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Review

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CLASSICS IN CHEMICAL NEUROSCIENCE: BUPRENORPHINE

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ABSTRACT: Buprenorphine has not only had an interdisciplinary impact on our understanding of key neuroscience topics like opioid pharmacology, pain signaling, and reward processing, but has also been a key influence in changing the way that substance use disorders are approached in modern medical systems. From its leading role in expanding outpatient treatment of opioid use disorders to its continued influence on research into next-generation analgesics, buprenorphine has been a continuous player in the ever-evolving societal perception of opioids and substance use disorder. To provide a multifaceted account on the enormous diversity of areas where this molecule has made an impact, this article discusses buprenorphine's chemical properties, synthesis and development, pharmacology, adverse effects, manufacturing information, and historical place in the field of chemical neuroscience.
KEY WORDS: buprenorphine, opioid use disorder, Suboxone, MAT, OUD

INTRODUCTION

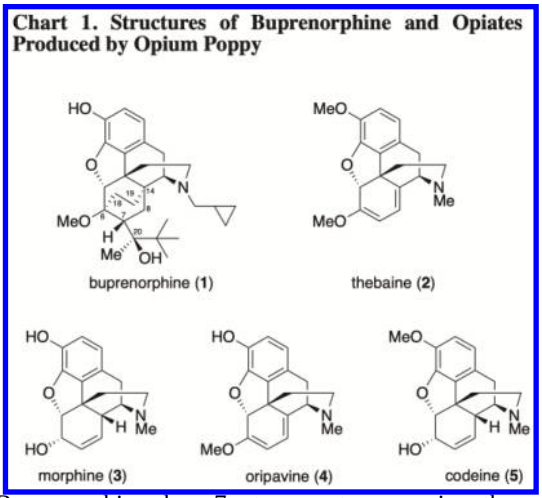
While all neuropsychiatric disorders present daunting biological challenges arising from the sheer complexity of the central nervous system, research on substance use disorder (SUD) has historically found itself fraught by equally challenging complexities arising from a completely different type of system – a sociopolitical one. Throughout history, opioids have been paraded through the intersection where biology and politics meet, sometimes hated, sometimes heralded. Viewed over time, one can almost see rhetorical ruts being worn into the pavement there, as the same arguments are repeatedly marshalled to take up their side of the cause. But in recent decades, one opioid molecule has found itself somewhat ill-suited to stay within the confines of these pre-defined paths, making an impressive wake in its passage. That molecule is buprenorphine, a mu opioid receptor (μOP) partial agonist.

Buprenorphine's unique mechanism of action, especially its lower risk for inducing respiratory depression as compared to other opioids, has enabled it to form the foundation of the office-based opioid treatment (OBOT) approach for opioid use disorder (OUD), a therapeutic intervention that was once a legal anathema in the United States. Furthermore, investigations stemming from the specific pharmacological profile of buprenorphine have been instrumental in opening the door to investigations of next-generation opioid therapeutics. As one of the primary treatments for OUD, this compound has already made an enormous, life-saving impact on millions of individuals. However, without careful study of the anomalous pharmacologic properties of this otherwise modestly successful opioid analgesic medication, buprenorphine's potential to advance both basic neuroscience and clinical psychiatry might easily have been missed.

CHEMICAL PROPERTIES AND SYNTHESIS

The drug commonly known as buprenorphine carries the IUPAC name *N*-cyclopropylmethyl-6,14-*endo*-ethano-7-(2-hydroxy-3,3-dimethyl-2-butyl)-tetrahydronororipavine.

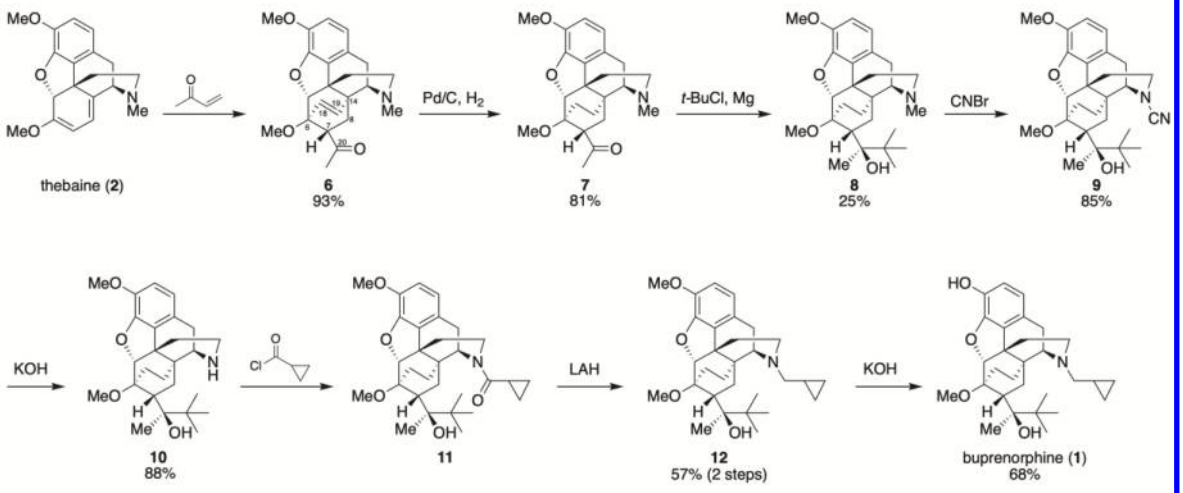
Chart 1. Structures of Buprenorphine and Opiates Produced by Opium Poppy



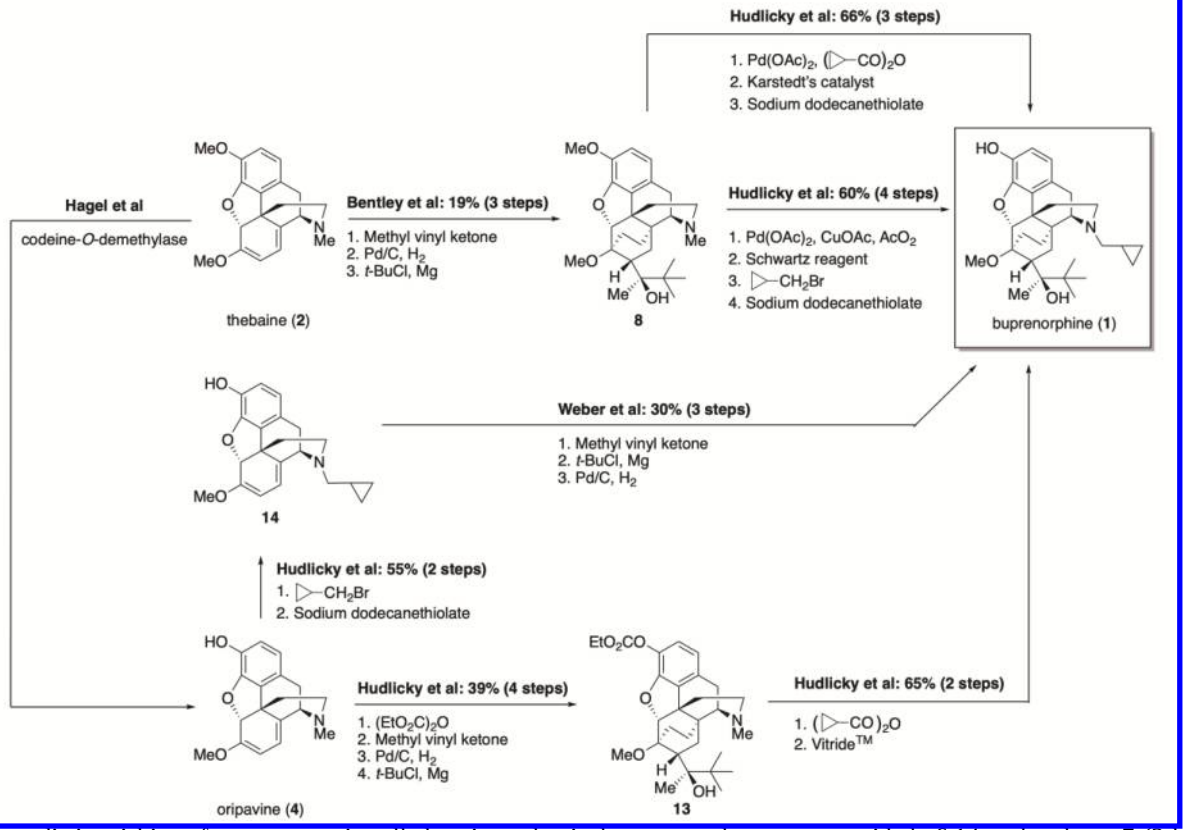
Buprenorphine has 7 stereocenters, carries the molecular formula of $C_{29}H_{41}NO_4$, and has a molecular weight of 467.65 g/mol. The free-base has a melting point of 209 ºC, though it is commonly manufactured as the hydrochloride salt.[1] With 2 hydrogen bond donors, 5 hydrogen bond acceptors, 5 rotatable bonds, a topological polar surface area of 62.16 Å^2, and ClogP of 3.809, buprenorphine meets all of Lipinski's rules of five.[2–4]

Buprenorphine (**1**, Chart 1) is a semisynthetic derivative of the natural product thebaine (**2**), which is isolated from the opium poppy, with a concentration of 41 μg/g detectable in the Indian poppy seed.[5] In support of production, cultivars of the poppy have been bred to produce a larger percentage of thebaine (1.68% by mass of dried poppy capsules) and with no morphine (**3**).[6] In a separate effort, Millgate and coworkers created a mutant poppy strain that arrests the biosynthesis pathway at thebaine and oripavine (**4**), preventing conversion to codeine (**5**) or morphine.[7] Structurally, buprenorphine is quite different from thebaine, containing a *N*-cyclopropylmethyl (CPM) instead of an *N*-methyl, an additional ring, and a hydroxybutane tail. At present, each of

Scheme 1. Bentley's Semi-Synthesis of Buprenorphine



Scheme 2. Improved Synthetic Routes to Buprenorphine



these distinguishing features are installed using classical organic synthesis approaches.

In initial work by Bentley and coworkers, the synthetic portion of the semi-synthesis began with thebaine's diene moiety, which readily reacted with methyl vinyl ketone in a Diels-Alder cycloaddition to provide the *endo* product, with no evidence of addition at C8 (Scheme 1).[8,9] Following recrystallization, it was determined that the 7α product was obtained as the major product, 6,14-*endo*-etheno-7-acetyl-tetrahydrothebaine (**6**), while the mother liquor contained approximately 1.5% of the 7β product.[9] Following the reduction of the internal double bond via Pd/C hydrogenation to 6,14-*endo*-ethano-7-acetyl-tetrahydrothebaine (**7**), a Grignard addition of *tert*-butyl magnesium chloride into the 7-acetyl group provided 6,14-*endo*-ethano-7-(2-hydroxy-3,3-dimethyl-2-butyl)-tetrahydrothebaine (**8**).[1] *N*-demethylation occurred via reaction with cyanogen bromide to yield the *N*-cyano-desmethyl intermediate **9**, and basic hydrolysis was utilized to provide the secondary amine 6,14-*endo*-ethano-7-(2-hydroxy-3,3-dimethyl-2-butyl)-tetrahydronorthebaine (**10**).[1] Acylation of the amine with cyclopropyl carbonyl chloride provided the amide **11**, which was subsequently reduced with lithium aluminum hydride to yield *N*-cyclopropylmethyl-6,14-*endo*-ethano-7-(2-hydroxy-3,3-dimethyl-2-butyl)-tetrahydronorthebaine (**12**).[1] Finally, *O*-demethylation with potassium hydroxide in ethylene glycol resulted in the desired product, *N*-cyclopropylmethyl-6,14-*endo*-ethano-7-(2-

hydroxy-3,3-dimethyl-2-butyl)-tetrahydronororipavine (**1**), with an overall yield of 5%.[1]

Alternative routes developed since this initial attempt have shortened the synthesis from eight total steps to six (Scheme 2). Hudlicky's approach also has the benefit of avoiding the use of the toxic reagent cyanogen bromide through use of a palladium-catalyzed acylation with cyclopropanecarboxylic anhydride or acetic anhydride, which also removes the *N*-methyl group.[10,11] Hudlicky's group also demonstrated that it was possible to utilize oripavine (**4**) as the starting material, protecting the phenol as ethyl carbonate **13**. An alternative route utilizes (bromomethyl)cyclopropane to install the *N*-CPM group to avoid an additional reduction step.[12] Finally, Weber and coworkers have modified one of Hudlicky's routes, avoiding the use of protecting groups to provide the desired product in 5 steps from oripavine, installing the *N*-CPM prior to the Diels-Alder reaction to provide intermediate **14**.[10,13] In an enzymatically-assisted approach, *O*-demethylation of the 3-methoxy group has been employed to provide oripavine in one step from thebaine.[14] Despite these improvements, the route developed by Bentley is still the method applied for the industrial production of buprenorphine.[11]

PRE-CLNICAL PHARMACOLOGY

In vitro studies of buprenorphine identify it predominantly as a partial agonist at μOP, although it also exhibits strong binding to both the kappa opioid receptor (κOP) and delta opioid receptor (δOP). In terms of its affinity for these targets, buprenorphine demonstrated K_is of 0.08 nM, 0.44 nM, and 0.82 nM against μOP, κOP, and δOP respectively, as determined by radioligand displacement with 0.25 nM [^{3}H]DAMGO for μOP, 1 nM [^{3}H]U69,593 for κOP, and 0.2 nM [^{3}H]naltrindole for δOP in cell membranes isolated from rhesus brain tissue.[15] In a cell model expressing cloned human receptors, it exhibited a μOP EC_{50} of 2.3 nM, with a maximum possible effect (MPE) of 66% in relationship to DAMGO, and no measurable δOP or κOP EC_{50}s, due to low stimulation overall (<20%).[16–18] Additionally, buprenorphine has been shown to be a partial agonist at the human nociceptin opioid peptide receptor (NOP)—EC_{50} of 35 nM with an MPE of 60% as compared to nociceptin.[19]

In addition to its low intrinsic efficacy and mixed pattern of pharmacologic activity across these major opioid receptor types, buprenorphine's downstream signaling bias at μOP and effects on receptor internalization are also worth noting. In HEK cells transfected with mouse μOP, buprenorphine was shown to inhibit both forskolin- and morphine-induced cyclic AMP (cAMP) formation by μOP.[20] However, it does not appear to induce β-arrestin recruitment at this same receptor. This stands in contrast to other opioid analgesics like morphine and fentanyl, which recruit β-arrestin to μOP at sub-micromolar concentrations, as determined in a bioluminescence resonance energy transfer (BRET) assay in HEK cells transfected with μOP.[21] Furthermore, buprenorphine antagonizes the recruitment of β-arrestin by DAMGO, suggesting it may act as an antagonist in the assay.[21] Buprenorphine's apparent bias against this pathway is particularly notable because β-arrestin recruitment to μOP has been closely studied as a potential mediator of opioid-induced respiratory depression, although this hypothesis has recently been called into question.[22–24] Using a FLAG-tagged μOP (mouse), treatment with buprenorphine resulted in a 10% increase in cell-surface μOPs, in contrast to morphine which led to a 17% decrease in cell-surface μOPs; the increase caused by buprenorphine could be further potentiated by pertussis toxin (PTX) treatment after 18 hours.[25] This element of its profile has also been a source of significant interest, as opioid-induced receptor internalization has been proposed as an important mediator of tolerance.[26]

Amongst these various *in vitro* effects of buprenorphine on opioid signaling, rodent studies have predominantly identified μOP activity as the key mediator of buprenorphine's antinociceptive and reward effects *in vivo*. In μOP knockout mice buprenorphine-mediated antinociception is blunted, while δOP, κOP, and NOP knockouts produce no differentiation from wild-type animals in tail-flick assays.[27] Furthermore, mice lacking μOP exhibit reduced conditioned place preference (CPP) in response to buprenorphine.[28,29] However, activity at κOP also appears to have relevance to some of buprenorphine's psychoactivity, particularly in regard to classical tests of antidepressant-like and anxiolytic effects such as the forced swim test, sucrose preference test, and dark/light emergence test. Using these behavioral metrics, buprenorphine generally decreases stress response in wild-type animals, μOP knockout mice, and δOP knockout mice, while κOP knockout mice do not show these altered stress behaviors.[30,31] The relevance of these effects to stress-induced drug-seeking is less clear; while buprenorphine has been found to reduce such behavior during extinction conditions following acute cocaine or heroin injections, it has not prevented reinstatement of drug-seeking following footshock stress.[32] Furthermore, buprenorphine administration does not recapitulate the increased stress response phenotypes exhibited by δOP knockout mice, possibly due to buprenorphine's lower *in vivo* efficacy at rodent δOP as compared to rodent μOP or κOP.[15,33] Nevertheless, δOP and κOP have been proposed to be relevant contributors to the rewarding effects of buprenorphine itself, as μOP knockout

Table 1. Transcription Pattern Following Treatment with Buprenorphine or Morphine (From Belkaï et al.)

Drug		Buprenorphine			Morphine		
Time Point		30 min	1 h	4 h	30 min	1 h	4 h
Nucleus Accumbens	c-Fos	0.76*	1	1	1	1	2.02*
	μOP	1	1	0.9	1.1	1	0.9
	κOP	1.3	1.1	0.8	1.3	1.2	1
	δOP	0.9	1	1	1.1	1.1	1
	POMC	-	-	-	-	-	-
	PENK	1.4*	1.2	1	1	1.3*	1
	PDYN	1	1	1	1	1	1
Dorsal Striatum	c-Fos	1	1	1.4	1	1	2.13*
	μOP	1	1	1.1	1.2	1	0.8
	κOP	1	1.2	1.1	1	1.56*	0.6
	δOP	0.9	0.9	1.1	1.28*	1	1.1
	POMC	0.8	1	0.53*	1	1.1	0.8*
	PENK	1	1.2	0.8	1	1.47*	0.55*
	PDYN	1	1	1	1	1	0.53*
Thalamus	c-Fos	1.1	1.45*	1.89*	1	1.1	1.91*
	μOP	1.1	1.1	1.1	1	1.1	1.1
	κOP	1.1	1.3	0.6	1.2	1	0.9
	δOP	1.4	-	1.1	1.3	-	1.1
	POMC	-	-	-	-	-	-
	PENK	0.6	1	0.6	0.9	0.8	0.8
	PDYN	-	-	-	-	-	-

Transcription of each gene is determined for each brain region via quantitative real-time polymerase chain reaction. Value provided in table is the ratio of the change compared to saline at the indicated time point.[32]
Red text indicates an increase compared to saline while blue text indicates a decrease compared to saline.
-: not determined
*significant change compared to saline ($p < 0.05$)

mice exhibit naloxone-sensitive CPP in response to buprenorphine administration, a finding consistent with the proposed role of δOP to facilitate association of reward with drug stimulus conditions.[33,34] Finally, in a study of nonhuman primates, NOP was implicated in alcohol use disorder (AUD) as both buprenorphine and an NOP agonist were both able to reduce ethanol self-administration without decreasing food intake.[35] This stands in contrast to naltrexone, an opioid antagonist commonly prescribed for AUD, which decreased both ethanol and food intake in this model.[35]

In regard to functional modification of reward responsivity in rodent models, significant differences between buprenorphine and μOP full agonists have appeared when evaluating changes in neuronal activation, opioid receptor gene expression, and gene expression of proopiomelanocortin (POMC), proenkephalin (PENK), and prodynorphin (PDYN) across various rat brain regions (Table 1).[36] Briefly, morphine increased c-Fos gene expression (a marker of neuronal activation) in the nucleus accumbens, dorsal striatum, and the thalamus. In contrast, buprenorphine decreased expression of c-Fos in the nucleus accumbens and increased c-Fos expression in both the thalamus and dorsal striatum.[36] Morphine administration also resulted in increased expression of κOP and δOP in the dorsal striatum, whereas buprenorphine did not alter expression of μOP, δOP, or κOP in any of the regions analyzed.[36] When considering endorphin-related transcription, both morphine and buprenorphine decreased expression of POMC in the dorsal striatum, while morphine temporarily increased, then decreased, PENK in the dorsal striatum and buprenorphine increased PENK in the nucleus accumbens.[36] Morphine also caused a decrease in PDYN in the dorsal striatum, while there was no change in the buprenorphine condition.[36] One additional transcriptional change worth noting is that buprenorphine administration can increase expression of tyrosine hydroxylase, which catalyzes the rate-limiting step in the biosynthesis of dopamine.[37] This alteration is consistent with independent observations of buprenorphine-induced increases in dopamine concentrations in rodent brain tissue.[38]

MANUFACTURING AND INDICATIONS

Buprenorphine-containing products are currently available as both monotherapy options and formulations in combination with naloxone (Table 2). Buprenorphine monotherapy is available as a buccal film, IV/IM injectable, and transdermal patch for use as an analgesic for severe chronic pain that does not respond to typical non-opioid or immediate-release opioid treatments. The approved products for this indication are Belbuca, Butrans, and Buprenex.[39–41] Sublocade and Probuphine are buprenorphine-only extended release (XR) subcutaneous injectables and subdermal implants, respectively, indicated for use as maintenance therapies for OUD; buprenorphine-only sublingual tablets are available generically for this application as well.[42,43] Zubsolv is a combination sublingual tablet containing a 4:1 ratio of buprenorphine: naloxone and can be used for induction or maintenance therapy in OUD.[44] Bunavail, a buccal film, contains a 6:1 ratio of buprenorphine: naloxone and can be used for induction or maintenance therapy for OUD.[45] Due to its formulation as a buccal film, smaller doses of buprenorphine are used in Bunavail than in equivalent sublingual formulations. Suboxone is provided as a sublingual film, has a 4:1 ratio of buprenorphine: naloxone, and is indicated for maintenance therapy of OUD.[46]

Table 2. Commercially Available Formulations of Buprenorphine

Name Manufacturer	Formulation	Uses	Strengths Available	
			Buprenorphine	Naloxone
Belbuca BioDelivery Systems	Buccal Film	Analgesic	75 μg	n/a
			150 μg	n/a
			300 μg	n/a
			450 μg	n/a
			600 μg	n/a
			750 μg	n/a
			900 μg	n/a
Butrans Purdue Pharma	Transdermal Patch	Analgesic	5 μg/h	n/a
			7.5 μg/h	n/a
			10 μg/h	n/a
			20 μg/h	n/a
Buprenex Reckitt Benckiser	IV or IM Injection	Analgesic	0.3 mg/mL	n/a
Sublocade Indivior	SC Extended-Release Injection	OUD Maintenance	100 mg	n/a
			300 mg	n/a
Probuphine Titan Pharmaceuticals	Implant	OUD Maintenance	80 mg/implant[a]	n/a
Zubsolv Orexo Inc	Sublingual Tablet	OUD Induction and Maintenance	0.7 mg	0.18 mg
			1.4 mg	0.36 mg
			2.9 mg	0.71 mg
			5.7 mg	1.4 mg
			8.6 mg	2.1 mg
			11.4 mg	2.9 mg
Bunavail BioDelivery Systems	Buccal Film	OUD Induction and Maintenance	2.1 mg	0.3 mg
			4.2 mg	0.7 mg
			6.3 mg	1 mg
Suboxone Indivior	Sublingual Film	OUD Maintenance	2 mg	0.5 mg
			4 mg	1 mg
			8 mg	2 mg
			12 mg	3 mg

[a]Four probuphine implants are typically implanted at once

EXPERIMENTAL APPLICATIONS AND INFLUENCES

Beyond the well-established and approved applications of buprenorphine in treatment of OUD and chronic pain, the unique pharmacology of this molecule also continues to provide inspiration to individuals seeking to expand its potential range of applications, as well as those endeavoring to discover the next generation of improved opioid therapeutics.

In terms of expanding the clinical applications of buprenorphine itself, several clinical trials have investigated buprenorphine's effect on stimulant use disorders. In a double-blind study combining Suboxone (buprenorphine/naloxone) with naltrexone, while the addition of Suboxone did not achieve its primary outcome of number of days of cocaine use during the evaluation period, there was an effect on the number of patients who were greater than 75% abstinent during the study compared to naltrexone alone.[47] A separate randomized, double-blind study comparing buprenorphine and bupropion showed a greater decrease in methamphetamine craving when given buprenorphine.[48] Furthermore, buprenorphine has also been studied in patients with severe depression who did not have an SUD diagnosis. In one approach, ultra-low doses of buprenorphine (<0.8 mg) were shown to significantly reduce suicidal ideation after 2 weeks, as compared to placebo in a double-blind trial.[49] In an randomized, unblinded trial, a single high dose of buprenorphine was shown to reduce suicidal ideation in patients with co-morbid OUD and suicidal tendencies.[50] Intriguingly, buprenorphine's reduction in depressive symptoms was even found to persist when given in combination with a μOP antagonist, suggesting an alternative

mechanism of action for this application.[51] Finally, in a double-blind study of patients with obsessive compulsive disorder, patients who augmented their existing treatment with buprenorphine showed a decrease in symptoms compared to placebo after 9 weeks.[52]

When considering buprenorphine's influences on future analgesic therapies, one of the most prominent efforts to broaden the therapeutic window for opioid analgesics has focused on the generation of G-protein biased agonists at μOP.[53] In a double-blind clinical trial, the biased μOP agonist TRV130 was found to be significantly different from morphine regarding induction of respiratory depression at low doses, while higher doses did cause transient respiratory depression that appeared to resolve somewhat more rapidly than that caused by morphine.[54] TRV130 also caused decreased nausea compared to morphine.[54] However, TRV130 was judged to lack clinical differentiation from current opioid analgesics in terms of safety, and was narrowly denied approval by FDA. Other analgesic development efforts have focused on the importance and utility of generating a mixed opioid efficacy profile like that of buprenorphine.[55] This low-selectivity approach is currently being explored using both multifunctional ligands and multi-component mixtures.[56]

ANALOGUE DEVELOPMENT AND STRUCTURE-ACTIVITY RELATIONSHIPS

Following on the synthesis of buprenorphine, multiple structural analogues of buprenorphine have been developed (Chart 2), including several that have resulted in commercialized products. These compounds have rarely been compared head to head and have often been evaluated using differing cell lines and species-specific receptors, making direct comparisons difficult. A didehydro derivative of buprenorphine, HS-599 (**15**), is a potent and long-acting antinociceptive that possesses significantly higher affinity for μOP compared to κOP and δOP, and also does not induce CPP, indicating that HS-599 may lack the rewarding properties of buprenorphine and morphine.[57] In the hot plate assay, HS-599 was 130x more effective than morphine, reaching 100% MPE at 0.2 μmol/kg but only reached 55% MPE under more intense nociceptive stimulation (up to 10 μmol/kg at 55 ºC).[58] Another didehydro analogue of buprenorphine, etorphine (**16**), has an *n*-propyl group in place of the *tert*-butyl as well as an *N*-methyl instead of *N*-CPM. Unlike buprenorphine and HS-599, etorphine is a full μOP agonist, and is approved for veterinary use.[17,19,59,60] Approximately 1000x more potent than morphine, its effects are apparent rapidly (within 10 min when given IM) and has a short duration of action (less than 2 hours) and thus was predicted to be "particularly liable for abuse."[61] Unlike morphine, etorphine causes rapid receptor internalization ($t_{1/2}$ = 6 min) as demonstrated in a model system using HEK cells transfected with a FLAG-tagged μOP receptor.[62] Its rapid onset and high potency/efficacy, however, makes it an appealing choice for sedation of large animals, such as elephants and rhinoceros. Dihydroetorphine (**17**), which possesses a reduced internal C18-19 bridge as opposed to the alkene of its parent molecule, is approved for use in China for the treatment of pain relief. Like etorphine, dihydroetorphine is extremely potent (1000-12000x stronger than morphine), and was initially considered as potentially less prone to development of OUD as compared to morphine.[17,59,63] Unfortunately, it has still been diverted for its ability to mitigate heroin-withdrawal symptoms and was subsequently restricted for use.

In contrast to the partial or full agonism associated with many other buprenorphine analogues, diprenorphine (**18**) is a potent pan-opioid antagonist, with sub-nanomolar activity at μOP, κOP, and δOP.[64] As it is the strongest commercially-available opioid antagonist approved for veterinary use, it is used to block the effects of etorphine and is commonly supplied alongside it. Though diprenorphine is not approved for therapeutic use in humans, [^{11}C]diprenorphine is occasionally used for PET scan studies to image opioid receptors due to its high affinity.[65,66]

Several additional analogues have pharmacologic profiles that make them attractive candidates for development as human therapeutics. BU10119 (**19**) has a phenyl group in place of the *tert*-butyl group and is a potent μOP, κOP, and NOP antagonist with minimal partial agonist activity.[67,68] Interestingly, this pharmacological profile appeared supportive of anxiolytic and antidepressant-like activity in mouse models, and further pre-clinical development of BU10119 is anticipated in regard to these efforts.[67] Despite its low efficacy at μOP, it does produce CPP that is blocked by a μOP antagonist.[67] Thienorphine (**20**) has an ethyl-2-thienyl group in place of the *tert*-butyl group and is a partial κOP agonist and poor μOP agonist (20% MPE).[19,69] It is currently in Phase II clinical trials for OUD treatment.[70] Thienorphine has a long duration of action, with antinociceptive effects observed at 8 hours following subcutaneous administration.[71] Its closely related analogue, TH-030418 (**21**), likewise possesses a thienyl substituent (ethyl-3-thienyl) but has an *N*-methyl instead of *N*-CPM and. induces severe respiratory depression in mice (LD_{50} = 6.77 mg/kg).[71,72]

Several other buprenorphine analogues which are not used commercially or being considered for therapeutic use are nevertheless noteworthy for the insights they have provided into structure-activity relationships at opioid receptors. The compounds UMB94 (**22**) and UMB97 (**23**) have hydroxylated C18-19 bridges, with a hydrogen in place of the *tert*-butyl group as well as an *N*-methyl instead of *N*-CPM. The placement of the hydroxyl provides either partial- or full-μOP agonist activity, with C19 hydroxylation (**22**) associated with partial μOP-agonism, full δOP agonism, and weak partial agonism of κOP.[19] In contrast, C18 hydroxylation (**23**) imparts full agonism at μOP, full agonism at δOP, and weak partial agonism of κOP.[19]

In another set of structure-activity relationship (SAR) experiments, Husbands and Lewis set out to determine the effect of the conformation of buprenorphine's C20 *tert*-butyl group through generating ring-constrained analogues. Instead of methyl vinyl ketone, the Diels-Alder reaction was performed with 2-methylenecyclopentanone and either *N*-methyl or *N*-CPM to form the spirocycle, reducing the ketone with lithium aluminum hydride to form **24** and **26,** or dialkylating at the alpha-keto position then reducing the ketone to form **25** or **27**; the generated alkylated analogue **25** possessed minimal μOP agonist activity (20% MPE) and some κOP/δOP agonist activity (~40% MPE) while the unalkylated versions (**24**, **26**) were a potent agonist for both κOP and δOP.[18] Similarly, ring-fused analogues BU46 (**28**) and BU47 (**29**) are also active, though the alpha-hydroxy analogue is an μOP antagonist while the beta-hydroxy analogue is a full μOP agonist as well as 12x more active at κOP than the alpha-hydroxy compound based on *in vivo* efficacy studies.[73]

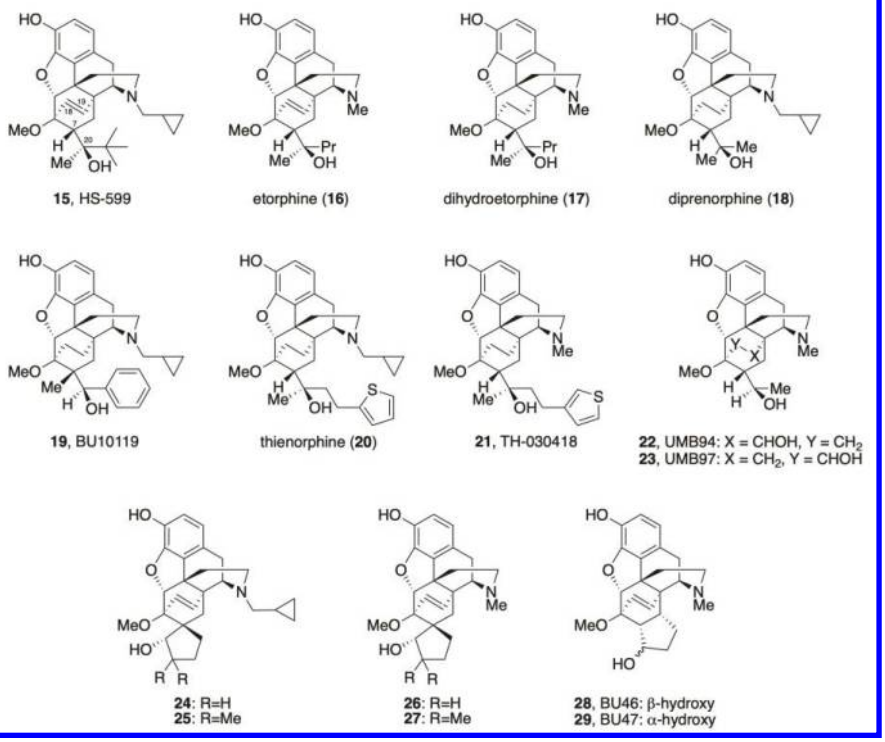
Despite the lack of consistency in the *in vitro* assays, some SAR trends can be identified (Table 3). One primary theme in the analogues is the importance of the identity of the *N*-alkyl group for μOP activity—*N*-methyl analogues appear to be full agonists of μOP while *N*-CPM leads to partial μOP agonism.

Table 3. Activity of Buprenorphine and Related Compounds at Opioid Receptors

Compound	μOP			δOP			κOP		
	EC_{50} (nM)	MPE (%)	K_i (nM)	EC_{50} (nM)	MPE (%)	K_i (nM)	EC_{50} (nM)	MPE (%)	K_i (nM)
Buprenorphine (**1**)[a]	0.08 ± 0.01	38 ± 8	0.08 ± 0.02	NS	12 ± 7	0.42 ± 0.04	0.04 ± 0.01	10 ± 4	0.11 ± 0.05
HS-599 (**15**)[b]	-	-	0.57 ± 0.08	-	-	32.0 ± 4	-	-	8.5 ± 0.9
etorphine (**16**)[c,d,e]	0.31 ± 0.05	109 ± 2	0.362 ± 0.003	10.0 (6.2-16.1)	74 ±4	1.62 ± 0.01	0.4 ± 0.3	90	3.75 ± 0.74
dihydroetorphine (**17**)[c,d]	0.26 ±0.07	112 ±3	0.00969 ± 0.00045	8.3 (5.1-13.5)	81 ± 5	3.23 ± 1.15	-	-	2.24 ± 0.93
diprenorphine (**18**)[d,f]	NS	8 ± 2	0.072	113 (34-375)	36 ± 4	0.23	-	-	0.017
BU10119 (**19**)[g]	NS	2 ± 4	0.10 ± 0.02	NS	0 ± 4	0.25 ± 0.18	NS	-2 ± 1	0.04 ± 0.01
thienorphine (**20**)[h]	1.9 ± 0.4	19 ± 4	0.22 ± 0.07	NS	2 ± 2	0.69 ± 0.03	0.3 ± 0.2	75 ± 5	0.14 ± 0.06
TH-030418 (**21**)[i]	-	-	0.56 ± 0.05	-	-	0.73 ± 0.20	-	-	0.60 ± 0.28
UMB94 (**22**)[h]	43 ± 12	63 ± 14	20 ± 3.7	88 ± 2.4	130 ± 8	25 ± 4.6	240 ± 5	75 ± 24	26 ± 10
UMB97 (**23**)[h]	12 ± 1	97 ± 11	4.3 ± 2.8	57 ± 18	140 ± 26	120 ± 16	720 ± 8	47 ± 19	230 ± 170
24[j]	2.8 ± 1.1	32 ± 19.0	0.32 ± 0.05	0.3 ± 0.1	104.5 ± 12.5	0.69 ±0.15	0.04 ± 0.0	89.0 ± 3.0	1.04 ± 0.01
25[j]	4.2 ± 1.4	21.0 ± 1.0	0.59 ± 0.03	1.1 ± 0.2	45.5 ± 2.5	5.42 ± 0.54	0.1 ± 0.04	40.0 ± 6.0	3.12 ±0.20
26[j]	3.7 ± 0.50	87 ± 14.0	0.26 ± 0.16	6.1 ± 1.8	111.0 ± 6.0	5.52 ± 0.25	10.5 ± 3.0	88.0 ± 1.0	0.87 ± 0.13
27[j]	0.8 ± 0.03	99.5 ± 18.5	0.50 ± 0.11	18.6 ± 5.2	100 ± 1.5	8.47 ± 0.51	1.6 ± 0.4	21.0 ± 1.0	1.28 ± 0.01
BU46 (**28**)[k]	0.21± 0.04	49.4 ± 1.5	0.60 ± 0.05	-	-	0.86 ± 0.08	0.18 ± 0.04	77.9 ± 6.5	1.02 ± 0.10
BU47 (**29**)[k]	0.40 ± 0.07	51.0 ± 1.6	0.88 ± 0.20	-	-	1.45 ± 0.19	2.02 ± 0.52	54.2 ± 3.2	2.75 ± 0.10

NS: nonstimulatory
–: not determined
[a] EC_{50}s and MPE determined via measurement of [^{35}S] GTPγS binding to membranes of CHO cells transfected with μOP (rat), δOP (mouse), or κOP (human) and compared to full agonism by DAMGO (μOP), DPDPE (δOP), or U50,448H (κOP). K_is determined by competition with [^{3}H]diprenorphine.[16]
[b] K_is determined by competition with [^{3}H]DAMGO for μOP, [^{3}H]deltorphin II for δOP, and [^{3}H]U-69593 for κOP in rat brain membrane preparations (μOP and δOP) or guinea pig brain membrane preparations for κOP.[57]
[c] K_is determined by competition with [^{3}H]DAMGO for μOP, [^{3}H]DPDPE for δOP, and [^{3}H]U-69593 for κOP in rat brain homogenate membranes.[59]
[d] EC_{50}s and MPE determined via measurement of [^{35}S]GTPγS binding to membranes of C6 glioma cells transfected with rat μOP or δOP compared to full agonism by 10 μM fentanyl for μOP or 10 μM SNC-80 for δOP.[17]
[e] KOR EC_{50} and MPE determined via determination of inhibition of forskolin-stimulated adenylyl cyclase activity in HEK cells expressing mouse κOP. MPE expressed as percent activity of endogenous ligand, dynorphin.[60]
[f] K_is determined by competition with [^{3}H]DAMGO for μOP, [^{3}H]naltrindole for δOP, and [^{3}H]U-69593 for κOP in transfected cells expressing either rat (μOP in COS-7 cells) or mouse receptors (δOP in CHO cells and κOP in PC-12 cells).[64]
[g] K_is determined by competition with [^{3}H]diprenorphine in cells expressing rat (μOP and δOP) or human (κOP) receptors. EC_{50} and MPE determined via [^{35}S]GTPγS binding compared to DAMGO (μOP), DPDPE (δOP), or U-69593 (κOP).[68]
[h] K_is determined by competition with [^{3}H]DAMGO for μOP, [^{3}H]DPDPE for δOP, and [^{3}H]U-69593 for κOP in cloned receptors. EC_{50}s and MPEs determined in [^{35}S]GTPγS binding assay compared to DAMGO, SNC-80, or dynorphin A for μOP, δOP, or κOP, respectively.[19]
[i] K_is determined by competition with [^{3}H]diprenorphine in cells expressing cloned μOP, δOP, or κOP.[71]
[j] K_is determined by competition with [^{3}H]DAMGO for μOP, [^{3}H]DPDPE for δOP, and [^{3}H]U-69593 for κOP in CHO cells expressing human receptors. EC_{50} and MPE determined in [^{35}S]GTPγS binding assay in CHO cells compared to DAMGO for μOP, DPDPE for δOP, and U-69593 for κOP.[18]
[k] K_is determined via ligand displacement of [^{3}H]DAMGO for μOP, [^{3}H]DPDPE for δOP, and [^{3}H]CI977 for κOP in mouse brain homogenates. EC_{50}s and MPE determined via [^{35}S]GTPγS binding assay compared to 10 μM fentanyl in SH-SY5Y cells (μOP) and compared to U-69593 in CHO cells transfected with κOP (human).[73]

Chart 2. Selected Analogs of Buprenorphine Demonstrating the Structure Activity Relationships



Furthermore, modeling studies have supported the concept that steric bulk adjacent to C20 prevents full stimulation of κOP. For example, the spirocyclic methyl groups of **25** have been shown to closely mimic the arrangement of buprenorphine's *tert*-butyl group, resulting in partial agonism at κOP. In contrast, analogue **24,** which lacks these methyl groups, acts as a full agonist at κOP.

DRUG METABOLISM AND PHARMACOKINETICS

Buprenorphine is most commonly administered sublingually, as its oral bioavailability is approximately 15%.[74] When given

sublingually in either an ethanolic solution or as a tablet, bioavailability increases to 28-51%.[74] Compton and coworkers noted that when given as a tablet, patients experienced fewer "opioid effects" than when provided as an ethanolic solution.[75] Sublingual combination products containing naloxone generally report no differences from monotherapy due to the low sublingual bioavailability of naloxone.[76,77]

Buprenorphine's half-life is approximately 20 hours.[74] C_{max} and t_{max} vary from patient to patient, but drug concentrations remain consistently elevated for 12 hours following dosing.[74] Notably, this long half-life is not seen when buprenorphine is administered IV, suggesting that the terminal elimination rate is limited by absorption from the oral mucosa.[74] Although buprenorphine is not readily bioavailable through the dermis, patches for use in chronic pain patients incorporate the drug into an adhesive matrix for extended release.[78] Following administration, buprenorphine is extensively protein-bound to alpha- and beta-globulins (96%) and has a large volume of distribution (188 L when given IV, which is increased approximately tenfold when given sublingually).[74] The clearance following IV administration is calculated to be 62.5 L/h.[79]

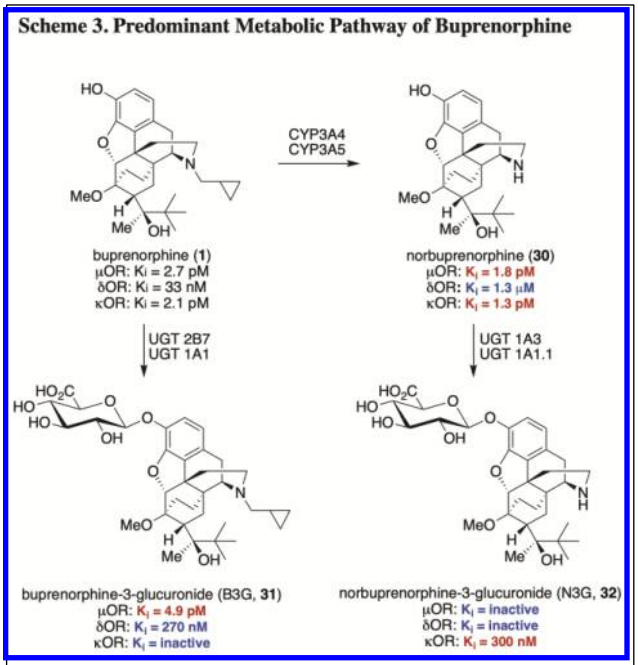
Several preclinical studies have indicated that buprenorphine is not a substrate for p-glycoprotein. Hassan and coworkers generated *mdr1a/b* knockout mice, which showed no change in buprenorphine's maximal antinociceptive response and area under the curve (AUC) compared to wildtype mice in a hot plate assay.[80] Furthermore, buprenorphine's brain to plasma ratio is high in rodents, ranging from 3.0 (at 15 min) to 10.5 (at 6 h) and there is a definitive difference in drug half-life in blood and brain (30 min and 1.1 h, respectively), indicating that buprenorphine is effectively retained in rat brain tissue.[81] Buprenorphine's apparent lack of affinity for Pgp has been observed in humans as well; cancer patients with upregulated Pgp demonstrated no difference in buprenorphine response as compared to controls.[82]

In humans, buprenorphine's primary metabolite is norbuprenorphine (**30**), formed through *N*-dealkylation by CYP3A4 and CYP3A5 (with some contributions from as CYP2C8 and CYP2C9) (Scheme 3).[83] Norbuprenorphine also possesses opioid activity, with 1/3rd the antinociceptive activity as buprenorphine as determined pre-clinically in an acetic acid writhing assay.[83] Unlike buprenorphine, norbuprenorphine is considered a full μOP agonist (81% MPE compared to DAMGO in CHO cells expressing rat μOP).[16] Norbuprenorphine is also a partial κOP agonist (60% MPE).[16,83] Also unlike buprenorphine, norbuprenorphine is a substrate for Pgp.[84] Perhaps most importantly, animal studies and some human reports suggest norbuprenorphine carries a greater risk of respiratory depression than the parent molecule.[85–89]Both buprenorphine and norbuprenorphine can be glucuronidated, buprenorphine by UGT2B7 and UGT1A1 and norbuprenorphine by UGT1A3 and UGT1A1.1.[83] The glucuronide metabolites are typically considered inactive, Brown and coworkers demonstrated that both buprenorphine-3-glucuronide (**31**, B3G) and norbuprenorphine-3-glucuronide (**32**, N3G) have some opioid activity.B3G showed some antinociceptive effects (20% MPE) and N3G showed slight antinociceptive effects (10% MPE) in a tail-flick assay; N3G also caused a decrease in tidal volume compared to saline in rodent models.[83] B3G's effects were mediated through μOP, δOP, and NOP, but not κOP, while N3G did not bind μOP or δOP, but did bind κOP and NOP.[83] Norbuprenorphine and N3G both displayed sedative effects, whereas B3G did not.[83]

Other drugs metabolized by CYP3A4 include several HIV protease inhibitors (e.g. ritonavir, saqanavir, indinavir), antifungals such as ketoconazole, SSRIs like fluoxetine and fluvoxamine, and several benzodiazepines (diazepam and flunitrazepam), which could prevent *N*-dealkylation of buprenorphine. Though one study reported that no alterations in *N*-dealkylation were observed in patients taking both buprenorphine and flunitrazepam, a separate study showed that ritonavir and indinavir did inhibit *N*-dealkylation of buprenorphine.[74] Conversely, individuals taking inducers of CYP3A4, such as phenobarbital and rifampicin, should be monitored closely for the development of opioid withdrawal symptoms at the end of the dosing interval.[74]

Most buprenorphine is eliminated through the feces, with less than 30% being excreted in the urine.[74] In the feces, buprenorphine and norbuprenorphine exist as the unglucuronidated forms, suggesting that B3G and N3G enter the bile, are secreted into the intestines, and hydrolyzed back to the parent forms before being eliminated.[74] No alterations were seen in AUCs of buprenorphine in renally-impaired patients, though increases in B3G and norbuprenorphine were observed.[74] Patients with impaired liver function should be monitored closely, given that buprenorphine metabolism is predominately mediated by liver enzymes.[74] In one study of patients with hepatitis, patients who received buprenorphine showed increases in alanine aminotransaminase (ALT) and aspartate transaminase (AST), both of which are biomarkers of liver distress.[74]

Scheme 3. Predominant Metabolic Pathway of Buprenorphine



K_i determined in human opioid receptors in CHO membrane preparations via ligand displacement of [^{3}H]-diprenorphine.[83]

Blue text indicates less affinity compared to buprenorphine while red text indicates more affinity compared to buprenorphine.

DOSING, CLINICAL PHARMACOLOGY, AND ADVERSE EFFECTS

Buprenorphine dosing is dependent on both the formulation used and the condition being treated. When used for treatment of pain, buccal and transdermal buprenorphine doses should be determined based on prior opioid history, using lower initial doses for opioid naïve patients, and applying product-specific conversions from oral morphine equivalents for opioid-tolerant patients.[39–41] When used for treatment of pain, buprenorphine

doses should be titrated for analgesic efficacy and tolerability.[39–41] When used for treatment of OUD, patients can be induced on a dose of 2-4 mg, increasing the dose in 2-4 mg increments every 60-90 min up through stabilization of withdrawal symptoms.[90] Because buprenorphine's partial agonism at μOP can lead to pharmacologically-precipitated withdrawal, induction is recommended to begin once mild-to moderate withdrawal symptoms have appeared.[90] Once dose stabilization has been achieved, during maintenance therapy for OUD, daily buprenorphine doses typically range from 8-24 mg.[91] Combination therapies with buprenorphine and naloxone are typically preferred for maintenance treatment of OUD since the presence of the opioid antagonist naloxone dissuades IV use.

The efficacy of buprenorphine in treatment of OUD compares favorably to other OUD treatment approaches, including potentially lower rates of all-cause mortality as compared to treatment with methadone, as found in a meta-analysis of cohort studies.[92] In an open-label randomized, controlled trial comparing use of buprenorphine/naloxone with extended release naltrexone (another major outpatient treatment approach for OUD) buprenorphine/naloxone demonstrated higher rates of successful initiation (94% vs. 72%), lower risk of relapse at 24 weeks (57% vs. 65%), higher rates of opioid-negative urine samples and opioid-abstinent days, and similar rates of opioid craving and adverse effects overall.[93]

As a partial agonist at μOP, buprenorphine induces a side effect profile qualitatively similar to that of other μOP agonists, albeit with a frequently reduced degree of severity.[94] Patients typically report symptoms of constipation and sedation especially during treatment induction, with prospective studies suggesting 1-5% of patients on buprenorphine report constipation.[94,95] In a double-blind, cross-over study of buprenorphine used for chronic back pain, transdermal buprenorphine did not cause significantly more constipation-related adverse events than placebo.[96]

When considering euphoric effects and abuse liability buprenorphine/naloxone did not produce any significant differences compared to placebo on a visual analog scale, (for 'high', 'good effect', 'bad effect', 'liking,' or 'sick'), nor did buprenorphine alone, in a double-blind, laboratory human subjects study.[97] However, a risk of abuse and diversion is still present, as illustrated in a survey of individuals using illicit opioids. In this study, 76% reported using diverted buprenorphine. Interestingly, the majority reported using the drug for treatment of withdrawal symptoms or to stop using other opioids.[98] Injection drug users were more likely to obtain buprenorphine in order to stop using other opioids than non-injection drug users (80% vs 47%) while non-injection drug users were more likely than injection drug user to obtain the drug in order to get high (69% vs 32%). A separate secondary data analysis of individuals in residential recovery centers likewise indicated mixed motivations for buprenorphine diversion, with more than 80% of those obtaining illicit buprenorphine reporting use for its euphoric effects.[99]

In regard to effects on the cardiovascular system, IM buprenorphine/naloxone caused slightly higher blood pressure readings, though the effect was not clinically significant.[97] Buprenorphine has been reported to block hERG channel activity *in vitro*; however, multiple human studies, both prospective and double-blind, have concluded that at clinically-relevant doses of buprenorphine, no significant effect is observed.[100,101] At supraclinical doses (4x and 8x typical doses) QTc elongation is observed, though not enough to be considered a likely cause of arrhythmia.[100,101]

Notably, buprenorphine's decreased risk of respiratory depression has led to a clinical preference for its use compared to methadone.[102,103] However, when combined with CNS depressants such as benzodiazepines or alcohol, the risk of severe respiratory depression returns due to an enhanced effect of these two compounds.[102,103] In a post-mortem analysis of buprenorphine related deaths, benzodiazepines and alcohol were found in 82% and 58% of cases, respectively.[103] In a separate survey of patients on medication assisted therapy (MAT), 36% of buprenorphine patients reported daily use of benzodiazepines and 67% of patients reported some benzodiazepine use during treatment.[102] Patients were more likely to experience opioid toxicity when combining benzodiazepines with methadone than with buprenorphine, but 1.2% of buprenorphine patients did report experiencing an overdose.[102]

The use of buprenorphine during pregnancy invokes several additional considerations. In a meta-analysis of buprenorphine and methadone exposure and neonatal outcomes, use of opioids by a pregnant mother was associated with negative outcomes in the child, such as low birthweight, small head circumference, and preterm birth as well as neonatal abstinence syndrome.[104] However, discontinuation of opioid use during pregnancy is not recommended due to the effect of stress on the fetus. Use of MAT (buprenorphine or methadone) during pregnancy is thus associated with improved outcomes with respect to birthweight, head circumference, gestational age, and the mother's abstinence from illicit opioid use.[104] The long-term effects of the mother's use of MAT on the child are still unclear, but some studies suggest possible disruptions in the drug-reward pathway as well as potential hyperactivity and impaired memory processing.[105]

When comparing the use of methadone with buprenorphine in pregnant mothers with OUD, significant differences between the two drugs are observed.[106] A prospective study on opioid-dependent pregnant women revealed that neonatal abstinence syndrome occurred in 62.5% of infants born to mothers using methadone, compared to 41.2% born to mothers using buprenorphine.[106] Furthermore, the withdrawal symptoms were significantly worse in the methadone group, with 80% vs 57% of infants requiring morphine treatment.[106] Expectant mothers on methadone were also more likely to have used heroin during their pregnancies (35% vs 12.9%).[106] A separate double-blind study observed that infants exhibiting symptoms of neonatal abstinence syndrome required less morphine and required a shorter duration of treatment if exposed to buprenorphine compared to methadone.[107] Finally, neonatal outcomes with respect to birthweight, length, and head circumference were improved when mothers were treated with buprenorphine versus methadone, despite similar rates of premature delivery in both prospective and double-blind studies.[90,104]

HISTORY AND IMPORTANCE IN NEUROSCIENCE

The long history of opiates, their use in medicine, and their attendant risks have been well-documented in this series.[108–110] Overall, due to the side effects of morphine use, much research was performed throughout the 20th century to design a new therapeutic which would retain morphine's analgesic properties avoid its associated risks. Initial research focused on simplification of the morphinan structure, but this strategy did not lead to an improved compound.[9] Ultimately, buprenorphine was developed in subsequent work at Reckitt and Colman (now

Reckitt Benckiser) in the 1960s.[111] In this effort, Bentley and coworkers postulated that more complex and more rigid structures would allow for biased activity as the new structures would fail to access certain receptor pockets and thus exhibit more selective effects.[9]

Following positive initial data, trials on human patients began in 1971, leading to the UK approving buprenorphine in 1978 as a treatment for severe pain.[111] It was initially provided as an IV injection, but a sublingual formulation was released in 1982.[111] Buprenorphine (Buprenex, a low-dose injectable solution) was approved for use in treating chronic pain in the United States in 1985 and distributed by Norwich-Eaton.[111]

While initially indicated for pain management, buprenorphine has become far better known for its role in treating OUD. In France, approximately half of the buprenorphine supply was used off-label for treatment of OUD in the 1980s.[111] France became the first country to approve buprenorphine for treatment of OUD in 1995.[111] However, in the US, formal FDA approval of buprenorphine as an agent for OUD treatment did not occur 2002.[111] While certainly notable, the long gap between initial synthesis and application of buprenorphine as MAT for treatment of OUD is only the latest saga in a long-standing debate over the appropriate scope of opioids for use in SUD treatment in the US.

A useful point to pick up this debate is around the turn of the 20th century, following morphine's isolation from the opium poppy and the concomitant development of the hypodermic needle in the 1800s.[109] In the early 1900s, the use of opiates had become so commonplace that heroin (initially intended as a treatment for opium addiction) could be obtained from the Sears Roebuck catalog. Patent medicines, too, were a common source of opiates.[110] Women were commonly prescribed opiates as a treatment for feminine complaints as well as for pain-relief during labor.[110] Around 1914, an estimated 0.4% of the population was addicted to opioids.[112] In an attempt to curb the rising rates of addiction, the Harrison Narcotics Tax Act was passed – this legislation, in conjunction with the Supreme Court cases U.S. v Doremus, Webb v U.S., and U.S. v Behrman, confirmed the ability of the government to regulate opiate prescribing for treatment of addiction, especially in regard to prohibition of the use of maintenance doses of opiates for this purpose.[112]

This prohibitive stance remained the status quo for decades, until methadone made the first significant shift toward normalization of maintenance therapy. Methadone had originally been developed in the late 1930's as an analgesic alternative to morphine. As early as the 1940's, investigators noted a development of tolerance to methadone's analgesic and sedative effects along with methadone's ability to reduce symptoms of morphine withdrawal.[113] By 1965, Dole and Nyswander reported on the use of oral methadone as a treatment for heroin dependence—in the article, they noted that unlike other opioids, methadone could be given once daily and result in a complete remission from drug craving.[114] Eventually, in the 1970's, concerned that Vietnam veterans would return dependent on heroin , the Nixon administration passed the Comprehensive Drug Abuse Prevention and Control Act of 1970, which was designed to repeal parts of the Harrison Act that made it illegal to treat narcotic addiction. Ultimately, this reform permitted the approval of methadone as a maintenance therapy in 1972. At that time, additional regulations were passed to allow the dispensing of methadone to addicts through Opioid Treatment Programs (OTPs), which consisted of hospital pharmacies and physicians licensed by the DEA and FDA.[115]

These intensive programs, often requiring daily visits to the OTP site, remained the dominant model for treatment until the 20th century came to a close. The passage of the Drug Addiction Treatment Act of 2000 (DATA2000) finally allowed for buprenorphine to be legally administered, prescribed, or dispensed for SUD treatment.[116] However, unlike methadone, this legislation allowed for buprenorphine to be provided outside the restrictions placed on OTPs, such that patients could more easily access this therapy in outpatient settings, potentially including their usual doctor's office. Although buprenorphine is a schedule III drug, qualified physicians must still obtain a waiver to prescribe buprenorphine through OBOT, due to the strict requirements of the Narcotic Addict Treatment Act of 1974. This waiver under DATA2000 is commonly known as an "X waiver" due to the physician being provided with a prescriber number beginning with an X, following the physician's approval to participate in the program once they have taken an 8-hour training course.[117] Non-physician prescribers can now also register for a waiver to provide buprenorphine through OBOT, with an additional 16 hours of training required for gaining approval.[117]

Interestingly, despite the loosened restrictions affording by DATA2000, Reckitt & Colman received orphan disease status for OUD treatment after arguing that they wouldn't be able to recoup costs, thus receiving protection from generic competition for 7 years.[111] In 2009, Reckitt & Colman released a new formulation of Suboxone, formulated in a film to prevent a decrease in profits due to generics.[111] With current examples of clinical and commercial successes in this arena being all too rare, buprenorphine continues to demonstrate its value, as more than 750,000 prescriptions of buprenorphine were filled in the United States in the fourth quarter of 2012 and over 22 tons of buprenorphine were consumed globally in 2017.[107,118]

Although regulatory challenges to expand opioid-based OUD treatment were a point of real concern during development, achieving commercial and clinical success of buprenorphine once these barriers had been addressed was perhaps less difficult than initially assumed. A recent National Survey on Drug Use and Health (NSDUH) estimated that 1.9 million civilian, non-institutionalized adults (0.8%) met the criteria for OUD while a further 11.5 million adults (4.7%) had misused opiates.[119] In patients with an opioid prescription, these rates are even higher, with 12.5% reporting misuse and 16.7% reporting an OUD diagnosis.[119] These elevated rates for opioid misuse and OUD diagnosis secondary to prescription opioid use, alongside the ongoing overdose crisis associated with long-term opioid use in chronic non-cancer pain, seem likely to make buprenorphine a continuing source of clinical value throughout the near future.

Nevertheless, several outstanding concerns with buprenorphine provide space for innovation and successful translation of fundamental neuroscience and neuropharmacologic investigations into improved therapeutic approaches for OUD. Most saliently, although the risk is diminished as compared to full opioid agonists, buprenorphine still carries with it the class-wide risk for fatal respiratory depression upon overdose, alone and in combination with other CNS depressants.[87] Furthermore, the optimal approach for treatment of acute pain in the context of chronic buprenorphine therapy for OUD remains an area of active concern and debate.[120,121] Similarly, patients, providers, and payers have widely divergent opinions on the desirability of lifetime

treatment with buprenorphine, highlighting ongoing tensions regarding indefinite use of MAT for OUD .[122–125]

If any of these issues are to be solved by a hypothetical future intervention, buprenorphine will likely have significant influence on its own obsolescence as SAR studies around buprenorphine have provided a great deal of insight into what structural features are required for modifying the efficacy and bias of signaling through μOP . Furthermore, the relationship between partial μOP agonism and receptor internalization, receptor desensitization, and β-arrestin recruitment has also been a valuable contribution to the field of neuroscience by improving our understanding of opioid-mediated reward and influencing next-generation approaches to analgesic therapy.[126,127] Whether the next generation of analgesics and OUD therapeutics can further optimize outcomes through modifying the magnitude, duration, and relative effect on opioid receptor intracellular signaling pathways, or by avoiding direct action at opioid receptors altogether is a topic of great interest for the future of neuropsychiatry – and one that will not be answered without reference to the unique pharmacologic insights and novel therapeutic models that buprenorphine has generated.

ABBREVIATIONS

SUD, substance use disorder; OBOT, office based opioid treatment; OUD, opioid use disorder; CPM, cyclopropylmethyl; μOP, mu opioid receptor; κOP, kappa opioid receptor; δOP, delta opioid receptor; MPE, maximum possible effect; NOP, nociceptin opioid peptide receptor; BRET, bioluminescence resonance energy transfer; CPP, conditioned place preference; cAMP, cyclic AMP; AUD, alcohol use disorder; POMC, proopiomelanocortin; PENK, proenkephalin; PDYN, prodynorphin; SAR, structure-activity relationship; IV, intravenous; IM, intramuscular; SC, subcutaneous; Pgp, p-glycoprotein; AUC, area under the curve; CNS, central nervous system; MAT, medication assisted therapy; XR, extended release; DEA, Drug Enforcement Agency; FDA, Food and Drug Administration; OTP, opioid treatment programs

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REFERENCES

(1) Bentley, K. W. Thebaine and Oripavine Derivaties. GB1136214, 1965.
(2) National Center for Biotechnology Information. Buprenorphine, CID=644073.
(3) PerkinElmer. ChemDraw Professional 16.0. 2017.
(4) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings. *Adv. Drug Deliv. Rev.* **2012**, *64*, 4–17.
(5) Paul, B. D.; Dreka, C.; Knight, E. S.; Smith, M. L. Gas Chromatographic/Mass Spectrometric Detection of Narcotine, Papaverine, and Thebaine in Seeds of Papaver Somniferum. *Planta Med.* **1996**, *62*, 544–547.
(6) Fist, A. J.; Byrne, C. J.; Gerlach, W. L. Papaver Somniferum Strain with High Concentration of Thebaine and Oripavine. US006067749A, 2000.
(7) Millgate, A. G.; Pogson, B. J.; Wilson, I. W.; Kutchan, T. M.; Zenk, M. H.; Gerlach, W. L.; Fist, A. J.; Larkin, P. J. Morphine-Pathway Block in Top1 Poppies. *Nature* **2004**, *430*, 413–414.
(8) Bentley, K. W. A Process for the Production of a Derivative of Thebaine. GB902659, 1961.
(9) Bentley, K. W.; Hardy, D. G. Novel Analgesics and Molecular Rearrangements in the Morphine-Thebaine Group. I.. Ketones Derived from 6,14-Endo-Ethenotetrahydrothebaine. *J. Am. Chem. Soc.* **1967**, *89*, 3267–3273.
(10) Machara, A.; Werner, L.; Endoma-Arias, M. A.; Cox, D. P.; Hudlicky, T. Improved Synthesis of Buprenorphine from Thebaine and/or Oripavine via Palladium-Catalyzed N-Demethylation/Acylation and/or Concomitant O-Demethylation. *Adv. Synth. Catal.* **2012**, *354*, 613–626.
(11) Hudlicky, T. Recent Advances in Process Development for Opiate-Derived Pharmaceutical Agents. *Can. J. Chem.* **2015**, *93*, 492–501.
(12) Werner, L.; MacHara, A.; Adams, D. R.; Cox, D. P.; Hudlicky, T. Synthesis of Buprenorphine from Oripavine via N-Demethylation of Oripavine Quaternary Salts. *J. Org. Chem.* **2011**, *76*, 4628–4634.
(13) Weber, B. T.; Roux, L. Improved Method of Manufacturing Buprenorphine and Analogues Thereof from Oripavine. WO2016078833A1, 2016.
(14) Hagel, J. M.; Facchini, P. J. Dioxygenases Catalyze the O-Demethylation Steps of Morphine Biosynthesis in Opium Poppy. *Nat. Chem. Biol.* **2010**, *6*, 273–275.
(15) Negus, S. S.; Bidlack, J. M.; Mello, N. K.; Furness, M. S.; Rice, K. C.; Brandt, M. R. Delta Opioid Antagonist Effects of Buprenorphine in Rhesus Monkeys. *Behav. Pharmacol.* **2002**, *13*, 557–570.
(16) Huang, P.; Kehner, G. B.; Cowan, A.; Liu-Chen, L. Y. Comparison of Pharmacological Activities of Buprenorphine and Norbuprenorphine: Norbuprenorphine Is a Potent Opioid Agonist. *J. Pharmacol. Exp. Ther.* **2001**, *297* (2), 688–695.
(17) Lee, K. O.; Akil, H.; Woods, J. H.; Traynor, J. R. Differential Binding Properties of Oripavines at Cloned μ- and δ-Opioid Receptors. *Eur. J. Pharmacol.* **1999**, *378*, 323–330.
(18) Husbands, S. M.; Lewis, J. W. Structural Determinants of Efficacy for κ Opioid Receptors in the Orvinol Series: 7,7-Spiro Analogues of Buprenorphine. *J. Med. Chem.* **2000**, *43*, 139–141.
(19) Wu, H.; Smith, T. A.; Huang, H.; Wang, J. B.; Deschamps, J. R.; Coop, A. Functionalization of the 6,14-Bridge of the Orvinols. Part 3: Preparation and Pharmacological Evaluation of 18- and 19-Hydroxyl Substituted Orvinols. *Bioorganic Med. Chem. Lett.* **2007**, *17*, 4829–4831.
(20) Blake, A. D.; Bot, G.; Freeman, J. C.; Reisine, T. Differential Opioid Agonist Regulation of the Mouse μ Opioid Receptor. *J. Biol. Chem.* **1997**, *272*, 782–790.
(21) Kuo, A.; Magiera, J.; Rethwan, N.; Andersson, Å.; Leen Lam, A.; Wyse, B.; Meutermans, W.; Lewis, R.; Smith, M. In Vitro Profiling of Opioid Ligands Using the CAMP Formation Inhibition Assay and the β-Arrestin2 Recruitment Assay: No Two Ligands Have the Same Profile. *Eur. J. Pharmacol.* **2020**, *872*, 172947.
(22) Raehal, K. M.; Walker, J. K. L.; Bohn, L. M. Morphine Side Effects in β-Arrestin 2 Knockout Mice. *J. Pharmacol. Exp. Ther.* **2005**, *314*, 1195–1201.

(23) Kliewer, A.; Gillis, A.; Hill, R.; Schmidel, F.; Bailey, C.; Kelly, E.; Henderson, G.; Christie, M. J.; Schulz, S. Morphine-Induced Respiratory Depression Is Independent of β-Arrestin2 Signalling. *Br. J. Pharmacol.* [Online early access] DOI:10.1111/bph.15004. Published Online: Feb 12, 2020 bpspubs.onlinelibrary.wiley.com/doi/full/10.1111/bph.15004 (accessed Apr 16, 2020).

(24) Hill, R.; Disney, A.; Conibear, A.; Sutcliffe, K.; Dewey, W.; Husbands, S.; Bailey, C.; Kelly, E.; Henderson, G. The Novel μ-Opioid Receptor Agonist PZM21 Depresses Respiration and Induces Tolerance to Antinociception. *Br. J. Pharmacol.* **2018**, *175*, 2653–2661.

(25) Zaki, P. A.; Keith, D. E.; Brine, G. A.; Carroll, F. I.; Evans, C. J. Ligand-Induced Changes in Surface μ-Opioid Receptor Number: Relationship to G Protein Activation? *J. Pharmacol. Exp. Ther.* **2000**, *292*, 1127–1134.

(26) Williams, J. T.; Ingram, S. L.; Henderson, G.; Chavkin, C.; von Zastrow, M.; Schulz, S.; Koch, T.; Evans, C. J.; Christie, M. J. Regulation of μ-Opioid Receptors: Desensitization, Phosphorylation, Internalization, and Tolerance. *Pharmacol. Rev.* **2013**, *65* (1), 223–254.

(27) Grinnell, S. G.; Ansonoff, M.; Marrone, G. F.; Lu, Z.; Narayan, A.; Xu, J.; Rossi, G.; Majumdar, S.; Pan, Y. X.; Bassoni, D. L.; Pintar, J.; Pasternak, G. W. Mediation of Buprenorphine Analgesia by a Combination of Traditional and Truncated Mu Opioid Receptor Splice Variants. *Synapse* **2016**, *70*, 395–407.

(28) Matthes, H. W. D.; Maldonadot, R.; Simonin, F.; Valverdet, O.; Slowet, S.; Befort, K.; Dierich, A.; Meur, M. Le; Dolle, P.; Tzavarall, E.; Hanounell, J.; Roquest, B. P.; Kieffer, B. L. Loss of Morphine-Induced Analgesia, Reward Effect and Withdrawal Symptoms in Mice Lacking the Mu-Opioid-Receptor Gene. *Nature* **1996**, *383*, 819–823.

(29) Marquez, P.; Baliram, R.; Kieffer, B. L.; Lutfu, K. The Mu Opioid Receptor Is Involved in Buprenorphine-Induced Locomotor Stimulation and Conditioned Place Preference. *Neuropharmacology* **2007**, *52*, 1336–1341.

(30) Wee, S.; Koob, G. F. The Role of the Dynorphin-κ Opioid System in the Reinforcing Effects of Drugs of Abuse. *Psychopharmacology (Berl).* **2010**, *209*, 121–135.

(31) Falcon, E.; Browne, C. A.; Leon, R. M.; Fleites, V. C.; Sweeney, R.; Kirby, L. G.; Lucki, I. Antidepressant-like Effects of Buprenorphine Are Mediated by Kappa Opioid Receptors. *Neuropsychopharmacology* **2016**, *41*, 2344–2351.

(32) Sorge, R. E.; Rajabi, H.; Stewart, J. Rats Maintained Chronically on Buprenorphine Show Reduced Heroin and Cocaine Seeking in Tests of Extinction and Drug-Induced Reinstatement. *Neuropsychopharmacology* **2005**, *30*, 1681–1692.

(33) Chung, P. C. S.; Kieffer, B. L. Delta Opioid Receptors in Brain Function and Diseases. *Pharmacol. Ther.* **2013**, *140* (1), 112–120.

(34) Ide, S.; Minami, M.; Satoh, M.; Uhl, G. R.; Sora, I.; Ikeda, K. Buprenorphine Antinociception Is Abolished, but Naloxone-Sensitive Reward Is Retained, in μ-Opioid Receptor Knockout Mice. *Neuropsychopharmacology* **2004**, *29*, 1656–1663.

(35) Flynn, S. M.; Epperly, P. M.; Davenport, A. T.; Cami-Kobeci, G.; Husbands, S. M.; Ko, M. C.; Czoty, P. W. Effects of Stimulation of Mu Opioid and Nociceptin/Orphanin FQ Peptide (NOP) Receptors on Alcohol Drinking in Rhesus Monkeys. *Neuropsychopharmacology* **2019**, *44*, 1476–1484.

(36) Belkaï, E.; Crété, D.; Courtin, C.; Noble, F.; Marie-Claire, C. Comparison of the Transcriptional Responses Induced by Acute Morphine, Methadone and Buprenorphine. *Eur. J. Pharmacol.* **2013**, *711*, 10–18.

(37) Boundy, V. A.; Gold, S. J.; Messer, C. J.; Chen, J.; Son, J. H.; Joh, T. H.; Nestler, E. J. Regulation of Tyrosine Hydroxylase Promoter Activity by Chronic Morphine in TH9.0-LacZ Transgenic Mice. *J. Neurosci.* **1998**, *18*, 9989–9995.

(38) Brown, E. E.; Finlay, J. M.; Wong, J. T. F.; Damsma, G.; Fibiger, H. C. Behavioral and Neurochemical Interactions between Cocaine and Buprenorphine: Implications for the Pharmacotherapy of Cocaine Abuse. *J. Pharmacol. Exp. Ther.* **1991**, *256*, 119–126.

(39) U.S. Food and Drug Administration website. Biodelivery Sciences International. Belbuca (buprenorphine buccal film) [package insert] https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021306s035lbl.pdf (accessed Jan 8, 2020).

(40) U.S. Food and Drug Administration website. Purdue Pharma. Butrans (buprenorphine transdermal patch) [package insert] https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021306s035lbl.pdf (accessed Jan 8, 2020).

(41) U.S. Food and Drug Administration website. Indivior. Buprenex (buprenorphine hydrochloride) [package insert] https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/018401s025lbl.pdf (accessed Jan 8, 2020).

(42) U.S. Food and Drug Administration website. Indivior. Sublocade (buprenorphine extended-release injection for subcutaneous use) [package insert] https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209819s009lbl.pdf (accessed Jan 8, 2020).

(43) U.S. Food and Drug Administration website. Titan Pharmaceuticals. Probuphine (buprenorphine implant) [package insert] https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/204442s009lbl.pdf (accessed Jan 8, 2020).

(44) U.S. Food and Drug Administration website. Orexo Inc. Zubsolv (buprenorphine and naloxone sublingual tablet) [package insert] https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/204242s017lbl.pdf (accessed Jan 8, 2020).

(45) U.S. Food and Drug Administration website. Biodelivery systems incorporated. Bunavail (buprenorphine and naloxone buccal film) [package insert] https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/205637s020lbl.pdf (accessed Jan 8, 2020).

(46) U.S. Food and Drug Administration website. Indivior. Suboxone (buprenorphine and naloxone sublingual film) [package insert] https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022410s038lbl.pdf (accessed Jan 8, 2020).

(47) Ling, W.; Hillhouse, M. P.; Saxon, A. J.; Mooney, L. J.; Thomas, C. M.; Ang, A.; Matthews, A. G.; Hasson, A.; Annon, J.; Sparenborg, S.; Liu, D. S.; McCormack, J.; Church, S.; Swafford, W.; Drexler, K.; Schuman, C.; Ross, S.; Wiest, K.; Korthuis, P. T.; Lawson, W.; Brigham, G. S.; Knox, P. C.; Dawes, M.; Rotrosen, J. Buprenorphine + Naloxone plus Naltrexone for the Treatment of Cocaine Dependence: The Cocaine Use Reduction with Buprenorphine (CURB) Study. *Addiction* **2016**, *111*, 1416–1427.

(48) Ahmadi, J.; Sahraian, A.; Biuseh, M. A Randomized Clinical Trial on the Effects of Bupropion and Buprenorphine on the Reduction of Methamphetamine Craving. *Trials* **2019**, *20*, 1–7.

(49) Yovell, Y.; Bar, G.; Mashiah, M.; Baruch, Y.; Briskman, I.; Asherov, J.; Lotan, A.; Rigbi, A.; Panksepp, J. Ultra-Low-Dose Buprenorphine as a Time-Limited Treatment for Severe Suicidal Ideation: A Randomized Controlled Trial. *Am. J. Psychiatry* **2016**, *173*, 491–498.

(50) Ahmadi, J.; Jahromi, M. S.; Ehsaei, Z. The Effectiveness of Different Singly Administered High Doses of Buprenorphine in Reducing Suicidal Ideation in Acutely Depressed People with Co-Morbid Opiate Dependence: A Randomized, Double-Blind, Clinical Trial. *Trials* **2018**, *19*, 1–8.

(51) Fava, M.; Memisoglu, A.; Thase, M. E.; Bodkin, J. A.; Trivedi, M. H.; De Somer, M.; Du, Y.; Leigh-Pemberton, R.; DiPetrillo, L.; Silverman, B.; Ehrich, E. Opioid Modulation with Buprenorphine/Samidorphan as Adjunctive Treatment for Inadequate Response to Antidepressants: A Randomized Double-Blind Placebo-Controlled Trial. *Am. J. Psychiatry* **2016**, *173*, 499–508.

(52) Ahmadpanah, M.; Reihani, A.; Ghaleiha, A.; Soltanian, A.; Haghighi, M.; Jahangard, L.; Sadeghi Bahmani, D.; Holsboer-Trachsler, E.; Brand, S. Buprenorphine Augmentation Improved Symptoms of OCD, Compared to Placebo - Results from a Randomized, Double-Blind and Placebo-Controlled Clinical Trial. *J. Psychiatr. Res.* **2017**, *94*, 23–28.

(53) Madariaga-Mazon, A.; Marmolejo-Valencia, A. F.; Li, Y.; Toll, L.; Houghten, R. A.; Martinez-Mayorga, K. Mu-Opioid Receptor Biased Ligands: A Safer and Painless Discovery of Analgesics? *Drug Discov. Today* **2017**, *22*, 1719–1729.

(54) Soergel, D. G.; Subach, R. A.; Burnham, N.; Lark, M. W.; James, I. E.; Sadler, B. M.; Skobieranda, F.; Violin, J. D.;

Webster, L. R. Biased Agonism of the Mu-Opioid Receptor by TRV130 Increases Analgesia and Reduces on-Target Adverse Effects versus Morphine: A Randomized, Double-Blind, Placebo-Controlled, Crossover Study in Healthy Volunteers. *Pain* **2014**, *155*, 1829–1835.

(55) Manglik, A.; Lin, H.; Aryal, D. K.; McCorvy, J. D.; Dengler, D.; Corder, G.; Levit, A.; Kling, R. C.; Bernat, V.; Hübner, H.; Huang, X. P.; Sassano, M. F.; Giguère, P. M.; Löber, S.; Duan, D.; Scherrer, G.; Kobilka, B. K.; Gmeiner, P.; Roth, B. L.; Shoichet, B. K. Structure-Based Discovery of Opioid Analgesics with Reduced Side Effects. *Nature* **2016**, *537*, 185–190.

(56) Azzam, A. A. H.; McDonald, J.; Lambert, D. G. Hot Topics in Opioid Pharmacology: Mixed and Biased Opioids. *Br. J. Anaesth.* **2019**, *122*, e136–e145.

(57) Lattanzi, R.; Negri, L.; Giannini, E.; Schmidhammer, H.; Schutz, J.; Improta, G. HS-599: A Novel Long Acting Opioid Analgesic Does Not Induce Place-Preference in Rats. *Br. J. Pharmacol.* **2001**, *134*, 441–447.

(58) Lattanzi, R.; Negri, L.; Schmidhammer, H.; Giannini, E. Antinociceptive Activity of a Novel Buprenorphine Analogue. *Life Sci.* **2002**, *70*, 2177–2185.

(59) Wang, D.-X.; Lu, X.-Q.; Qin, B.-Y. Dihydroetorphine Is a M-Receptor-selective Ligand. *J. Pharm. Pharmacol.* **1995**, *47*, 669–673.

(60) Gharagozlou, P.; Hashemi, E.; DeLorey, T. M.; Clark, J. D.; Lameh, J. Pharmacological Profiles of Opioid Ligands at Kappa Opioid Receptors. *BMC Pharmacol.* **2006**, *6*, 1–7.

(61) Jasinski, D. R.; Griffith, J. D.; Carr, C. B. Etorphine in Man. I. Subjective Effects and Suppression of Morphine Abstinence. *Clin. Pharmacol. Ther.* **1975**, *17*, 267–272.

(62) Keith, D. E.; Murray, S. R.; Zaki, P. A.; Chu, P. C.; Lissin, D. V.; Kang, L.; Evans, C. J.; Von Zastrow, M. Morphine Activates Opioid Receptors without Causing Their Rapid Internalization. *J. Biol. Chem.* **1996**, *271*, 19021–19024.

(63) Ohmori, S.; Hayashi, T.; Kawase, M.; Saito, S.; Morimoto, Y. Pharmacokinetic and Pharmacodynamic Evaluations of a Potent Analgesic, Dihydroetorphine, in Hairless Rat. *J. Pharmacol. Exp. Ther.* **2001**, *296*, 528–536.

(64) Raynor, K.; Kong, H.; Chen, Y.; Yasuda, K.; Yu, L.; Bell, G. I.; Reisine, T. Pharmacological Characterization of the Cloned κ-, δ-, and p-Opioid Receptors. *Mol. Pharmacol.* **1994**, *45*, 330–334.

(65) Willoch, F.; Schindler, F.; Wester, H. J.; Empl, M.; Straube, A.; Schwaiger, M.; Conrad, B.; Tölle, T. R. Central Poststroke Pain and Reduced Opioid Receptor Binding within Pain Processing Circuitries: A [11C]Diprenorphine PET Study. *Pain* **2004**, *108*, 213–220.

(66) Jones, A. K. P.; Cunningham, V. J.; Ha-kawa, S.; Fujiwara, T.; Luthra, S. K.; Silva, S.; Derbyshire, S.; Jones, T. Changes in Central Opioid Receptor Binding in Relation to Inflammation and Pain in Patients with Rheumatoid Arthritis. *Rheumatology* **1994**, *33*, 909–916.

(67) Almatroudi, A.; Ostovar, M.; Bailey, C. P.; Husbands, S. M.; Bailey, S. J. Antidepressant-like Effects of BU10119, a Novel Buprenorphine Analogue with Mixed κ/μ Receptor Antagonist Properties, in Mice. *Br. J. Pharmacol.* **2018**, *175* (14), 2869–2880.

(68) Cueva, J. P.; Roche, C.; Ostovar, M.; Kumar, V.; Clark, M. J.; Hillhouse, T. M.; Lewis, J. W.; Traynor, J. R.; Husbands, S. M. C7β-Methyl Analogues of the Orvinols: The Discovery of Kappa Opioid Antagonists with Nociceptin/Orphanin FQ Peptide (NOP) Receptor Partial Agonism and Low, or Zero, Efficacy at Mu Opioid Receptors. *J. Med. Chem.* **2015**, *58*, 4242–4249.

(69) Li, J. X.; Becker, G. L.; Traynor, J. R.; Gong, Z. H.; France, C. P. Thienorphine: Receptor Binding and Behavioral Effects in Rhesus Monkeys. *J. Pharmacol. Exp. Ther.* **2007**, *321*, 227–236.

(70) Hao, W. A Study of Thienorphine Hydrochloride Tablets in Relapse Prevention Treatment of Opioid Dependence. Identification No. NCT03656120. https://clinicaltrials.gov/ct2/show/NCT03656120 (accessed Jan 9, 2020).

(71) Yu, G.; Yan, L. Di; Li, Y. L.; Wen, Q.; Dong, H. J.; Gong, Z. H. TH-030418: A Potent Long-Acting Opioid Analgesic with Low Dependence Liability. *Naunyn. Schmiedebergs. Arch. Pharmacol.* **2011**, *384*, 125–131.

(72) Dai, W.; Xiao, D.; Gao, X.; Zhou, X. B.; Fang, T. Y.; Yong, Z.; Su, R. bin. A Brain-Targeted Ampakine Compound Protects against Opioid-Induced Respiratory Depression. *Eur. J. Pharmacol.* **2017**, *809*, 122–129.

(73) Traynor, J. R.; Guo, L.; Coop, A.; Lewis, J. W.; Woods, J. H. Ring-Constrained Orvinols as Analogs of Buprenorphine: Differences in Opioid Activity Related to Configuration of C 20 Hydroxyl Group. *J. Pharmacol. Exp. Ther.* **1999**, *291*, 1093–1099.

(74) Elkader, A.; Sproule, B. Buprenorphine: Clinical Pharmacokinetics in the Treatment of Opioid Dependence. *Clin. Pharmacokinet.* **2005**, *44*, 661–680.

(75) Compton, P.; Ling, W.; Moody, D.; Chiang, N. Pharmacokinetics, Bioavailability and Opioid Effects of Liquid versus Tablet Buprenorphine. *Drug Alcohol Depend.* **2006**, *82*, 25–31.

(76) Johnson, R. E.; McCagh, J. C. Buprenorphine and Naloxone for Heroin Dependence. *Curr. Psychiatry Rep.* **2000**, *2*, 519–526.

(77) Chiang, C. N.; Hawks, R. L. Pharmacokinetics of the Combination Tablet of Buprenorphine and Naloxone. *Drug Alcohol Depend.* **2003**, *70*, 39–47.

(78) Hans, G.; Robert, D. Transdermal Buprenorphine - A Critical Appraisal of Its Role in Pain Management. *J. Pain Res.* **2009**, *2*, 117–134.

(79) Mendelson, J.; Upton, R. A.; Everhart, E. T.; Jacob, P.; Jones, R. T. Bioavailability of Sublingual Buprenorphine. *J. Clin. Pharmacol.* **1997**, *37*, 31–37.

(80) Hassan, H. E.; Myers, A. L.; Coop, A.; Eddington, N. D. Differential Involvement of P-Glycoprotein (ABCB1) in Permeability, Tissue Distribution, and Antinociceptive Activity of Methadone, Buprenorphine, and Diprenorphine: In Vitro and in Vivo Evaluation. *J. Pharm. Sci.* **2009**, *98*, 4928–4940.

(81) Pontani, R. B.; Vadlamani, N. L.; Misra, A. L. Disposition in the Rat of Buprenorphine Administered Parenterally and as a Subcutaneous Implant. *Xenobiotica* **1985**, *15*, 287–297.

(82) Wang, J.; Cai, B.; Huang, D. X.; Yang, S. D.; Guo, L. Decreased Analgesic Effect of Morphine, but Not Buprenorphine, in Patients with Advanced P-Glycoprotein+ Cancers. *Pharmacol. Reports* **2012**, *64*, 870–877.

(83) Brown, S. M.; Holtzman, M.; Kim, T.; Kharasch, E. D. Buprenorphine Metabolites, Buprenorphine-3-Glucuronide and Norbuprenorphine-3-Glucuronide, Are Biologically Active. *Anesthesiology* **2011**, *115*, 1251–1260.

(84) Brown, S. M.; Campbell, S. D.; Crafford, A.; Regina, K. J.; Holtzman, M. J.; Kharasch, E. D. P-Glycoprotein Is a Major Determinant of Norbuprenorphine Brain Exposure and Antinociception. *J. Pharmacol. Exp. Ther.* **2012**, *343*, 53–61.

(85) Ohtani, M.; Kotaki, H.; Nishitateno, K.; Sawada, Y.; Iga, T. Kinetics of Respiratory Depression in Rats Induced by Buprenorphine and Its Metabolite, Norbuprenorphine. *J. Pharmacol. Exp. Ther.* **1997**, *281*, 428–433.

(86) Alhaddad, H.; Cisternino, S.; Declèves, X.; Tournier, N.; Schlatter, J.; Chiadmi, F.; Risède, P.; Smirnova, M.; Besengez, C.; Scherrmann, J. M.; Baud, F. J.; Mégarbane, B. Respiratory Toxicity of Buprenorphine Results from the Blockage of P-Glycoprotein-Mediated Efflux of Norbuprenorphine at the Blood-Brain Barrier in Mice. *Crit. Care Med.* **2012**, *40*, 3215–3223.

(87) Seldén, T.; Ahlner, J.; Druid, H.; Kronstrand, R. Toxicological and Pathological Findings in a Series of Buprenorphine Related Deaths. Possible Risk Factors for Fatal Outcome. *Forensic Sci. Int.* **2012**, *220*, 284–290.

(88) Mégarbane, B.; Hreiche, R.; Pirnay, S.; Marie, N.; Baud, F. J. Does High-Dose Buprenorphine Cause Respiratory Depression? Possible Mechanisms and Therapeutic Consequences. *Toxicol. Rev.* **2006**, *25*, 79–85.

(89) Strang, J.; Knight, A.; Baillie, S.; Reed, K.; Bogdanowicz, K.; Bell, J. Exploratory Analyses with New Lyophilized Buprenorphine and Sublingual Buprenorphine. *Int. J. Clin. Pharmacol. Ther.* **2018**, *56*, 81–85.

(90) Kampman, K.; Jarvis, M. American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. *J. Addict. Med.* **2015**, *9* (5), 358–367.

(91) Hillhouse, M.; Canamar, C. P.; Doraimani, G.; Thomas, C.; Hasson, A.; Ling, W. Participant Characteristics and Buprenorphine Dose. *Am. J. Drug Alcohol Abuse* **2011**, *37*, 453–459.
(92) Sordo, L.; Barrio, G.; Bravo, M. J.; Indave, B. I.; Degenhardt, L.; Wiessing, L.; Ferri, M.; Pastor-Barriuso, R. Mortality Risk during and after Opioid Substitution Treatment: Systematic Review and Meta-Analysis of Cohort Studies. *BMJ* **2017**, *357*, j1550.
(93) Lee, J. D.; Nunes, E. V.; Novo, P.; Bachrach, K.; Bailey, G. L.; Bhatt, S.; Farkas, S.; Fishman, M.; Gauthier, P.; Hodgkins, C. C.; King, J.; Lindblad, R.; Liu, D.; Matthews, A. G.; May, J.; Peavy, K. M.; Ross, S.; Salazar, D.; Schkolnik, P.; Shmueli-Blumberg, D.; Stablein, D.; Subramaniam, G.; Rotrosen, J. Comparative Effectiveness of Extended-Release Naltrexone versus Buprenorphine-Naloxone for Opioid Relapse Prevention (X:BOT): A Multicentre, Open-Label, Randomised Controlled Trial. *Lancet* **2018**, *391*, 309–318.
(94) Lange, W. R.; Fudala, P. J.; Dax, E. M.; Johnson, R. E. Safety and Side-Effects of Buprenorphine in the Clinical Management of Heroin Addiction. *Drug Alcohol Depend.* **1990**, *26*, 19–28.
(95) Griessinger, N.; Sittl, R.; Likar, R. Transdermal Buprenorphine in Clinical Practice - A Post-Marketing Surveillance Study in 13179 Patients. *Curr. Med. Res. Opin.* **2005**, *21* (8), 1147–1156.
(96) Gordon, A.; Callaghan, D.; Spink, D.; Cloutier, C.; Dzongowski, P.; O'Mahony, W.; Sinclair, D.; Rashiq, S.; Buckley, N.; Cohen, G.; Kim, J.; Boulanger, A.; Piraino, P. S.; Eisenhoffer, J.; Harsanyi, Z.; Darke, A. C.; Michalko, K. J. Buprenorphine Transdermal System in Adults with Chronic Low Back Pain: A Randomized, Double-Blind, Placebo-Controlled Crossover Study, Followed by an Open-Label Extension Phase. *Clin. Ther.* **2010**, *32* (5), 844–860.
(97) Stoller, K. B.; Bigelow, G. E.; Walsh, S. L.; Strain, E. C. Effects of Buprenorphine/Naloxone in Opioid-Dependent Humans. *Psychopharmacology (Berl).* **2001**, *154*, 230–242.
(98) Bazazi, A. R.; Yokell, M.; Fu, J. J.; Rich, J. D.; Zaller, N. D. Illicit Use of Buprenorphine/Naloxone among Injecting and Noninjecting Opioid Users. *J. Addict. Med.* **2011**, *5* (3), 175–180.
(99) Walker, R.; Logan, T. K.; Chipley, Q. T.; Miller, J. Characteristics and Experiences of Buprenorphine-Naloxone Use among Polysubstance Users. *Am. J. Drug Alcohol Abuse* **2018**, *44*, 595–603.
(100) Fareed, A.; Patil, D.; Scheinberg, K.; Blackinton Gale, R.; Vayalapalli, S.; Casarella, J.; Drexler, K. Comparison of QTc Interval Prolongation for Patients in Methadone versus Buprenorphine Maintenance Treatment: A 5-Year Follow-Up. *J. Addict. Dis.* **2013**, *32*, 244–251.
(101) Harris, S. C.; Morganroth, J.; Ripa, S. R.; Thorn, M. D.; Colucci, S. Effects of Buprenorphine on QT Intervals in Healthy Subjects: Results of 2 Randomized Positive- and Placebo-Controlled Trials. *Postgrad. Med.* **2017**, *129*, 69–80.
(102) Nielsen, S.; Dietze, P.; Lee, N.; Dunlop, A.; Taylor, D. Concurrent Buprenorphine and Benzodiazepines Use and Self-Reported Opioid Toxicity in Opioid Substitution Treatment. *Addiction* **2007**, *102*, 616–622.
(103) Häkkinen, M.; Launiainen, T.; Vuori, E.; Ojanperä, I. Benzodiazepines and Alcohol Are Associated with Cases of Fatal Buprenorphine Poisoning. *Eur. J. Clin. Pharmacol.* **2012**, *68*, 301–309.
(104) Brogly, S. B.; Saia, K. A.; Walley, A. Y.; Du, H. M.; Sebastiani, P. Prenatal Buprenorphine versus Methadone Exposure and Neonatal Outcomes: Systematic Review and Meta-Analysis. *Am. J. Epidemiol.* **2014**, *180*, 673–686.
(105) Kvello, A. M. S.; Andersen, J. M.; Øiestad, E. L.; Steinsland, S.; Aase, A.; Mørland, J.; Bogen, I. L. A Monoclonal Antibody against 6-Acetylmorphine Protects Female Mice Offspring from Adverse Behavioral Effects Induced by Prenatal Heroin Exposure. *J. Pharmacol. Exp. Ther.* **2019**, *368*, 106–115.
(106) Lacroix, I.; Berrebi, A.; Garipuy, D.; Schmitt, L.; Hammou, Y.; Chaumerliac, C.; Lapeyre-Mestre, M.; Montastruc, J. L.; Damase-Michel, C. Buprenorphine versus Methadone in Pregnant Opioid-Dependent Women: A Prospective Multicenter Study. *Eur. J. Clin. Pharmacol.* **2011**, *67*, 1053–1059.
(107) Jones, H. E.; Johnson, R. E.; Jasinski, D. R.; O'Grady, K. E.; Chisholm, C. A.; Choo, R. E.; Crocetti, M.; Dudas, R.; Harrow, C.; Huestis, M. A.; Jansson, L. M.; Lantz, M.; Lester, B. M.; Milio, L. Buprenorphine versus Methadone in the Treatment of Pregnant Opioid-Dependent Patients: Effects on the Neonatal Abstinence Syndrome. *Drug Alcohol Depend.* **2005**, *79*, 1–10.
(108) Burns, S. M.; Cunningham, C. W.; Mercer, S. L. DARK Classics in Chemical Neuroscience: Fentanyl. *ACS Chem. Neurosci.* **2018**, *9*, 2428–2437.
(109) Devereaux, A. L.; Mercer, S. L.; Cunningham, C. W. DARK Classics in Chemical Neuroscience: Morphine. *ACS Chem. Neurosci.* **2018**, *9*, 2395–2407.
(110) Presley, C. C.; Lindsley, C. W. DARK Classics in Chemical Neuroscience: Opium, a Historical Perspective. *ACS Chem. Neurosci.* **2018**, *9*, 2503–2518.
(111) Campbell, N. D.; Lovell, A. M. The History of the Development of Buprenorphine as an Addiction Therapeutic. *Ann. N. Y. Acad. Sci.* **2012**, *1248*, 124–139.
(112) Redford, A.; Powell, B. Dynamics of Intervention in the War on Drugs: The Buildup to the Harrison Act of 1914. *Indep. Rev.* **2016**, *20*, 509–530.
(113) Isbell, H.; Wikler, A.; Eddy, N. B.; Wilson, J. L.; Moran, C. F. Tolerance and Addition Liability of 6-Dimethylamino-4-4-Diphenyl-Heptanone-3 (Methadon). *J. Am. Med. Assoc.* **1947**, *135*, 888–894.
(114) Dole, V. P.; Nyswander, M. A Medical Treatment for Diacetylmorphine (Heroin) Addiction. *J. Am. Med. Assoc.* **1965**, *193* (646–650), 241.
(115) Institute of Medicine. *Federal Regulation of Methadone Treatment*; National Academies Press: Washington, DC, 1995.
(116) Diversion Control Division. DEA Requirements for DATA Waived Physicians (DWPs) https://www.deadiversion.usdoj.gov/pubs/docs/dwp_buprenorphine.htm (accessed Dec 18, 2019).
(117) Substance Abuse and Mental Health Services Administration. Apply for a Practitioner Waiver https://www.samhsa.gov/medication-assisted-treatment/training-materials-resources/apply-for-practitioner-waiver (accessed Dec 18, 2019).
(118) International Narcotics Control Board. *Narcotic Drugs: Estimated World Requirements for 2019*; 2018.
(119) Han, B.; Compton, W. M.; Blanco, C.; Crane, E.; Lee, J.; Jones, C. M. Prescription Opioid Use, Misuse, and Use Disorders in U.S. Adults: 2015 National Survey on Drug Use and Health. *Ann. Intern. Med.* **2017**, *167*, 293–301.
(120) Goel, A.; Azargive, S.; Lamba, W.; Bordman, J.; Englesakis, M.; Srikandarajah, S.; Ladha, K.; Di Renna, T.; Shanthanna, H.; Duggan, S.; Peng, P.; Hanlon, J.; Clarke, H. The Perioperative Patient on Buprenorphine: A Systematic Review of Perioperative Management Strategies and Patient Outcomes. *Can. J. Anesth.* **2019**, *66*, 201–217.
(121) Anderson, T. A.; Quaye, A. N. A.; Ward, E. N.; Wilens, T. E.; Hilliard, P. E.; Brummett, C. M. To Stop or Not, That Is the Question Acute Pain Management for the Patient on Chronic Buprenorphine. *Anesthesiology* **2017**, *126*, 1180–1186.
(122) Dakwar, E.; Kleber, H. D. Naltrexone-Facilitated Buprenorphine Discontinuation: A Feasibility Trial. *J. Subst. Abuse Treat.* **2015**, *53*, 60–63.
(123) Stein, M. D.; Conti, M. T.; Herman, D. S.; Anderson, B. J.; Bailey, G. L.; Noppen, D. Van; Abrantes, A. M. Worries About Discontinuing Buprenorphine Treatment: Scale Development and Clinical Correlates. *Am. J. Addict.* **2019**, *28* (4), 270–276.
(124) Weinstein, Z. M.; Gryczynski, G.; Cheng, D. M.; Quinn, E.; Hui, D.; Kim, H. W.; Labelle, C.; Samet, J. H. Tapering off and Returning to Buprenorphine Maintenance in a Primary Care Office Based Addiction Treatment (OBAT) Program. *Drug Alcohol Depend.* **2018**, *189*, 166–171.
(125) O'Neil, M. G. Methadone or Buprenorphine for Maintenance Therapy of Opioid Addiction: What's the Right Duration? *Medscape*. https://www.medscape.com/viewarticle/819875 (accessed Apr 6, 2020).
(126) Grim, T. W.; Acevedo-Canabal, A.; Bohn, L. M. Toward Directing Opioid Receptor Signaling to Refine Opioid Therapeutics. *Biol. Psychiatry* **2020**, *87*, 15–21.
(127) Viscusi, E. R.; Webster, L.; Kuss, M.; Daniels, S.; Bolognese, J. A.; Zuckerman, S.; Soergel, D. G.; Subach, R. A.; Cook, E.; Skobieranda, F. A Randomized, Phase 2 Study Investigating TRV130, a Biased Ligand of the -Opioid Receptor, for the

Intravenous Treatment of Acute Pain. *Pain* **2016**, *157*, 264–272.

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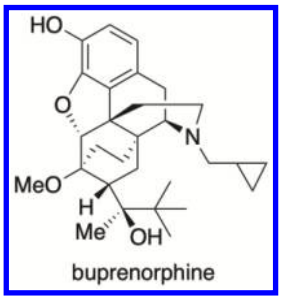
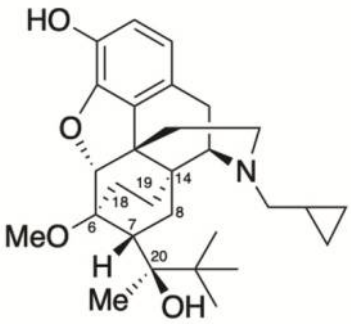


Classics in Chemical Neuroscience: Buprenorphine
Jillian L. Kyzer, Cody J. Wenthur

Chart 1. Structures of Buprenorphine and Opiates Produced by Opium Poppy



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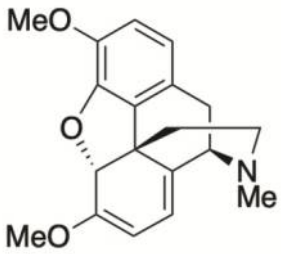
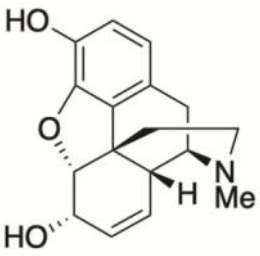
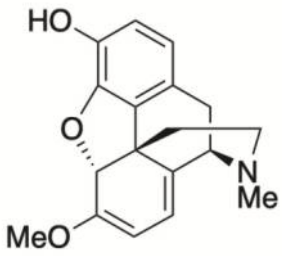


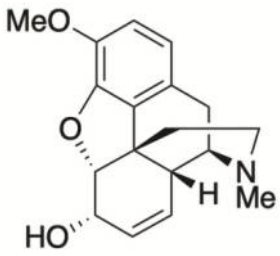
thebaine (**2**)



morphine (**3**)



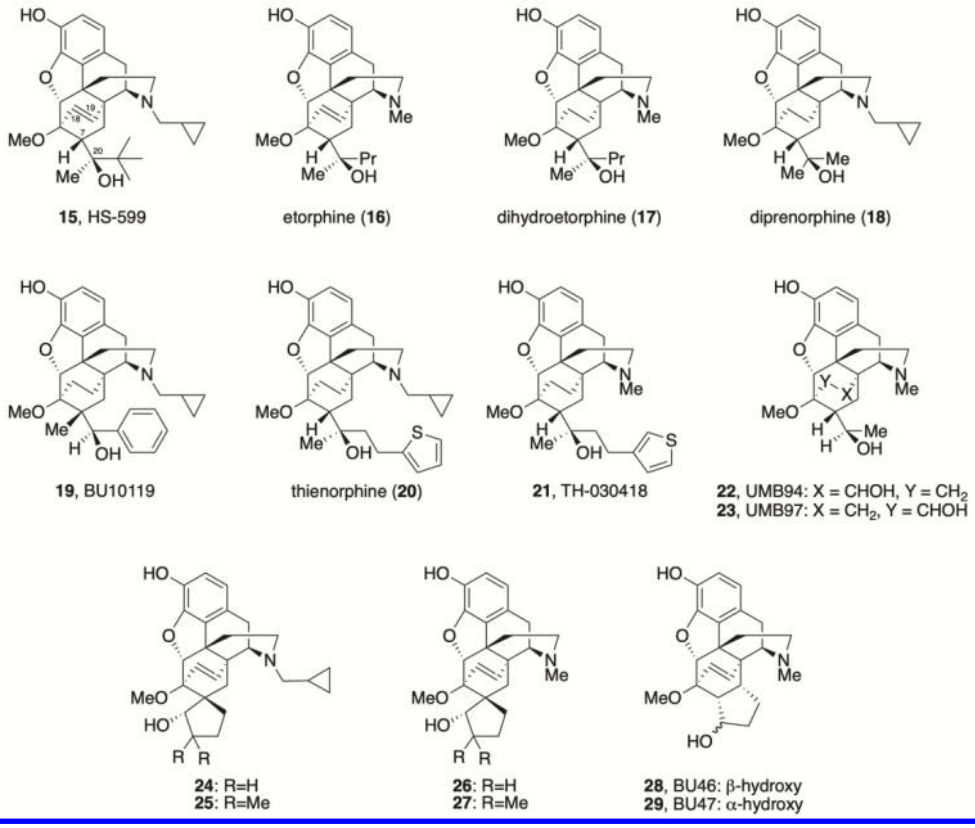
oripavine (**4**)



codeine (**5**)

117x107mm (300 x 300 DPI)

Chart 2. Selected Analogs of Buprenorphine Demonstrating the Structure Activity Relationships



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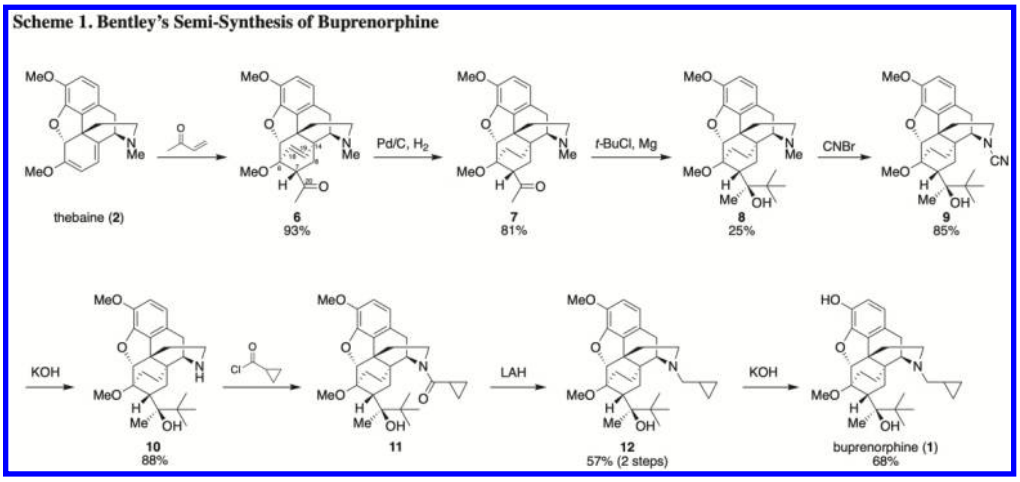

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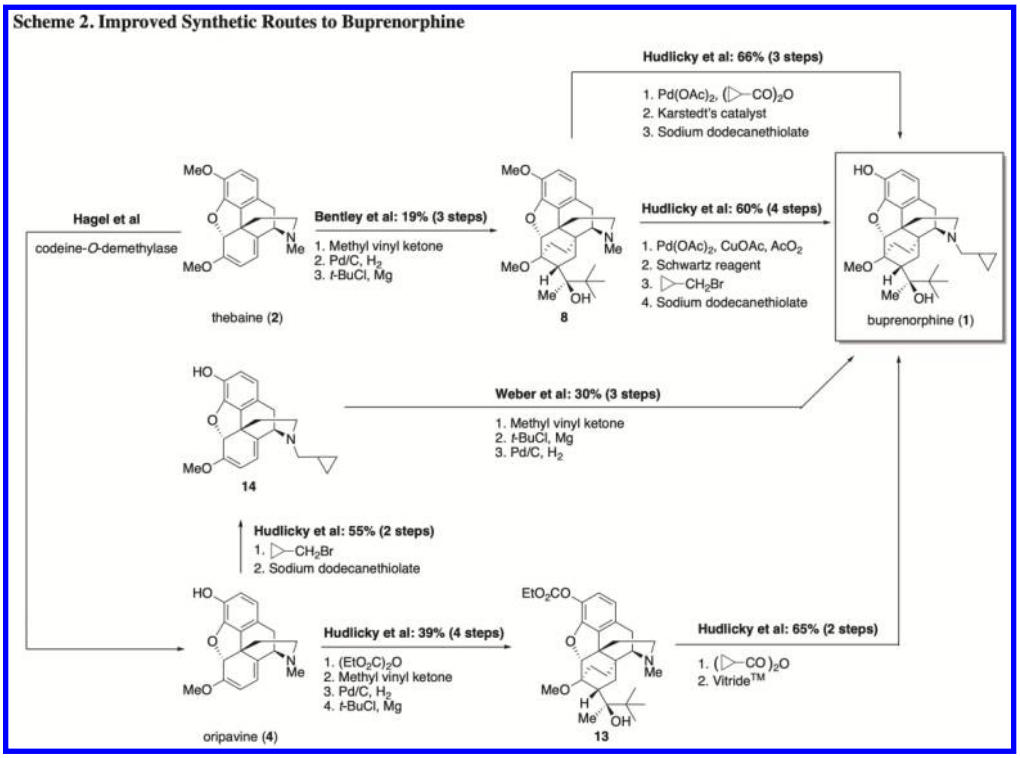

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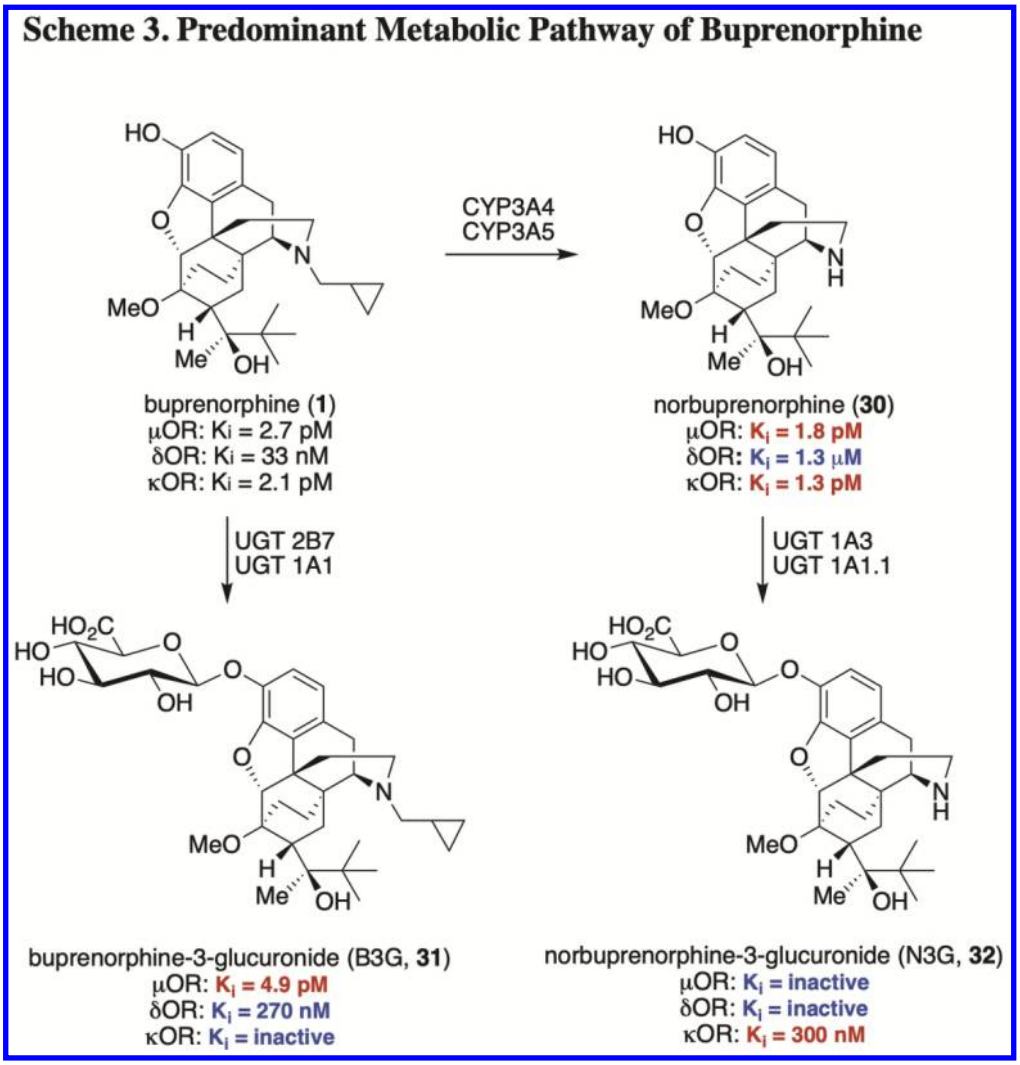
Scheme 3. Predominant Metabolic Pathway of Buprenorphine



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