Management of patients with Opioid Use Disorder

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Learning Objectives

• Understand the current situation of the opioid epidemic
• Learn risk factors for developing opioid addiction
• Learn how to manage patients with opioid addiction
Terminology

- **Addiction** - a chronic, relapsing brain disease, characterized by compulsive drug seeking and use, despite harmful consequences; synonymous with substance dependence
- **Opioid misuse** - inappropriate or illegitimate use of opioids, including use of prescription opioids in any way other than as prescribed
- **Opioid dependence** - strictly refers to the DSM-IV definition of substance dependence in which opioids are the substance of dependence. Expressly does NOT refer to physical dependence, which is a distinct phenomenon
- **Opioid Abuse** - maladaptive pattern of drug use that result in harm or place in the individual at risk of harm
- **Opioid use disorders** - refers to either opioid abuse or opioid dependence; the plural form encompasses both diagnoses (opioid use disorders)

Withdrawal

- **Spontaneous withdrawal** (usually called withdrawal) occurs when a physically dependent individual suddenly stops or significantly decreases opioid usage. The time frame for withdrawal is heavily dependent on the half-life of the drug being taken. Withdrawal from heroin, an opioid with a relatively short half-life, is fairly quick and very intense. Heroin withdrawal typically begins 6 to 12 hours after the last dose, peaks between 36 and 72 hours, and lasts about 5 days. It may be several months before the patient feels completely “normal” again. As a rule, withdrawal from opioids with longer half-lives, such as methadone or buprenorphine, has a later onset, is more protracted, and lasts longer.
- **Precipitated withdrawal** occurs when a full agonist, such as heroin, is displaced from opioid receptors by an antagonist, such as naloxone. Precipitated withdrawal is similar to regular withdrawal but is more intense and has a much faster onset. In some cases, a partial agonist such as buprenorphine can precipitate withdrawal. Buprenorphine is more likely to precipitate withdrawal if
  - The patient has a high level of physical dependence.
  - There has been a short time interval between the last dose of the full agonist and the first dose of buprenorphine.
  - A high dose of buprenorphine is used.
  - The full agonist has a long half-life, as is the case with methadone.
Opiates versus Opioids

- Opiates are drugs derived from opium (morphine, codeine, thebaine and opium)
- *Opioid* is used for the *entire family* of opiates including natural, synthetic and semi-synthetic
- Semi-synthetics: synthesized from naturally occurring opiates: heroin, oxycodone (ocy, Perc), buprenorphine, hydromorphone (dilaudid), oxymorphone, hydrocodone (Vicodin)
- Synthetic opioids: fentanyl, meperidine (demerol), methadone, W-18 and krokodil

The Opioid Epidemic in Numbers

- Roughly 21 million people in the United States aged 12 and older have used prescription drugs for nonmedical reasons at least once in their lifetimes
- Since 2003, more deaths have been associated with opioid overdose than cocaine or heroin use combined
- Studies have shown that up to 45% of chronic pain patients on opioid therapy reported aberrant drug–related behaviors, including the use of alternative routes of administration of oral formulations, concurrent use of alcohol/illicit drugs, and the repeated use of opioid therapy despite adverse effects.
- The United States is the biggest opioid consumer globally, accounting for almost 100 percent of the world total for hydrocodone (*e.g.*, Vicodin) and 81 percent for oxycodone (*e.g.*, Percocet)
The opioid Epidemic

- The opioid epidemic began with compassionate doctors trying to end “the suffering of millions of people in pain”

- Opium’s addictive properties and deadly potential were known for centuries. Morphine addiction caused enough societal problems in the early 1900s that for more than 50 years American Doctors rarely prescribed opiate-based drugs

- Pain management leaders and the government experts believed they had to keep talking about how safe opioid therapy was.” They thought they were fighting bias against opioids and the need to eliminate pain
Brief History

• In the 1800s, people could get opioids fairly freely. They were available over the counter.
• Bayer began selling heroin, a chemical derived from opium, for pain relief and cough suppression.
• Within one year, reports revealed that people were developing a tolerance to the drug.
• By 1910, Americans were crushing opioid pills and inhaling them for pleasure
• Four years later, Congress passed the Harrison Narcotics Act, making opioids available only by prescription.

A Capsule History of Pain Management
Marcia L. Meldrum, PhD JAMA. 2003;290(18):

“The introduction of surgical anesthesia was one of the greatest revolutions of modern medicine, but not all physicians were immediately enthusiastic. There was an extended debate over the ethics of operating on an unconscious patient in both Europe and the United States about the possibility that the relief from pain might actually retard the healing process. Religious writers called anesthesia a violation of God’s law, whom they believed inflicted pain to strengthen faith and to teach the new mother the need for self-sacrifice for her children. But the surgeons could not long resist their new power to perform longer and more complex procedures, and most patients thought anesthesia a divine blessing.”
A LETTER THAT CHANGED THE GAME

• In the late 1970s, researchers from Boston Medical Center analyzed the medical records of hospitalized patients who had received narcotics. They found that of 11,882 patients who received narcotics, only four showed "reasonably well documented" symptoms of addiction and only one major instance of addiction.

• Jane Porter and Hershel Jick wrote a five-sentence letter to the editor in the New England Journal of Medicine describing the analysis in 1980.

• "We conclude that despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction."

ADDITION RARE IN PATIENTS TREATED WITH NARCOTICS

To the Editor: Recently, we examined our current files to determine the incidence of narcotic addiction in 39,946 hospitalized medical patients who were monitored consecutively. Although there were 11,882 patients who received at least one narcotic preparation, there were only four cases of reasonably well documented addiction in patients who had no history of addiction. The addiction was considered major in only one instance. The drugs implicated were meperidine in two patients, Percodan in one, and hydrocodone in one. We conclude that despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction.

Jane Porter
Hershel Jick, M.D.
Boston Collaborative Drug Surveillance Program

Waltham, MA 02154

Boston University Medical Center

Building Momentum for Pain Relief

• The letter became one of the most prominent resources for pain-relief advocates who claimed that less than 1% of patients treated with opioids became addicted.
• It has been cited by more than 900 studies since it was published.
• During the next decade, researchers laid the groundwork for drug companies to make aggressive and exaggerated claims about the safety and efficacy of opioids.

An Era of Pain

• As a society we learned to dislike pain
• We get laughing gas when we have teeth pulled and powerful painkillers after surgery
• We learned “Chemical coping”
Risks Factors for Developing an Opioid Addiction

- Accessibility of drugs
- Types of drugs
- Genetic Predisposition
- Chronic Pain issues
- Mental Health Issues
- Environment/communities
- Types of drugs
- Accessibility of drugs
Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system

Joseph A. Boscarino1,2,3, Margaret Rukstalis1, Stuart N. Hoffman1, John J. Han5, Porat M. Erlich4, Glenn S. Gerhard7 & Walter F. Stewart1,8

1 Center for Health Research, Geisinger Health System, Danville, PA, USA; 2 Department of Medicine and Pediatrics, Mount Sinai School of Medicine, New York, NY, USA; 3 Department of Psychiatry, Temple University School of Medicine, Philadelphia, PA, USA; 4 Department of Neurology, Geisinger Health System, Danville, PA, USA; 5 Department of Twin Medicine, Geisinger Health System, Danville, PA, USA; 6 Department of Medicine, Temple University School of Medicine, Philadelphia, PA, USA; 7 Weis Center for Research, Geisinger Health System, Danville, PA, USA; 8 Department of Epidemiology (Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA)
Methods

- Using electronic health records, the authors identified outpatients receiving 4+ physician orders for opioid therapy in the past 12 months for non-cancer pain.
- Patients were recruited from a large US health-care system.
- They completed diagnostic interviews with 705 of these patients to identify opioid use disorders and assess risk factors.

Results

- Addiction was found in 26% of the population studied.
- Logistic regression:
  - Younger age (less than 65) (OR 2.33, P=0.001)
  - Opioid abuse history (OR 3.81, P<0.001)
  - High dependence severity (OR 1.85, P=0.001)
  - Major depression (OR 1.29, P=0.022)
  - Psychotropic medication use (OR 1.73, P=0.006)
Combined Risk Factors

- Four variables combined: age, depression, psychotropic medications and pain impairment OR = 8.01, $P < 0.001$.
- History of severe dependence and opioid abuse increased this risk substantially: OR = 56.36, $P < 0.001$.

Other Risk Factors

- Family history of addiction
- History of Trauma
- Other types of addiction
3- Management of Patients with OUD

Opioid Receptor

- Opioids work in the brain at specific “opioid receptors”
- Several types of opioid receptors but the main receptor is called “mu”
- Binding - full stimulation or effect at the receptor (agonist), or a partial effect (partial agonist) or block the effect of the receptor (antagonist)
Opioid Receptors and Activation effect

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>µ₁</td>
<td>Analgesia, euphoria</td>
</tr>
<tr>
<td>µ₂</td>
<td>Constipation, respiratory depression</td>
</tr>
<tr>
<td>Kappa</td>
<td>Dysphoria, hallucination, sedation</td>
</tr>
<tr>
<td>Delta</td>
<td>Analgesia through endorphin, enkephalin, and dynorphin system, GI motility.</td>
</tr>
</tbody>
</table>

- Abused opioids have primarily agonist effects at MOP-receptors (encoded by the mu opioid receptor gene [OPRM1]).
- **MOP-r are inhibitory G protein-coupled receptors with opioids as ligands**
Identifying those with OUD

- Preoperative evaluation to identify comorbidities and risk factors and recognize signs and symptoms of opioid misuse and opioid withdrawal
- Use of PMP

Tools

- The Current Opioid Misuse Measure: assesses a patient’s relative frequency of a thought or behavior in the past 30 days.
- The Screener and Opioid Assessment for Patients with Pain – Revised (SOAPP-R): predict future misuse based on past behavior or thoughts; this tool is only appropriate for patients under consideration for long-term opioid therapy.
- Look for aberrant symptoms
Opioid Risk Tool (ORT)

OPIOID RISK TOOL PATIENT FORM

Name: ____________________________
Age: ____________________

<table>
<thead>
<tr>
<th></th>
<th>Mark Each Box That Applies</th>
<th>Score of Female</th>
<th>Score of Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Family History of Substance Abuse</td>
<td>Alcohol</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Illegal Drugs</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Prescription Drugs</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>2. Personal History of Substance Abuse</td>
<td>Alcohol</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Illegal Drugs</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Prescription Drugs</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>3. Age (MAI and BDI 16-60)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>4. History of Preabuse Sexuality</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5. Psychological Disease</td>
<td>Attention Deficit Hyperactivity Disorder</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Obsessive Compulsive Disorder</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Bipolar Disorder</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Schizophrenia</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Total Score _______ Risk Category _______

Low Risk 0-3
Moderate Risk 4-7
High Risk >7

Brief, simple scoring tool that is validated in pain populations (Passik, et al, 2008). Validated for both male and female patients (Webster & Webster, 2005).

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Table 4. Difference between Chronic Pain and Opioid-abusing Patients

<table>
<thead>
<tr>
<th>Chronic Pain Patient</th>
<th>Opioid-abusing Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate use of opioid</td>
<td>Out of control with opioids</td>
</tr>
<tr>
<td>Opioids improve quality of life</td>
<td>Opioid impair quality of life</td>
</tr>
<tr>
<td>Aware of side effects</td>
<td>Unconcerned</td>
</tr>
<tr>
<td>Follows treatment plan</td>
<td>Does not follow plan</td>
</tr>
<tr>
<td>Has medication saved from previous prescriptions</td>
<td>Out of medication, “loses” prescriptions, has a “story”</td>
</tr>
</tbody>
</table>
Challenges

• We mostly rely on self report
• Sometimes these patients are seen in the setting of trauma/urgent care where information cannot be obtained

Box 1-2. Pain Management Goals of Therapy for Patients with Opioid Addiction

- Prevent withdrawal
- Treat symptoms
- Provide effective analgesia
- Prevent relapse to addiction
- Effective treatment of opioid addiction (maintenance opioid therapy)
- Treatment of psychiatric disorders such as anxiety

Patients on Methadone

• Patients on methadone maintenance therapy should receive their usual daily dose of methadone plus a different opioid agent for management of the acute pain
• If the exact usual dose of methadone cannot be confirmed with the patient’s methadone maintenance clinic, it is advisable to divide the total daily dose reported by the patient into three or four increment
• The usual oral daily dose should be cut in half when administered intravenously

Patients on Buprenorphine

• Buprenorphine could be discontinued for several days before the episode and supplemented with methadone to prevent withdrawal
• If it is not possible to discontinue the buprenorphine, use of an intravenous form of an opioid that binds strongly to mu receptors, such as fentanyl, is preferred
• It may be possible to increase the daily buprenorphine dose and split administration into four doses to achieve an analgesic effect.
Non opioid Alternatives for Perioperative Analgesia

- Limited data exist on the use of dexmedetomidine as an analgesic alternative or adjunct to opioids.
- α2-agonist approved for use in ICU
- Effective in the management of postoperative pain and withdrawal syndrome
- Infusion of dexmedetomidine during the intraoperative period reduced the need for morphine by 66% and was associated with a slower heart rate during recovery.

Buprenorphine

- Buprenorphine is a thebaine derivative that is legally classified as a narcotic
- When used as an analgesic, buprenorphine is usually given by injection, via a sublingual tablet, or as a transdermal patch, and doses are relatively low (compared with doses used in the treatment of opioid addiction). The typical analgesic dose of buprenorphine is 0.3–0.6 mg (intramuscular or intravenous), and its analgesic effects last about 6 hours.
- At low doses, buprenorphine is many times more potent than morphine.
Affinity, Intrinsic Activity, and Dissociation

- Buprenorphine has high affinity for, but low intrinsic activity at, mu receptors.
- Buprenorphine displaces morphine, methadone, and other full opioid agonists from receptors.
- It is difficult for opioid antagonists (e.g., naloxone) to displace buprenorphine and precipitate withdrawal.
- Buprenorphine has a slow dissociation rate from the mu opioid receptor, which gives rise to its prolonged suppression of opioid withdrawal and blockade of exogenous opioids.
Bioavailability

- Buprenorphine has poor gastrointestinal (GI) bioavailability, and fair sublingual bioavailability.

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Buprenorphine Bioavailability Relative to Intravenous Route of Administration</th>
<th>Buprenorphine Bioavailability Relative to Intramuscular Route of Administration</th>
<th>Buprenorphine Bioavailability Relative to Sublingual Solution Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>100%</td>
<td>____</td>
<td>____</td>
</tr>
<tr>
<td>IM</td>
<td>70%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Sublingual sol</td>
<td>49%</td>
<td>70%</td>
<td>100%</td>
</tr>
<tr>
<td>Sublingual tab</td>
<td>29%</td>
<td>42%</td>
<td>50-70%</td>
</tr>
</tbody>
</table>
Abuse Liability

- Epidemiological studies and human laboratory studies indicate that buprenorphine is abusable
- Diversion of sublingual tablets to injection route
- In nonphysically dependent opioid users, acute parenteral doses of buprenorphine produce typical mu agonist opioid effects
- In individuals who are physically dependent, parenteral buprenorphine can cause precipitated withdrawal

Potential for Physical Dependence

- Repeated administration of buprenorphine produces or maintains opioid physical dependence
- The withdrawal syndrome associated with buprenorphine discontinuation may be significantly milder in intensity, and the onset of withdrawal signs and symptoms slower, than that seen with full mu agonists
Buprenorphine Safety Profile

- Poor GI bioavailability: swallowing the tablets will result in a milder effect compared with administering them sublingually (1/5th as potent when swallowed vs. when sublingually.)
- Overdose of buprenorphine does not appear to cause lethal respiratory depression in noncompromised individuals
- Some cases of respiratory depression induced by buprenorphine in individuals not physically dependent on opioids or when buprenorphine is taken in combination with other sedative drugs

Maintenance Treatment

- Results from studies suggest that buprenorphine in a dose range of 8–16 mg a day sublingually is as clinically effective as approximately 60 mg a day of oral methadone, although it is unlikely to be as effective as full therapeutic doses of methadone (e.g., 120 mg per day) in patients requiring higher levels of full agonist activity for effective treatment.
Different types of Buprenorphine

- Buprenorphine is available under the trade names, Suboxone, Subutex, Zubsolv (typically used for opioid addiction), Temgesic (sublingual tablets for moderate to severe pain), Norspan and Butrans (transdermal preparation used for chronic pain)
- Buprenorphine has been introduced in most European countries as a transdermal formulation (marketed as Transtec) for the treatment of chronic pain not responding to non-opioids.

Combining Naloxone and Buprenorphine

- Sublingual naloxone has relatively low bioavailability, while sublingual buprenorphine has good bioavailability
- Both naloxone and buprenorphine have poor GI bioavailability.
Intake Process

- Establish that the patient has OUD
- Verify the patient's list of medications, illicit drugs, and alcohol use
- Conduct a brief psychosocial assessment
- Conduct lab testing: liver function tests, urine toxicology screen, pregnancy test
- Have patient review and sign consent forms and treatment agreement
- Determine when and where to start induction
- Provide education to the patient about the induction, stabilization, and maintenance processes
- Advise patients not to use opioids for appropriate amount of time to prevent precipitated withdrawal
- Preparing for Induction

Induction

- Patients should be in mild to moderate withdrawal.
- Patient who are dependent on short-acting opioids should abstain from 12 to 24 hours
- It will take 36 to 72 hours for those dependent on methadone.
- Use Clinical Opioid Withdrawal Scale (COWS) - to evaluate the patient's withdrawal symptoms prior to induction
- When patients have a COWS score about 12 or 13 (mild to moderate withdrawal), they are ready for their first dose.
- Patients who are maintained on high doses of methadone should be tapered down to a 30 mg daily dose (ideally) just prior to transfer and maintained on this dose for a week.
Induction Day 1

• Opioid-dependent patients should be inducted with a 4mg buprenorphine dose, observed for 1-2 hours, then given a second 4mg dose if withdrawal symptoms reappear.
• In some instances a 2mg dose is preferred to minimize the chances of precipitated withdrawal.
• A maximum dose of 8 mg is allowed for Day 1.
• It's helpful to allow a 2-4 hour window of office time on the first day of induction.

Induction Day 2/Follow up

• Increase dose in case of craving or withdrawal
  – Give their Day 1 dose + 4mg
  – wait 1-2 hours and increase the dose in 2-4mg increments in case of withdrawal symptoms.
  – The total recommended dose for Day 2 should not exceed 16mg.
• Recommended dose is 16 mg, any dose above 16 mg should be justified.
Managing Withdrawal Symptoms

- Anxiolytics (use very carefully and in limited quantities). Alpha 2 agonists are preferred.
- Non-opioid pain relievers (NSAIDs or acetaminophen), while considering risks vs. benefits
- Antidiarrheal agents
- Antiemetics and Antispasmodics

Maintenance Phase

- The maintenance phase will continue indefinitely for most patients (SAMHSA 2004). Long-term maintenance is recommended due to high relapse rates. For example, in one study of 255 individuals, approximately 87% relapsed at 3 months (Ling 2009).
Characteristics of naloxone:

- It is a short acting opioid receptor antagonist that works broadly across most classes of opioids.
- It binds with high affinity to opioid receptors as a competitive antagonist.

Characteristics of naloxone:

- It is used in low doses to reverse opioid side-effects such as respiratory depression, sedation and hypertension without significantly reversing analgesia.
- At high doses, it blocks opioid analgesia and causes precipitated opioid withdrawal.
- It is approximately 45% protein-bound, primarily to albumin.
- It is rapidly metabolized by glucuronidase and to naloxone-3-glucuronide in the liver and then excreted primarily in urine.
Advantages of buprenorphine – naloxone maintenance therapy:

- Compared to methadone, it diminishes the risk for respiratory depression from overdose.
- It produces only mild withdrawal symptoms even upon abrupt termination as compared with methadone.
- It provides a better safety margin for office–based practices compared with other opioid addiction treatment maintenance therapies.
- Its feasibility for office–based practice allows for it to reach a larger population base.
- It has similar success rates for treating opioid addiction to those from specialized treatment centers using methadone.
- It is proven to be cost-effective when taking into account improvement in the quality of life of the patient, as compared to no treatment.
- Patients were more likely to report abstinence, be involved in a 12 step recovery program, be employed, and have improved psychosocial functional status (for example, they are less likely to be unhappy, have negative personality changes, or do regretful things/hurt family).

Rationales for using bup/nal in pain management:

- There are no current published studies which show effectiveness of bup/nal for pain relief in non-opioid dependent chronic pain patients.
- This may be because buprenorphine only partially activates the mu opioid receptor in low doses and only reaches a plateau as doses are increased in terms of analgesic effect.
- High dose buprenorphine functions as an opioid antagonist and further limits its analgesic affect which further limits the drugs ability to provide adequate pain relief in patients without opioid dependence or addiction.
Rationales for using bup/nal in pain management:

- Buprenorphine diminishes the risk for addiction and abuse of opioid medications in chronic pain patients
- Patients on high-dose opioids may develop opioid tolerance and/or opioid–induced hyperalgesia and often require alternative treatment for pain relief
- Buprenorphine/naloxone could be used to help taper patients off/lower their high-dose opioids

Rationales for using bup/nal in pain management:

Bup/nal therapy in pain patients with opioid dependence
- One study showed that chronic pain patients who had already converted from full agonist opioid therapy to buprenorphine/naloxone therapy experienced a 2.3 point pain reduction (on a 0–10 pain scale) within 60 days of the switch
- A primary care retrospective chart review study found that patients who had nonmalignant chronic pain as well as opioid dependence showed a reduced pain level if they stayed on buprenorphine/naloxone therapy and eventually required lower doses of it over time.
- Several randomized clinical trials showed evidence that chronic pain patients with opioid dependence experienced a 12.7% reduction of pain with buprenorphine/naloxone therapy
Possible mechanisms of bup/nal therapy in pain patients with opioid dependence

- Recent studies have shown that buprenorphine is anti-nociceptive through activation of the mu opioid receptor
- Additionally, buprenorphine exerts an anti-hyperalgesic effect with a longer halftime than its analgesic effects in humans
- Buprenorphine has been shown to reverse hyperalgesia induced by opioids through "buprenorphine induced anti-nociception"
- Buprenorphine's kappa receptor antagonism competes with the effect of spinal dynorphin – an endogenous kappa receptor agonist that increases following opioid exposure and contributes to opioid induced hyperalgesia. Thus, buprenorphine decreases the effect of spinal dynorphin resulting in decreased opioid induced hyperalgesia.

Buprenorphine alone in pain patients without opioid dependence

- One study showed the transdermal buprenorphine significantly alleviated chronic back pain in opioid naive patients
- Other studies have shown that transdermal buprenorphine was effective in reducing nonmalignant persistent pain, but it was only effective in 11% of the study subjects. Additionally, 41% of patients in that same study discontinued the treatment due to unacceptable side effects/inadequate pain relief
- Some studies have shown overall improvement in quality of life when administering transdermal buprenorphine patches, but with only moderate pain reduction.
- A similar study found that administering buprenorphine patches to osteoarthritis patients help to improve sleep and motor movement, but did not functionally reduce pain for these patients.
- Some studies have shown that buprenorphine alleviated pain in cancer patients and can improve the quality of life in these patients.
Buprenorphine alone in pain patients with opioid dependence

- By contrast using buprenorphine alone in patients with opioid dependence lead to good/complete pain relief, improved duration of sleep, improved quality-of-life and reduced the need for additional sublingual buprenorphine (transdermal buprenorphine used in this study).
- 80% of the participants reported good pain relief and 70% of them moved onto a buprenorphine/naloxone therapy
- randomized clinical trials have shown that chronic pain patients placed on sublingual buprenorphine after failing other opioid therapies experienced substantial pain relief (66–82% pain reduction)

Clinical uses of Buprenorphine/Naloxone

A flowchart illustrating the clinical effect of buprenorphine/naloxone (bup/na) on various categories of chronic pain patients with or without opioid dependence or addiction. OIH: opioid-induced hyperalgesia
methadone in pain management

- It's a full agonist at the mu opioid receptor and antagonist at the glutaminergic NMDA receptor.
- The NMDA receptor plays an important role in neuronal excitation, memory, opioid tolerance, and opioid induced hyperalgesia and activation of this receptor is one mechanism by which methadone may be effective in treating neuropathic pain.
- Methadone inhibits reuptake of serotonin and norepinephrine making it useful in treating other pain arising from other etiologies as well.
- It has a number of adverse pharmacological properties that make it rather difficult to use in managing pain including:
  - A long and unpredictable half-life (13–58 hours)
  - Individual serum levels may vary greatly (ranging from 41–95% with an average bioavailability of about 80%)
  - It interacts frequently with other medications
  - May produce significant cardiac toxicity with increased QTC intervals,
  - May cause hypoxia and severe pulmonary edema when used concurrently with benzodiazepines.

Bup/nal versus methadone in pain management

- A randomized clinical trial comparing the two treatments in opioid dependent pain patients found that both increased treatment retention rate and the analgesic effect did not significantly differ between these two drugs, but methadone was superior in reducing illicit opioid use.
- The same study showed that subjects receiving buprenorphine/naloxone had better improvement in mood, energy, personality, and the psychological component of chronic pain as compared to those on methadone
- Suboxone is likely to be superior to methadone in at least two patient populations: pregnant women with opioid dependence and newborn babies to opioid dependent mothers (fewer neonatal abstinence symptoms and higher birth weight), as well as in patients with renal failure.
Probability of Continuing Use

• The likelihood of long-term use increases based on the length of the initial prescription, according to the CDC
• The likelihood of long-term use increases sharply after the third and fifth days of opioid prescription and spikes after the 31st day
• According to the CDC, long term use also increases with a second prescription of refill, a 700 MME cumulative dose and an initial 10 or 30 day supply
Virginia’s Board of Medicine Opioid Prescription Regulations

- The medical record should document the presence of one or more recognized medical indications for prescribing an opioid analgesic.
- Treatment of a patient who has a history of substance use disorder should, if possible, involve consultation with an addiction specialist before opioid therapy is initiated (and follow-up as needed).
- Prescribing physicians are required to request information from the state’s PMP at the time of initiating a new course of treatment to a human patient that includes the prescribing of opioids anticipated to last more than 14 consecutive days.
- For acute pain, the amount given should not be more than a 7-day supply, and 14 days after surgery.
- Opioid therapy should be presented to the patient as a therapeutic trial or test for a defined period of time (usually no more than 90 days) and with specified evaluation points.
- The physician should regularly review the patient’s progress and should be obtained from family members.
- Periodic drug testing.

Prescribing Opioids for Chronic Pain

The second part of the new Virginia regulations covers opioid prescription for chronic pain. Providers must conduct a physical exam of the patient and take an oral history. The doctor or other prescriber must also evaluate the patient’s mental health. Mental health can be a key factor in determining the probability the patient who uses opioids will become addicted.

There are nine evaluation items that must be recorded:
1. Current treatment for pain and past treatments
2. How intense the pain is and the scope of the pain
3. The diseases and conditions (such as injury) that are causing the patient’s pain
4. How the pain is affecting the patient’s physical and emotional health – including his/her quality of life and daily activities such as sleeping, eating, and walking
5. The patient’s history of addiction, substance abuse, and psychiatric problems – and those of any family members
6. The results of a urine test to determine what drugs are in the patient’s system or a serum medication test
7. A Prescription Monitoring Program (PMP) query – as defined in the Virginia Code
8. The risk of substance abuse based on the patient’s prior history
9. A request to see and examine prior medical reports and records

Prescribers of opioids are also required to review the safe and best way to store controlled medications that contain opioids and the proper way to dispose of them. Prescribers must also discuss with patients, where the opioid prescriptions are not effective, a methodology for terminating the use of the opioids.
Conclusion

• Improving prescribing practices and the way pain is treated is one avenue to help prevent misuse, addiction and overdose, while ensuring legitimate access to pain management.