Opioids: Overview, Uses and Management of Acute and Chronic Pain

A Peer-Reviewed Publication
Written by Dr. Nicholas B. Hill

Educational Objectives
At the conclusion of this educational activity participants will be able to:
1. Discuss opioid agnostics and antagonists.
2. Describe the pharmacokinetics of opioids.
3. Discuss the mechanisms of pain.
4. Identify opioid dependence and screening for narcotic abuse and screening for narcotic abuse.
5. Ensure safe prescribing methods in your practice.

Author Profile
Dr. Nicholas B. Hill is a comprehensive oral and maxillofacial surgeon currently practicing just outside of the greater Philadelphia Pennsylvania area. Dr. Hill is dedicated to his patients comfort and focuses on achieving long lasting solutions pertaining to their overall oral health and wellbeing. Prior to his recent associateship position at Bala Institute of Oral Surgery, he completed a four year residency at Temple University Hospital Oral and Maxillofacial Surgery. He also completed a one year oral and maxillofacial surgery internship at John Peter Smith Hospital in Fort Worth Texas and a one year general practice residency after completion of dental school at West Virginia University. Dr. Hill received his doctorate of dental surgery from West Virginia University School of dentistry. He received his Bachelor of Science degree in animal and veterinary sciences at West Virginia University in three and a half years. Dr. Hill serves as an attending in the department of oral and maxillofacial surgery at the Capital Health System in Trenton New Jersey as well as an adjunctive faculty attending at Temple University Hospital oral and maxillofacial surgery department. Dr. Hill can be reached at nicholasbhill@gmail.com.

Author Disclosure
Dr. Nicholas B. Hill has no commercial ties with the sponsors or providers of the unrestricted educational grant for this course.

Abstract
Opioids are among the world’s oldest known drugs used in acute, chronic and palliative care. Pain is treatable in patients with the correct understanding of physiology and its triggers. Opioids play a major and important role in management of pain. Understanding opioids as well as alternative medications that are non-narcotic dependent can help any practitioner manage their patients more effectively and safely. Patients undergoing surgical procedures of any type may require pain medicine and more so than not an opioid is the recommended choice. The last thing a physician should ever do is not adequately control a patient’s pain post operatively and in today’s world, many patients are already taking high doses of opioids to control other ailments. Given the extensiveness of areas encompassing pain, opioids and management, this educational course will provide a clear understanding and a multimodal approach for treating pain.

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Information shared in this CE course is developed from clinical research and represents the most current information available from evidence based dentistry.

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References:

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Abstract
Opioids are among the world’s oldest known drugs used in acute, chronic and palliative care. Pain is treatable in patients with the correct understanding of physiology and its triggers. Opioids play a major and important role in management of pain. Understanding opioids as well as alternative medications that are non-narcotic dependent can help any practitioner manage their patients more effectively and safely. Patients undergoing surgical procedures of any type may require pain medicine and more so than not an opioid is the recommended choice. The last thing a physician should ever do is not adequately control a patient’s pain post operatively and in today’s world, many patients are already taking high doses of opioids to control other ailments. Given the extensiveness of areas encompassing pain, opioids and management, this educational course will provide a clear understanding and a multimodal approach for treating pain.

History:
Opioids originate from a plant indigenous to the Indochina region called the papaver somniferum. Opium contains approximately 12% morphine, an alkaloid, which is frequently processed chemically to produce heroin for the illegal drug trade and for legal medicinal use in some countries. The sap of the opium plant also includes the alkaloid codeine and its similarly structured cousin thebaine. It also contains non-analgesic alkaloids such as papaverine and noscapine. The Sumerian, Assyrian, Egyptian, Indian, Minoan, Greek, Roman, Persian and Arab empires all made widespread use of opium, which was the most potent form of pain relief available, allowing ancient surgeons to perform prolonged surgical procedures. Opium is derived from the Greek word for “juice” and is obtained from the poppy of papaver somniferum. The main producer of opioids is Afghanistan with the United States being the number one consumer of opioids worldwide. Opioids wholesale price at approximately $3000 per kilogram and retail in price around $16,000 per kilogram.

Table 1a. Classification

<table>
<thead>
<tr>
<th>Natural Alkaloids of Opium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenanthrenes</td>
</tr>
<tr>
<td>Benzyloquinolines</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Synthetic Derivatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylpiperidines</td>
</tr>
<tr>
<td>Propianilides</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Semi-Synthetic Derivatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>diacetylmorphine (heroin), hydromorphone (Dilaudid™), oxymorphone, hydrocodone, oxycodone</td>
</tr>
</tbody>
</table>

Opioid medications are used to provide analgesia and euphoria. Clinicians must understand that narcotic medications do not produce amnesia and that an opioid medication used alone provides inferior sedation technique. Opioids produce excellent analgesia but they do not cause a patient to lose sensations of touch, proprioception and consciousness. Patients who are given opioids alone will still retain awareness of the procedure and their memory will remain clear.

Structure:
Opioids can be classified as natural, synthetic or semi-synthetic substances which produce their effect by binding to receptors causing a morphine-like effect. (Table 1a) An agonist is a chemical that binds to a receptor and activates the receptor to produce a biological response. Whereas an agonist causes an action, an antagonist blocks the action of the agonist and an inverse agonist causes an action opposite to that of the agonist. Opioids produce analgesia without loss of touch, proprioception or consciousness as previously mentioned. The chemical structure of the opioid molecule is what determines its potency. Levo-isomers are considered to be the most active (left orientation of a molecule). Morphine is a naturally occurring levo-isomer (L-morphine). To make a semisynthetic opioid, the morphine molecule will be changed by minor modifications. Potency and rate of equilibration between plasma and the site of the drug are the main pharmacodynamic differences between opioids. (Table 1b)

Table 1b. Common Opioid Agonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>1</td>
</tr>
<tr>
<td>Meperidine</td>
<td>0.1</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>75-125</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>500-1000</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>10-25</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>250</td>
</tr>
</tbody>
</table>
Table 1b shows some of the most commonly used opioid agonists and relates their potency.

**Mechanism of Action:**

There are many stereospecific opioid receptors noted in Table 2 within the central nervous system; mainly Mu, Kappa and Delta receptors. Opioids act as agonists at these stereospecific receptors in the central nervous system (CNS) and outside the CNS in peripheral nervous system (PNS). Decrease in neurotransmission is the principal effect of opioids. This results in a decrease in release of acetylcholine, dopamine, norepinephrine and substance P from presynaptic neurotransmitters (Table 3). The effect of opioid receptor activation is increased potassium conductance, leading to hyperpolarization of cellular membranes. The two main effects and side effects of opioids, analgesia and depression of ventilation respectively, are the results of depression of cholinergic transmission in the CNS. Again, this causes opioid induced inhibition of acetylcholine release from nerve endings. The reader is referred to many available texts that describe peripheral and central pain mechanisms in depth.

**Table 2. Opioid Receptor Classification**

<table>
<thead>
<tr>
<th>Features</th>
<th>Mu 1</th>
<th>Mu 2</th>
<th>Kappa</th>
<th>Delta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effects</td>
<td>Analgesia</td>
<td>Analgesia</td>
<td>Analgesia</td>
<td>Analgesia</td>
</tr>
<tr>
<td>Euphoria</td>
<td>Depression of ventilation</td>
<td>Dysphoria, Sedation</td>
<td>Depression of ventilation</td>
<td></td>
</tr>
<tr>
<td>Low abuse potential</td>
<td>Physical dependence</td>
<td>Low abuse potential</td>
<td>Physical dependence</td>
<td></td>
</tr>
<tr>
<td>Miosis</td>
<td>Miosis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bradycardia</td>
<td>Bradycardia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothermia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary retention</td>
<td>Diuresis</td>
<td>Urinary retention</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. **Examples of Pain Modulating Neurotransmitters**

<table>
<thead>
<tr>
<th>Excitatory</th>
<th>Inhibitory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutamate</td>
<td>Enkephalins</td>
</tr>
<tr>
<td>Aspartate</td>
<td>Angiotensin</td>
</tr>
<tr>
<td>Vasoactive intestinal polypeptide</td>
<td>Substance P</td>
</tr>
<tr>
<td>Cholecystokinin</td>
<td>Somatostatin</td>
</tr>
<tr>
<td>Gastrin releasing peptide</td>
<td></td>
</tr>
<tr>
<td>Angiotensin peptide</td>
<td></td>
</tr>
<tr>
<td>Substance P</td>
<td></td>
</tr>
<tr>
<td>Angiotensin peptide</td>
<td></td>
</tr>
<tr>
<td>Substance P</td>
<td></td>
</tr>
<tr>
<td>Enkephalins</td>
<td></td>
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<tr>
<td>Angiotensin peptide</td>
<td></td>
</tr>
<tr>
<td>Substance P</td>
<td></td>
</tr>
<tr>
<td>Somatostatin</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1.** Demonstrates how an action potential is not produced as an opioid binds to a stereospecific receptor in the CNS and/or PNS. An efflux of potassium is produced but an influx of calcium is not produced, therefore causing an inhibitory effect which does not result in neurotransmission.

The receptors for opioids (Table 2) are listed as mu, delta and kappa. These receptors ultimately cause a decrease in neuronal activity by inhibition of adenyl cyclase and inhibition of ion movement across calcium and potassium channels. Similar to local anesthetics, the effects of opioids are not only dose related, but also related to their pKa, lipid solubility and percentage of protein binding (Table 4). Based on these receptors, drugs can be divided into four (4) groups; agonists, antagonists, agonist-antagonists and partial agonists. Pure agonists have affinity for binding plus efficacy. Pure antagonists have affinity for binding but have no efficacy. Mixed agonist-antagonists produce agonist effect at one receptor and an antagonist effect on another. Partial agonists have affinity for binding but with low efficacy (Figure 2).

**Table 4**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Action Affected</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>pKa (opioids are weak bases)</td>
<td>Onset</td>
<td>Lower pKa = rapid onset of action</td>
</tr>
<tr>
<td>Lipid solubility</td>
<td>Potency</td>
<td>Increase lipid solubility = Increased potency</td>
</tr>
<tr>
<td>Protein binding</td>
<td>Duration</td>
<td>Increased protein = Duration increased</td>
</tr>
</tbody>
</table>
Pharmacokinetics:
Pharmacokinetics refers to how the drug interacts and what it does to the body at a receptor, and its effects at a cellular and organ system level i.e. CNS, respiratory, genitourinary, placenta/fetus, gastrointestinal systems (Table 5). There are four main categories to remember when drugs are given either intravenously or orally. These are absorption, distribution, metabolism and excretion. Understanding these concepts will help a clinician control either the loading dose or maintenance dose of the drug. Clearance of opioids principally occurs by hepatic metabolism, but large differences in lipid solubility account for pharmacokinetic differences. Analgesia is most effective when opioids are administered before the painful stimulus occurs. This should be taken into consideration when administering an opioid to patients before surgical stimulus is performed. One of the most important factors to take into consideration when dosing patients appropriately with pain medicine is to obtain a thorough history and physical. This will allow the practitioner to understand and be better at controlling patients’ effective dose and titratability.

Opioids cause little reduction in cerebral blood flow. Patients who experience nausea and vomiting to opioid administration varies among the population but is commonly seen with either intravenous or oral administration. The area of the brain responsible for nausea and vomiting is the area postrema of the medulla. There is also evidence of dopaminergic and serotonin activity that also causes nausea. Miosis (constriction of pupils) is a process that occurs by most mu and kappa receptor agonists. The area of the brain responsible for this process is called the Edinger-Westphal nucleus. The Edinger Westphal nucleus is the accessory parasympathetic cranial nerve nucleus of the third (III) cranial nerve (oculomotor nerve). A physician may notice constriction of the pupils or pin point pupils with patients who are overdosed on opioids. If opioids are administered too quickly intravenously, production of muscle rigidity could occur. This process could also be exacerbated with simultaneous use of nitrous oxide and in the elderly population. Peripheral vasodilation does occur with opioid administration and patients should be monitored judiciously. Blood pressure needs to be monitored very closely to assess postural hypotension in patients who are supine and in erect positions. Bradycardia can also occur with administration of opioids. As noted before in Table 3, all mu receptor agonists cause a decrease in heart rate.

Table 5.

<table>
<thead>
<tr>
<th>Side Effects of opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>Urinary retention</td>
</tr>
<tr>
<td>Depression of ventilation</td>
</tr>
<tr>
<td>Sedation</td>
</tr>
<tr>
<td>Central nervous system excitation</td>
</tr>
<tr>
<td>Activation of latent viral infections</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
</tr>
<tr>
<td>Water retention</td>
</tr>
</tbody>
</table>

Opioid Agonists-Antagonists:
These drugs bind to mu receptors and produce little or no effect. Often a small agonistic effect will occur at the kappa and delta receptors. Dysphoric effects can occur just as they can in opioid agonists. The main advantages of opioid agonist-antagonists are the ability to produce analgesia with minimal ventilatory depression and a low risk for physical dependence. These drugs include Pentazocine, Butorphanol, Nalbuphine, Buprenorphine and Nalorphine.

Figure 2.

**Agonists and Antagonists**

<table>
<thead>
<tr>
<th>Agonists</th>
<th>Drugs that occupy receptors and activate them.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antagonists</td>
<td>Drugs that occupy receptors but do not activate them. Antagonists block receptor activation by agonists.</td>
</tr>
</tbody>
</table>

Agonist alone

<table>
<thead>
<tr>
<th>Full activation</th>
</tr>
</thead>
</table>

Agonist + antagonist

<table>
<thead>
<tr>
<th>Less activation</th>
</tr>
</thead>
</table>

Antagonist alone

<table>
<thead>
<tr>
<th>No activation</th>
</tr>
</thead>
</table>
**Opioid Antagonists:**
The creation of an opioid antagonist is achieved with little modification of an opioid agonist. The opioid receptor’s affinity for an opioid antagonist results in displacement of the opioid agonist from the mu receptors. Naloxone is the treatment for reversal of opioid agonists. Naloxone has no analgesic activity at all and is a competitive antagonist at mu, kappa and sigma receptors. It displaces morphine and other opioids from the receptor site and reverses all actions of the opioid quickly. Naloxone is given (1-4 ug/kg IV) and quickly reverses the analgesic and depression ventilatory state. Its duration of action is anywhere from 30-45 minutes. This short duration may require re-administration of the antagonist to prevent return of the depressive states. Nausea and vomiting is common after opioid antagonist administration. Following administration, an increase in blood pressure could be noticed.

![Naloxone](image)

**FDA Pregnancy Categories**
The FDA has established five categories to indicate the potential of a drug to cause birth defects if used during pregnancy. The categories are determined by the reliability of documentation and the risk to benefit ratio. They do not take into account any risks from pharmaceutical agents or their metabolites in breast milk. (Drugs.com)

The categories are:

**Category A**
Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).

**Category B**
Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

**Category C**
Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

**Category D**
There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

**Category X**
Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

**Category N**
FDA has not classified the drug.

**Medications:**

**Acetaminophen:**
- 325mg, 500mg, 650mg
- Effective oral analgesic and antipyretic
- Weak anti-inflammatory activity
- New intravenous formulation developed in 2010
- Mechanism not completely understood
- Main mechanism inhibition of COX (cyclooxygenase)
- Recent findings show highly selective for COX-2
- Max dose:
  - Tylenol™ containing products: cumulative dose 4g/ day
  - Tylenol extra strength™: do not exceed 3g/day
- Pregnancy Category B
- Crosses placenta
- Excreted in breast milk
- Caution: Glucose-6-phosphate-dehydrogenase deficiency
  Alcoholics
  Risk for Stevens Johnson syndrome (rare)

**Codeine:**
- Schedule II
- Antitussive
- 15mg, 30mg, 60mg oral solution 30mg/5ml
- About 1/10th the potency of morphine
- Lower efficacy than morphine
- About 10% converted to morphine
- 10% of patients do not possess this enzyme (typically women)
- Pregnancy Category C/D
- Excreted in breast milk
- **Black box warning:** respiratory depression and death reported in children who received codeine following tonsillectomy and or adenoidectomy that were also ultra-rapid metabolizers of codeine due to CYP2D6 polymorphism (up to 7% of Caucasians and up to 30% Asian and African populations)
- Caution: Asthma, inflammatory bowel disease, respiratory impairment
Hydrocodone (Zohydro ER™): *NEW*
- Schedule II
- 10mg, 15mg, 20mg, 30mg, 40mg, 50mg
- Indicated for use in chronic pain patients
- New drug
- Increase risk of addiction, abuse and misuse with opioids
- Should be reserved for use in patients for whom alternative treatment options ineffective
- NOT approved for as needed (PRN) for pain relief

Figure 4.

Side effects of Hydrocodone

Central
- Drowsiness
- Dizziness
- Lightheadedness
- Fuzzy thinking
- Anxiety
- Abnormally happy or sad mood

Skin
- Rash
- Itching

Respiratory
- Slowed or irregular breathing
- Chest tightness

Gastric
- Nausea
- Vomiting

Urinary
- Difficulty urinating

Hydrocodone with acetaminophen:
- Schedule III
- Vicodin™, Lor cet™, Hycet™, Norco™, Lortab™ Elixir, Vicodin™ ES, Xodol™, Zamicet™
- Moderate to severe pain
- Antitussive
- Avoid in hepatic impairment patients
- Pregnancy category C
- New dosage limit (January 2014): no more than 325mg/dosage unit for prescription medications that contain acetaminophen
- Still DO NOT EXCEED 4000mg of Tylenol™ a day

Oxycodone:
- About 10x potency of codeine
- Moderate to severe pain
- Not to be used with severe asthma or breathing problems or blockage in stomach
- Controlled release formulation (OxyContin™)

Figure 5.

Side effects of Oxycodone

Central
- Hallucination
- Confusion
- Fainting
- Dizziness
- Loss of appetite
- Drowsiness
- Headache
- Mood changes

Skin
- Hives
- Rash
- Flushing
- Sweating
- Itching

Respiratory
- Difficulty breathing
- Slowed breathing

Gastric
- Nausea
- Vomiting

Urinary
- Difficulty urinating

NSAIDS (Nonsteroidal anti-inflammatory)
- Nonspecific inhibitors of COX-1 and COX-2
- NSAID drug classes
  - Acetic acids: diclofenac, indomethacin, ketorolac
  - COX-2 Inhibitors: celecoxib
  - Fenamates: meclofenamate
  - Oxicams: meloxicam, piroxicam
  - Propionic acids: ibuprofen, naproxen
  - Pyrazolones: phenylbutazone
  - Salicylates: aspirin, salsalate
- COX (cyclooxygenase) converts arachidonic acid to prostaglandins and leukotriene
- COX-2 primarily associated with inflammation and is primary target of NSAIDS
- NSAIDS also reduce prostaglandin production
- Associated with pyrogen interleukin-1 è antipyretic action
- COX-2 promotes thrombosis

Preoperative Phase:
A rapid and smooth recovery is something all clinicians try to achieve with their patients; optimizing all phases of the perioperative period including:
- Patient education
- Using minimally invasive techniques
- Controlling post-operative pain
- Aggressive rehabilitation (if applicable)
- Improve functional mobility and harmony
Patient education plays a huge role in controlling post-operative pain. This includes providing the patient with pamphlets before surgery and verbal instructions by the dentist, nurses, assistant(s)/staff before and on the day of surgery. “Psychological preparation of patients undergoing surgery has been shown to shorten hospital stays and to reduce the need for post-operative analgesics.” A thorough history and physical should be taken the day of consultation by the physician to identify challenging populations. This includes:
- Opioid tolerant
- Elderly
- Physically limited

A well thought-out plan should be in place for how patients will be managed post-operatively. Opioid tolerant patients are at an increased risk for high post-operative opioid requirements. It is of the utmost importance to give the patient or have the patient take his or her baseline dose and then additional medication to cover the surgical and breakthrough pain for the day of surgical intervention as well as during the post-operative phase.

### Postoperative Phase:
Any of the non-opioid over the counter medications has the potential for abuse and misuse by patients as well as opioid derived medications. Recommended doses are always outlined on the box of the medication prescribed or purchased over the counter. These should always be followed and read by the patient. Special care should be taken by all patients and prescribing dentists and physicians relating to adverse effects and interactions with other medications the patients may be taking. There are no specific and outlined guidelines that exist for “best” postoperative pain management following dental and oral surgical procedures. A clinician can only keep up to date by reading recent case based and or literature reviews as well as taking continuing education classes. Table 6 outlines adverse physiologic effects that patients can have following surgical procedures relating to postoperative pain. These should be taken into consideration at all times when patients undergo an operation.

The CDA, CDC and WebMD™ have published guidelines prescribing post-operative medications for pregnant patients as well as safe antibiotics. A pregnant patient’s obstetric gynecologist must also be contacted and provide written medication recommendations that should be placed in the patient's chart after the patient gets clearance from the surgeon or dentist.

Larrazabal and Penarrocha’s research shows that patients with poor oral hygiene who smoke preoperatively and postoperatively experience more pain in the postoperative phase than do patients who had better oral hygiene and did not smoke. The length of the surgical procedure also plays a huge role in the amount of patient’s postsurgical pain perception. Re-visitation of the patient’s pain symptomatology is one of the first steps in management of a patient’s continued postoperative pain diagnosis. This could occur for a number of reasons including other sites of pathology, neurogenic, TMJ and intracranial dysfunctions.

### Table 6. Adverse Physiologic Effects of Postoperative Pain

<table>
<thead>
<tr>
<th>Pulmonary system (decreased lung volume)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atelectasis</td>
</tr>
<tr>
<td>Ventilation to perfusion mismatching</td>
</tr>
<tr>
<td>Arterial hypoxemia</td>
</tr>
<tr>
<td>Hypercapnia</td>
</tr>
<tr>
<td>Pneumonia</td>
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</table>

<table>
<thead>
<tr>
<th>Cardiovascular system (sympathetic nervous system stimulation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic hypertension</td>
</tr>
<tr>
<td>Tachycardia</td>
</tr>
<tr>
<td>Myocardial ischemia</td>
</tr>
<tr>
<td>Cardiac dysrhythmias</td>
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<table>
<thead>
<tr>
<th>Endocrine system</th>
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</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
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<tr>
<td>Sodium and water retention</td>
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<td>Protein catabolism</td>
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<table>
<thead>
<tr>
<th>Immune system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased immune function</td>
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<tr>
<td>Coagulation system</td>
</tr>
<tr>
<td>Increased platelet adhesiveness</td>
</tr>
<tr>
<td>Decreased fibrinolysis</td>
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<tr>
<td>Hypercoagulation</td>
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<table>
<thead>
<tr>
<th>Genitourinary system</th>
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<tbody>
<tr>
<td>Urinary retention</td>
</tr>
</tbody>
</table>

### Opioid Tolerance:
Dependence is defined as the propensity to experience an abstinence syndrome after discontinuation of a drug or administration of an antagonist drug (need to keep taking the drug to avoid withdrawal symptoms). Addiction is a chronic condition characterized by the compulsive use of a substance resulting in harm whether physical, psychological or social and continued use despite that harm (intense craving and compulsive use). Opioid tolerance, dependence and addiction are all manifestations of brain changes that come from chronic opioid use and abuse. Addiction, however, entails a wide ranging, complex and longer lasting brain abnormality. The medications used to treat these issues above such as methadone; LAAM (levomethadyl acetate), buprenorphine and naltrexone act on the same brain structures as opioids but have protective and/or normalizing effects. For an opioid dependent and addicted patient, pharmacotherapies cannot be used alone but in conjunction with psychosocial treatments. These patients need to understand that there is a huge brain origin component of addiction and
that their illness has a biological basis. These patients more importantly need to realize that they are not “bad” people. When our brain recognizes pain and an opioid is administered to treat this pain, the same response and triggers of opioid receptors also gives patients the feeling of reward and pleasure. These rewards and pleasures are the same that we experience when we eat or have sexual experiences. However, in the absence of pain, a person can become motivated to abuse the opioid based on these biochemical processes mentioned above. The area of the brain responsible for the rewarding mechanism occurs in the ventral tegmental area in the nucleus accumbens and prefrontal cortex.

Withdrawal of a drug is related to its time course and the elimination half-life of the opioid. Symptoms can appear in 6 to 12 hours and reach a peak 24 to 72 hours following cessation of a drug. Withdrawal symptoms are listed below (Table 7).

<table>
<thead>
<tr>
<th>Table 7. Withdrawal Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset by feelings of anxiety, nervousness, irritability</strong></td>
</tr>
<tr>
<td>Chills and hot flushes</td>
</tr>
<tr>
<td>Wetness including salivation, lacrimation, rhinorrhea and diaphoresis</td>
</tr>
<tr>
<td>Piloerection</td>
</tr>
<tr>
<td>Nausea, vomiting, abdominal cramps, insomnia</td>
</tr>
</tbody>
</table>

Continuing research to understand everything there is to know about dependence, addiction and the medications used in treating these symptoms is ongoing although it is clear that all of the current treatments help manage these types of patients. Research does show that one of the primary driving factors for dependence comes from withdrawal of the drug itself. Tolerance of opioids occurs when repeated exposure of the drug causes the brain cell opioid receptors to become less responsive to the opioid stimulation. Dependence occurs in an area at the base of the brain called the locus ceruleus.

**Facts pertaining to opioids:**

It is true that more than 150 people die from drug overdose in the United States every day. The rate of overdose related deaths has more than tripled since the early 90's. It was reported in 2008 that most of the drug related overdose deaths were caused by prescription drugs. Over a half of million people in 2009 were treated by the emergency department relating to misuse of prescription painkillers. These deaths are most commonly from drugs that are prescribed from educated physicians, with internal medicine, primary care and dentists being at the top of the list. The CDC has implemented an operational prescription drug monitoring program in more than 36 states that electronically tracks suspected abuse. State policies are available to all practitioners and should be strictly followed so that we can reverse this epidemic prescription battle.

**Opioids in your practice:**

It is not uncommon for practitioners to keep commonly prescribed narcotic medications in their office for ease of availability to patients post surgery. Intravenous opioids as well as general anesthetics, benzodiazepines and emergency cart medications are also kept available as well and stored for later use. These medications should be recorded immediately as they arrive and opened for storage. A detailed log should be kept of the drugs that are currently in your office, expiration dates and the time and date that these drugs were recorded. Emergency cart drugs should be locked during non-business hours in a crash case or cart and opened during intravenous sedations or general anesthetics. Paralytic drugs are commonly kept in a refrigerator that must be lockable. These medications need to be immediately available for emergency situations if they were to arise. Narcotic medications, especially, should be locked and stored in a double lockable cabinet that only the practitioner can unlock. Again, a detailed description of locked storage for particular schedules of medications can be reviewed on the DEA website. Intravenous medications or those in PO form (taken by mouth) should only be drawn up and dispensed by the practitioner.

Practitioners will have to obtain a DEA number for administration of certain classes of medications. These classes (I-V) of controlled substances can be obtained by visiting and reviewing the DEA website as well as instructions for obtaining a DEA number for prescribing. Once a DEA number is obtained, the certificate registration number must be readily available for office inspections. Records for scheduled drugs must be maintained for a minimum of 2 years. A very common misperception is that a single DEA number can be used from state to state as well as from office to office. The answer to this question is no. Therefore, he or she must obtain a separate DEA registration for each state. This amendment was issued to make it easier for practitioners to understand the requirements of the Controlled Substances Act (CSA) and its implementing regulations. This is documented again on the DEA Diversion website under 21 U.S.C. § 822(e). When a prescription is written by a prescriber, there are mandatory written requirements that must be present for the medication to be filled including:

1. Drug name
2. Strength
3. Dosage form
4. Quantity prescribed
5. Directions for use
6. Number of refills (if any) authorized
7. Prescriber’s name and practice name
8. Doctor’s signature
9. License number
10. DEA number
11. Appropriate script paper/pad
Conclusion:
This course is intended to make clear the concepts behind opioid physiology and recommendations to manage your patients more effectively and safely. Management of pain can seem relentless at times and difficult to obtain. Opioid restrictions are continuing to be more strictly regulated with the amount of abuse potential from patients as well as the abuse from overprescribing physicians. It is of the utmost importance to realize the harm that can happen to a patient with overdose and overuse. Continuing education is a must to practicing clinicians to understand the physiology of all medications that they prescribe and use on a day in and day out basis.

References
10. Figure 2. <http://www.zazzle.com/chart_of_the_side_effects_of_opioid_hydrocodone_poster-228470819736833146>

Author Profile
Dr. Nicholas B. Hill is a comprehensive oral and maxillofacial surgeon currently practicing just outside of the greater Philadelphia Pennsylvania area. Dr. Hill is dedicated to his patients comfort and focuses on achieving long lasting solutions pertaining to their overall oral health and wellbeing. Prior to his recent associateship position at Bala Institute of Oral Surgery, he completed a four year residency at Temple University Hospital Oral and Maxillofacial Surgery. He also completed a one year oral and maxillofacial surgery internship at John Peter Smith Hospital in Fort Worth Texas and a one year general practice residency after completion of dental school at West Virginia University. Dr. Hill received his doctorate of dental surgery from West Virginia University School of dentistry. He received his Bachelor of Science degree in animal and veterinary sciences at West Virginia University in three and a half years. Dr. Hill serves as an attending in the department of oral and maxillofacial surgery at the Capital Health System in Trenton New Jersey as well as an adjunctive faculty attending at Temple University Hospital oral and maxillofacial surgery department. Dr. Hill can be reached at nicholasbhill@gmail.com

Author Disclosure
Dr. Nicholas B. Hill has no commercial ties with the sponsors or providers of the unrestricted educational grant for this course.
Questions

1. Miosis or constriction of the pupils is caused by which of the following receptors?
   a. Mu
   b. Kappa
   c. Sigma
   d. a & b

2. Which one of the following is not a natural derivative of opium?
   a. Morphine
   b. Codeine
   c. Papaverine
   d. Fentanyl

3. Opioids can be classified as natural, synthetic or semi-synthetic substances which produce their effect by binding to receptors causing:
   a. Increased release of acetylcholine
   b. Morphine like effects
   c. Antagonism at the Mu receptor
   d. Mydriasis of the pupils

4. Which one of the following medications is not an agonist?
   a. Morphine
   b. Vicodin®
   c. Tylenol®
   d. Naloxone

5. Opioids act at which receptors?
   a. Mu
   b. Kappa
   c. Delta
   d. All of the above

6. Which one of the following does not happen during binding of an opioid to a receptor?
   a. An efflux of potassium
   b. An efflux of calcium
   c. cAMP levels decrease
   d. The hyperpolarized neuron is less likely to now fire an action potential

7. The pKa determines which of the following properties of a drug?
   a. Onset
   b. Potency
   c. Duration
   d. None of the above

8. Lipid solubility determines which of the following properties of a drug?
   a. Onset
   b. Potency
   c. Duration
   d. None of the above

9. Protein binding determines which of the following properties of a drug?
   a. Onset
   b. Potency
   c. Duration
   d. None of the above

10. Analgesia is most effective when opioids are taken:
    a. After the procedure
    b. During the procedure
    c. Before the procedure
    d. Before and after the procedure

11. Analgesia occurs at which of the following opioid receptors?
    a. Mu1 and Mu2
    b. Kappa
    c. Delta
    d. All of the above

12. Withdrawal of opioids causes which of the following symptoms?
    a. Nervousness
    b. Chills and hot flushes
    c. Nausea/vomiting
    d. All of the above

13. Which of the following statements is incorrect?
    a. Schedule I drugs can be prescribed in the United States
    b. Narcotic prescriptions must be signed by the prescriber
    c. Emergency drugs and narcotic medications must be locked in a single or double cabinet
    d. Records for scheduled drugs must be kept for a minimum of 2 years

14. Which of the following is mandatory on a prescription?
    a. Drug name
    b. Number of refills
    c. DEA license if applicable and license number of prescriber
    d. All of the above

15. Which of the following statements is true?
    a. COX-2 is associated with inflammation and is the target of NSAIDS
    b. Oxycodone is about ten times more potent than codeine
    c. As of January 2014 the new limit for acetaminophen is 325mg in narcotic medications
    d. All of the above

16. Which of the following statements is incorrect?
    a. Clearance of opioids primarily occurs by hepatic metabolism
    b. Respiratory depression is not a major side effect of opioids and Mu receptor agonists
    c. Opioids should be titrated incrementally and slowly when administered
    d. All of the above

17. The area of the brain mostly responsible for nausea and vomiting is the:
    a. Hypothalamus
    b. Cerebral cortex
    c. Postrema of the medulla
    d. Frontal cortex

18. Which area of the brain is responsible for miosis (constriction) of the pupils?
    a. Cranial nerve I (olfactory nerve complex)
    b. Cranial nerve III (Edinger-Westphal nucleus)
    c. Cranial nerve V (trigeminal nucleus)
    d. None of the above

19. Which of the following can occur during administration of opioids?
    a. Hypotension
    b. Bradycardia
    c. Respiratory depression
    d. All of the above

20. Naloxone produces which of the following actions?
    a. Competitive antagonist at Mu, Kappa, and Sigma receptors
    b. Has no analgesic activity
    c. Reverses the analgesic and depression ventilatory state of opioids
    d. All of the above

21. Opioid receptors are found in which of the following?
    a. Peripheral nervous system
    b. Central nervous system
    c. Gastrointestinal system
    d. All of the above

22. Which of the following statements is true?
    a. Using operational prescription drug monitoring programs help track prescription abuse
    b. More than 150 people die every day from overdose
    c. Most drug related deaths are from prescription drugs
    d. All of the above statements are correct

23. Which of the following countries consumes the most opioids?
    a. Serbia
    b. Australia
    c. Holland
    d. United States

24. The opioid receptor most responsible for dysphoria is which of the following?
    a. Mu1
    b. Mu2
    c. Kappa
    d. Delta

25. Respiratory depression can be enhanced and worsen when opioids are synergistically combined with which of the following?
    a. Valium®
    b. Other narcotic medications
    c. Propofol
    d. All of the above
26. A 75 year old patient comes into your office for a procedure using intravenous conscious sedation. After a thorough medical history and prior consultation you notice that the patient is also taking oxycodone 5mg for chronic back pain 3-4 times a day. Consent is obtained, patient is hooked up to required monitors, and IV access is obtained. You administer 50mcg of fentanyl and 2 mg of Versed®. You finish your procedure and notice that it is taking a much longer time for the patient to recover and awake to full awareness. Which of the following is the most likely reason for this?

a. The patient ate a cookie in the morning
b. Liver function is decreased in older patients
c. The patient is also taking other narcotic medications
d. Both b and c

27. Which of the following statements is false?

a. Blood pressure should be monitored closely with opioid administration
b. Opioids cause peripheral vasodilation
c. Opioids should be injected quickly and forcefully
d. Bradycardia can occur with opioid administration

28. The maximum cumulative dose for Tylenol® containing products is:

a. 1mg/day
b. 2mg/day
c. 3mg/day
d. 4mg/day

29. Which of the following medications is transferred and excreted through breast milk?

a. Tylenol®
b. Hydrocodone
c. Codeine
d. All of the above

30. Which of the following medications would be most appropriate for a patient with alcoholic liver cirrhosis?

a. Oxycodone 5mg
b. Tylenol® #3
c. Vicodin® 5/325mg
d. Percocet® 5/325mg
Opioids: Overview, Uses and Management of Acute and Chronic Pain

Educational Objectives

1. Discuss opioid agonists and antagonists.
2. Describe the pharmacokinetics of opioids.
3. Discuss the mechanisms of pain.
4. Identify opioid dependence and screening for narcotic abuse and screening for narcotic abuse.
5. Ensure safe prescribing methods in your practice.

Course Evaluation

1. Were the individual course objectives met?
   - Objective #1: Yes No
   - Objective #2: Yes No
   - Objective #3: Yes No

   Please evaluate this course by responding to the following statements, using a scale of Excellent = 5 to Poor = 0.

2. To what extent were the course objectives accomplished overall?  S 4 3 2 1 0
3. Please rate your personal mastery of the course objectives. S 4 3 2 1 0
4. How would you rate the objectives and educational methods? S 4 3 2 1 0
5. How do you rate the author’s grasp of the topic? S 4 3 2 1 0
6. Please rate the instructor’s effectiveness. S 4 3 2 1 0
7. Was the overall administration of the course effective? S 4 3 2 1 0
8. Please rate the usefulness and clinical applicability of this course. S 4 3 2 1 0
9. Please rate the usefulness of the supplemental webography. S 4 3 2 1 0
10. Do you feel that the references were adequate? Yes No
11. Would you participate in a similar program on a different topic? Yes No
12. If any of the continuing education questions were unclear or ambiguous, please list them.
13. Was there any subject matter you found confusing? Please describe.
14. How long did it take you to complete this course?
15. What additional continuing dental education topics would you like to see?

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