The Role of Buprenorphine in Pain and Addiction

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Disclosure

- I am involved in 3 clinical trials, but do not receive any financial support from them.
- The content of this presentation is non-commercial and does not represent any conflict of interest or commercial bias.
Objectives

- Introduction the problems with opiates use
- Introduction of CDC guideline
- Introduction of Buprenorphine
- Buprenorphine in opioid use disorder
- Buprenorphine in pain
- Management strategies in patients on buprenorphine
What is Pain

Pain: an unpleasant sensory and emotional experience associated with actual or potential issue damage, or described in terms of such damage.

Pain is the most highly modulated experience.

Central Modulation

Inhibitory or facilitating processes in spinal cord (ascending) or brain (descending)

Opioid analgesics enhance inhibition initially, may facilitate as late phenomena (hyperalgesia)

Addictive illness facilitates via multiple mechanisms

Key Facts of Chronic Pain

• Pain ≥ 3-6 months, beyond the period of normal tissue healing
  – Examples: low back pain, other msk pain, fibromyalgia, neuropathy, headache
• Common (11-40%) and costly ($600b)
• Biological basis increasingly well-understood
  – Genetic predisposition
  – Peripheral and central sensitization
• Heavily impacted by psychosocial factors
  – Significant comorbidity with depression, anxiety, PTSD
• Not just a symptom: it’s a chronic disease

Bair, Arch Int Med, 2003; McWilliams, Pain, 2003.
Chronic Pain and Prescription Opioids

- 11% of Americans experience daily (chronic) pain
- Opioids frequently prescribed for chronic pain
- Primary care providers commonly treat chronic, non-cancer pain
  - account for ~50% of opioid pain medications dispensed
  - report concern about opioids and insufficient training
**Effect and Burden of Chronic Pain**

*Figure 1: The effect and burden of chronic pain*

Chronic pain affects every aspect of a patient’s life, contributing to a loss of both physical and emotional function, affecting a patient’s levels of activity (ability to work at home and job and engage in social and recreational pursuits); additionally, there are often serious economic consequences as a result of health-care bills and potential loss or decrease in financial income.

AL is one of the 5 states that have the highest number of prescription painkillers per 100 people: 128-143, in 2012. The other 4 are OK, WV, TN and KY.
Sharp Increase in Opioid Prescriptions and related Deaths from 2000-2014 in the U.S

Thus more overdose deaths than heroin

Why are there so many people who overdosed on opioids?
Rise in Opioid-Related Deaths

- According to the CDC, more than 33,000 people died from opioid overdose in the U.S. in 2015—one of many signs of the rising trend in opioid abuse.

- Annual opiate overdose deaths exceed traffic fatalities since 2008 and continue to rise.

- A significant proportion involve prescription medications.
The other tragedy behind Prince's death

By Chris Johnson

Updated 6:00 PM ET, Mon July 11, 2016

Photos: Celebrities who died from painkillers and heroin

Rock superstar Prince, known as "The Purple One," died at his Paisley Park home in Minnesota in April of what the medical examiner called a "self-administered" overdose of the painkiller fentanyl, one of the most powerful of all opioids. Prince was 57 years old.
Mechanisms for CDC to release Opioid Prescribing Guidelines for Chronic Pain

- Significant increase in opioids Rx and its-related overdose death
- Previous opioid prescribing guidelines have been developed by several states and agencies but were inconsistent
- Most recent national guidelines are several years old and don’t incorporate the most recent evidence
- Need for clear, consistent recommendations
- Does not include active cancer treatment, palliative care, and end-of-life care

www.cdc.gov/drugoverdose
12 recommendations in 3 conceptual areas

- Determining when to initiate or continue opioids for chronic pain
- Opioid selection, dosage, duration, follow-up, and discontinuation
- Assessing risk and addressing harms of opioid use

Dowell, JAMA, 2016
Summary of 12 Recommendations

- Non-pharmacologic therapy and non-opioid pharmacologic therapy are preferred for treatment of chronic pain.
- Opioids should be used only when benefits for pain and function are expected to outweigh risks.
- Before starting opioids, clinicians should establish treatment goals with patients and consider how opioids will be discontinued if benefits do not outweigh risks.
- If opioids are used, they should be combined with non-pharmacologic therapy and non-opioid pharmacologic therapy, as appropriate.
- When opioids are used, clinicians should prescribe the lowest effective dosage, carefully reassess benefits and risks when considering increasing dosage to 50 morphine milligram equivalents or more per day.
- Avoid concurrent opioids and benzodiazepines whenever possible.
- Clinicians should evaluate benefits and harms of continued opioid therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids.
- Clinicians should review prescription drug monitoring program data (PDMP), when available, for high-risk combinations or dosages.
- For patients with opioid use disorder, clinicians should offer or arrange evidence-based treatment, such as medication-assisted treatment with buprenorphine or methadone.
Pain, Opioids and Addiction are Related

Problems with Opioids

- Pain relief (short term)
- Hyperalgesia
- Medication toxicity
- Dependence
- Tolerance
- Withdrawal
- Addiction

3-26%
What is an Addict?

• Someone who says he/she is an addict
• Someone who asks for pills all the time
• Someone with weak will power
• Someone who is not smart enough to stop
• The last patient you ever want to deal with
What is Addiction

General Idea:
Continued use of a substance or engagement in an activity despite obvious harm.
What is Addiction

• A primary, chronic disease of brain reward, motivation, memory and related circuitry.
• Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations.
• This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.
What is Addiction

- Like other chronic diseases, addiction often involves cycles of relapse and remission.
- Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.
“Pleasure Circuit”

- **Cortex (logic)**
- **Amygdala (emotions)**
- **Hippocampus (memory)**
- **Ventral Pallidum (motivation)**

**Nucleus Accumbens (striatum)**

- Amphetamine
- Cocaine
- Opiates
- Cannabinoids
- Phencyclidine
- Ketamine

**Ventral Tegmental Area (midbrain)**

- Opiates
- Ethanol
- Barbiturates
- Benzodiazepines
- Nicotine
- Cannabinoids

DOPAMINE!!!
“Pleasure Circuit” (Addict)

- Cortex (logic)
- Ventral Tegmental Area (midbrain)
- Nucleus Accumbens (striatum)
- Amygdala (emotions)
- Hippocampus (memory)
- Ventral Pallidum (motivation)

Stress (glutamate) from Amygdala

Cues (CRF/Norepi) from Hippocampus

Dopamine from Nucleus Accumbens

VTA

Addictive substances:
- Amphetamine
- Cocaine
- Opiates
- Opiates
- Cannabis
- Phencyclidine
- Ketamine

Opiates
- Ethanol
- Barbiturates
- Benzodiazepines
- Nicotine
- Cannabinoids
Why do people develop opioid use disorder?

Repeated exposure to opioids leads to neuronal adaptations in Meso-limbic dopaminergic system.

Mediate tolerance, withdrawal, craving and addiction.
If you suspect opioid use disorder (OUD)

- Discuss with your patient and provide an opportunity to disclose concerns.
- Assess for OUD using DSM-5 criteria. If present, offer or arrange medication-assisted treatment.
  - Buprenorphine through an office-based buprenorphine treatment provider or an opioid treatment program specialist
  - Methadone maintenance therapy from an opioid treatment program specialist
  - Oral or long-acting injectable formulations of naltrexone (for highly motivated non-pregnant adults)
No new molecules were approved for any type of substance use disorders in 2016.

Methadone, naltrexone, and buprenorphine—all of which interact with opioid receptors—have been the mainstay of medication-assisted treatment for opioid use disorder for decades.

As buprenorphine has become more popular in recent years, more companies have started to explore alternative formulations of the medication that require less frequent follow-up.
**Buprenorphine Properties**

- Partial-μ receptor agonist: very high affinity to the receptors
  - Less reinforcing than a full agonist \( \rightarrow \) not enough to cause intense euphoria \( \rightarrow \) less abuse potential and physical dependence
  - When other opioids are on board, could precipitate withdrawal
  - but can be used for opiate detoxication as well due to less severe/shorter duration of withdrawal symptoms

- Half-life 24-48 hrs, so long duration of action (24-72hr) and dissociate from receptors at a slow rate \( \rightarrow \) so enable daily or 3/wk dosing

- Side effects: respiratory suppression (can not be reversed by naloxone), nausea, dizziness, dysphoria

- Strong safety profile
  - Little respiratory depression
  - Little overdose potential
(1) It can displace or block morphine binding to μ-receptor thus contributes to reduced opioid dependence.

(2) Buprenorphine agonist activity on μ receptor is the primary contributing factor to its analgesic signaling events.

(3) Buprenorphine interacts with nociceptin/ORL1 with much lower affinity and thus is unlikely to contribute to analgesic effects at therapeutic doses. It is conceivable that buprenorphine interactions with other similar receptors could contribute secondary analgesia.

(4) Buprenorphine is a potent antagonist of θ-opioid receptor and this interaction could contribute to reduced tolerance and antidepressant like activity.
Binding affinity for opioid receptors

<table>
<thead>
<tr>
<th>Opioid receptor</th>
<th>Ki (nM)</th>
<th>Agonist/antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>μ</td>
<td>1.5</td>
<td>Partial agonist</td>
</tr>
<tr>
<td>δ</td>
<td>6.1</td>
<td>Antagonist</td>
</tr>
<tr>
<td>κ</td>
<td>2.5</td>
<td>Antagonist</td>
</tr>
<tr>
<td>Nociceptin or ORL1</td>
<td>77.4</td>
<td>Agonist</td>
</tr>
</tbody>
</table>

ORL I: opioid receptor-like 1
Partial Agonist and Clinically Observed Affinity

- **Full Agonist (Methadone)**
- **Partial Agonist (Buprenorphine)**
- **Antagonist (Naloxone)**

Affinity levels:
- **Low Affinity**: Morphine, Oxycodone, hydrocodone
- **High Affinity**: Buprenorphine, Hydromorphone, Methadone, Fentanyl(s)
- **Ceiling** effect: typical dose 12-16mg, daily

- **Withdrawal**

![Suboxone Withdrawal Timeline]

- Physical symptoms at their worst
  - Bodily aches and pains, insomnia, and mood swings
- Depression
- Cravings and depression
- Symptoms can last several months

Suboxone Withdrawal Timeline:

- Last dose
- 72hrs
- 1wk
- 2wk
- 1mo
Moderate to severe pain

- **Buprenex** (buprenorphine) iv or im
- **Butrans** (buprenorphine) transdermal patch

Opioid use disorder

- **Bunavail** (buprenorphine and naloxone) buccal film
- **Suboxone** (buprenorphine and naloxone) tablet/film
- **Zubslov** (buprenorphine and naloxone) tablets
- **Subutex** (buprenorphine) tablet—really one indication—Pregnancy
Is Buprenorphine just exchanging one drug for another

- Stabilize neuronal circuitry
  - Mu occupation/blockade
  - Cross-tolerant
- Prevent withdrawal and craving
- Prevent spread of HIV and HCV
- Prevent criminal activity
- Decrease or Extinguish compulsive behavior
- Decrease deaths
- Decrease overall chaos
- Increase retention in treatment
- Increase engagement in socially productive roles
- Increase employment opportunity

3P, 3D, 3I

EBM has clearly indicated that MAT can help improve overall function and help patients to live a ‘normal’ and productive life

The answer is probably Not ……
Transdermal buprenorphine is approved and indicated for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period.

Pain relief with buprenorphine seems equivalent to that of morphine, hydromorphone, fentanyl and methadone, but less side effects and discontinuations relative to other opioids.

Buprenorphine effectively relieves neuropathic pain and offers distinct benefit.

Probably due to its κ-receptor antagonist, buprenorphine seems to have antidepressants and antianxiety properties, which also helps in pain management.

Slow onset with transdermal formulations and ability to adjust initial dose levels may limit the utility in some cases.

There are no large RCT comparing buprenorphine with other opioids. Many were case studies.

Keys To Success

• Experience using buprenorphine for pain
  – The training for pain/addiction does not provide this and often leads to poor pain control and side effect limitations
• Pain psychology counseling
  – Very high incidence of trauma, abuse and unresolved grief in the chronic pain population
• Interdisciplinary Care Team Meetings
• Identification and simultaneous treatment of SUD and other medical and psychological comorbidities
Pain Management in Patients on Buprenorphine

Due to its partial agonistic activity on μ-receptor and high affinity, it is an issue how to treat this sub-population who are on buprenorphine, but need surgical procedures. Thus patients require special consideration when it comes to acute pain management.

Again, there are no RCT. Recommendations are currently based on case reports/studies and physicians’ experiences

A few options:
- Non-opioid analgesics are preferred while buprenorphine is continued.
- Discontinue buprenorphine therapy at least 72 hours prior to the operative procedure.
- Replace buprenorphine with methadone
- Consider adding opioids with higher affinity than buprenorphine
- Divide daily dose of buprenorphine into every 6 or 8 hr dosing cycle.

### Comparison of safety profile of buprenorphine with other opioids

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Constipation</th>
<th>Sedation</th>
<th>Respiratory distress</th>
<th>Tolerance</th>
<th>Addiction</th>
<th>Hyperalgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td></td>
<td>+++</td>
<td>+++</td>
<td>?</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td></td>
<td>yes</td>
</tr>
<tr>
<td>Methadone</td>
<td></td>
<td>+++</td>
<td></td>
<td>?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>limited</td>
<td>Anit-hyperalgesia</td>
</tr>
</tbody>
</table>

**In addition:**
- Low clearance through renal path, so could be used in CKD patients
- Safe opioid option for seniors
- Minimal DDI and minimal influence on PK

Work-up for Initiating Buprenorphine Therapy

- Take a complete medical history
- Review psychiatric history
- Review substance abuse history (including alcohol and tobacco use)
- Get a complete list of all medications (current and historical) and repeat regularly
- Urine Drug Screen
- Basic Labs (CBC, Chem profile, Thyroid fxn, etc)
- Carefully educate the patient as to risks, benefits and expectations.
Buprenorphine Treatment Agreements

- NOT contracts
- Informed consent; you and your patient’s responsibilities
  - One prescriber, one pharmacy
  - Take as prescribed, no changes on one’s own
  - Urine drug testing
  - How medicines are refilled, replacement Rx
  - Conditions for stopping buprenorphine
UAB Outpatient Psychiatry
Agreement for Treatment with Buprenorphine

- I agree not to be on any other mood altering or addictive drugs such as Xanax or Adderall during buprenorphine treatment. However, if you are prescribed by another physician, please let the other physician write me a letter to explain it including the length you need to be taking them-no unnecessary other controlled Rx.
- I agree not to be working with another MD for suboxone or subutex or methadone treatment at the same time- one prescriber
- I agree not to refill my medications early- no early refill
- I agree to follow up with appointments. If no show> 2 appts/yr, w/o cancellation, I understand that this may lead to termination-compliance to reduce relapse.
- I understand that if a Urine Drug Screen is ordered I must obtain that day or risk termination-UDS request.
- I understand that I must keep a clean Urine Drug Screen. A single positive Drug screen may cause me to be terminated-0 tolerance of positive UDS.
- I understand that lost, stolen or destroyed medication does not assure an early refill or more medication-store medications safely.
- I agree not to take more than my prescribed dose of medication-compliance.
- I agree that if I want a dose changed, I must come in to talk to my physician first before changing the dose-no self-Rx.
- I agree to attend recovery meetings including AA, NA and/or CA meetings in the community at least 2-3 times weekly-meetings required.
- I agree that suboxone or subutex treatment is not definite. Thus the plan of taper off will be discussed between me and my provider during the treatment-no definite.
Urine Drug Testing

• Useful for checking for adherence to rx’d drugs and for presence of substances not rx’d
• “A tool not an oracle”
• Send screening immunoassay; discuss unexpected results; if still unclear, send confirmatory test (GCMS/LCMS); if still unclear, consider ddx
• Know your toxicologist
• Be mindful of cost
• Insist to see results before Rx is filled sometime

Prescription Drug Monitoring Programs (PDMP)

- State-by-state, lots of variability
- Tells you three things that predict OD:
  - Dose
  - multiple rx’s
  - opioid and benzo co-rx
Success Rates

• Patients report reduced OUD (clean UDS) and improvement in quality of life in 40 – 70%
• Family members frequently say “Thank you for giving me my [wife/husband/parent/child] back
• Patient usually “comes to” by the second month
• However, this is the beginning of a long process

Berland, et al; Am J Therapeutics 2013
Recovery is a multi-disciplinary work

- Address the physical, emotional and cognitive management of chronic pain, in conjunction with medical management
- Address the relationship between chronic pain and depression, anger and other emotional states
- Manage and educate on addictive behaviors and addictive thinking, as well as relapse prevention
- Clients on maintenance doses of MAT will be expected to pursue 12-Step based counseling and ultimately to taper off the medication, but Seppala says of this group, “They will be taking the medication for probably months.”
Concerning Behaviors

• Examples include:
  – Unexpected urine results
  – Running out early/other rx problems
  – Multiple prescribers
  – Belligerent behavior

• All have a differential diagnosis

• Tips for evaluating these behaviors:
  – Detailed exploration with patient
  – Re-education
  – Closer monitoring, small prescriptions (is this a pattern? does the patient divert/misuse Rx?)
  – Involvement of family/friends/pharmacy
Some updates

In May 2016, the FDA approved the long-acting buprenorphine implant (Probuphine), which has a duration of action for six months.

A monthly subcutaneous depot injection of buprenorphine is being developed by Indivisor PLC, a spinoff from Reckitt Benckiser and the maker of Subutex and Suboxone tablets. The company announced positive results from a phase 3 clinical trial in August 2016 and is planning to file a new drug application with the FDA in 2017.

In addition, Insys Therapeutics is developing a sublingual spray formulation for buprenorphine, naloxone, and a combination of both drugs.

For newer medications to treat opioid withdrawal, the company US Worldmeds LLC, in collaboration with NIDA, is currently testing lofexidine—an antihypertensive medication that has been available in United Kingdom for treating opioid withdrawal for years—in a phase 3 trial. Like clonidine, which is often used in detoxification of opioid addiction, lofexidine inhibits the heightened noradrenergic activity associated with opioid withdrawal and relieves associated symptoms.
Take Home Points

• Pain is a significant disease and affects patient’s life
• Medication toxicity, opioids in particular, is frequently the result of over prescribing
• Not every patient who overuses medication is an addict
• Medication-assisted withdrawal and treatment, including Buprenorphine, requires some expertise and patience, but can dramatically improve quality of life and safety
• Do not forget to treat your patient with compassion and understanding, and non-judgmental.
Thank you
Recognizing Opioid Use Disorder

1. Opioids are often taken in longer amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

DSM-5.