# Buprenorphine update 2021

## Journal of Opioid Management

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www.bupe2021.com

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## Disclosures

- NO FINANCIAL
- Massachusetts General Hospital
  - MGH/Charlestown Monument Street Counseling Center
  - Pain Management Center at MGH (Anesthesiology DACCPM)
  - HOME BASE Veteran and Family Care (Medical Director)
- Harvard Medical School
  - Assistant Professor of Psychiatry
- Board Certified:
  - American Board of Anesthesiology (ABA)
  - American Board of Psychiatry and Neurology (ABPN)
  - ABPN – Addiction Psychiatry

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## Objectives

- Understand unique features of buprenorphine at the receptor/cellular level
- Apply this to clinical settings including:
  MOUD
  Perioperative/periprocedural settings
  Chronic Pain
  Acute Pain
- Realize competing goals of analgesia vs relapse prevention
- Discuss dose timing for best outcome given buprenorphine products
- Demonstrate some practical strategies and a guideline

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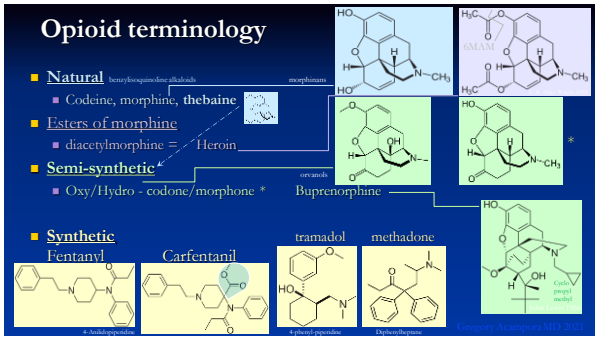
Opioid terminology
Natural
benzylisoquinoline alkaloids
morphinans
Codeine, morphine, thebaine
Esters of morphine
diacetylmorphine = Heroin
6MAM
Semi-synthetic
oripavols
Oxy/Hydro - codone/morphone *
Buprenorphine
Synthetic
Fentanyl
Carfentanil
tramadol
methadone
4-Anilidopiperidine
4-phenyl-piperidine
Diphenylheptane
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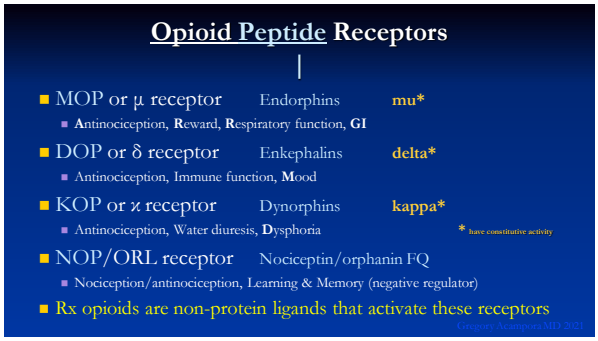
Opioid Peptide Receptors
MOP or μ receptor
Endorphins
mu*
Antinociception, Reward, Respiratory function, GI
DOP or δ receptor
Enkephalins
delta*
Antinociception, Immune function, Mood
KOP or κ receptor
Dynorphins
kappa*
Antinociception, Water diuresis, Dysphoria
* have constitutive activity
NOP/ORL receptor
Nociceptin/orphanin FQ
Nociception/antinociception, Learning & Memory (negative regulator)
Rx opioids are non-protein ligands that activate these receptors
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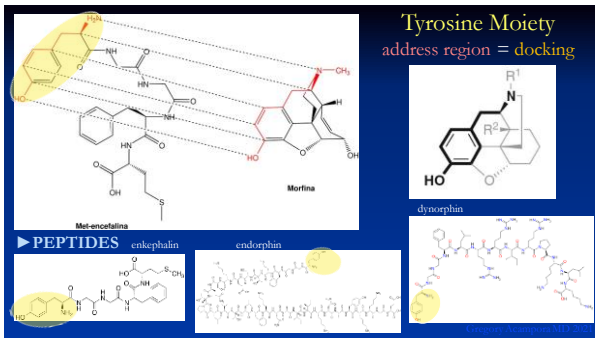
Tyrosine Moiety
address region = docking
Morfina
Met-encefalina
dynorphin
PEPTIDES
enkephalin
endorphin
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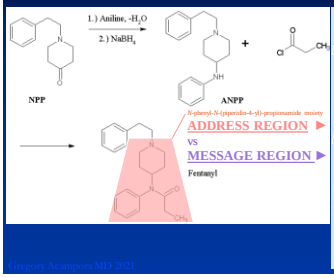
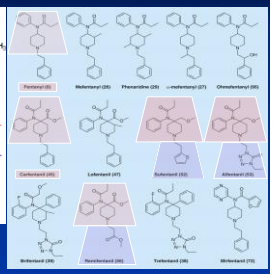
## NPP & ANPP precursor & "the fentanyls"

4-anilidopiperidine scaffold



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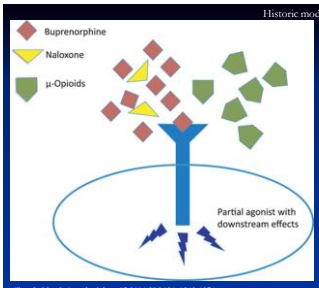
## Historic models




Chen L, Mao J; Anesthesiology 05 2014, Vol.120, 1262-1274

▲ [Competition] for the opioid receptor:

Binding affinity is a widely used measure of a drug's relative potency. However, published data for MOR binding affinity of clinically relevant opioid drugs are incomplete and often inconsistent, precluding the systematic ranking of binding affinity to this

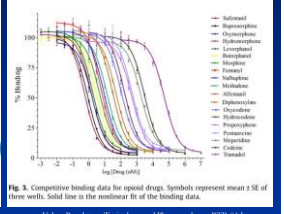



Fig. 3. Competitive binding data for opioid drugs. Symbols represent mean ± SE of three wells. Solid line is the nonlinear fit of the binding data.

Volpe: Regulatory Toxicology and Pharmacology : RTP; 06 Jan 2011, 59(3):383-390

▲IN VITRO!

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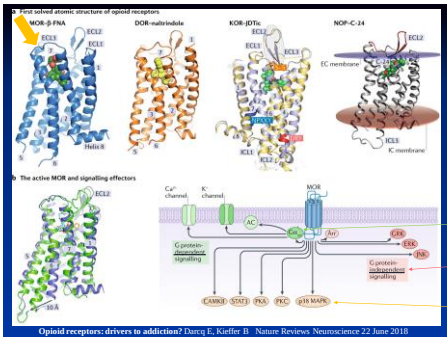


**Opioid receptors: drivers to addiction?** Darcq E, Kieffer B . Nature Reviews Neuroscience 22 June 2018

Folded seven-(pass)-transmembrane receptors:

- N-terminus (external)
- 3 ext and 3 int loops (Gα)
- C-terminus: prox (Gβγ)+ distal phos AAs

▲ PharmcoDynamics (PD)

Binding of **opioid** causes receptor phosphorylation: G-protein heterotrimer split: (Gα) inhibit adenylyl cyclase (Gβγ) modulate ion gates = **analgesia**

GRK & βarr2: internalization + proinflamm ("effectors") desensitization and redirection of signaling

Invokes intracellular response and ∆ CREB (DNAtxcept)

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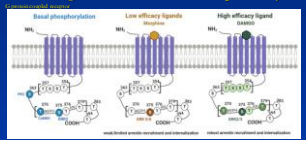
PharmcoKinetics (PK) leads to **At the receptor** PharmcoDynamics (PD)

- Molecular docking and formation of "strong or weak" bonds leads to:
  between the helices TM3 to TM7
- Phosphorylation of specific receptor amino acid residues (IL x 3, distal C-terminus) :
  - Via G protein, directly reduce AC and hyperpolarize ionophores blocking pain signal
  - Effectors: β-arrestin promotes receptor internalization blocking G protein
  - Regulators: intracellular redirection of signalling
- Rx opioids are GPCR ligands that affect these pathways variably !

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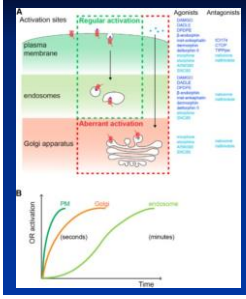
## Opioid Receptor signaling compartmentalization




Spatiotemporal Landscape of OR Activation in the Cell

- **Peptide** agonists (dark blue) drive a "**regular**" activation pattern, with two sequential waves of receptor activation, 1st in plasma membrane;
- ◄**then in endosomes following internalization of the receptor** "desensitized path"
- **Non-peptide** agonist (light blue) distorts this pattern by activating a ◄Golgi-localized internal OR pool (direct "**aberrant**" activation).

Stoeber et al., 2018, Neuron 98, 963–976 June 6, 2018 ª 2018 Elsevier Inc.
Van Gaalel Pharmacol., 28 November 2018

Distinct (SIGNAL BIAS) receptor compartmentalization and activation paths by peptide (dark blue) and non-peptide (light blue) antagonists

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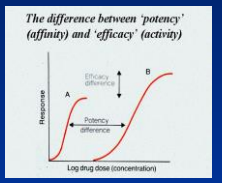
## Affinity Efficacy$_i$ Potency

- Affinity = ability to link and form bonds in receptor (PharmcoDynamics)
  - $(1/K_i)$ $K_i$ affinity constant is the opposite of $K_d$ dissociation constant
- Intrinisic Efficacy (ε) (PK + PD)
  - maximum **activity** regardless of dose
  - Affected by receptor density / reserve / SIGNAL BIAS
- Potency (PK/PD !)
  - amount needed to produce a given effect $EC_{50}/ED_{50}/Kd$




►Receptor binding and dissociation, individual molecule selectivity, potency, and intrinsic efficacy contribute to individual opioid pharmacodynamic profiles

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## Buprenorphine is unique ☺

- Highly lipophilic
- High binding affinity and long dwell time
- *LOW maximal "activity" (ε) (ε cyclo propyl methyl group positioning)
- BUP can produce analgesia with only 5–10% of receptors occupied
- Long acting analgesia from 8-12 hours despite $t_{1/2}$ 4-6 h
  - CNS Clearance is slower than plasma clearance, which accounts for the difference between plasma $t_{1/2}$ and the duration of analgesia
- Analgesia is largely mediated through mu receptors in the dorsal horn
- Reduced (no?) respiratory depression – resp depression comes from NorBUP

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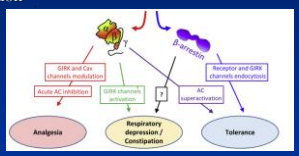
## Buprenorphine is uniquely unique

- BUP does not induce receptor internalization
- BUP does not induce desensitization
- μOR G protein/β-arrestin ratio = SIGNAL BIAS (leftward) ►




- HI G protein inhibition of AC and ionophores = **analgesia!**
- LOW β-arrestin recruitement = **limited respiratory depression & tolerance**
  - Buprenorphine failed to recruit β-arrestin-2 binding at doses of 10 Mm
  - Respiratory depression is likely due to NorBUP 3-G-NorBUP

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## How did we arrive at doses? MOUD vs analgesia?

- Buprenorphine was developed as "ideal opioid" for analgesia: (see 2019 ref)
  - adequate analgesia, limited side effects, limited tolerance
- Buprenorphine applications for MOUD as alternative to heroin or methadone overshadowed analgesia
- Partial antagonist profile deemed safer – initial dosing was up to 32mg/d
- Recent growing attention to treating ACUTE PAIN for those on MOUD
- OPIOID CRISIS
- Better understanding of μ opioid receptor function is explaining what was observed in lab and clinically: A MED WITH STRANGE QUALITIES

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## Opioid receptor availability vs ADDED BUP dose (Extrapolated from 2003 PET data)

[heroin dependent volunteers]

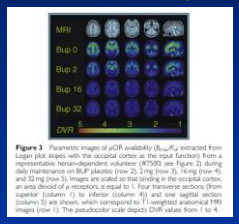
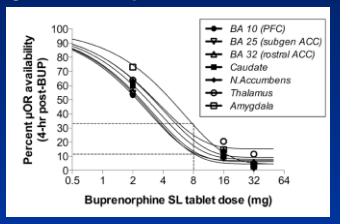



Figure 3 Parametric images of μOR availability ($B_{max}/K_d$ extracted from Logan plot slopes with the occipital cortex as the input function) from a representative heroin-dependent volunteer (#7500; see Figure 2) during daily maintenance on BUP placebo (row 2), 2 mg (row 3), 16 mg (row 4), and 32 mg (row 5). Images are scaled so that binding in the occipital cortex, an area devoid of μ receptors, is equal to 1. Four transverse sections (from superior (column 1) to inferior (column 4)) and one sagittal section (column 5) are shown, which correspond to T1-weighted anatomical MRI images (row 1). The pseudocolor scale depicts DVR values from 1 to 4.




Greenwald 2003 Greenwald et al. 2014



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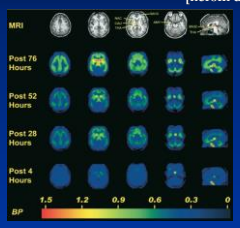
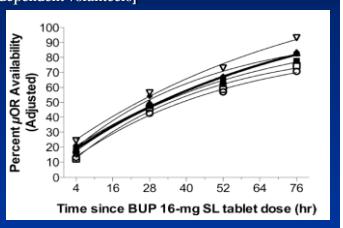
## Opioid receptor availability vs HELD BUP16 dose (Extrapolated from 2003 PET data)

[heroin dependent volunteers]




Greenwald 2007 Greenwald et al. 2014



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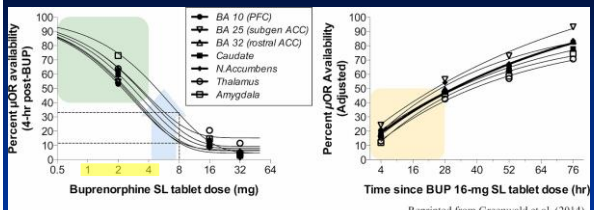
## [ 11 C]-carfentanil Positron Emission Tomography (PET)

Mathematical (simulated) estimation

in vivo μOR availability




Reprinted from Greenwald et.al. (2014)



Greenwald, *Drug Alcohol Depend.* 2014 November 1; 0: 1–11.



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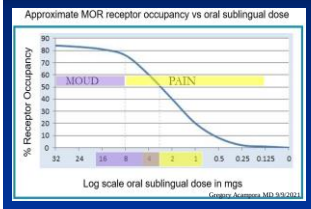
## BUP works best in an optimal range




- Protect OUD population from craving/relapse
  - ~75% occupied effectively eliminates euphoria [2-3 ng/ml]
  - ~50% occupied effectively eliminates crave/withdraw ~1 ng/ml
- Provides adequate analgesia with 10-60% occupied receptor
- Post OP GYN patients selected ~1000µg/d (IV PCA) for adequate pain relief Oda 2009
  - BUP SL equivalent = 3mg/d

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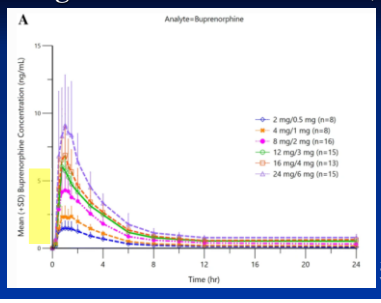
## Sublingual dose and serum levels (ng/ml)




Drugs in R&D (2019) **volume 19**, pages255–265

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## ZUBSOLV & BUNAVIL (BUP/NLX)

| Zubsolv sublingual tablets dosage strength | Corresponding Suboxone sublingual tablet dosage |
|---|---|
| 1.4 mg/0.36 mg | 2 mg/0.5 mg |
| 5.7 mg/1.4 mg | 8 mg/2 mg |
| 8.6 mg/2.1 mg | 12 mg/3 mg |
| 11.4 mg/2.9 mg | 16 mg/4 mg |

| Bunavil buccal film dosage strength | Corresponding Suboxone sublingual tablet dosage strength |
|---|---|
| 2.1 mg/0.3 mg | 4 mg/1 mg |
| 4.2 mg/0.7 mg | 8 mg/2 mg |
| 6.3 mg/1 mg | 12 mg/3 mg |

- Bunavil ® film provides **greater bioavailability by unidirectional mucoadhesive structure**
- Bunavil ® **Duration is longer and may be due to buccal fat reservoir**
- The buccal patch is associated with reduced constipation thought to be due to reduced norbuprenorphine plasma levels

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## BELBUCA & BUTRANS (BUP only)

- Dosage forms: 75, 150, 300, 450, 600, 750, 900mcg (1000mcg = 1mg)

**Table 1. Buprenorphine Plasma Pharmacokinetic Parameters (mean±SD)**

| | BUP-121 60 µg | BUP-117 75 µg | BUP-117 300 µg | BUP-117 300 µg | BUP-115 500 µg | BUP-118 900 µg | BUP-120 900 µg | BUP-117 1200 µg |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | BUP |
| Cmax (ng/mL) | 0.07± 0.02 | 0.17±0.30 | 0.37±0.10 | 0.47±0.47 | 0.55±0.12 | 1.32±0.41 | 1.36±0.42 | 1.43±0.45 |

50-60% bioavailability FDA.gov

BUTRANS

- Dosage forms: 5, 7.5, 10, 15, 20mcg/hour transdermal patch
- BUTRANS IS NOT TO BE USED FOR OUD

| Single 7-day Application | AUC$_{0-t}$ (pg.h/mL) | $C_{max}$ (pg/mL) |
|---|---|---|
| BUTRANS 5 mcg/hour | 12087 (37) | 176 (67) |
| BUTRANS 10 mcg/hour | 27035 (29) | 191 (34) |
| BUTRANS 20 mcg/hour | 54294 (36) | 471 (49) |
| **Multiple 7-day Applications** | **AUC$_{TAU,ss}$ (pg.h/mL)** | **$C_{max,ss}$ (pg/mL)** |
| BUTRANS 10 mcg/hour, steady-state | 27543 (33) | 224 (35) |

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## SUBLOCADE I

| Pharmacokinetic parameters | SUBUTEX daily stabilization | | SUBLOCADE | | |
|---|---|---|---|---|---|
| Mean | 12 mg (steady-state) | 24 mg (steady-state) | 300 mg# (1st injection) | 100 mg* (steady-state) | 300 mg* (steady-state) |
| $C_{max,ss}$ (ng/mL) | 1.71 | 2.91 | 2.19 | 3.21 | 6.54 |
| $C_{max,ss}$ (ng/mL) | 5.35 | 8.27 | 5.37 | 4.88 | 10.12 |
| $C_{min,ss}$ (ng/mL) | 0.81 | 1.54 | 1.25 | 2.48 | 5.01 |

After inj, peak and median $T_{max}$ occurred at 24h The plasma buprenorphine concentrations decreased slowly to a plateau. Steady-state was achieved at **4-6 months**. Observed mean buprenorphine concentrations levels for $C_{avg}$, $C_{max}$ and $C_{min}$ are presented in Table

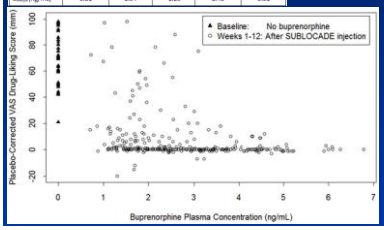


Figure Drug Liking VAS vs. Plasma [BUP] after 18 mg Hydromorphone INJ.

Withdrawal symptoms were controlled corresponding to plasma levels = 1 ng/ml

Subjective effects of exogenous opioid agonist controlled when 70-80%+ µOR were occupied plasma levels = 2.3 ng/ml These results were pivotal in defining target buprenorphine plasma concentrations of at least 2-3 ng/ml, which drove the clinical development of BUP-XR

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209819s012lbl.pdf

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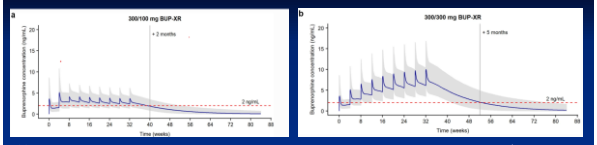
## SUBLOCADE II




The data indicate that administration of 2 monthly doses of 300 mg followed by 100 mg monthly (300/100-mg dosing regimen) achieved target concentrations of 2 ng/mL from the first injection. From the second injection onwards, plasma concentrations were sustained above 2 ng/mL over the entire treatment duration in the majority of subjects. Administration of 300 mg monthly (300/300-mg dosing regimen) provided higher buprenorphine plasma concentrations in the range of 5-10 ng/ml

PLEASE NOTE TIME TO 2ng/ml upon cessation of depot: 2m (300/100) vs 5m (300/300)

Clin Pharmacokinet **60**, 2021 527–540

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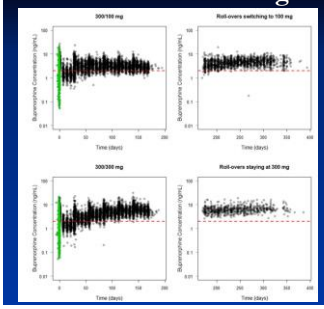
## Note range variability




**Top panel**: 300/100 mg of BUP-XR in Study 2 (tablet run-in) and 300/100-mg roll-over subjects after they received one or multiple subcutaneous injections of 100 mg of BUP-XR
**Bottom panel**: 300/300 mg of BUP-XR in Study 2 and 300/300-mg roll-over subjects who remained taking 300 mg of BUP-XR in Study 3 (film run-in).
Rollovers: Study 2 participants who were enrolled in Study 3.
Concentrations measured after sublingual dosing during the run-in are shown in green; concentrations measured after BUP-XR dosing are shown in black.
The horizontal red dashed line indicates **2 ng/mL**

Clin Pharmacokinet **60,** 2021 527–540

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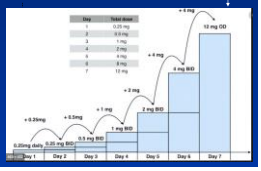
## Clinical "pearls"

- Analgesic vs MOUD dose targets are strategically different!
- You can add FAO ► BUP
- You must START low when adding BUP ► FAO – think "Bernese"
- AVOID high dose BUP vs FAO battle (resp depr)
- PAY ATTENTION TO DOSE TIMING !
- Small doses of BUP go a long way for ANALGESIA
- There is a pain-place for BUP de novo
- NorBUP shouldn't be ignored
- Don't forget adjuvants

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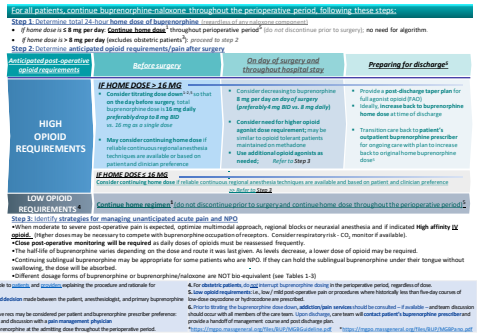
Mass General Brigham

**Figure 1.**
**MGB** Recommendations for the **Perioperative Management of Home Buprenorphine-Naloxone** (Suboxone®) and other buprenorphine

Modified ACAMPORA 10.13.2021

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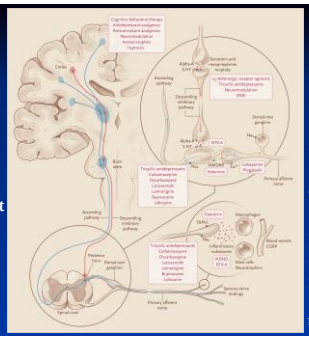
**Cortex**
CBT, SNRI, AED
Acetaminophen,
Neuromodulation

**Spinal Cord & Primary Afferent**
Lamotrigine,
Oxcarbazepine, TCA,
Tizanidine
Bupivacaine, Lidocaine



NON-OPIOID ANALGESICS & LOCI

**Pre & Post Synaptic**
Tizanidine, TCA, SNRI
Gabapentinoids
Ketamine
Capsaicin
Botulinum Toxin
Neuromodulation

N Engl J Med 2019;380:2440-8.



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## References 2021


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- Treating chronic pain — Drugs. 2018 August ; 78(12): 1211–1228
- BUP unique — Pain Ther (2020) 9:4154 doi.org/10.1007/s40122-019-00143-6
- Good Synopsis — Pain Ther (2020) 9:41–54 doi.org/10.1007/s40122-019-00143-6
- SUBUTEX — Clin Pharmacokinet **60,** 2021 527–540 doi.org/10.1007/s40262-020-00939
- Cellular Signaling — Cell Signal 2021 Apr;80
- *https://mgpo.massgeneral.org/files/BUP/MGBGuideline.pdf
  *https://mgpo.massgeneral.org/files/BUP/MGBPano.pdf


You can contact me: gacampora@mgh.harvard.edu

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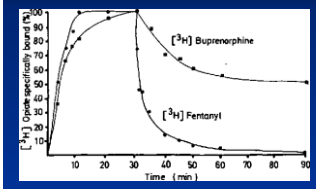
## Fentanyl is "potent" but note FAST offset




- This graph is edifying. Synthetic opioids have very high affinity but Fentanyl "dwell" time is limited
- FAST OFFSET can be felt as triggering!
- PK/PD!



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