Buprenorphine: Not Just Another Opioid – Understanding the Worlds Most Interesting Opioid

BUPE2024

Andrea Rubinstein, MD
Pain Therapeutics Consulting

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Objectives

At the end of this presentation participants should have a deeper understanding of what makes buprenorphine:

- Unique
- Safer than traditional opioids for the treatment of pain that requires opioid therapy
- As effective for pain as traditional opioids
- Safe to continue throughout the perioperative period

2

I have nothing to disclose

3

Thought Experiment:
Can we design a more perfect opioid?

Safe

- Less or no respiratory depression
- Non-reinforcing
- No dose adjustment for age
- No dose adjustment for liver / kidney

Effective

- Highly effective
- No tolerance
- No hyperalgesia

Versatile

- NPO
- Schedule III
- Large dose range
- Generic

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Buprenorphine and Safety

5

Spoiler

JAMA Network | Open

Original Investigation | Substance Use and Addiction

Trends and Characteristics of Buprenorphine-Involved Overdose Deaths Prior to and During the COVID-19 Pandemic

Lauren J. Tanz, ScD; Christopher M. Jones, PharmD, DrPH; Nicole L. Davis, PhD; Wilson M. Compton, MD; Grant T. Baldwin, PhD; Beth Han, MD, PhD; Nora D. Volkow, MD

74,474 deaths related to opioid overdose
Buprenorphine was found in only 1,955 (2.6%) of all people who died of opioid overdose
97% had at least one other substance

58 deaths in the US over 2 years where buprenorphine was the only drug found at autopsy

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British Journal of Pharmacology (2009), 157, 851–863

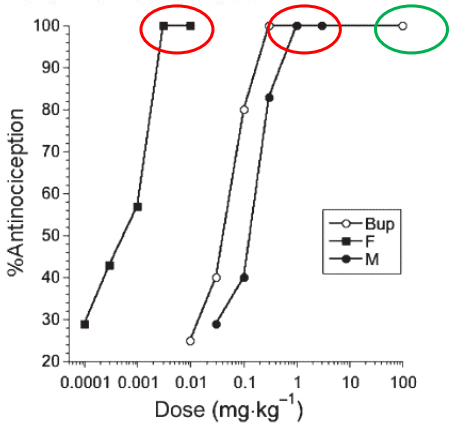
0007-1188/09
www.brjpharmacol.org

RESEARCH PAPER

Identification of an additional supraspinal component to the analgesic mechanism of action of buprenorphine

Zhe Ding and Robert B Raffa

Department of Pharmaceutical Sciences, Temple University School of Pharmacy, Philadelphia, PA, USA



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British Journal of Anaesthesia 94 (6): 825–34 (2005)
doi:10.1093/bja/aei145 Advance Access publication April 15, 2005

BJA

PAIN

Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats

A. Dahan[1]*, A. Yassen[2], H. Bijl[1], R. Romberg[1], E. Sarton[1], L. Teppema[1], E. Olofsen[1] and M. Danhof[2]

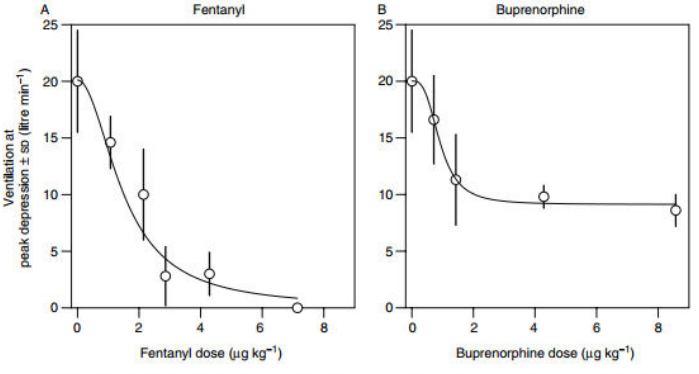

Fig 4 Dose–response relationships for (A) fentanyl and (B) buprenorphine. The response is the peak ventilatory depression. The line through the data is the fit to the Hill equation. 0 μg kg^{-1} is placebo. Data are mean (SD).

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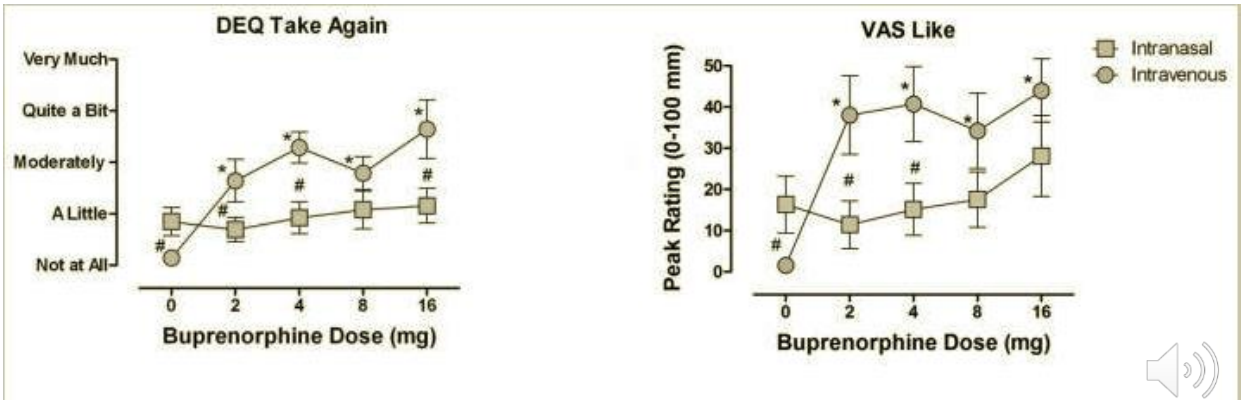
The Reinforcing and Subjective Effects of Intravenous and Intranasal Buprenorphine in Heroin Users

Jermaine D. Jones, Ph.D.[1,*], **Gabriela Madera, B.A.**[1], and **Sandra D. Comer, Ph.D.**[1]

Pharmacol Biochem Behav. 2014 July ; 122: 299–306. doi:10.1016/j.pbb.2014.04.012.



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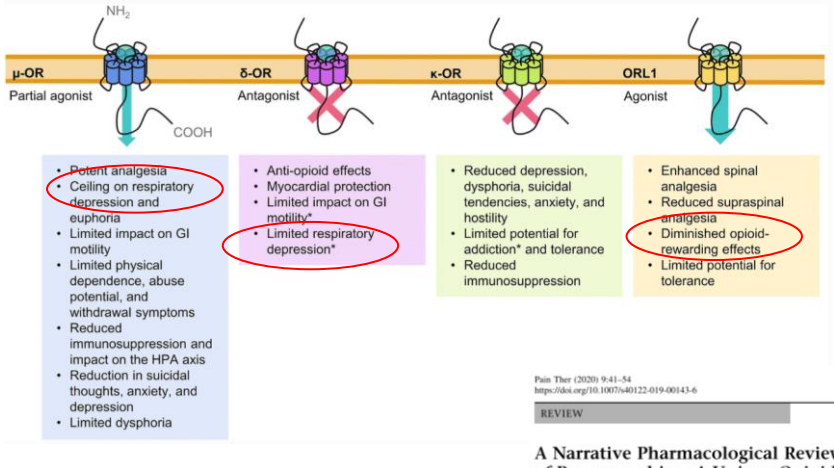
Buprenorphine is Promiscuous



Pain Ther (2020) 9:41–54
https://doi.org/10.1007/s40122-019-00143-6
REVIEW

A Narrative Pharmacological Review of Buprenorphine: A Unique Opioid for the Treatment of Chronic Pain

Jeffrey Gudin · Jeffrey Fudin

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Therapeutics and Clinical Risk Management

Dovepress

open access to scientific and medical research

Open Access Full Text Article

REVIEW

Safe Use of Opioids in Chronic Kidney Disease and Hemodialysis Patients: Tips and Tricks for Non-Pain Specialists

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management

Opioid	Physico-Chemical Properties [40]			Metabolism [39]	Elimination [39]
	Vd (L/kg)	PPB (%)	MW (g/mol)		
Morphine sulphate	3.2	35	758.8	Phase 2 metabolism via glucuronidation by UGT2B7 (90%) to: -M3G without analgesic activity, but possibly neurotoxic -M6G with analgesic activity. Minor conversion to normorphine.	70–80% excreted in the urine 10% excreted in the feces <10% excreted in urine as unchanged drug.
Codeine	2.6	7	406.4	Phase 2 metabolism via glucuronidation by UGT2B7 and UGT2B4 (80%) to C6G Phase 1 metabolism: -via CYP3A4 (N-demethylation) to norcodeine (10%) without analgesic properties -via CYP2D6 (O-demethylation) to morphine (5–10%)	90% excreted by kidneys 10% excreted in urine as unchanged drug.
Buprenorphine	8.3	96	467.6	Extensive first-pass hepatic metabolism. Phase 1 metabolism via CYP3A4 and CYP3A5 to norbuprenorphine. Phase 2 metabolism via glucuronidation to the inactive compounds B3G and N3G	Metabolites are primarily eliminated via feces. Only 10–30% of the dose is excreted in urine.
Fentanyl citrate	4	80–85	336.5	Extensive hepatic metabolism into inactive metabolites. Phase 1 metabolism via CYP3A4 to norfentanyl (99%)	<7% excreted unchanged in the urine. <1% excreted unchanged in the feces.
Hydromorphone hydrochloride	1.22	7.1	321.8	Extensive first-pass hepatic metabolism (62%) Phase 2 metabolism: Glucuronidation via UGT2B7 to H3G with no analgesic activity (possibly causes neuroexcitation, agitation, and confusion) Minor Phase 1 metabolism via CYP3A4 and CYP2C9 to norhydromorphone	Mainly eliminated through the urine as H3G. 7% excreted unchanged in the urine. 1% excreted unchanged in the feces.
Oxycodone hydrochloride	2.6	45	405.9	Phase 1 metabolism: -via CYP3A4 and CYP3A5 (N-demethylation) to noroxycodone, and then via CYP2D6 to noroxymorphone -via CYP2D6 (O-demethylation) to oxymorphone, and then via CYP3A4 to noroxymorphone	Mainly eliminated through the urine: 23% unbound noroxycodone 10% conjugated oxymorphone 9% free and conjugated oxycodone <1% oxymorphone
Tramadol	3	20	299.8	Extensive first-pass hepatic metabolism Phase 1 metabolism: -via CYP3A4 and CYP2B6 (N-demethylation) to N-desmethyl-tramadol (M2) -via CYP2D6 (O-demethylation) to O-desmethyltramadol (M1)	90% excreted in the urine (30% as unchanged drug) 10% excreted in the feces
Tapentadol hydrochloride	6.7	20	221.3	Phase 2 metabolism via glucuronidation (97%). Minor contribution of Phase 1 metabolism via CYP2C9 (13%) to N-desmethyl tapentadol and CYP2D6 (2%) to hydroxyl tapentadol. All metabolites are inactive.	99% renal excretion of tapentadol and its metabolites. 3% excreted in urine as unchanged drug.
Methadone	2–6	60–90	309.5	Extensive first-pass hepatic metabolism into inactive metabolites. N-demethylation Metabolism by different CYP450 enzymes: CYP2C19, CYP3A7, and CYP2C8 preferentially metabolize (R)-methadone; CYP2B6, CYP2D6, and CYP2C18 preferentially metabolize (S)-methadone; CYP3A4 does not have an enantiomer preference	Excreted in the feces and urine after extensive biotransformation. 20% excreted unchanged in the urine.

Abbreviations: Vd, volume of distribution; PPB, plasma protein binding; WS, water solubility; MW, molecular weight; B3G, buprenorphine-3-glucuronide; N3G, norbuprenorphine-3-glucuronide; H3G, hydromorphone-3-glucuronide; H6G, hydromorphone-6-glucuronide; C6G, codeine-6-glucuronide.
Notes: Green: safe use in CKD; Yellow: use with caution in CKD; Orange: not recommended in CKD

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Buprenorphine and Efficacy

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Spoiler …

Annals of Internal Medicine®

Clinical Guidelines | 14 February 2023

The Use of Opioids in the Management of Chronic Pain: Synopsis of the 2022 Updated U.S. Department of Veterans Affairs and U.S. Department of Defense Clinical Practice Guideline FREE

Authors: Friedhelm Sandbrink, MD, Jennifer L. Murphy, PhD, Melanie Johansson, MD, Juli L. Olson, DC, DACM, Ellen Edens, MD, MPE, Jamie Clinton-Lont, MSN, AGPCNP-BC, James Sall, PhD, and Christopher Spevak, MD, MPH, JD VA/DoD Guideline Development Group | AUTHOR, ARTICLE, & DISCLOSURE INFORMATION

Recommendations:

This guideline is intended for clinicians who may be considering opioid therapy to manage patients with chronic pain. This synopsis reviews updated recommendations for the initiation and continuation of opioid therapy; dose, duration, and taper of opioids; screening, assessment, and evaluation; and risk mitigation. New additions are highlighted, including recommendations about the use of buprenorphine instead of full agonist opioids; assessing for behavioral health conditions and factors associated with higher risk for harm, such as pain catastrophizing; and the use of pain and opioid education to reduce the risk for prolonged opioid use for postsurgical pain.

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Br. J. Pharmac. (1977), **60**, 547–554

THE ANIMAL PHARMACOLOGY OF BUPRENORPHINE, AN ORIPAVINE ANALGESIC AGENT

A. COWAN[1], J.C. DOXEY & E.J.R. HARRY
Department of Pharmacology, Reckitt & Colman, Dansom Lane, Kingston-upon-Hull HU8 7DS

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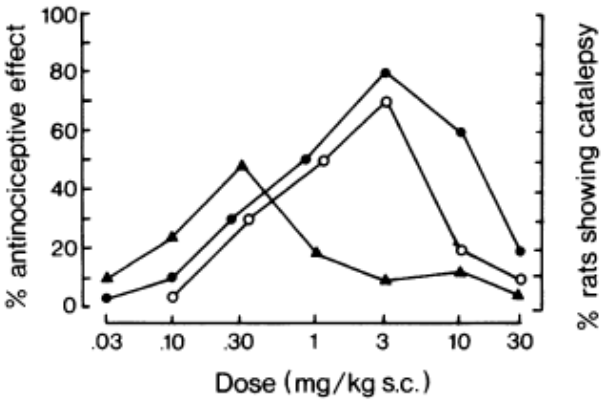
Br. J. Pharmac. (1977), **60**, 537–545

AGONIST AND ANTAGONIST PROPERTIES OF BUPRENORPHINE, A NEW ANTINOCICEPTIVE AGENT

A. COWAN[1], J.W. LEWIS & I.R. MACFARLANE
Department of Pharmacology, Reckitt & Colman, Dansom Lane, Kingston-upon-Hull HU8 7DS



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Journal of Clinical Pharmacy and Therapeutics
Journal of Clinical Pharmacy and Therapeutics, 2014 doi: 10.1111/jcpt.12196

Commentary

The clinical analgesic efficacy of buprenorphine

R. B. Raffa* PhD, M. Haidery* PharmD, H.-M. Huang* PharmD, K. Kalladeen* PharmD, D. E. Lockstein* PharmD, H. Ono* PharmD, M. J. Shope* PharmD, O. A. Sowunmi* PharmD, J. K. Tran* PharmD and J. V. Pergolizzi†‡§ Jr MD
Temple University School of Pharmacy, Philadelphia, PA, †Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, ‡Department of Anesthesiology, Georgetown University School of Medicine, Washington, DC, and §Department of Pharmacology, Temple University School of Medicine, Philadelphia, PA, USA

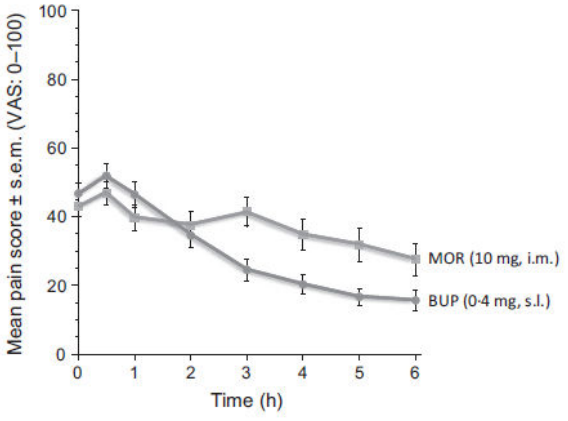

Fig. 2. The analgesic efficacy of s.l. buprenorphine (0·4 mg) was compared with that of i.m. morphine (10 mg) in a randomized, double-blind study of post-op pain of 101 patients (mean age: 40–45 years). Pain was measured using a 10-cm pain scale (0 = none, 10 = as much as imaginable). Buprenorphine produced the same pain relief as did morphine during the first 2 h and modestly greater pain relief from 2 to 6 h. Redrawn from Edge *et al.*[22]

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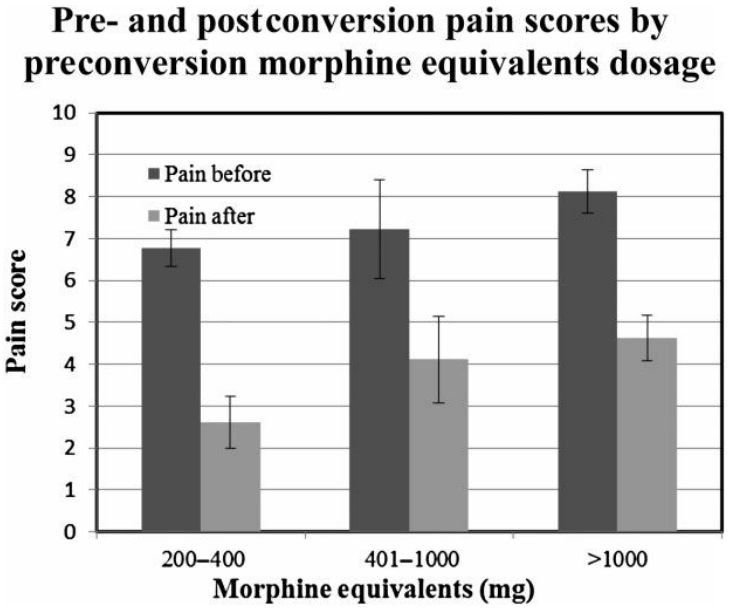

Daitch, D et al. *Conversion from High-Dose Full-Opioid Agonists to Sublingual Buprenorphine Reduces Pain Scores and Improves Quality of Life for Chronic Pain Patients. Pain* Medicine 2014

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Pain 118 (2005) 15–22

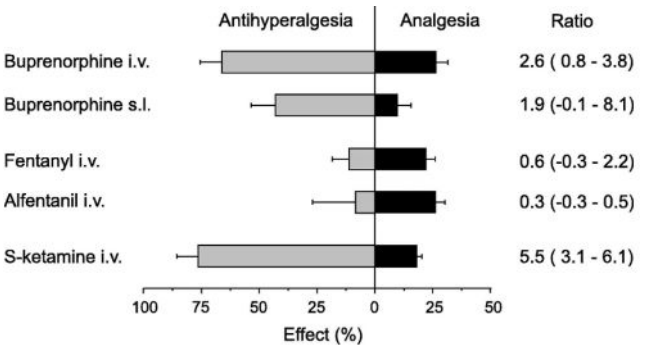
PAIN

www.elsevier.com/locate/pain

Research papers

Different profiles of buprenorphine-induced analgesia and antihyperalgesia in a human pain model

Wolfgang Koppert[a,*], Harald Ihmsen[a], Nicole Körber[a], Andreas Wehrfritz[a], Reinhard Sittl[a], Martin Schmelz[b], Jürgen Schüttler[a]



Ratios of antihyperalgesic and analgesic effects after application of the respective medication, based on the areas under the curve of the individual ratings ($AUC_{antihyperalgesia}/AUC_{analgesia}$). The data for fentanyl, alfentanil and S-ketamine are re-analyzed from previous studies (Koppert et al., 2001; Tröster et al., 2004). Data are expressed as mean and SD (n=12–15 each).

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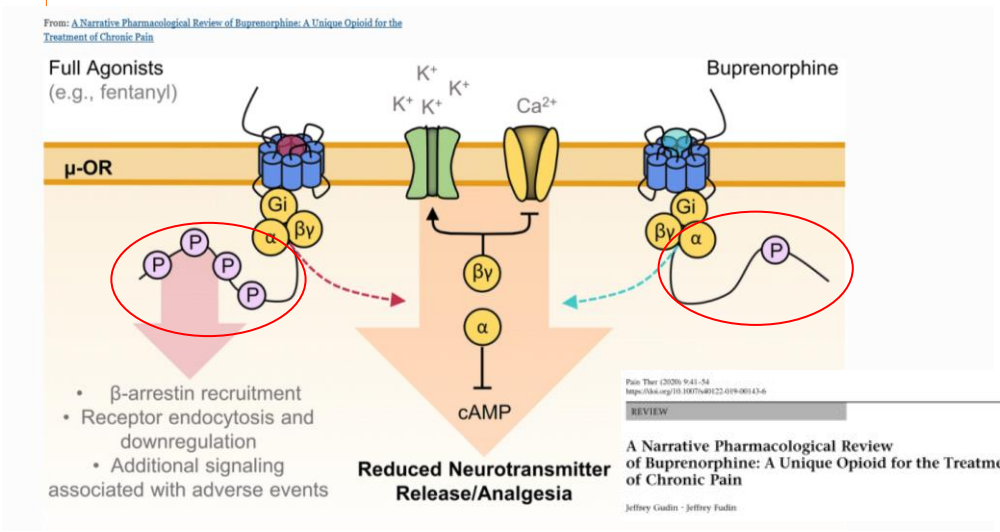
Buprenorphine tolerance



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Buprenorphine Versatility

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Buprenorphine Formulations

Formulation	Dose range	Brand/Generic	FDA approval
Transdermal	5-20 mcg/hr (120-480 mcg/day)	Generic	Pain
Transbuccal	75 -900 mcg (150-1800 mcg per day)	Brand	Pain
Sublingual	2-8 mg 1-32 mg per ay	Generic	Opioid Use Disorder

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Perioperative Concerns

22

Spoiler…..

BJA

British Journal of Anaesthesia, 123 (2): e333–e342 (2019)

doi: 10.1016/j.bja.2019.03.044
Advance Access Publication Date: 29 May 2019
Special Article

Perioperative Pain and Addiction Interdisciplinary Network (PAIN) clinical practice advisory for perioperative management of buprenorphine: results of a modified Delphi process

Akash Goel[1,2], Saam Azargive[1,3], Joel S. Weissman[2,4], Harsha Shanthanna[5], John G. Hanlon[1], Bana Samman[1], Mary Dominicis[1], Karim S. Ladha[1], Wiplove Lamba[6], Scott Duggan[3], Tania Di Renna[1], Philip Peng[1], Clinton Wong[7], Avinash Sinha[8], Naveen Eipe[9], David Martell[10], Howard Intrater[11], Peter MacDougall[9], Kwesi Kwofie[12], Mireille St-Jean[13], Saifee Rashiq[14], Kari Van Camp[15], David Flamer[1], Michael Satok-Wolman[15] and Hance Clarke[1,15,*]

The major recommendation of this practice advisory is:

- to continue buprenorphine therapy in the perioperative period.
- It is rarely appropriate to reduce the buprenorphine doseirrespective of indication or formulation.
- If analgesia is inadequate after optimization of adjunct analgesic therapies, we recommend initiating a full mu agonist while continuing buprenorphine at some dose

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Binding affinity at the mu receptor

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A fine point…

Buprenorphine on top of another opioid is different than another opioid on top of buprenorphine.

Doses of buprenorphine particularly above 2 mg sl may precipitate withdrawal in patients on other opioids if few opioid receptors are available

Other opioids given on top of buprenorphine will bind at other open opioid receptors if available. They do not cause withdrawal and their effect is not blocked by buprenorphine

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Anaesth Intensive Care 2013; **41**: 222-230

Pain relief and opioid requirements in the first 24 hours after surgery in patients taking buprenorphine and methadone opioid substitution therapy

P. E. MACINTYRE*, R. A. RUSSELL†, K. A. N. USHER‡, M. GAUGHWIN§, C. A. HUXTABLE**

Department of Anaesthesia, Pain Medicine and Hyperbaric Medicine, Royal Adelaide Hospital, North Terrace, Adelaide, South Australia 5000, Australia

First 24-hour postoperative analgesic drugs given and duration of treatment

	All BOST patients, n=22	BOST given*, n=11	BOST not given*, n=11	All MOST patients, n=29	MOST given*, n=22	MOST not given*, n=7
PCA opioid ordered, %						
Morphine	22.7	18.2	27.3	75.9	68.2	100
Fentanyl	77.3	81.8	72.7	24.1	31.8	0
First 24-hour PCA morphine equivalents, mg (mean±SD)	200.3±128.6	155.2±135.5	245.5±109.3†	221.2±138.2	202.0±138.0	281.6±129.9
Paracetamol, %	100	100	100	100	100	100
NSAID, %	31.8	18.2	45.5	44.8	36.4	71.4
Ketamine infusion, %	63.6	27.3	100	58.6	54.5	71.4
Days requiring PCA (mean±SD)	3.4±2.6	2.2±1.4	4.6±3.0	3.51±2.38	2.7±1.6	6.0±2.8
Days requiring APS supervision (mean±SD)	4.5±3.3	3.0±1.7	5.9±3.9	5.1±3.4	4.0±2.5	8.7±3.4

* Given or not given on the first day after surgery. † The mean PCA morphine equivalent dose was significantly higher ($P=0.02$) in patients who did not receive buprenorphine the first day after surgery compared with those who did receive buprenorphine. BOST=buprenorphine opioid substitution therapy, MOST=methadone opioid substitution therapy, PCA=patient-controlled analgesia, SD=standard deviation, NSAID=non-steroidal anti-inflammatory drugs, APS=acute pain service.

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Thought Experiment: Can we design a more perfect opioid?

Safe	Effective	Versatile
No Respiratory depression	Highly Effective	NPO
Liver/kidney	No tolerance	Schedule III
Non-reinforcing	No Hyperalgesia	Large dose range
no dose adjustment for age		

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Clinical Concerns…

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Dose/Risk Separation

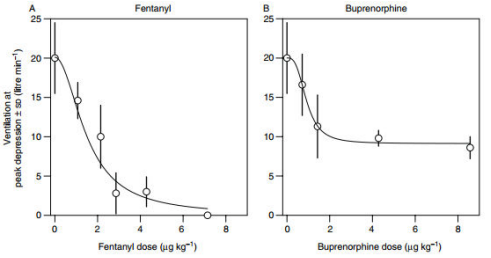
Respiratory depression is the primary dose limiting risk when using opioids

What happens when respiratory depression does not change with dose?

We can titrate to optimal dose rather than lowest effective dose.

allows patient to self select optimal dose

dose goes down over time in most cases



* This assumes buprenorphine is being used a sa single agent without other centrally acting drugs

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Equianalgesic Dosing

- Published equipotency charts are highly variable
- 1:25 to 1:100
- Buprenorphine acts at multilple receptors that may not be possible to affect with other opioids
- Some of buprenorphine's effect are anti-hyperalgesic not just analgesic
- Buprenorphine affects tolerance
- Proceed with caution

* This assumes buprenorphine is being used a sa single agent without other centrally acting drugs

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acta Anaesthesiologica Scandinavica
An international journal of anaesthesiology, intensive care, pain, and critical emergency medicine
SSAI

Comparison of the ventilatory effects of morphine and buprenorphine in children

K. HAMUNEN, K. T. OLKKOLA, E.-L. MAUNUKSELA

First published: July 1993 | https://doi.org/10.1111/j.1399-6576.1993.tb03744.x | Citations: 24

The decrease in ventilatory rate and acute change in the arteriolar oxygen saturation and the increase in end-tidal CO_2 levels were statistically significantly greater in magnitude and duration after buprenorphine than after morphine. For both drugs, the time, duration and magnitude of ventilatory changes varied appreciably between individuals. No child had apnea or hypoventilation requiring assistance.

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Buprenorphine and mood

Buprenorphine Completed Phase 3 Trials for Depression / Major Depressive Disorder (MDD) / Depressive Disorder Treatment

Back to Buprenorphine

INDICATIONS	STATUS	PURPOSE	PHASE
• DBCOND0018735 (Depression) • DBCOND0030181 (Major Depressive Disorder (MDD)) • DBCOND0024243 (Depressive Disorder)	Completed	Treatment	3

Show 10 entries Search

CLINICALTRIALS.GOV IDENTIFIER	TITLE	DRUGS
NCT01407575	Buprenorphine for Treatment Resistant Depression	• Buprenorphine (DB00921) • Naloxone (DB01183)

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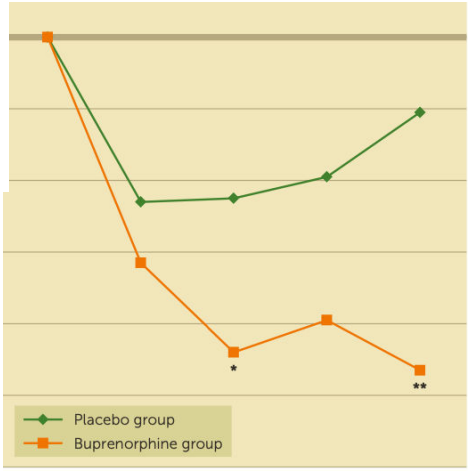
Buprenorhine and mood

Ultra-Low-Dose Buprenorphine as a Time-Limited Treatment for Severe Suicidal Ideation: A Randomized Controlled Trial

Yoram Yovell, M.D., Ph.D., Gali Bar, Ph.D., Moti Mashiah, M.D., Yehuda Baruch, M.D., Irina Briskman, M.D., Jack Asherov, M.D., Amit Lotan, M.D., Amihai Rigbi, Ph.D., Jaak Panksepp, Ph.D.



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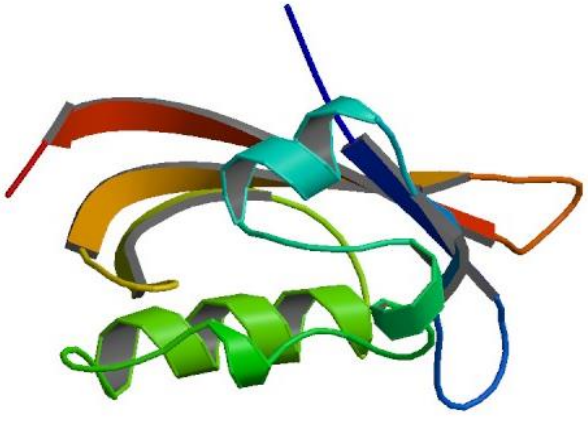
QT prolongation



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Medical Principles and Practice

Review

Med Princ Pract 2018;27:401–414
DOI: 10.1159/000492616

Received: October 22, 2017
Accepted: August 2, 2018
Published online: August 2, 2018

Opioids and Cardiac Arrhythmia: A Literature Review

Mina Behzadi[a] Siyavash Joukar[a, b] Ahmad Beik[b]

Significance of the Study

- Opioids are widely used throughout the world and statistics show that sales of prescription opioids in the United States nearly quadrupled from 1999 to 2014. One of the most common side effects of opioids is their influence on the electrical activity of the heart. In this review, results and reports from previous studies are investigated. We confirm that from the perspectives of prolongation of QT interval and arrhythmogenicity, opioids such as methadone even in low doses are high-risk drugs, tramadol and oxycodone show intermediate risk and opioids such as morphine and buprenorphine are low-risk drugs. This review may serve to increase the understanding of physicians and pharmacists regarding effects of opioids on heart electrical activity and their safety levels to decide on prioritizing the administration of these drugs in different patients, especially in opioid-dependent persons. It can also be a guide for students and researchers interested in studies on opioid drugs.

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New FDA statement on QT prolongation

- **5.14 QTc Prolongation**
- Thorough QT studies with buprenorphine products have demonstrated QT prolongation ≤ 15 msec. This QTc prolongation effect does not appear to be mediated by hERG channels. Based on these two findings, buprenorphine is unlikely to be pro-arrhythmic when used alone in patients without risk factors. The risk of combining buprenorphine with other QT-prolonging agents is not known.
- Consider these observations in clinical decisions when prescribing SUBUTEX to patients with risk factors such as hypokalemia, bradycardia, recent conversion from atrial fibrillation, congestive heart failure, digitalis therapy, baseline QT prolongation, subclinical long-QT syndrome, or severe hypomagnesemia.

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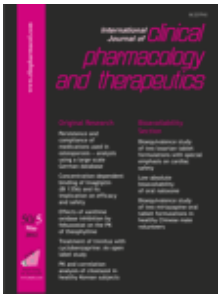
And what about Naloxone?

Low absolute bioavailability of oral naloxone in healthy subjects

Kevin Smith[1], Michael Hopp[2], Gill Mundin[1], Simon Bond[3], Paul Bailey[1], Jo Woodward[1], David Bell[4]



- Naloxone is an abuse deterrent only
- Full reversal dose is 1-2 mg
- Naloxone is 10% orally bioavailable if you take 0.5 you get 0.05 mg

International Journal of Clinical Pharmacology and Therapeutics, Volume 50 - May (360 - 367)

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Good things to Know

- You don't need a special license to prescribe for pain in any formulation
- Does not show up as opiates on standard toxicology screen. Must be ordered separately
- Patients often "forget" to take it
- Butrans™ and Belbuca ™ do not usually require abstinence due to low dose – the 2 mg rule of thumb

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"Few studies have compared buprenorphine to other opioids for the treatment of chronic pain. Even fewer data are available to guide clinicians on how pharmacologic, clinical, and patient characteristics may affect buprenorphine's effectiveness in treating chronic pain . . . Clearly, more research about formulation, dosing, and clinical characteristics will be crucial to guide buprenorphine treatment for chronic pain . . . this recommendation is exciting, but underdeveloped, and many questions about implementation remain."

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Questions or Comments:

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707-978-0163

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