally, it could explain a recent case finding that ketamine, which resensitizes mu-opioid

receptors and attenuates opioid withdrawal, could potentially be used to accelerate buprenorphine induction.[69-72]

Assumption 3

We hypothesize that prebuprenorphine opioid balance will predict the outcome of the initial buprenorphine dose (ie, postbuprenorphine opioid balance). This model requires standardized, concurrent measurement of both agonist and withdrawal effects, as the first author has shown with an instrument (Opiate32 questionnaire) that has 16 items each for agonist symptoms and withdrawal symptoms to calculate this balance score.[73] This instrument has repeatedly proven sensitive to doses of several opioid agonists (buprenorphine, methadone, hydromorphone, and fentanyl), naloxone-precipitated opioid withdrawal, and spontaneous opioid (buprenorphine and methadone) discontinuation.[73-77]

Assumption 4

We acknowledge that outcomes of buprenorphine induction (described herein as average responses) are influenced by individual difference factors beyond chronicity or type of opioid use, which are yet to be determined, and could include genetic variation (eg, in molecular signaling pathways), other substance use, and neuropsychiatric conditions. However, this error variance exceeds the scope of this discussion.

PROPOSED TESTS OF THE WORKING MODEL

Figure 1 (inset) illustrates that, in a person who is physically dependent on opioids and, thus, can experience both agonist and withdrawal effects, opioid balance is positively related to mu-opioid receptor occupancy. Figure 1 (main panel) shows that when preinduction opioid balance is positive (ie, greater residual agonist effect and mu-opioid receptor occupancy), the probability of buprenorphine-precipitated withdrawal is greater following pre-exposure to agonists with high ALE values such as fentanyl and is less with agonists with low ALE values such as morphine.

Residual agonist effects of opioids with high ALE values (eg, fentanyl, hydromorphone) are predicted to shift the postbuprenorphine opioid balance score toward greater withdrawal probability and/or severity compared to residual heroin and its central nervous system-acting metabolite morphine (lower ALE value). This outcome is expected from assumption 2 because opioids with higher ALE values promote mu-opioid receptor activation, yielding a desensitized state. This reduction in mu-opioid

receptor reserve makes it more likely that buprenorphine will displace (through its higher affinity) and produce less agonist action (due to its lower intrinsic efficacy) compared with the prior opioid. Accordingly, the most favorable outcome is that buprenorphine agonist actions will be attenuated, and the least favorable outcome is that withdrawal effects predominate. The likelihood/severity of withdrawal effects is expected to be greater for fentanyl than for morphinan or semisynthetic opioids (eg, morphine, oxycodone, and hydrocodone) when there is greater prebuprenorphine opioid balance (ie, minimal physiologic withdrawal). If the patient has consumed large daily doses of a high ALE-value agonist, this will lead to agonist accumulation, and the desensitized state may take longer to reverse, which would manifest as a more positive opioid balance; under these conditions, intermediate-dose buprenorphine might displace the residual agonist but will not achieve sufficient agonist signaling in the desensitized state to prevent withdrawal symptoms. In this situation, buprenorphine microdosing might promote mu-opioid receptor resensitization while not triggering withdrawal symptoms; conversely, high-dose buprenorphine could be used to maximize agonist signaling and resensitization.

In contrast, the ease of buprenorphine induction is not expected to differ between various opioids when there is significant preinduction withdrawal (in our clinical experience, more so when there are physiological withdrawal signs) because buprenorphine uniformly suppresses withdrawal regardless of the preceding agonist.[78,79] Thus, microdosing is counterproductive (insufficient agonist signaling due to low buprenorphine dosing) when the patient is experiencing preinduction withdrawal symptoms, regardless of how the withdrawal symptoms developed—from abstinence, naloxone, or prior doses of buprenorphine.

Figure 2 illustrates further clinical implications of the working model on the basis of the studies summarized in Tables 1 and 2. We emphasize that the following approximations are a starting point and require evaluation in controlled studies. Consistent with prior mu-opioid–receptor brain imaging findings, we hypothesize that when the residual opioid continues to produce agonist effects, which we estimate to occur when >20% of mu-opioid receptors are occupied, intermediate buprenorphine initiation doses (about 1 to <16 mg) will increase the likelihood of withdrawal effects ("donut hole" in Figure 2), whereas lower initial buprenorphine doses (≤0.5 mg) will likely produce minimized effects of any kind but, through gradual increase over time, could achieve a therapeutic level.[75,77,79,80] In microdosing, the
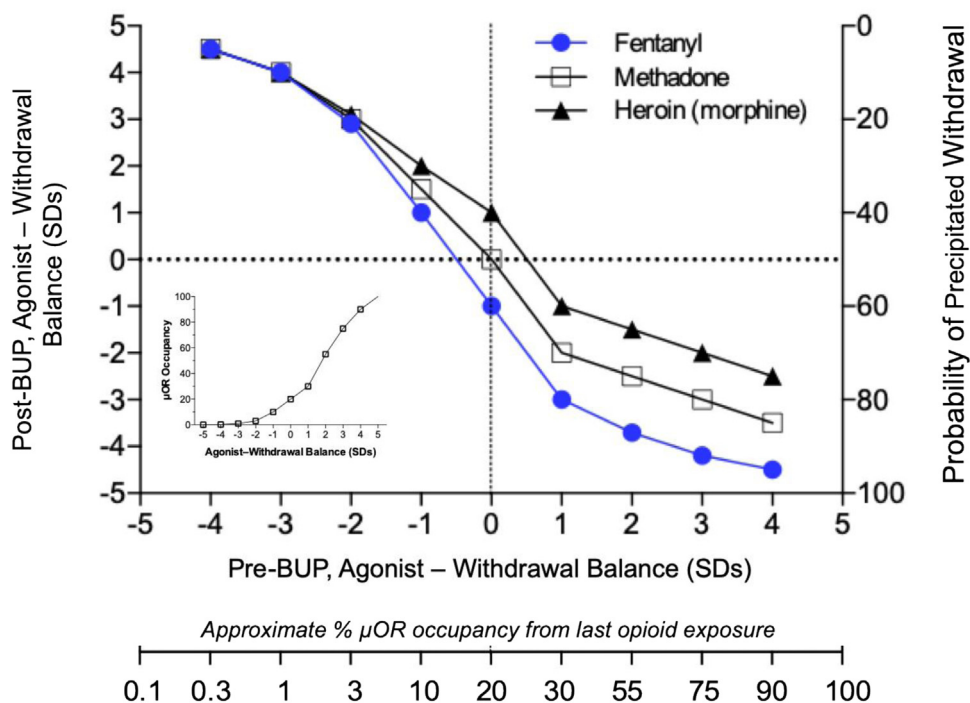
Figure 1. Neuropharmacologic working model. The upper X-axis depicts the clinical symptom state produced by residual opioid use prior to the buprenorphine (BUP) starting dose. Zero "opioid balance" represents that neither withdrawal nor agonist effects predominate (neutral state); negative scores indicate withdrawal, and positive scores indicate agonist effects. This clinical state reflects the difference of total opioid agonist symptoms minus total opioid withdrawal symptoms ("agonist-withdrawal balance"), indexed in SD units relative to 0 (neutral state; text). The lower X-axis depicts the estimated percentage of mu-opioid receptors (μORs) occupied by the last opioid used. The inset displays that opioid balance is sigmoidally related to μOR occupancy.[79] The left Y-axis shows the predicted clinical outcome (opioid balance in standard deviation units) after the BUP starting dose. The right Y-axis (note the reverse scale) shows the estimated probability of an initial moderate BUP dose to precipitate withdrawal (negative opioid balance). The model predicts that the clinical outcome (post-BUP opioid balance) is a function of preinitiation opioid balance. Negative opioid balance at baseline is related to greater post-BUP agonist balance (upper left quadrant) (ie, successful induction). In contrast, a greater baseline agonist effect from residual opioid exposure, with correspondingly greater percent μOR occupancy, is associated with greater post-BUP withdrawal symptom severity (ie, BUP-precipitated withdrawal; lower right quadrant). The model also predicts that pre-exposure to heroin/morphine (low affinity, lipophilicity, and μOR intrinsic efficacy value) leads to easier BUP induction, whereas fentanyl (high affinity, lipophilicity, and μOR intrinsic efficacy value) is associated with more difficult BUP induction; this is reflected in the curve shift. Although specific values are estimates that need to be empirically tested, the form of these functions should remain similar in principle. Each drug curve describes an average response profile, allowing the possibility that other testable factors could modulate BUP induction response (ie, shift the curve; assumption 4).

buprenorphine dose is very low, and the magnitude of the agonist effect (and presumably stimulation of receptor resensitization) is also low; hence, the minimum sufficient buprenorphine dose to transition to a full therapeutic dose remains unclear.

SUPPORT FOR THE WORKING MODEL: CLINICAL SCENARIOS

Scenario 1

Clinicians have observed that some patients (who are not experiencing spontaneous opioid withdrawal) who were administered an initial moderate buprenorphine dose (4 to 8 mg) experienced prominent withdrawal symptoms, and when the same patient received larger follow-up buprenorphine doses (eg, 16 mg all at once), withdrawal scores decreased.[36] Notably, buprenorphine causes minimal mu-opioid–receptor desensitization or internalization and can suppress its precipitated withdrawal.[46,58,74,81] In our model, if buprenorphine precipitates withdrawal, that initial dose becomes the residual opioid, and subsequent buprenorphine (particularly higher) doses should promote mu-opioid–receptor resensitization, adding cumulative agonist effect and suppressing withdrawal effects from the first dose. Thus, buprenorphine macrodosing can be effective even after the first dose produces withdrawal
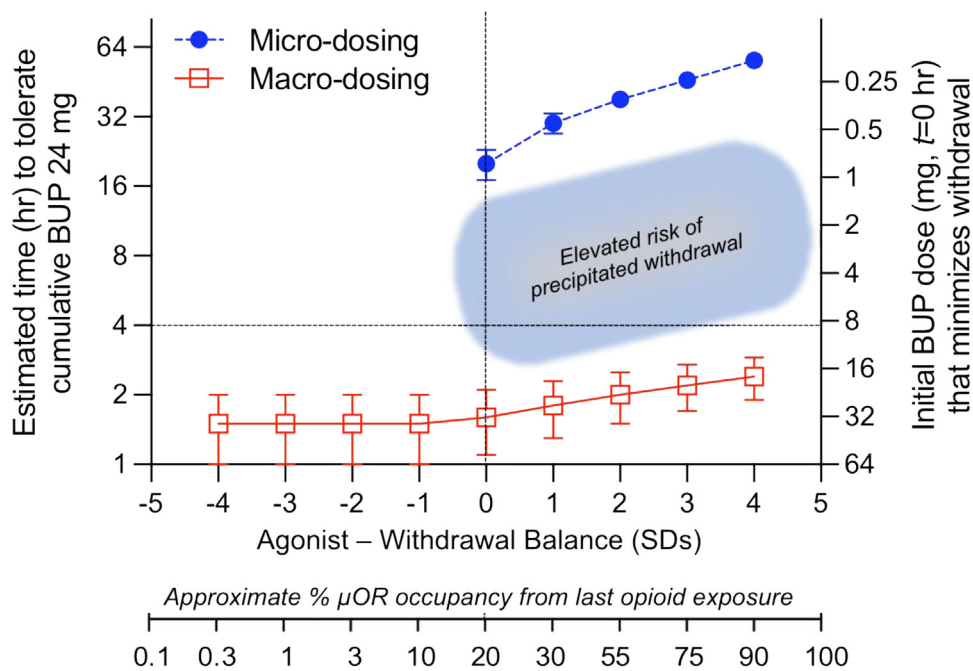
Figure 2. Clinical implications of the neuropharmacologic model for buprenorphine (BUP) initiation dosing on the basis of literature (Tables 1 and 2). The dual X-axes are identical to those in Figure 1. The right Y-axis estimates the initial BUP dose that minimizes precipitated opioid withdrawal relative to the preinitiation opioid balance or mu-opioid–receptor occupancy. The left Y-axis estimates the time required for the patient to tolerate a cumulative 24 mg dose of sublingual BUP. The horizontal dashed line at 4-hour time to cumulative 24 mg (an arbitrary cutoff) reflects that BUP macrodosing may be accomplished acutely in the ED setting. The model suggests that when there is residual agonist effect from prior opioid use, intermediate BUP starting doses will increase the risk of precipitated withdrawal (shaded area). In contrast, higher starting doses (>16 mg sublingual) or small starting doses (<0.5 mg sublingual) will be better tolerated with less chance of precipitated withdrawal. Intermediate BUP doses may be sufficient to displace enough residual agonist to precipitate withdrawal but insufficient to maximally stimulate spare functional mu-opioid receptors, resulting in a worsened agonist-withdrawal balance. When significant baseline withdrawal is present, macrodosing should result in a positive agonist balance, and microdosing, although unlikely to precipitate opioid withdrawal, is also unlikely to sufficiently replace the residual agonist, and abstinence withdrawal will persist. As described in Figure 1, these curves may shift depending on the ALE value of the last opioid used.

symptoms, which is consistent with the clinical experience of the present authors.[21,82]

Scenario 2

In methadone-maintained inpatient volunteers (100 mg/day), Rosado et al[83] tested ascending doses of buprenorphine (4, 8, 16, and 32 mg sublingual) in separate sessions, each administered 24 hours after methadone, to identify a person-specific threshold dose for buprenorphine-precipitated withdrawal. Remarkably, in phase 1, 3 of 10 participants tolerated up to 32-mg buprenorphine without precipitated withdrawal and were not studied further. In phase 2, for the continuing 7 participants, when his or her threshold dose for precipitated withdrawal (4 mg [n=4], 8 mg [n=2], and 16 mg [n=1]) was halved and given 2 hours apart, self-reported withdrawal was absent, but some objective signs were detected. Among the 10 participants, the median buprenorphine threshold dose for precipitated

withdrawal was 8 mg. (The investigators did not test the effects of administering additional buprenorphine doses to subjects after the development of precipitated withdrawal.) The working model anticipates this scenario: methadone has an intermediate ALE value, but lipophilicity is similar to buprenorphine, logP=4.77 and 4.98.[45] Methadone has a 15-fold lower mu-opioid–receptor affinity than buprenorphine (Ki=3.38 versus 0.22 nM), making methadone vulnerable to displacement and precipitated withdrawal when buprenorphine is initiated.[44] The model also predicts that, for the same person, a lower buprenorphine initiation dose will minimize withdrawal effects (whereas promoting mu-opioid–receptor resensitization), thereby priming the patient for buprenorphine agonist effects. However, it is presently unknown which individual difference factors determine such dramatic variability in triggering bothersome opioid withdrawal symptoms during buprenorphine induction.

Scenario 3

Buprenorphine induction following fentanyl exposure has been sporadically observed to be difficult or variable within 24 hours since the last fentanyl use.[84-86] We contend that physical dependence on fentanyl, rather than acute exposure, is pivotal. The model predicts difficulty with buprenorphine induction because fentanyl has a high ALE value and chronic fentanyl use increases its distribution into adipose tissue and steady release back into the circulation and brain ("reservoir effect").[87] Thus, chronic fentanyl use will prolong its terminal elimination, increase opioid agonist balance, and delay the onset of withdrawal symptoms, although limiting the functional mu-opioid receptors available for buprenorphine to act on. Fentanyl induces strong mu-opioid–receptor desensitization relative to other opioids with similar efficacy; thus, until fentanyl has cleared the brain, mu-opioid–receptor resensitization, which is thought to be needed for ideal buprenorphine clinical effects, is suppressed.[46,87,88]

During buprenorphine induction after fentanyl pre-exposure, 2 high-affinity lipophilic agonists compete for binding at mu-opioid receptors. Although lipophilicity is similar for buprenorphine and fentanyl (logP=4.98 and 4.28, respectively), mu-opioid–receptor affinity is approximately 6-fold higher for buprenorphine than for fentanyl (K_i=0.22 versus 1.35 nM).[44,45,89] The canonical view is that buprenorphine should displace fentanyl (and opioids with lower ALE values) and buprenorphine's lower intrinsic efficacy (partial mu-opioid–receptor agonism) should decrease opioid agonist balance and increase the risk of precipitated withdrawal. However, this viewpoint does not account for the rapid resensitization of mu-opioid receptors and maximization of cumulative agonist signaling that buprenorphine macrodosing may produce.

Scenario 4

1. In a representative microdose induction strategy (although there is wide protocol variation; Table 2), pharmacologic crossover involves gradually increasing buprenorphine doses while maintaining or tapering doses of the prior opioid agonist.[11,13,41,66,82,90-92] We postulate that tapering the dose of the prior opioid (methadone in scenario 2 and fentanyl in scenario 3) might facilitate buprenorphine induction by lowering opioid agonist balance (and underlying tolerance and physical dependence) toward a neutral state and that gradually increasing buprenorphine doses (eg, at 2-hour intervals) resensitizes mu-opioid receptors (which occurs within

minutes in vitro), thereby reducing the risk of withdrawal effects. However, this conjecture suggests that the alternative scenario of maintaining the prior opioid dose while increasing buprenorphine doses would increase the risk of withdrawal, which it does not appear to do.[11,13,41,82,93,94] Thus, we hypothesize that the rate at which buprenorphine resets mu-opioid receptors may play a more important role in successful induction than that played by the rate at which the prior agonist dose is reduced, even with opioids with high ALE values.

DISCUSSION

We present a working model based on evidence and theory to educate physicians regarding the neuropharmacologic complexities of buprenorphine induction. This model offers proposed solutions and testable hypotheses and highlights the need for systematic investigation to advance understanding and clinical practice in this important care sphere. To emphasize the translation of this working model to clinical care, Figure 3 illustrates a clinical decision tool, and the figure in Appendix E1 illustrates an empirically based range of macrodosing and microdosing protocols that could assist physicians.

Successful buprenorphine induction requires reaching therapeutic levels of mu-opioid–receptor occupancy that relieve opioid withdrawal and craving and produce full-agonist blockade.[79] Achieving this state requires neuroadaptations to reconstitute functional mu-opioid receptors and downstream signaling to a sufficient degree at which the partial agonist buprenorphine can produce a positive agonist balance. We propose that the magnitude of these neuroadaptations is proportional to the duration, dose, and ALE value of the prebuprenorphine agonist. Thus, prolonged heavy use of fentanyl would produce more profound tolerance and dependence and mu-opioid–receptor downregulation than those produced by opioids with low ALE. The implication is that people using fentanyl likely face a greater neuroadaptive hurdle (tolerance reversal) to be stabilized on a therapeutic buprenorphine dose.

Clinically, the challenge involves matching opioid balance with the appropriate buprenorphine dose. Microdosing avoids withdrawal symptoms and achieves a therapeutic state by gradually escalating buprenorphine doses to nudge mu-opioid receptors toward resensitization and promoting buprenorphine agonist signaling. During interdose intervals of induction, mu-opioid–receptor upregulation is hypothesized to occur so the individual can tolerate larger subsequent doses such that buprenorphine
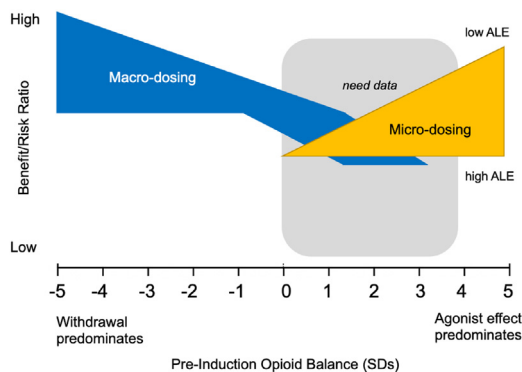
Figure 3. Clinical decision tool for buprenorphine induction. When the patient's preinduction opioid balance (X-axis) is negative (withdrawal predominates), macrodosing has a high benefit-to-risk ratio (Y-axis) and is the ideal intervention regardless of the prior opioid (height of polygon depicts error variance related to the affinity, lipophilicity, and μOR intrinsic efficacy value of the prior opioid); in contrast, microdosing is contraindicated because agonist substitution occurs too slowly. The benefit-to-risk ratio for macrodosing decreases to moderate levels (becomes less favorable) as preinduction opioid balance shifts toward an agonist state, more so when the prior opioid has a high affinity, lipophilicity, and μOR intrinsic efficacy value. When there is a mild- to moderate-positive opioid (agonist-predominant) balance, both macrodosing and microdosing are possible; however, more empirical data are needed in this range. At a higher agonist balance, microdosing has a more favorable benefit-to-risk ratio, although the benefit may be limited if patients drop out of treatment because of the slower pace of induction. Microdosing has a higher benefit-to-risk ratio if the prior opioid has a lower affinity, lipophilicity, and μOR intrinsic efficacy value. Note that extended microdosing would need to occur outside the ED.

maintenance can proceed. An important question is how to avoid opioid deficit withdrawal when small buprenorphine doses are used while the residual agonist is being metabolized. To address this, buprenorphine could be coadministered with a low-ALE value agonist during gradual dose-escalation to maximize the activation of spare functional mu-opioid receptors so that withdrawal is not experienced while not inhibiting mu-opioid receptor resensitization. This approach has been used extensively in pain medicine and hospital-based medicine (reviews by Powell et al[95] and Spreen et al[96]); however, issues remain regarding optimal timing, dose, and legality of use in patients with opioid use disorder. Presently, there are no successful reports of microdosing among ED patients. With all induction procedures, the individual is ultimately expected to stop full-agonist use and tolerate a full dose of buprenorphine (eg, >8 mg sublingual). The exact point when low-dose buprenorphine induction can be declared

successful is unknown; a case of delayed microdosing failure was recently published, highlighting this uncertainty.[72]

Successful induction depends on buprenorphine agonist signaling and reversal of tolerance to the prior opioid. Persistent exposure to full agonist is expected to impede tolerance reversal proportionate to its dose and ALE value. Thus, opioid abstinence should accelerate buprenorphine induction, whereas persistent exposure to full agonists with high ALE values will prolong it. Rotation away from agonists with high ALE values (eg, fentanyl to morphine) should facilitate tolerance reversal. Likewise, at a given moment during induction, the most effective buprenorphine dose (maximal stimulation of mu-opioid–receptor resensitization and maximal signaling) falls just below the threshold dose where withdrawal symptoms predominate. The clinical challenge is that evidence highlights a significant variation in buprenorphine threshold dose to precipitate withdrawal in opioid-dependent individuals. The risk is that using fixed-dosing protocols may lead to many patients being needlessly misdosed. Importantly, during subtherapeutic dosing, there is minimal mu-opioid–receptor blockade and no protection from full-agonist overdose. Also, microdosing outside the hospital setting risks continued use of illicit opioids and possible overdose. Finally, adhering to multiday buprenorphine uptitration may be difficult for many persons with opioid use disorder living in the community without close support. Estimating the risks and benefits of outpatient microdose treatment should balance the risk of withdrawal symptoms against the risk of prolonged vulnerability to overdose. As most patients will undergo multiple attempts to stabilize on buprenorphine, the cumulative time spent in a state of buprenorphine exposure without protection deserves consideration. Notably, in opioid agonist therapy with methadone, it is a standard of care to initiate treatment at low doses and titrate over time, such that initial doses block craving but do not fully protect against overdose. Thus, microdosing does not fundamentally differ from opioid agonist therapy titration in this regard. Although traditional buprenorphine induction eliminates the need for slow dose-titration, the clinical tradeoff is that patients must first experience opioid deficit withdrawal prior to induction.

It is critical to address clinicians' and patients' concerns regarding precipitating withdrawal; otherwise, physicians may be reluctant to undertake buprenorphine induction. It has been consistently observed that buprenorphine treats buprenorphine-precipitated withdrawal.[18,74,81] This property underlies the development of macrodosing

strategies. The rationale is that the magnitude of agonist signaling and tolerance reversal are dose-related; thus, larger buprenorphine doses are predicted to accelerate induction. During macrodosing, most patients will experience rapid symptom improvement and opioid blockade that is sustained after ED discharge. In the patient who experiences precipitated withdrawal (incidence in most studies is very low), higher buprenorphine concentrations maximize mu-opioid–receptor binding and push the binding-dissociation equilibrium toward the activated "on" state.[79] Although relative effectiveness and optimal dosing for this strategy are unknown, a large case series provides strong evidence for safety and tolerability, although the increasing prevalence of fentanyl needs to be considered.[21]

Individuals with physiologic withdrawal before buprenorphine should experience primarily agonist effects of buprenorphine, whereas those without withdrawal (positive opioid balance) could experience a time-varying combination of withdrawal effects and buprenorphine agonism, possibly ranging from severe distress to neutral (withdrawal and agonist effects cancel out) to synergistic agonist effects. The minimum amount of withdrawal required for most opioid-dependent individuals to experience an agonist-predominant outcome is unknown. Most macrodose guidelines suggest some physiologic signs of withdrawal (eg, Clinical Opiate Withdrawal Scale [COWS] score >7) as a prerequisite, whereas some allow for macrodosing with a lower Clinical Opiate Withdrawal Scale.[34,36,97] Buprenorphine has a ceiling effect for respiratory depression but not other effects (eg, analgesia). Reported macrodoses vary widely from 16 to 120 mg sublingual but generally start at 16 mg with titration. The capacity of intravenous buprenorphine dosing (which yields rapid and high plasma concentrations) to promote agonist-predominant effects is also unknown.

In patients dependent on opioids with lower ALE values, there is evidence for both macrodosing and microdosing as viable alternative strategies. However, in patients dependent on opioids with high ALE values, prospective data are lacking. Perhaps the most important is how often and when do bothersome withdrawal symptoms occur during induction among individuals using fentanyl and, when symptoms develop, how severe are they? Recent data from a multicenter trial of buprenorphine induction at 25 US EDs found precipitated withdrawal to be rare (≈1%) among >800 unique patients undergoing ED induction.[98] Despite anecdotal reports, to date, there are no prospective high-quality data that suggest that buprenorphine-precipitated withdrawal incidence is greater among fentanyl users. Reasons for this discrepancy between case reports and prospectively collected data are unclear.

In the absence of compelling data to the contrary, the clear conclusion for most ED clinicians is to continue buprenorphine inductions using established guidelines, such as those disseminated by the American College of Emergency Physicians, and if withdrawal symptoms occur, to treat with additional buprenorphine until a positive agonist balance has been achieved.[35] Microdosing remains an invaluable tool for hospitalist physicians rotating patients from a full agonist to buprenorphine but currently has no established role in the ED.

In conclusion, this proposed model offers a theoretical framework, hypotheses, and suggestions for empirical evaluation (including precursor studies in animals to validate this model and designing comparative trials) and practical guidance for clinicians working in this challenging area.[99,100] Although buprenorphine induction is an acute intervention, effective induction offers a critical bridge to longer-term care that is essential to combating the opioid crisis.

Author affiliations: From the Department of Psychiatry and Behavioral Neurosciences, School of Medicine, and Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, MI (Greenwald); the Department of Emergency Medicine, Highland Hospital—Alameda Health System, University of California, San Francisco, CA (Herring); the Department of Emergency Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA (Perrone); the Department of Emergency Medicine, Rutgers New Jersey Medical School, Newark, NJ (Nelson); and the Department of Psychiatry, Vancouver General Hospital and University of British Columbia, Vancouver, British Columbia, Canada (Azar).

REFERENCES

1. Sharma A, Kelly SM, Mitchell SG, et al. Update on barriers to pharmacotherapy for opioid use disorders. *Curr Psychiatry Rep*. 2017;19:35.
2. Castillo M, Conte B, Hinkes S, et al. Implementation of a medical student-run telemedicine program for medications for opioid use disorder during the COVID-19 pandemic. *Harm Reduct J*. 2020;17:88.
3. Hood JE, Banta-Green CJ, Duchin JS, et al. Engaging an unstably housed population with low-barrier buprenorphine treatment at a syringe services program: lessons learned from Seattle, Washington. *Subst Abus*. 2020;41:356-364.
4. Jakubowski A, Fox A. Defining low-threshold buprenorphine treatment. *J Addict Med*. 2020;14:95-98.
5. Monico LB, Oros M, Smith S, et al. One million screened: scaling up SBIRT and buprenorphine treatment in hospital emergency departments across Maryland. *Am J Emerg Med*. 2020;38:1466-1469.
6. Peck KR, Ochalek TA, Badger GJ, et al. Effects of interim buprenorphine treatment for opioid use disorder among emerging adults. *Drug Alcohol Depend*. 2020;208:107879.
7. Wiercigroch D, Sheikh H, Hulme J. A rapid access to addiction medicine clinic facilitates treatment of substance use disorder and reduces substance use. *Subst Abuse Treat Prev Policy*. 2020;15:4.
8. Snyder H, Kalmin MM, Moulin A, et al. Rapid adoption of low-threshold buprenorphine treatment at California emergency departments participating in the CA Bridge Program. *Ann Emerg Med*. 2021;78:759-772.
9. Wenzel K, Fishman M. Mobile van delivery of extended-release buprenorphine and extended-release naltrexone for youth with OUD: an adaptation to the COVID-19 emergency. *J Subst Abuse Treat*. 2021;120:108149.
10. De Aquino JP, Fairgrieve C, Klaire S, et al. Rapid transition from methadone to buprenorphine utilizing a micro-dosing protocol in the outpatient veteran affairs setting. *J Addict Med*. 2020;14:e271-e273.
11. Klaire S, Zivanovic R, Barbic SP, et al. Rapid micro-induction of buprenorphine/naloxone for opioid use disorder in an inpatient setting: a case series. *Am J Addict*. 2019;28:262-265.
12. Martin L, Lennox R, Regenstreif L, et al. Case report: "striving to skip the withdrawal" using buprenorphine/naloxone microdosing for hospitalized patients. *Can J Addict*. 2019;10:35-40.
13. Terasaki D, Smith C, Calcaterra SL. Transitioning hospitalized patients with opioid use disorder from methadone to buprenorphine without a period of opioid abstinence using a microdosing protocol. *Pharmacotherapy*. 2019;39:1023-1029.
14. Weimer MB, Guerra M, Morrow G, et al. Hospital-based buprenorphine micro-dose initiation. *J Addict Med*. 2021;15(3):255-257.
15. D'Onofrio G, O'Connor PG, Pantalon MV, et al. Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence: a randomized clinical trial. *JAMA*. 2015;313:1636-1644.
16. D'Onofrio G, Chawarski MC, O'Connor PG, et al. Emergency department-initiated buprenorphine for opioid dependence with continuation in primary care: outcomes during and after intervention. *J Gen Intern Med*. 2017;32:660-666.
17. Srivastava A, Kahan M, Njoroge I, et al. Buprenorphine in the emergency department: randomized clinical controlled trial of clonidine versus buprenorphine for the treatment of opioid withdrawal. *Can Fam Physician*. 2019;65:e214-e220.
18. Guo CZ, D'Onofrio G, Fiellin DA, et al. Emergency department-initiated buprenorphine protocols: a national evaluation. *J Am Coll Emerg Physicians Open*. 2021;2:e12606.
19. Clinical guidelines: national practice guideline 2020: focused update. American Society of Addiction Medicine. Accessed February 21, 2021. https://www.asam.org/quality-care/clinical-guidelines/national-practice-guideline
20. Use of medication-assisted treatment in emergency departments. Substance Abuse and Mental Health Services Administration. Accessed February 17, 2021. https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/pep21-pl-guide-5.pdf
21. Herring AA, Vosooghi AA, Luftig J, et al. High-dose buprenorphine induction in the emergency department for treatment of opioid use disorder. *JAMA Netw Open*. 2021;4:e2117128.
22. Welsh C, Sherman SG, Tobin KE. A case of heroin overdose reversed by sublingually administered buprenorphine/naloxone (Suboxone). *Addiction*. 2008;103:1226-1228.
23. Herring AA, Schultz CW, Yang E, et al. Rapid induction onto sublingual buprenorphine after opioid overdose and successful linkage to treatment for opioid use disorder. *Am J Emerg Med*. 2019;37:2259-2262.
24. Phillips RH, Salzman M, Haroz R, et al. Elective naloxone-induced opioid withdrawal for rapid initiation of medication-assisted treatment of opioid use disorder. *Ann Emerg Med*. 2019;74:430-432.
25. Edwards FJ, Wicelinski R, Gallagher N, et al. Treating opioid withdrawal with buprenorphine in a community hospital emergency department: an outreach program. *Ann Emerg Med*. 2020;75:49-56.
26. Antoine D, Huhn AS, Strain EC, et al. Method for successfully inducting individuals who use illicit fentanyl onto buprenorphine/naloxone. *Am J Addict*. 2021;30:83-87.
27. Berg ML, Idrees U, Ding R, et al. Evaluation of the use of buprenorphine for opioid withdrawal in an emergency department. *Drug Alcohol Depend*. 2007;86:239-244.
28. Dunkley CA, Carpenter JE, Murray BP, et al. Retrospective review of a novel approach to buprenorphine induction in the emergency department. *J Emerg Med*. 2019;57:181-186.
29. Hu T, Snider-Adler M, Nijmeh L, et al. Buprenorphine/naloxone induction in a Canadian emergency department with rapid access to community-based addictions providers. *CJEM*. 2019;21:492-498.
30. Kaucher KA, Caruso EH, Sungar G, et al. Evaluation of an emergency department buprenorphine induction and medication-assisted treatment referral program. *Am J Emerg Med*. 2020;38:300-304.
31. LeSaint KT, Klapthor B, Wang RC, et al. Buprenorphine for opioid use disorder in the emergency department: a retrospective chart review. *West J Emerg Med*. 2020;21:1175-1181.
32. Cao SS, Dunham SI, Simpson SA. Prescribing buprenorphine for opioid use disorders in the ED: a review of best practices, barriers, and future directions. *Open Access Emerg Med*. 2020;12:261-274.
33. Cisewski DH, Santos C, Koyfman A, et al. Approach to buprenorphine use for opioid withdrawal treatment in the emergency setting. *Am J Emerg Med*. 2019;37:143-150.
34. Fox L, Nelson LS. Emergency department initiation of buprenorphine for opioid use disorder: current status, and future potential. *CNS Drugs*. 2019;33:1147-1154.
35. Hawk K, Hoppe J, Ketcham E, et al. Consensus recommendations on the treatment of opioid use disorder in the emergency department. *Ann Emerg Med*. 2021;78:434-442.
36. Herring AA, Perrone J, Nelson LS. Managing opioid withdrawal in the emergency department with buprenorphine. *Ann Emerg Med*. 2019;73:481-487.

37. Moe J, O'Sullivan F, Hohl CM, et al. Short communication: systematic review on effectiveness of micro-induction approaches to buprenorphine initiation. *Addict Behav.* 2021;114:106740.

38. Wax PM, Stolbach AI, Schwarz ES, et al. ACMT position statement: buprenorphine administration in the emergency department. *J Med Toxicol.* 2019;15:215-216.

39. Kornfeld H, Reetz H. Transdermal buprenorphine, opioid rotation to sublingual buprenorphine, and the avoidance of precipitated withdrawal: a review of the literature and demonstration in three chronic pain patients treated with Butrans. *Am J Ther.* 2015;22:199-205.

40. Hämmig R, Kemter A, Strasser J, et al. Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method. *Subst Abuse Rehabil.* 2016;7:99-105.

41. Azar P, Nikoo M, Miles I. Methadone to buprenorphine/naloxone induction without withdrawal utilizing transdermal fentanyl bridge in an inpatient setting–Azar method. *Am J Addict.* 2018;27:601-604.

42. Dong R, Wang H, Li D, et al. Pharmacokinetics of sublingual buprenorphine tablets following single and multiple doses in Chinese participants with and without opioid use disorder. *Drugs R D.* 2019;19:255-265.

43. Harris DS, Mendelson JE, Lin ET, et al. Pharmacokinetics and subjective effects of sublingual buprenorphine, alone or in combination with naloxone: lack of dose proportionality. *Clin Pharmacokinet.* 2004;43:329-340.

44. Volpe DA, McMahon Tobin GA, Mellon RD, et al. Uniform assessment and ranking of opioid μ receptor binding constants for selected opioid drugs. *Regul Toxicol Pharmacol.* 2011;59:385-390.

45. Peckham EM, Traynor JR. Comparison of the antinociceptive response to morphine and morphine-like compounds in male and female Sprague-Dawley rats. *J Pharmacol Exp Ther.* 2006;316:1195-1201.

46. McPherson J, Rivero G, Baptist M, et al. μ-opioid receptors: correlation of agonist efficacy for signalling with ability to activate internalization. *Mol Pharmacol.* 2010;78:756-766.

47. Kelly E, Sutcliffe K, Cavallo D, et al. The anomalous pharmacology of fentanyl. Br J Pharmacol. Published online May 24, 2021. https://doi.org/10.1111/bph.15573

48. Zhang J, Ferguson SS, Barak LS, et al. Role for G protein-coupled receptor kinase in agonist-specific regulation of mu-opioid receptor responsiveness. *Proc Natl Acad Sci USA.* 1998;95:7157-7162.

49. Claing A, Laporte SA, Caron MG, et al. Endocytosis of G protein-coupled receptors: roles of G protein-coupled receptor kinases and beta-arrestin proteins. *Prog Neurobiol.* 2002;66:61-79.

50. Arttamangkul S, Heinz DA, Bunzow JR, et al. Cellular tolerance at the μ-opioid receptor is phosphorylation dependent. *eLife.* 2018;7:e34989.

51. Kovoor A, Celver JP, Wu A, et al. Agonist induced homologous desensitization of mu-opioid receptors mediated by G protein-coupled receptor kinases is dependent on agonist efficacy. *Mol Pharmacol.* 1998;54:704-711.

52. Ferguson SS. Evolving concepts in G protein-coupled receptor endocytosis: the role in receptor desensitization and signaling. *Pharmacol Rev.* 2001;53:1-24.

53. von Zastrow M. Regulation of opioid receptors by endocytic membrane traffic: mechanisms and translational implications. *Drug Alcohol Depend.* 2010;108:166-171.

54. Williams JT, Ingram SL, Henderson G, et al. Regulation of μ-opioid receptors: desensitization, phosphorylation, internalization, and tolerance. *Pharmacol Rev.* 2013;65:223-254.

55. von Zastrow M, Svingos A, Haberstock-Debic H, et al. Regulated endocytosis of opioid receptors: cellular mechanisms and proposed roles in physiological adaptation to opiate drugs. *Curr Opin Neurobiol.* 2003;13:348-353.

56. Gainetdinov RR, Premont RT, Bohn LM, et al. Desensitization of G protein-coupled receptors and neuronal functions. *Annu Rev Neurosci.* 2004;27:107-144.

57. Keith DE, Anton B, Murray SR, et al. mu-opioid receptor internalization: opiate drugs have differential effects on a conserved endocytic mechanism in vitro and in the mammalian brain. *Mol Pharmacol.* 1998;53:377-384.

58. Zaki PA, Keith DE Jr, Brine GA, et al. Ligand-induced changes in surface mu-opioid receptor number: relationship to G protein activation? *J Pharmacol Exp Ther.* 2000;292:1127-1134.

59. Alvarez VA, Arttamangkul S, Dang V, et al. μ-opioid receptors: ligand-dependent activation of potassium conductance, desensitization, and internalization. *J Neurosci.* 2002;22:5769-5776.

60. Tanowitz M, von Zastrow M. A novel endocytic recycling signal that distinguishes the membrane trafficking of naturally occurring opioid receptors. *J Biol Chem.* 2003;278:45978-45986.

61. Koch T, Widera A, Bartzsch K, et al. Receptor endocytosis counteracts the development of opioid tolerance. *Mol Pharmacol.* 2005;67:280-287.

62. Anselmi L, Jaramillo I, Palacios M, et al. Ligand-induced μ opioid receptor internalization in enteric neurons following chronic treatment with the opiate fentanyl. *J Neurosci Res.* 2013;91:854-860.

63. Law PY, Erickson LJ, El-Kouhen R, et al. Receptor density and recycling affect the rate of agonist-induced desensitization of mu-opioid receptor. *Mol Pharmacol.* 2000;58:388-398.

64. Dang VC, Williams JT. Chronic morphine treatment reduces recovery from opioid desensitization. *J Neurosci.* 2004;24:7699-7706.

65. Roman-Vendrell C, Yu YJ, Yudowski GA. Fast modulation of μ-opioid receptor (MOR) recycling is mediated by receptor agonists. *J Biol Chem.* 2012;287:14782-14791.

66. Callan J, Pytell J, Ross J, et al. Transition from methadone to buprenorphine using a short-acting agonist bridge in the inpatient setting: a case study. *J Addict Med.* 2020;14:e274-e276.

67. Virk MS, Arttamangkul S, Birdsong WT, et al. Buprenorphine is a weak partial agonist that inhibits opioid receptor desensitization. *J Neurosci.* 2009;29:7341-7348.

68. Zadina JE, Chang SL, Ge LJ, et al. Mu opiate receptor down-regulation by morphine and up-regulation by naloxone in SH-SY5Y human neuroblastoma cells. *J Pharmacol Exp Ther.* 1993;265:254-262.

69. Gupta A, Devi LA, Gomes I. Potentiation of μ-opioid receptor-mediated signaling by ketamine. *J Neurochem.* 2011;119:294-302.

70. Jovaisa T, Laurinena G, Vosylius S, et al. Effects of ketamine on precipitated opiate withdrawal. *Medicina (Kaunas).* 2006;42:625-634.

71. Lalanne L, Nicot C, Lang JP, et al. Experience of the use of ketamine to manage opioid withdrawal in an addicted woman: a case report. *BMC Psychiatry.* 2016;16:395.

72. Hailozian C, Luftig J, Liang A, et al. Synergistic effect of ketamine and buprenorphine observed in the treatment of buprenorphine precipitated opioid withdrawal in a patient with fentanyl use. *J Addict Med.* Published online November 16, 2021. https://doi.org/10.1097/ADM.0000000000000929

73. Schuster CR, Greenwald MK, Johanson CE, et al. Measurement of drug craving during naloxone-precipitated withdrawal in methadone-maintained volunteers. *Exp Clin Psychopharmacol.* 1995;3:424-431.

74. Greenwald MK, Schuh KJ, Stine SM. Transferring methadone-maintained outpatients to the buprenorphine sublingual tablet: a preliminary study. *Am J Addict.* 2003;12:365-374.

75. Greenwald MK, Johanson CE, Moody DE, et al. Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology.* 2003;28:2000-2009.

76. Greenwald MK. Opioid craving and seeking behavior in physically dependent volunteers: effects of acute withdrawal and drug

reinforcement opportunity. *Exp Clin Psychopharmacol.* 2005;13:3-14.

77. Greenwald MK, Johanson CE, Bueller J, et al. Buprenorphine duration of action: mu-opioid receptor availability and pharmacokinetic and behavioral indices. *Biol Psychiatry.* 2007;61:101-110.

78. Coe MA, Lofwall MR, Walsh SL. Buprenorphine pharmacology review: update on transmucosal and long-acting formulations. *J Addict Med.* 2019;13:93-103.

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

80. Moss RB, Pryor MM, Baillie R, et al. Higher naloxone dosing in a quantitative systems pharmacology model that predicts naloxone-fentanyl competition at the opioid mu receptor level. *PLoS One.* 2020;15:e0234683.

81. Oakley B, Wilson H, Hayes V, et al. Managing opioid withdrawal precipitated by buprenorphine with buprenorphine. *Drug Alcohol Rev.* 2021;40:567-571.

82. Azar P, Wong JSH, Jassemi S, et al. A case report: rapid micro-induction of buprenorphine/ naloxone to administer buprenorphine extended-release in an adolescent with severe opioid use disorder. *Am J Addict.* 2020;29:531-535.

83. Rosado J, Walsh SL, Bigelow GE, et al. Sublingual buprenorphine/ naloxone precipitated withdrawal in subjects maintained on 100 mg of daily methadone. *Drug Alcohol Depend.* 2007;90:261-269.

84. Spadaro A, Sarker A, Hogg-Bremer W, et al. Reddit discussions about buprenorphine associated precipitated withdrawal in the era of fentanyl. *Clin Toxicol(Phila).* 2022;60:694-701.

85. Silverstein SM, Daniulaityte R, Martins SS, et al. "Everything is not right anymore": buprenorphine experiences in an era of illicit fentanyl. *Int J Drug Policy.* 2019;74:76-83.

86. Varshneya NB, Thakrar AP, Hobelmann JG, et al. Evidence of buprenorphine-precipitated withdrawal in persons who use fentanyl. *J Addict Med.* Published online November 23, 2021. https://doi.org/10.1097/ADM.0000000000000922

87. Huhn AS, Hobelmann JG, Oyler GA, et al. Protracted renal clearance of fentanyl in persons with opioid use disorder. *Drug Alcohol Depend.* 2020;214:108147.

88. Bot G, Blake AD, Li S, et al. Fentanyl and its analogs desensitize the cloned mu opioid receptor. *J Pharmacol Exp Ther.* 1998;285:1207-1218.

89. Virk MS, Williams JT. Agonist-specific regulation of mu-opioid receptor desensitization and recovery from desensitization. *Mol Pharmacol.* 2008;73:1301-1308.

90. Avdeef A, Barrett DA, Shaw PN, et al. Octanol-, chloroform-, and propylene glycol dipelargonat-water partitioning of morphine-6-glucuronide and other related opiates. *J Med Chem.* 1996;39:4377-4381.

91. Rozylo J, Mitchell K, Nikoo M, et al. Case report: successful induction of buprenorphine/ naloxone using a microdosing schedule and assertive outreach. *Addict Sci Clin Pract.* 2020;15:2.

92. Hamata B, Griesdale D, Hann J, et al. Rapid micro-induction of buprenorphine/naloxone for opioid use disorder in a critically ill intubated patient: a case report. *J Addict Med.* 2020;14:514-517.

93. Raheemullah A, Lembke A. Buprenorphine induction without opioid withdrawal: a case series of 15 opioid-dependent inpatients induced on buprenorphine using microdoses of transdermal buprenorphine. *Am J Ther.* 2019;28:e504-e508.

94. Robbins JL, Englander H, Gregg J. Buprenorphine microdose induction for the management of prescription opioid dependence. *J Am Board Fam Med.* 2021;34(suppl):S141-S146.

95. Powell VD, Rosenberg JM, Yaganti A, et al. Evaluation of buprenorphine rotation in patients receiving long-term opioids for chronic pain: a systematic review. *JAMA Netw Open.* 2021;4(9):e2124152.

96. Spreen LA, Dittmar EN, Quirk KC, et al. Buprenorphine initiation strategies for opioid use disorder and pain management: a systematic review. *Pharmacotherapy.* 2022;42:411-427.

97. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs.* 2003;35:253-259.

98. D'Onofrio G, Perrone JP, Herring AA, et al. Low incidence of precipitated withdrawal in ED-initiated buprenorphine, despite high prevalence of fentanyl use. Paper presented at: Society for Academic Emergency Medicine Annual Meeting; May 10-13, 2022; New Orleans, LA.

99. Wong JSH, Nikoo M, Westenberg JN, et al. Comparing rapid micro-induction and standard induction of buprenorphine/naloxone for treatment of opioid use disorder: protocol for an open-label, parallel-group, superiority, randomized controlled trial. *Addict Sci Clin Pract.* 2021;16:11.

100. Emergency department-initiated buprenorphine validation network trial (NCT04225598). ClinicalTrials.gov. Accessed February 15, 2022. https://clinicaltrials.gov/ct2/show/NCT04225598

101. Zamani N, Hassanian-Moghaddam H. Intravenous buprenorphine: a substitute for naloxone in methadone-overdosed patients? *Ann Emerg Med.* 2017;69:737-739.

102. Brar R, Fairbairn N, Sutherland C, et al. Use of a novel prescribing approach for the treatment of opioid use disorder: buprenorphine/ naloxone micro-dosing–a case series. *Drug Alcohol Rev.* 2020;39:588-594.

103. Oretti R. A retrospective evaluation of inpatient transfer from high-dose methadone to buprenorphine substitution therapy. *J Subst Abuse Treat.* 2015;57:102-105.

104. Thakrar AP, Jablonski L, Ratner J, et al. Micro-dosing intravenous buprenorphine to rapidly transition from full opioid agonists. *J Addict Med.* 2022;16:122-124.

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