Buprenorphine update 2021
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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)
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  ■ Board Certified:
    ■ American Board of Anesthesiology (ABA)
    ■ American Board of Psychiatry and Neurology (ABPN)
    ■ ABPN – Addiction Psychiatry

Objectives
◼ Understand unique features of buprenorphine at the receptor/cellular level
◼ Apply this to clinical settings including:
  MOUD
  Perioperative/postprocedural 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
Opioid terminology

- Natural
  - Codeine, morphine, thebaine
- Esters of morphine
  - diacetylmorphine = Heroin
- Semi-synthetic
  - Oxy/Hydro - codeine/morphine + Buprenorphine
- Synthetic
  - Carfentanil, tramadol, methadone, fentanyl, carfentanil

**Opioid Peptide Receptors**

- MOP or μ receptor: Endorphins, μ*
  - Antinociception, Reward, Respiratory function, GI
- DOP or δ receptor: Enkephalins, δ*
  - Antinociception, Immune function, Mood
- KOP or κ receptor: Dynorphins, κ*
  - Antinociception, Water diuresis, Dysphoria
- NOP/ORL receptor: Nociceptin/orphanin FQ
  - Nociception/antinociception, Learning & Memory (negative regulator)

Rx opioids are non-protein ligands that activate these receptors

Tyrosine Moiety

Address region = docking

PEPTIDES: enkephalin, endorphin, dynorphin
NPP & ANPP precursor & “the fentanylls”

4-anilidopiperidine scaffold

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Historic models

Opioid receptors: drivers to addiction?

Darcq E, Kieffer B   Nature Reviews Neuroscience 22 June 2018

PharmacoDynamics (PD)

Binding of opioid causes

- Receptor phosphorylation
- G protein heterotrimer split
- 

Invokes intracellular response and Δ CREB (DNA transcrip)
At the receptor

PharmcoKinetics (PK) leads to

- Molecular docking and formation of “strong or weak” bonds leads to:
  - Phosphorylation of specific receptor amino acid residues
- Via G protein, directly reduce AC and hyperpolarize ionophores
- Effector: β-arrestin promotes receptor internalization; blocking G protein
- Regulators: intracellular inhibition of signaling

Rx opioids are GPCR ligands that affect these pathways variably!

Opioid Receptor signaling compartmentalization

Spatialtemporal 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
- Non-peptide agonists (light blue) distort this pattern by activating a Golgi-localized internal OR pool ("aberrant" activation)

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

Affinity  Efficacy  Potency

- **Affinity** = ability to link and form bonds in receptor
  - $K_a$: affinity constant is the opposite of $K_d$, dissociation constant

- **Intrinsic Efficacy** (ε) (PK + PD)
  - maximum activity regardless of dose
  - Adjusted by receptor density / reserve / SIGNAL BIAS

- **Potency** (PK/PD)
  - amount needed to produce a given effect
  - EC50/ED50

Receptor binding and dissociation, individual molecule selectivity, potency, and intrinsic efficacy contribute to individual opioid pharmacodynamic profiles
**Buprenorphine is unique**

- Highly lipophilic
- High binding affinity and long dwell time
- LOW maximal “activity” (ε cyclopropyl 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

**Buprenorphine is uniquely unique**

- BUP does not induce receptor internalization
- BUP does not induce desensitization
- µ OR G protein/β-arrestin ratio
  - SIGNAL/MAINS (leftward) ►

- HI G protein inhibition of AC and ionophores = analgesia!
- LOW β-arrestin recruitment = limited respiratory depression & tolerance
- Buprenorphine failed to recruit β-arrestin-2 binding at doses of 10 μm
- Respiratory depression is likely due to NorBUP, not BUP

**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
Opioid receptor availability vs ADDED BUP dose
(Extrapolated from 2003 PET data)
[heroin dependent volunteers]

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

Greenwald et al. 2014

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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
  - BUP SL equivalent = 3 mg/d

Sublingual dose and serum levels (ng/ml)

- Corresponding Suboxone sublingual tablet dosage

<table>
<thead>
<tr>
<th>ZUBSOLV &amp; BUNAVIL (BUP/NLX)</th>
<th>Corresponding Suboxone sublingual tablet dosage strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zubsolv sublingual tablet dosage strength</td>
<td>Bunavil buccal film dosage strength</td>
</tr>
<tr>
<td>1.4 mg/0.36 mg</td>
<td>2.1 mg/0.3 mg</td>
</tr>
<tr>
<td>2.1 mg/0.5 mg</td>
<td>4 mg/1 mg</td>
</tr>
<tr>
<td>4.2 mg/0.7 mg</td>
<td>8 mg/2 mg</td>
</tr>
<tr>
<td>5.7 mg/1.4 mg</td>
<td>6.3 mg/1 mg</td>
</tr>
<tr>
<td>8 mg/2 mg</td>
<td>12 mg/3 mg</td>
</tr>
</tbody>
</table>

* Based on greater bioavailability by unidirectional mucoadhesive structure

- 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
BELBUCA & BUTRANS (BUP only)

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

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>Cavg (ng/ml)</th>
<th>Tmax (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>0.1</td>
<td>2.5</td>
</tr>
<tr>
<td>150</td>
<td>0.2</td>
<td>3.5</td>
</tr>
<tr>
<td>300</td>
<td>0.3</td>
<td>4.5</td>
</tr>
<tr>
<td>450</td>
<td>0.4</td>
<td>5.5</td>
</tr>
<tr>
<td>600</td>
<td>0.5</td>
<td>6.5</td>
</tr>
<tr>
<td>750</td>
<td>0.6</td>
<td>7.5</td>
</tr>
<tr>
<td>900</td>
<td>0.7</td>
<td>8.5</td>
</tr>
</tbody>
</table>

BUTRANS

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

SUBLOCADE I

- After inj and median T<sub>max</sub> occurred at 24h. The plasma buprenorphine concentration from initial drug to steady-state was achieved at 4-6 months. Observed mean buprenorphine concentrations were reported in Table.

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 which could be associated with the clinical development of BUP-XR.

Please note: Time to 2ng/ml upon cessation of depot: 2m (300/100) vs 5m (300/300)
Clinical “pearls”

- Analgesic vs MOUD dose targets are strategically different!
- You can add FAO • BUP
- You must start low when adding BUP • FAO – think “Berno”
- AVOID high dose BUP vs FAO battle (resp dept)
- PAY ATTENTION TO DOSE TIMING!
- Small doses of BUP go a long way
  - for ANALGESIA
- There is a pain-place for BUP de novo
- NoBUP shouldn’t be ignored
- Don’t forget adjuvants
References 2021

- **Bennett conversion** Pain Med 2016 May;17(5):899-907. doi: 10.1093/pm/pmw061
- **BUP & pain mechanisms** Synapse. 2016 October ;70(10):395-407
- **Workshop** Synapse. 2016 October ;70(10):395-407. doi:10.1002/syn.21914
- **Treating chronic pain** Drugs. 2018 August ;78(12):1211-1228
- **Botulinum Toxin** Neuroradiology. 2016 November ;60:527-530. doi:10.1007/s00251-015-2694-3

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References 2019


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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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2021