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

BUPE2021

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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

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I have nothing to disclose

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Thought Experiment: Can we design a more perfect opioid?

Safe	Effective	Versatile
• No Respiratory depression • No Liver/kidney • Non-reinforcing • No dose adjustment for age	• Highly Effective/ Potent • No tolerance • No Hyperalgesia • Large dose range • Flexible with other medications	• NPO • Schedule III • Easy titration • Easy to stop • Generic

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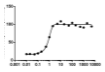
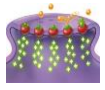
The mythology of buprenorphine…

It is just another opioid

It isn't analgesic



It has a ceiling effect



It blocks other opioids

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Myth #1: Buprenorphine is just another opioid

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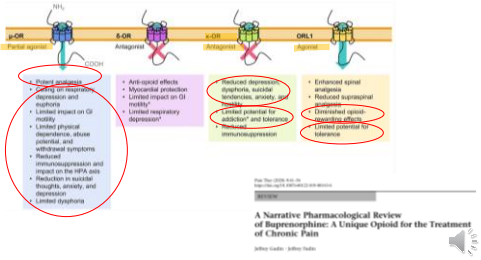
Buprenorphine is promiscuous



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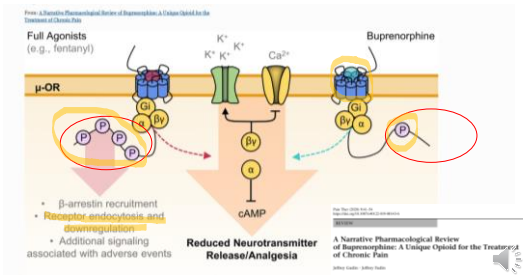
Buprenorphine binds differently



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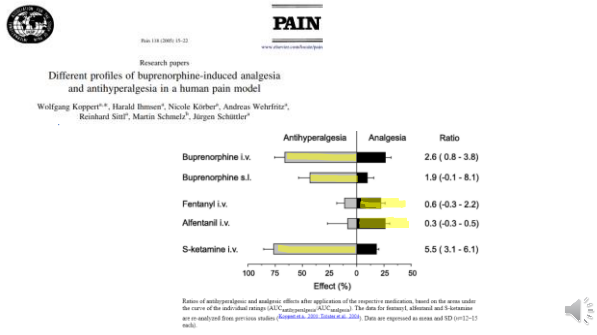

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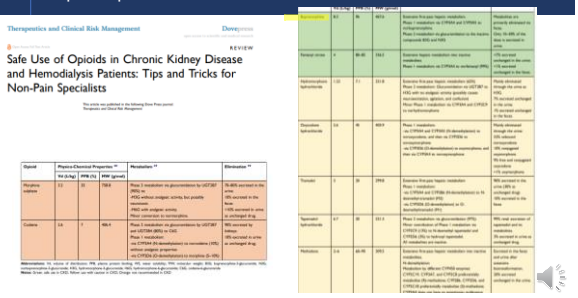
Buprenorphine metabolism



Therapeutics and Clinical Risk Management

REVIEW

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

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Thought Experiment: Can we design a more perfect opioid?

Safe	Effective	Versatile
• No Respiratory depression ☆ Liver/kidney ★ Non-reinforcing ★ No dose adjustment for age	• Highly Effective/Potent ★ No tolerance ★ No Hyperalgesia • Large dose range • Flexible with other medications	• NPO • Schedule III • Easy titration • Easy to stop • Generic

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Myth #2: Buprenorphine isn't (a very good) analgesic

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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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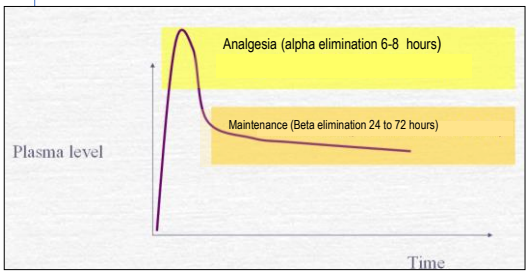
Buprenorphine has a double (half) life



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Formulations of Buprenorphine

- Transdermal Butrans™ Patch (generic)
- Transbuccal Belbuca™ lozenge
- Sublingual tablet and film Suboxone™ and Subutex™ (generic)
- Marketed in high dose form for OUD in the US since 2003



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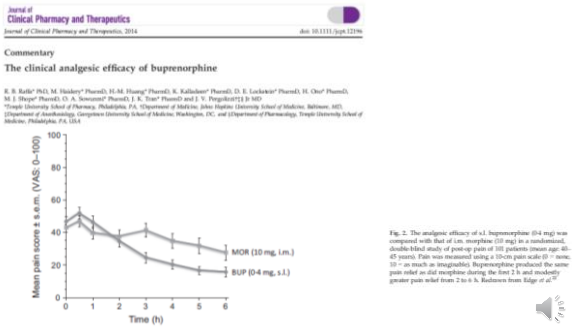

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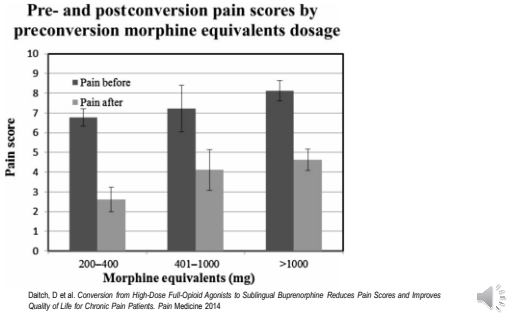

Daitch, D et al. *Conversion from High-Dose Full-Opioid Agonists to Sublingual Buprenorphine Reduces Pain Scores and Improves Quality of Life for Chronic Pain Patients. Pain* Medicine 2014

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GAP 4: Barriers include lack of coverage and reimbursement for buprenorphine as well as the lack of education and training on the proper usage of buprenorphine. There has been a lack of access to buprenorphine treatment for chronic pain.

- RECOMMENDATION 4A: Make buprenorphine treatment for chronic pain available for specific groups of patients, and include buprenorphine in third-party payer and hospital formularies.
- RECOMMENDATION 4B: Encourage CMS and private payers to provide coverage and reimbursement for buprenorphine treatment, both for OUD and for chronic pain. Encourage primary use of buprenorphine rather than use only after failure of standard mu agonist opioids such as hydrocodone or fentanyl, if clinically indicated.
- RECOMMENDATION 4C: Encourage clinical trials using buprenorphine for chronic pain to better understand indication, usage, and dosage.

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Thought Experiment: Can we design a more perfect opioid?

Safe	Effective	Versatile
• No Respiratory depression ★ Liver/kidney ☆ Non-reinforcing ★ No dose adjustment for age	★ Highly Effective ★ No tolerance ★ No Hyperalgesia ★ large dose range • Flexible with other medications	★ NPO ★ Schedule III ★ Easy titration • Easy to stop ☆ Generic

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Myth #3: Buprenorphine has a Ceiling Effect

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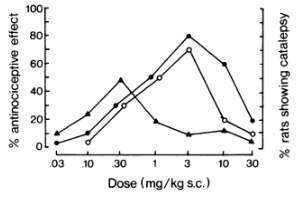
Br. J. Pharmac. (1977), **60**, 537–545

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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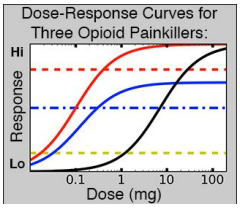
Ceiling Effect



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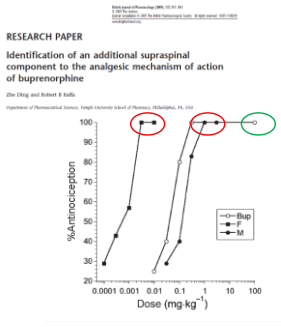

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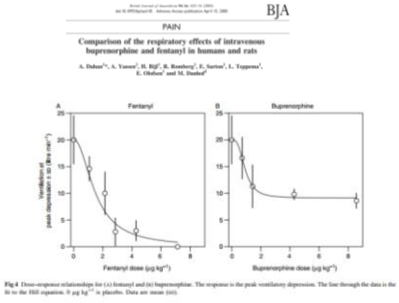

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Thought Experiment: Can we design a more perfect opioid?

Safe	Effective	Versatile
☆ No Respiratory depression	★ Highly Effective	★ NPO
☆ Liver/kidney	★ No tolerance	★ Schedule III
★ Non-reinforcing	★ No Hyperalgesia	★ Easy titration
★ no dose adjustment for age	★ large dose range	• Easy to stop
	• flexible with other medications	☆ Generic

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Myth #4: Buprenorphine blocks other opioids

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Concept: Opioid Blocking

"While patients are taking opioid pain medications, the administration of buprenorphine generally should be discontinued. Note that until buprenorphine clears the body, it may be difficult to achieve analgesia with short-acting opioids."

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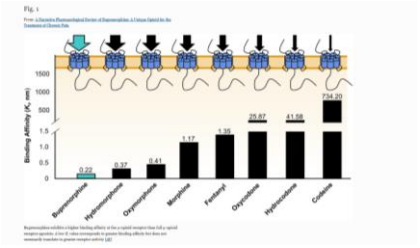

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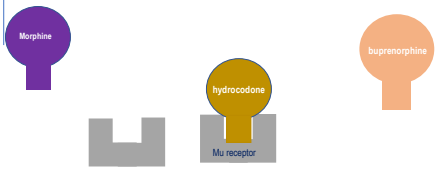
Binding affinity at the mu receptor



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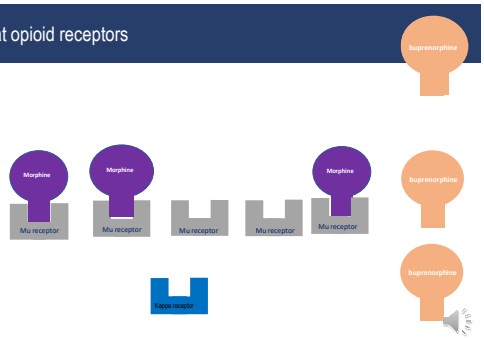
Binding affinity at opioid receptors



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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: 333-340

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	195.2±185.7	145.5±100.3†	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	72.7	100	58.6	54.5	71.4
Days requiring PCA (mean±SD)	3.4±2.6	3.5±1.8	4.8±3.0	3.5±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±4.9	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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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 Azargoo[1,3], Joel S. Weissman[1,4], Harsha Shanthanna[1], John G. Hanlon[1], Rana Samman[1], Mary Dominicis[1], Karim S. Ladha[1], Wiplove Lamba[1], Scott Duggan[1], Tania Di Renna[1], Philip Peng[1], Clinton Wong[1], Avinash Sinha[1], Steven Epe[1], David Martell[1], Howard Intrater[1], Peter MacDougall[1], Kwesi Kwofie[1], Mireille St-Jean[1], Saifee Rashiq[1], Karl Van Camp[1], David Fisher[1], Michael Satok-Wolman[1] and Hance Clarke[1,2,*]

The major recommendation of this practice advisory is:

- to continue buprenorphine therapy in the perioperative period.
- It is rarely appropriate to reduce the buprenorphine dose
- irrespective 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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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	Easy titration
no dose adjustment for age	large dose range	Easy to stop
	flexible with other medications	Generic

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A few other things to know…

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What about Stopping Buprenorphine?

- Buprenorphine is relatively easy to taper down
- Buprenorphine can be hard to discontinue from high dose and usually requires other formulations to get off
- Rarely people can not tolerate being off buprenorphine

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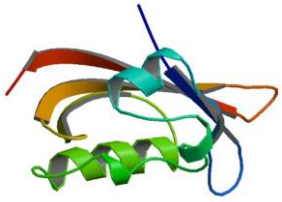
QT prolongation



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Medical Principles and Practice

Review

Opioids and Cardiac Arrhythmia: A Literature Review

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

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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What Is the Opiate Blocker in Suboxone?

By Robert Samora, eHow Contributor last updated June 26, 2013

Suboxone is a drug used mostly in the treatment of opiate addiction. Suboxone is the combination of two other drugs (naloxone and buprenorphine) to reduce the withdrawal symptoms of opiate addiction and to block the effects of any opiates used at the same time. Have a question? Get an answer from a doctor now!

Naloxone

Naloxone is the opiate blocker in Suboxone. When naloxone is being used, it stops the effects of opiates (such as euphoria).

Buprenorphine

Buprenorphine, the other component in Suboxone, reduces withdrawal symptoms (such as sweating and insomnia) and opiate cravings. It creates similar effects to opiates (like morphine), but without euphoria.

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And what about Naloxone?

Low absolute bioavailability of oral naloxone in healthy subjects

Kevin Smith, Michael Hopp, Gil Mundin, Simon Bondi, Paul Bailey, Jo Woodward, David Jett

- 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.
- Patients often "forget" to take it
- Patients dosing remains stable long term or decrease over time
- Butrans™ and Belbuca ™ do not usually require abstinence due to low dose
- Very hard to predict equianalgesic dose

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Questions or Comments:

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