Pain Management, Drug Diversion, & Controlled Substances Best Practices
Mark Garofoli PharmD, MBA, BCGP

Home Study Monograph
Pain Management, Drug Diversion, & Controlled Substances Best Practices

ACTIVITY DESCRIPTION
We live in an "Opioid Epidemic" where someone dies approximately every 15 minutes from prescription drug overdose. So just how do we end this "Opioid Epidemic" or at least, how do we as healthcare professionals contribute to the progress of society in the right direction? In this monograph, we will discuss overall pain management etiology, specific opioid medication pharmacological concepts, opioid overdose reversal treatments, and not only how to identify drug seeking and diversion behaviors, but possible actions to take when the behaviors are suspected. Unlike opioids, this monograph is intended to open one's eyes, elevate blood pressure and/or heart rate, and increase cognition (in relation to appropriate pain management).

TARGET AUDIENCE
The target audience for this activity is pharmacists, pharmacy technicians, and nurses in hospital, community, and retail pharmacy settings.

LEARNING OBJECTIVES
After completing this activity, the pharmacist and nurses will be able to:
• Describe the etiology and epidemiology of chronic pain.
• Identify non-pharmacological and pharmacological (both opioid and non-opioid) pain treatments.
• Describe when and how to initiation, continue, or discontinue opioid medications for the management of patients experiencing pain based on available pain management guidelines including the CDC Chronic Pain Opioid Guidelines. Concepts will include a review of patient evaluation and risk assessment tools; pain treatment objectives; patient and provider(s) agreements; urine screenings; pill counts; patient education on the safe use, storage and disposal of controlled substances; drug interactions; toxicities; & discontinuation and tapering of opioids.
• Explain how to be compliant with federal and state controlled substances laws.

After completing this activity, the pharmacy technician will be able to:
• Describe the etiology and epidemiology of chronic pain.
• Identify non-pharmacological and pharmacological (both opioid and non-opioid) pain treatments.
• Identify the best practices for the use of opioid medications based on available pain management guidelines including the CDC Chronic Pain Opioid Guidelines. Concepts will include a review of patient evaluation and risk assessment tools; pain treatment objectives; patient and provider(s) agreements; urine screenings; pill counts; patient education on the safe use, storage and disposal of controlled substances; drug interactions; toxicities; & discontinuation and tapering of opioids.
• Explain how to ensure that the best practices for the supply of, and education on, naloxone as an opioid overdose reversal treatment are in place within a pharmacy practice.
• Describe the best practices for identifying red flag patient drug seeking & diversion behaviors, and ultimately working with patients, prescribers, law enforcement, and others as appropriate, concerning patients suspected of drug seeking behavior and diversion.
PharmCon, Inc. is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

PharmCon, Inc. is approved by the California Board of Registered Nursing (Provider Number CEP 13649) and the Florida Board of Nursing (Provider Number 50-3515). Activities approved by the CA BRN and the FL BN are accepted by most State Boards of Nursing.

CE hours provided by PharmCon, Inc. meet the ANCC criteria for formally approved continuing education hours. The ACPE is listed by the AANP as an acceptable, accredited continuing education organization for applicants seeking renewal through continuing education credit. For additional information, please visit: http://www.nursecredentialing.org/RenewalRequirements.aspx

Universal Activity No.: 0798-0000-17-125-H04-P & T
Credits: 2.0 contact hour (0.2 CEU)

Release Date: 6/14/2017
freeCE Expiration Date: 6/14/2020
ACPE Expiration Date: 6/14/2020

ACTIVITY TYPE
Knowledge-Based Home Study Monograph

FINANCIAL SUPPORT BY
Pharmaceutical Education Consultants, Inc.
ABOUT THE AUTHOR
Dr. Mark Garofoli graduated from the University of Pittsburgh earning a PharmD in 2004, and later went on to earn an MBA from Strayer University in 2008. Mark is certified in Geriatric Care (BCGP), Immunizations, Medication Therapy Management (MTM), and Weapons of Mass Destruction (WMD) Response. He resides with his lovely wife, Dr. Gretchen Garofoli (also a FreeCE.com presenter), in Morgantown, WV where he is an assistant professor at the West Virginia University School of Pharmacy, Director of the Safe & Effective Management of Pain Program, and Coordinator of the West Virginia Expert Pain Management Panel, which developed the West Virginia Safe & Effective Management of Pain (SEMP) Guidelines available at the www.sempguidelines.org website.

FACULTY DISCLOSURE
It is the policy of PharmCon, Inc. to require the disclosure of the existence of any significant financial interest or any other relationship a faculty member or a sponsor has with the manufacturer of any commercial product(s) and/or service(s) discussed in an educational activity. Mark Garofoli reports no actual or potential conflict of interest in relation to this activity.

Peer review of the material in this CE activity was conducted to assess and resolve potential conflict of interest. Reviewers unanimously found that the activity is fair, balanced and lacks commercial bias.

Please Note: PharmCon, Inc. does not view the existence of relationships as an implication of bias or that the value of the material is decreased. The content of the activity was planned to be balanced and objective. Occasionally, faculty may express opinions that represent their own viewpoint. Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not intended as a substitute for the participant’s own research, or for the participant’s own professional judgement or advice for a specific problem or situation. Conclusions drawn by participants should be derived from objective analysis of scientific data presented from this activity and other unrelated sources.

Neither freeCE/PharmCon nor any content provider intends to or should be considered to be rendering medical, pharmaceutical, or other professional advice. While freeCE/PharmCon and its content providers have exercised care in providing information, no guarantee of its accuracy, timeliness or applicability can be or is made. You assume all risks and responsibilities with respect to any decisions or advice made or given as a result of the use of the content of this activity.
General Epidemiology

Research indicates that more than 1.5 billion people worldwide suffer from chronic pain. Chronic Pain (~100 Million) affects more Americans than diabetes (~26 Million), heart disease (~16 Million), and cancer (~12 Million) combined. Approximately 75 million Americans, one in every four, have suffered from pain that lasts longer than 24 hours and millions more suffer from acute pain. Chronic pain is the most common cause of long-term disability (Painmed.org, 2017). 75% of people who began their opioid abuse in 2000s stated that their first regular opioid was a prescription opioid (TJ Cicero, 2014). Approximately 2 million Americans live with prescription opioid abuse or dependence (SAMSHA, 2013). During 2015, a total of 52,404 drug overdose deaths occurred in the United States (MMWR, December 16, 2016). In 2015, 63.1% (33,091) of drug overdose deaths involved an opioid (MMWR, December 16, 2016). Therefore, approximately 90 Americans die every day due to opioid overdose, equating to one American dying approximately every 15 minutes. Additionally, in our country a baby is born addicted to opioids approximately every 25 minutes (Tolia, 2015). Studies have shown a strong and consistent linear relationship between the number of opioids sold and distributed with morbidity and mortality associated with these chemicals (Paulozzi LJ B. D., 2006). These staggering statistics demonstrate how bad this situation is, and why it has been generally regarded as a national epidemic (Paulozzi LJ J. C., 2011) (Jones CM, 2013).

Pain Overview

Pain Anatomy & Physiology

Nociception is the sensory nervous system's response to harmful stimuli. The general cascade of nociception begins with transduction where sensory is translated into electricity, as when a radio transduces radio waves into sound waves. The next part of nociception is conduction where the pain sensory moves from the peripheral nervous system into the central nervous system, as when heat from a hot cooking pan is conducted from the pan to a metal spoon touching the inside of the pan. Next is transmission where electricity is converted into neurotransmitters such as glutamate, norepinephrine, or dopamine, as when television signals are transmitted over open air to a receiver television. Next is perception where the neurotransmitters elicit a sensory experience within the thalamus of the brain, as is with one’s perception being different on any given topic such as a glass being half full or half empty. Finally, and sometimes included within the perception phase, is modulation where the brain adjusts pain sensory via the descending pathways (away from the brain) within the nervous system (all previous phases were in the ascending pathway, or to the brain), like one playing a trump card in pinochle or a joker card in poker.

Pain is typically understood to involve both the nervous system and the musculoskeletal system, yet it transcends to all the systems of the body such as the endocrine, cutaneous,
cardiovascular, and immunological systems. Within the endocrine system, pain related neurohormones are released from various points in the body such as the hypothalamus, pituitary gland, thyroid (thyroxine), adrenal glands (cortisol, DHEA, etc.), and the ovaries (estrogen/progesterone) or testes (testosterone). Each of these neurohormones plays a vital role in communicating with other systems of the body to facilitate responses to the experience of pain. Upon injury to the skin, the cutaneous system has activated skin receptors releasing vasodilators which affect the cardiovascular system (veins/arteries) and stimulate the immunological response of releasing cytokines and other mediators to ultimately stimulate nociceptors within the nervous system. The overall encompassing idea is that pain involves all the systems of the body.

**Pain Management Terminology**

Analgesia is derived from the Greek language meaning “without pain” or lack of pain. Anesthesia means lack of sensation. Chronic pain is defined as experiencing the sensation of pain for a period longer than the expected time to heal, but is commonly referred to as pain lasting greater than 3 months. Allodynia is a painful response to a normally unpainful stimulus. Hyperalgesia is an extremely painful response to a normally minimal painful stimulus. Tolerance develops when a higher dose is needed for the same response. Dependence develops when the body exhibits withdrawal symptoms upon discontinuation of the substance. Substance-use disorder or addiction is a medical condition where the brain exhibits changes relating to a craving for a substance.

**Diagnosis of Pain**

Subjective assessments include subjective pain scales (i.e. classic 1 to 10 rating) and/or functional pain assessments on topics such as activities of daily living (ADLs) or the “PQRST” assessment. Examples of activities of daily living include walking up sets of stairs within a home, completing tasks necessary for employment, or even merely walking outside to get the mail. The “PQRST” assessment includes questions revolving around what precipitates or palliates one’s pain (P), the quality (Q), the region and radiation (R), the severity (S), and the temporal factors (T) of one’s pain.

Objective assessments include physical exam findings, such as range of motion, dermatomes, or myotomes. Other objective findings include both laboratory results such as inflammation markers or vitamin levels, or radiological findings such as MRIs, X-Rays, or CT Scans.
Types of Pain

Nociceptive pain arises from noxious stimuli affecting thermal, mechanical, or chemical receptors (nociceptors) in normal tissues (Merck Manual, 2017). Nociceptive pain can be further classified into somatic or visceral. Somatic nociceptive pain involves the outer organs, and generally produces a localized aching or throbbing pain. Visceral nociceptive pain involves internal organs with examples including a localize tumor or Irritable Bowel Syndrome.

Neuropathic pain stems from an abnormal processing of sensory input by the Central Nervous System (CNS) and/or Peripheral Nervous System (PNS) (Merck Manual, 2017). Central neuropathic pain can occur because of injury to the CNS or PNS, such as is seen with phantom leg pain, or be the result of a dysregulation of the autonomic nervous system, such as is seen in complex regional pain syndrome (CRPS). Peripheral neuropathic pain manifests itself from damage to a specific nerve with an example being trigeminal neuralgia, or can be distributed among a regional grouping of nerves with examples being diabetic neuropathy or post-herpetic neuralgia.

Best Practices in Pain Management

Patient Education

Patient & Provider(s) Agreements

An umbrella strategy for reducing patient risk with the use of pain management medications is to have a thorough review of the mutually agreed upon pain management treatment plan between a patient and a provider within a patient and provider agreement, sometimes known as a contract or consent form. A patient and provider agreement is an invaluable tool to ensure progress towards specific, measurable, attainable, realistic, and timely goals. A patient and provider agreement can also serve as a roadmap for how to progress, or even cease, an agreed upon treatment plan.

Best practices amongst pain management specialists suggest a patient and provider agreement to include appropriate goals (i.e. improvement in function, reduction in pain, and end of therapy), periodic reassessment of a patient’s psychological state, risk, pain, function, and the treatment profile; drug interaction review; adverse effects of medications; proper medication storage and disposal of medications; prescription drug monitoring program (PDMP) results, urine drug screening and/or testing; naloxone education and supply as necessary; medication pill counts; medication risks to others if shared; and having a treatment co-manager if needed.
Treatment Goals

Pain Reduction and Function Improvement Treatment Goal

A pain management treatment plan, or any treatment plan in general, cannot facilitate successful treatment unless one has assessed a respective patient’s entire life situation. Conversely, an ineffective pain management treatment plan can often, decrease one's quality of life, or even cause the patient to display drug-seeking behaviors when they are in fact only seeking relief from chronic pain. (“Opioid Risk Assessment Tools”, 2016)

In addition to pain severity, pain can be evaluated and treated based on how it affects a patient’s functional status and performance of daily activities. The goal of pain management is to reduce pain and improve a patient’s daily social and physical function, not solely or merely reduce one’s subjective pain scale reporting. There are of course conversely some clinical circumstances where reductions in pain without improvement in function may end up being a more realistic goal as is often observed in palliative care (CDC, 2016).

End of Therapy Treatment Goal

Treatment goals should naturally include a time frame, or in other words, an end of therapy goal. Making any goal timely is an essential constituent of being a “SMART” goal in that the goal is Specific, Measurable, Attainable, Realistic, and Timely. In chronic pain management, end of therapy goals may be more difficult to develop since the resolution of the causation, or the elimination of pain, is not expected to occur. However, in the management of acute pain, it is recommended to develop an end of therapy goal for the use of any pain management medications based on the expected time frame of the healing process.

Proper Medication Storage & Disposal

A chief responsibility of all healthcare professionals is educating patients, and often, that education is on basic concerns that can greatly help a patient in everyday life. Educating patients on proper medication storage and disposal can involve straightforward information, yet sometimes is even debated amongst healthcare professionals. The most important aspects of proper medication storage can be summarized as consistently putting medications away, with a safety cap locked on, after every use in a cool, dry, and secure storage location out of the reach and sight of children and pets, and within a locked device if controlled substances are involved. (Education, 2016) Patients need to know that if someone accidentally takes an unintended medication or dosage, the Poison Center (1-800-222-1-222) should be contacted immediately or even the “911” emergency service if person is unconscious or having a seizure. Many medicine cabinets are installed in bathrooms, which some healthcare professionals may inadvertently recommend consistent storage within, even though the humidity of the bathroom shower and/or bath is not a suitable location to store medications unless the room is well ventilated.
The FDA recommends three different methods of medication disposal including disposal through a DEA sponsored Take-Back Program, a DEA-Authorized collector, or via a specific process within household trash. The FDA recommended process for disposal of medications within household trash is summarized as removing medications from original container and mixing with an undesirable substance (i.e. coffee grounds, dirt, etc.) in a sealable container or bag. Additionally, for a few dozen controlled substance medications, the FDA recommends removal from the home by flushing them down the toilet or sink (FDA Drug Disposal, 2016).

**Treatment Selection**

**Mental Health Assessments**

**Psychological Evaluation**

Another best practice within pain management is to perform an initial and annual psychological evaluation for patients taking medications with addictive properties. Life circumstances evolve for everyone, thus risk can also change over time, warranting ongoing monitoring of risk factors.

Currently the PHQ-2 depression screening instrument is not only one of the go-to screening tools for depression, but is also something that can be completed conversationally in a mere two questions. The purpose of the PHQ-2 is not to diagnose, but to be utilized as a brief initial screen for depression, where positive screening results should be further evaluated with the PHQ-9 to determine whether they meet criteria for a depressive disorder. The two main questions within the PHQ-2 screening tool revolved around how often the following occurred in the last two weeks: 1. Little interest or little pleasure in doing things, and 2. Feeling down, depressed, or hopeless. All healthcare professionals can easily familiarize themselves with the PHQ-2 brief depression screening to utilize as a tool for determining when to refer for an actual diagnosis.

**Opioid Risk Screenings**

It is vitally important to bear in mind that all patients being considered for opioid medications should be screened for risk of substance misuse regardless of his or her respective previous exposure to opioid medications. There is debate amongst healthcare professionals as to whether more in-depth research on the evidence of the opioid risk screenings may be needed, especially for use in populations beyond patients experiencing chronic pain. However, it is currently generally accepted as best practice to employ a risk screening for any patient currently taking or being considered for opioid medication (Chou R, 2009). One of the natural questions to arise regarding the results of an opioid risk screening, is whether higher risk results disqualify a patient from being a candidate for receiving opioid medications. Results of an opioid risk screening neither demand nor inhibit the use of opioid medications for a given patient, yet results more so emphasize the degree to which more patient education is needed on risk reduction strategies, while also suggesting when the utilization of opioid medications may be of higher risk.
One can classify the currently available opioid risk screenings into those to be utilized for opioid-naïve patients or those to be utilized for opioid-experienced patients. The screenings useful for patients being considered for opioid treatment include the Opioid Risk Tool (ORT), the Drug Abuse Screening Test (DAST), the Diagnosis, Intractability, Risk, & Efficacy Score (DIRE), and the Screener and Opioid Assessment for Patients with Pain (SOAPP). The SOAPP can be utilized for opioid-experienced patients as well. With that in mind, the opioid screenings useful for patient already receiving opioid treatment include the Current Opioid Misuse Measure (COMM), the Pain Medication Questionnaire (PMQ), and the Prescription Drug Use Questionnaire (PDUQ). (CDC, 2016)

**Drug Interaction Review**

**Drug-Drug, Pharmacokinetic, & Pharmacodynamic Interactions**

As the role of healthcare professionals expand, there are more and more cases of drug interaction screenings happening before a prescription is even written by hand or electronically. The scenario of pain management is no different than any other medical condition in that a review of possible drug interactions is pivotal for any and every patient to facilitate the highest level of patient care. Pain management medications interact with other medications just as often and easily as any other medications interact. Thus, a review of a patient’s entire medication profile to assess for drug interactions is pivotal to ensure the proper selection and dosage of a patient’s pain medication(s).

**Pharmacogenetic Interactions**

In addition to drug-drug, pharmacokinetic, and pharmacodynamic interactions, there can also be interactions due to a difference in one’s genetic composition. Pharmacogenics (PGx) is the study of the role of genetics in the human body’s response to medications. Numerous physiological systems of the human body, such as metabolic enzymes or drug receptors, can exhibit genetic variability resulting in altered drug-responses. For instance, if a patient’s genetic composition facilitates a change in how a patient metabolizes a pain medication, then the selection and dosage of the pain medication may need altered. Two of the most common hepatic cytochrome P450 (CYP450) enzymes that have shown involvement with pain management specific medications include 2C9 and 2D6. 2C9 substrates include pain medications such as ibuprofen and celecoxib, and 2D6 substrates include codeine, dextromethorphan, tramadol, duloxetine, venlafaxine, and tricyclic antidepressants. Pharmacogenetic testing can be performed to help forecast a patient’s response to a given medication before initializing the treatment plan. For example, a CYP2D6 poor metabolizer may not receive adequate analgesia from tramadol, whereas, an ultra-rapid metabolizer may experience unnecessary side effects because of having more of the active metabolites present.
**Adherence & Diversion Monitoring**

**Pill Counts**

Randomized and/or Scheduled Pill Counts (based on appointments, etc.) represent one of the tools to assess medication adherence and prevent and/or detect drug diversion. To ensure a proper continuum of care and efficient process, a healthcare professional should schedule any appointment-based pill counts within a minimum of 3 days of when the current prescription will run out of supply/refills (Safeguard, 2011). A patient presenting with an unexpected pill count, does not automatically mean a discontinuation of treatment, yet, a conversation between the healthcare professional(s) and the patient can aim to discuss the reasoning.

**Urine Drug Screens/Tests**

Urine drug screens and tests are important tools in facilitating not only truthful conversations between healthcare professionals and patients, but also in medication adherence monitoring and the detection of illicit substance use. In general, one must also remember that an illicit substance is either a substance that is illegal by law and/or a substance that is use either for an unintended purpose or by an unintended person. All healthcare professionals need the most up-to-date and comprehensive medication information, including both legal medications and illicit substances, to provide a high level of patient’s care.

Urine drug screenings are typically known as the “urine collection cup” method, and more specifically as the lower cost, yet qualitative examination. Urine drug screenings often include a strip on the cup labeled “OPI” which will show results for the most common structural class of opioids (phenanthrenes) including morphine, diacetylmorphine (Heroin), codeine, hydrocodone, and oxycodone, however missing other opioids such as methadone or fentanyl. Urine drug testings are typically known as the more sophisticated chemical testings (i.e. Gas Chromatography Mass Spec), and more specifically as the higher cost, yet quantitative examination. In general, a urine drug screening can neither legally confirm nor deny the absolute presence of a substance, but can indicate the need for more specific testing via urine drug testing, which specifically identify all present and amount of substances within the urine sample. Urine drug screens (not tests) have been conversationally compared to over-the-counter urine pregnancy tests in that there is not only a possibility for false negatives or false positives, but also that the over-the-counter urine pregnancy test may tell if one is pregnant, but certainly not to the specificity of the sex of the fetus.

Urine drug screens (i.e. the cups) are very frequently utilized within community, family practice, and primary care settings. Before administering a urine drug screen, a healthcare professional should be fully educated on cross-contaminants, testing time periods, and anticipated results based on the original substance and its respective metabolites. Asking a patient for a complete medication profile including prescription, over-the-counter, supplements, illicit substances, and even short-term medications can ensure that the results of a urine drug screening can be relied on, with a special concern for avoiding cross contaminants. The following chart highlights the
active metabolites of the specified opioid medications that would be expected within a urine drug testing (note: not screening).

<table>
<thead>
<tr>
<th>Opioid Ingested</th>
<th>Urine Drug Test Expected Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Based on Active Metabolites, not including inactive metabolites)</td>
</tr>
<tr>
<td>morphine</td>
<td>morphine &amp; hydromorphone*</td>
</tr>
<tr>
<td>hydromorphone</td>
<td>hydromorphone</td>
</tr>
<tr>
<td>hydrocodone</td>
<td>Hydrocodone, dihydrocodeone*, &amp; hydromorphone</td>
</tr>
<tr>
<td>codeine</td>
<td>codeine, hydrocodone*, dihydrocodeone*, morphine, &amp; hydromorphone</td>
</tr>
<tr>
<td>oxycodone</td>
<td>oxycodone &amp; oxymorphone</td>
</tr>
<tr>
<td>oxymorphone</td>
<td>oxymorphone</td>
</tr>
<tr>
<td>fentanyl</td>
<td>fentanyl</td>
</tr>
<tr>
<td>tramadol</td>
<td>tramadol</td>
</tr>
<tr>
<td>methadone</td>
<td>methadone</td>
</tr>
<tr>
<td>heroin</td>
<td>heroin, morphine, &amp; hydromorphone</td>
</tr>
</tbody>
</table>

*Very low levels  (Smith, Opioid Metabolism, 2009)

**Prescription Drug Monitoring Program (PDMP) Use**

Prescription drug monitoring programs (PDMPs), also known as Controlled Substance Monitoring Programs (CSMPs), are useful tools in monitoring medication adherence and avoiding drug abuse and diversion. PDMPs are not the panacea answer to preventing drug abuse and diversion, but are one major tool amongst others that needs to be universally and consistently utilized to reach its full potential. Yet with participation by prescribers and dispensers typically being voluntary, usage is well below half nationally (Brandeis University, October 2014). The day will hopefully come when both prescribing and dispensing computer software and electronic healthcare records automatically review a given state’s PDMP, but in the meantime, healthcare professionals have a moral responsibility to do no harm, which can be aided with the consistent review of a respective state’s PDMP.

**Pain Management Treatment Options**

**Non-pharmacological Treatment Options**

Non-pharmacological treatment options can be separated into two distinct groups of Active vs Passive treatments, which may help to facilitate conversations around acceptance and agreement upon a selected non-pharmacological treatment options between a healthcare professional and a patient. “Active” treatments require some form of action during the treatment on behalf of the patient, whereas “Passive” treatments do not necessarily actually require a patient do perform any action.
“Active” non-pharmacological treatments include Cardio and/or Resistance Exercise, Aquatic Exercise, Walking Aids, Yoga, Tai Chi, Qigong, Meditation, Hypnosis, Relaxation, Cognitive Behavioral Therapy, Acceptance & Commitment Therapy Biofeedback, Graded Motor Imagery, & Occupational or Physical Therapy. “Passive” non-pharmacological treatments include Nutrition, Heat or Cold, TENS or EMS Devices, Hyperbaric Oxygen, Spinal Manipulation (Chiropractor) or Massage, Ultrasound, Paraffin Wax, Infrared Light, Spinal Traction, and Acupuncture.

Pharmacological Treatment Options

Non-Opioids

Acetaminophen

Acetaminophen is an abbreviated name for n-acetyl-p-aminophenol. Additionally, the abbreviation “APAP” is extracted from n-Acetyl-P-AminoPhenol, and the brand proprietary name Tylenol® is extracted from n-acETYL-p-aminophENOL. Acetaminophen inhibits prostaglandin synthesis in the Central Nervous System (CNS), thus giving its antipyretic properties. The toxic metabolite via CYP1A2/2E1/3A4 metabolism is referred to as NAPQI, which is what derives the medication’s maximum recommended doses of 3 grams for over-the-counter use and patients >/= 65 years of age, 4 grams under prescriber supervision, and 2 grams for patients with liver or kidney impairment (Clinical Pharmacology. Internet Database.)

NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit lymphocytes, neutrophils, and prostaglandin synthesis in both the central nervous system (CNS) and the peripheral nervous system (PNS). NSAIDs can be useful in the treatment of inflammatory conditions such as rheumatoid arthritis, fever. NSAIDs can also be helpful in the management of gout due to the increased urinary excretion of urates. NSAIDs must be used with caution in asthma, due to the increased production of leukotrienes, and in impaired renal function, due to the decrease in glomerular filtration rate (GFR). The relative selectivity of each NSAID medication for either COX-1 or COX-2 inhibition is of importance for patients with either a higher risk of gastrointestinal issues or cardiovascular issues. In general, patients with a higher gastrointestinal risk should receive NSAIDs that are more COX-2 selective with the possible addition of a proton pump inhibitor, whereas patients with a higher cardiovascular risk should receive NSAIDs that are more COX-1 selective. Overall examples of NSAIDs (in relative order of COX-2 selectivity to COX-1 selectivity) include etodolac, meloxicam, celecoxib, diclofenac, sulindac, piroxicam, ibuprofen, naproxen, indomethacin, ketoprofen, ketorolac, and aspirin.
**L-methylfolate**

Folate is the natural version of synthetic folic acid, which is metabolized to dihydrofolate (DHF), and then tetrahydrofolate (THF), which is then metabolized by the methylenetetrahydrofolate reductase (MTHFR) enzyme to L-methylfolate, which is bioactive to assist in the formation of monoamines such as serotonin, norepinephrine and dopamine. Those monoamines help facilitate the body’s sensory status regarding conditions such as depression or pain sensation. Thus, a deficiency in L-methylfolate will result in an alteration of status in those medical conditions. L-methylfolate supplementation may increase monoamine synthesis and augment a patient’s depression therapy or pain management as demonstrated in several studies (Trippe B, 2016). L-methylfolate is available as multiple prescription products with doses of 3mg, 7.5mg, and 15mg, and ranging vastly in respective price ranges as compared to the unregulated non-FDA approved supplement versions available in various doses.

**Topical Formulations**

Topical medication formulations are very useful not only for the reducing one’s pain and improving function, but primarily in accomplishing those goals while avoiding systemic exposure and additional side effects. Examples of commonly utilized topical pain medications include topical NSAIDs, tricyclic antidepressant (doxepin) lidocaine +/- prilocaine, capsaicin, counterirritants (i.e. menthol, camphor, etc.), salicylates, or arnica.

**Tri-Cyclic Antidepressants (TCAs)**

Antidepressants exhibit their respective mechanisms of action on neurotransmitters within the nervous system, such as dopamine, serotonin, norepinephrine, and so on. Antidepressants that are observed to be effective in pain management have a mechanism of action involving norepinephrine (NE). Therefore, antidepressant medications ineffective in pain management include selective serotonin reuptake inhibitors (SSRIs), and to some degree trazodone (mainly affecting serotonin) and nefazodone (norepinephrine effects lost with chronic use).

Tricyclic antidepressants (TCAs) mainly affect norepinephrine, and thus are observed to be effective in pain management. Secondary amines have less side effects and shorter half-lives relative to tertiary amines such as amitriptyline. Secondary amines include both desipramine, the metabolite of imipramine, and nortriptyline, the metabolite of amitriptyline. Anticholinergic and antihistaminic related side effects of TCAs include orthostatic hypotension, drowsiness, & withdrawal upon abrupt discontinuation (Clinical Pharmacology. Internet Database.).
Serotonin & Norepinephrine Re-Uptake Inhibitors (SNRIs)

Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs) include duloxetine, venlafaxine, desvenlafaxine, milnacipran, & levomilnacipran. SNRIs exhibit their pain management mechanism of action on norepinephrine (NE). The relative scale of potency/action on NE ranks nortriptyline as the highest potency to act upon NE, followed by milnacipran, amitriptyline, duloxetine, venlafaxine, and desvenlafaxine (Vaishnavi SN, 2004). Common side effects of SNRIs include nausea, dry mouth, fatigue, and somnolence (Clinical Pharmacology. Internet Database.).

Atypical Antidepressants

Two atypical antidepressants that have been observed to be effective in pain management include bupropion and mirtazapine. Bupropion exhibits its mechanism of action as a norepinephrine & dopamine reuptake inhibitor, while mirtazapine exhibits its mechanism of action as a noradrenergic (alpha-blocking) & specific serotonergic antidepressant.

Anti-Epileptic Drugs (AEDs)

Epilepsy prevention medications exhibit their seizure management effects on the body’s nervous system by affecting the electrical current passed along neurons and their pain management effects on the body’s nervous system by increasing the Gamma-Amino-Butyric Acid (GABA) facilitated inhibition of pain sensation. First generation AEDs include carbamazepine, phenytoin, & valproic acid. Second generation AEDs include lamotrigine, levetiracetam, topiramate, oxcarbazepine, & zonisamide. Unique side effects of AEDs compared to other pain management medications include rashes and an increased bone fracture risk (Clinical Pharmacology. Internet Database.).

Gabapentinoids

Gabapentinoids act upon Gamma-Amino-Butyric Acid (GABA) channels, like benzodiazepines, ethanol, and sedative hypnotics. The action is on calcium channels, not the actual GABA Receptors, to ultimately increase GABA’s inhibition of pain sensation. Common Gabapentinoids include gabapentin, pregabalin, and a structural analog of GABA named baclofen (typically referred to as a muscle relaxant). Gabapentin’s maximum daily dosage is 3,600mg per day, while it can also be noted that it’s bioavailability decreases with higher than average doses. Gabapentin is highly lipophilic (crossed the Blood-Brain-Barrier) and is excreted unchanged in the urine. Common side effects of gabapentin include sedation/fatigue, dizziness, ataxia, & neuropathic edema (which ironically is not affectively treated with water pills). Gabapentin is a
classic example of the mantra for “start low, go slow” dosing, whereas Pregabalin has a relatively quicker dose titration period (Clinical Pharmacology. Internet Database.).

**Muscle Relaxants**

Muscle relaxant medications are intended to be used for the relief of muscle spasticity and spasms with acute pain, yet are not recommended for chronic everyday use. These medications are classified as either exhibiting action on muscle spasticity (stiffness) or musculoskeletal conditions (spasms).

Medications referred to as muscle relaxants observed to be effective for stiffness include tizanidine, baclofen, and dantrolene. Tizanidine is a structural analog of clonidine and is thus an alpha-2 agonist, best dosed at bedtime to avoid daytime drowsiness. Baclofen is a structural analog of Gamma-Amino-Butyric Acid (GABA). Dantrolene is the one true muscle relaxant exhibiting its actions on peripheral muscles.

Medications referred to as muscle relaxants observed to be effective for spasms include carisoprodol, cyclobenzaprine, orphenadrine, methocarbamol, metaxalone, and chlorzoxazone. Carisoprodol is metabolized to meprobamate, a barbiturate. Cyclobenzaprine is structurally related to amitriptyline and began its history of utilization as a TCA. Orphenadrine is a structural analog of diphenhydramine. Methocarbamol is a carbamate derivative of guaifenesin, a structural analog of mephenisin, a structural analog of mefenamic acid and began its history of utilization as a NSAID. Metaxalone has a relatively lower risk of sedation, and its bioavailability increases when taken with high fat meals. Chlorzoxazone has a unique side effect of turning urine orange, red, or purple (Clinical Pharmacology. Internet Database.).

**Opioids**

Opioid receptors naturally occurring in the human body include Mu, Kappa, Sigma, Delta receptors. Most current opioid pain medications exhibit analgesic effects as action on Mu opioid receptors.

**Morphine Milligram Equivalents (MMEs)**

One of the most important concepts for the selection and dosage of opioid pain medications is the morphine milligram equivalent (MME). The MME can be explained in a different paradigm involving citrus fruits such as oranges, grapefruits, lemons, and limes which all contain various amounts citrus or potency of citric acid. The relative comparison of how much “citrus” is in each citrus fruit could become known as the “citrus content equivalent”, much like the degree of
opioid potency in any opioid medications relative to morphine as a baseline standard. In essence, the role of the MME is to express an opioid’s potency.

To most easily utilize the MME conversation factors seen below, as adopted from the CDC Opioid Guidelines with 2017 updates, one can multiply the MME factor by the opioid dosage for a given patient to calculate the overall MMEs the patient is receiving. Typically, that total MME amount is divided by a given time frame to result in a Morphine Equivalent Daily Dose (MEDD), otherwise known as a daily MME. The CDC Chronic Pain Opioid Guidelines of 2016 state that a daily MME level $\geq 50$ should only be used with caution and a daily MME level $\geq 90$ should be avoided unless a clinician can carefully justify the titration. According to a study published in the Annals of Internal Medicine in 2010, the approximate adjusted hazard ratio (or relative likelihood of overdose) for a patient receiving $\geq 100$ morphine milligram equivalent (MME) of any opioid medication per day is eleven, thus showing the importance of healthcare professionals being familiar with the concept of MMEs. A table of MME Conversion Factors is provided below for reference, yet if a healthcare professional learns that morphine and hydrocodone each have an MME Conversion Factor of 1, while oxycodone has an MME Conversion Factor of 1.5, much of the commonly utilized opioid medications can have their MME easily calculated.

<table>
<thead>
<tr>
<th>Type of Opioid</th>
<th>MME Conversion Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine patch</td>
<td>12.6 (then divide by days)</td>
</tr>
<tr>
<td>Buprenorphine tab or</td>
<td>30 (for mg doses)</td>
</tr>
<tr>
<td>Codeine</td>
<td>0.15</td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td>0.25</td>
</tr>
<tr>
<td>Fentanyl patch</td>
<td>7.2 (then divide by days)</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>1</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>4</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>11</td>
</tr>
<tr>
<td>Meperidine</td>
<td>0.1</td>
</tr>
<tr>
<td>Methadone</td>
<td>4, 8, 10, &amp; 12</td>
</tr>
<tr>
<td>Morphine</td>
<td>1</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>1.5</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>3</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>0.37</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>0.4</td>
</tr>
<tr>
<td>Tramadol</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Adapted from: (CMS, 2015), (CDC, 2016)
**Opioid Metabolism**

It is important to understand how an opioid, or any medication, is metabolized in the human body considering pharmacogenetic differences and possible drug-drug interactions (Smith, Opioid Metabolism, 2009). The CYP2D6 enzyme is involved in the metabolism of codeine, hydrocodone, oxycodone, methadone and tramadol. The CYP3A4 enzyme is involved in the metabolism of oxycodone, methadone, tramadol, and fentanyl (Clinical Pharmacology. Internet Database.).

**Opioid Side Effects**

The package inserts of all opioid medications contain each of the following as possible side effects to opioid medications: constipation, neuralgia, itching, Sedation, Respiratory Depression, Bradycardia, Hypotension, QT Prolongation, Nausea & Vomiting, Central Sleep Apnea, Edema, Urine Retention, Miosis (Pupil Constriction), Myoclonus (muscle jerking), and Hypogonadism (decreased estrogen or testosterone).

One of the most common side effects of opioids is itching due to stimulation of the release of histamine. Second generation antihistamines such as loratadine, cetirizine, or fexofenadine can prevent/treat the itching side effect with minimal respective side effects. Another common side effect of opioids is sedation, which can be addressed by educating patients on the likelihood of feeling tired and/or confused to best accommodate their daily life. A basic yet incredibly important counseling point is to have patients avoid operating machinery or driving while adjusting to opioid medication dosage for an appropriate period. Another commonly observed side effect of opioids is constipation (i.e. opioid induced constipation). To best prevent or treat this side effect, healthcare professionals should encourage patients to utilize a diet with adequate fiber and fluid intake. When additional assistance is needed, a stepwise approach to preventing or treating the constipation is to use docusate with/without Senna, followed by Polyethylene Glycol-3350, followed by either a chloride channel activator (i.e. lubiprostone) if the constipation was present prior to opioid therapy, or a peripheral opioid antagonist (i.e. methylnaltrexone, naloxegol, etc.) if the constipation resulted from opioid therapy.

**Opioid Tapering, Conversion, & Rotation**

**Opioid Tapering**

The goal of opioid tapering is to safely decrease the need for the prescription opioid pain medication. Approaches to tapering range from a slow 10% reduction per week to a more aggressive 25-50% reduction every few days depending on the original MME dosage and duration of the opioid therapy. In general, a slower taper will produce fewer unpleasant symptoms of withdrawal. Opioid withdrawal symptoms are uncomfortable, but are not
dangerous, thus opioids can be stopped abruptly when the risks outweigh the benefits. (Association, 2014)

**Opioid Conversion**

If the same opioid medication is being converted from immediate-release (IR) to extended-release (ER) formulation, one can directly convert the IR MME daily dose to an ER MME daily dose. (Clinical Pharmacology. Internet Database.)

**Opioid Rotation**

First, calculate the MME based equianalgesic dose of the new opioid. Then determine the automatic dose reduction percentage.

If switching to methadone, then utilize a 75-90% dosage reduction. If switching to a new route of administration for the same drug, utilize a 25% dosage reduction. If the patient is receiving a higher risk MME dose, is not Caucasian, elderly, or medically frail, utilize a 50% dosage reduction. Additionally, assess patient pain severity to decide upon an additional increase or decrease of 15-30% to enhance pain management effectiveness or avoid causing withdrawal symptoms.

Continually assess the patient for effectiveness and safety of the new dosage. Healthcare professionals may want to provide a “rescue dose” supply at 5-15% of the total daily MME for as needed use by the patient during the opioid rotation (Fine P, 2009).

**Therapeutic Classes & Examples**

**Traditional Opioids**

Codeine (acetaminophen/codeine) has a higher chance of patients experiencing two of the more common opioid side effects of nausea/vomiting and constipation. Morphine is a Mu agonist and the control standard of opioid pain medications for relative dosage. Hydrocodone and its metabolite hydromorphone are both in the C2 class of medications, even though there is a four-fold difference in potency. Similarly, both oxycodone and its metabolite oxymorphone are in the C2 class of medications, even though there is a two-fold difference in potency. Oral pentazocine (with naloxone) is a weak Mu antagonist and a weak Kappa agonist. Dihydrocodeine is available as combination products with caffeine added along with either acetaminophen or aspirin. Fentanyl is a fully synthetic and highly potent opioid with numerous dosage forms. Meperidine is also a fully synthetic opioid. Buprenorphine is a partial Mu agonist and Kappa antagonist with a unique “ceiling effect” where relatively lower doses provide pain relief without progressing to a euphoric feeling or higher chance of respiratory depression. Buprenorphine also exhibits a very high relative affinity for Mu receptors. Buprenorphine is available alone for both pain management (mcg doses) and opioid-use disorder (mg doses) or in
combination with naloxone solely for opioid-use disorder (Clinical Pharmacology. Internet Database.).

**Mixed Action Opioids**

Tramadol is a weak Mu agonist and serotonin norepinephrine reuptake inhibitor (SNRI) with a maximum immediate release daily dose of 400mg and maximum extended release daily dose of 300mg. tramadol requires hepatic and renal impairment dosing adjustments, and a monitoring for serotonergic interactions and symptoms. Tapentadol is a weak Mu Agonist & norepinephrine reuptake inhibitor with a relatively faster onset and less serotonergic activity and concerns compared to tramadol. Levorphanol is a fully synthetic opioid with multiple mechanisms of action including being a Mu, Delta, & Kappa Agonist; NMDA Antagonist; serotonin and norepinephrine reuptake inhibitor (SNRI); Anticholinergic medication. Methadone is a Mu agonist; NMDA Antagonist; serotonin and norepinephrine reuptake inhibitor (SNRI). Methadone has two enantiomers with the D-methadone enantiomer exhibiting the primary analgesic effects. The pharmacokinetics of methadone include a half-life of 8 to 150 hours while being metabolized by CYP 3A4, 2B6, 2C9 2C19, 2D6, & PgP (Clinical Pharmacology. Internet Database.). These variable pharmacokinetic factors warrant a relatively very low initial dose (i.e. 15mg/day) with no dose titrations in the initial week of therapy, followed by a gradual increase of approximately 10mg/day each week (Webster, 2012).

**Naloxone**

**Naloxone General Information**

Naloxone is a reversal agent for opioid overdose as it reverses opioid induced respiratory depression. Naloxone is available in multiple formulations including a 0.4mg/ml IM injection, 0.4mg/ml auto-injection, 2mg/2ml intranasal solution, and the 4mg nasal spray. Candidates for the education and supply of naloxone include: (Instructions for Healthcare Professionals: Prescribing Naloxone, 2016)

- Current or past opioid-use disorder or opioid overdose
- Current higher risk dose opioid use (/>=50mg MME per day) or opioid rotation
- Receiving any opioid prescription for pain plus:
  - Respiratory Condition (i.e. Smoking, COPD, emphysema, asthma, sleep apnea, etc.)
  - Renal dysfunction, hepatic disease, cardiac illness, HIV/AIDS
  - Concurrent alcohol use
  - Concurrent sedative or antidepressant prescription
  - Who may have difficulty accessing EMS (i.e. distance, rural, etc.)
- Voluntarily request naloxone by oneself or a caregiver
Controlled Substances, Red Flags, & Best Practices in Drug Diversion

**Controlled Substance Classifications**

Knowing the respective controlled substance classes of opioid medications can be helpful for healthcare professionals to understand so as to ascertain what professionals can prescribe medications from various controlled substance classes based on state laws. The CIV, or C4, class contains tramadol and Pentazocine/naloxone products. The CIII, or C3, class contains acetaminophen/codeine and dihydrocodeine products along with buprenorphine products specifically utilized in pain management (As per DATA2000, not for substance-use disorder, or addiction). The CII, or C2, class contains Tapentadol, morphine, hydrocodone, hydromorphone, oxycodone, oxymorphone, Levorphanol, methadone, and fentanyl.

**Drug Enforcement Agency (DEA) Red Flags**

Healthcare professionals encounter situations that balance preventing drug diversion and ensuring appropriate patient care daily. The US Drug Enforcement Agency (DEA) developed these “red flags” as a resource of what to be on the lookout for as healthcare professionals in those precarious situations.

**Prescriber**

1. Cash only patients and/or no acceptance of worker’s compensation or private insurance
2. Prescribing of the same combination of highly-abused drugs
3. Prescribing the same, typically high, quantities of pain drugs to most or every patient
4. High number of prescriptions issued per day
5. Out-of-area patient population

**Dispenser**

1. Dispensing a high percentage controlled to non-controlled drugs
2. Dispensing high volumes of controlled substances generally
3. Dispensing the same drugs & quantities prescribed by the same prescriber
4. Dispensing to out-of-area or out-of-state patients
5. Dispensing to multiple patients with the same last name or address
6. Sequential prescription #s for highly diverted drugs from the same prescriber
7. Dispensing for patients of controlled substances from multiple practitioners
8. Dispensing for patients seeking early prescription fills
Once Drug Seeking or Diversion is Suspected

Working with healthcare professionals and other professionals concerning patients suspected of drug seeking behavior and diversion is often not something that many are comfortable pursuing. As with any other clinical or administrative decision, if one leaves out personal or judgmental biases, and proceeds with a calm, collected, knowledgeable, and well researched approach, the entire endeavor will lead itself to a path of success.

If uncertainty exists regarding the nature of the unintended result of a risk reduction action such as a PDMP review, a urine drug screen/test, or a random/scheduled pill count, the healthcare professional(s) may consider arranging for an in-person meeting with the identified patient to have an open conversation to clarify the patient’s actions and concerns. Prior to initiating that important conversation, a healthcare professional should research all aspects of the respective patient related scenario including opening communications with any other respective healthcare professionals involved directly or indirectly with the respective patient case. If abuse or diversion is confirmed, treatment can continue with alternative therapies (i.e. non-controlled substances) the patient should be referred to a substance-use disorder (addiction) specialist/program, or an entity that can facilitate that connection, and law enforcement if concern for the safety of others exists. Respect or all those directly or indirectly involved in the specific patient case should be upheld always, while also ensuring both a procession within mandated laws and an appropriate level of patient care.
References


Clinical Pharmacology. Internet Database. (n.d.).


Exam Questions:

1) All 50 US states have an active Prescription Drug Monitoring Program (PDMP).
   A) True
   B) False

2) Chronic pain is defined as experiencing the sensation of pain for a period longer than the expected time to heal, but is commonly referred to as pain lasting greater than:
   A) 1 month
   B) 3 months
   C) 6 months
   D) 1 year

3) A painful response to normally unpainful stimuli is known as:
   A) Allodynia
   B) Chronic Pain
   C) Nociceptive Pain
   D) Hyperalgesia

4) Examples of neuropathic pain include:
   A) Phantom leg pain
   B) Complex regional pain syndrome
   C) Trigeminal neuralgia
   D) All the above

5) Which of the following antidepressant medications would be expected to decrease pain and increase function within daily activities?
   A) Fluoxetine
   B) Trazodone
   C) Nortriptyline
   D) Paroxetine
6) Methadone interacts with which CYP450 enzyme(s)?

   A) 3A4
   B) 2C9 & 2C19
   C) 2D6
   D) All the above

7) If a patient is suspected of opioid abuse and asked to perform a urine drug screening, which of the following substances will test positive for the most typical “OPI” screening?

   A) Oxycodone
   B) Fentanyl
   C) Methadone
   D) All of the above

8) If a patient is prescribed, dispensed, and is actively taking codeine, which of the following opioids may test positive in a urine drug screening?

   A) Hydrocodone
   B) Codeine
   C) Hydromorphone
   D) All the above

9) Which of the following are possible side effects of opioid agonist medications according to respective package insert documentation?

   A) Itching
   B) Neuralgia
   C) Constipation
   D) All the above
   E) A & C

10) According to a study published in the Annals of Internal Medicine in 2010, what is the approximate adjusted hazard ratio (or relative likelihood of overdose) for a patient receiving >/= 100 morphine milligram equivalent (MME) of any opioid medication per day?

    A) 11
    B) 5
    C) 3
    D) 2
11) Best practices in pain management aimed at reducing risk include which of the following:

A) Use caution when prescribing or dispensing $\geq 50$ MME/day for any patient
B) Review the PDMP annually for a patient receiving an opioid medication
C) Educate patients on naloxone for those higher risk opioid dosing
D) All of the above
E) A & C
F) B & D

12) Best practices in pain management aimed at reducing risk include which of the following:

A) Opioid Risk Screening(s)
B) Treatment goals of improved function and reduced pain that are time bound or have an end of therapy target
C) Initial & annual psychological evaluation
D) All the above

13) DEA Red Flag scenarios that, whether alone or combined, may alert prescribers and dispensers to possible drug abuse or diversion include:

A) Patients requesting to pay only with cash
B) Patients receiving both Extended-Release & Immediate-Release formulations of an opioid medication
C) Out-of-Area patients
D) All of the above
E) A & C
F) B & C

14) A patient taking oxycodone 40mg at a dosage of one tablet twice daily is receiving how many Morphine Milligram Equivalents (MMEs) per day?

A) 40
B) 80
C) 120
D) 160

15) Which of the following medications is a prodrug metabolized by the CYP2D6 hepatic enzyme to its active metabolite?

A) Ibuprofen
B) Tramadol
C) Celecoxib
D) Methadone
16) Which of the following qualify a person as a candidate for consideration of supplying naloxone?

A) Opioid daily dosage \( \geq 50 \) MME  
B) Patient with any respiratory condition including being a tobacco smoker  
C) Patient also taking other sedatives such as benzodiazepines, muscle relaxers, hypnotics, or alcohol  
D) All the above

17) An appropriate treatment goal for pain management in all patient scenarios is complete elimination of the sensation of pain?

A) True  
B) False

18) Gabapentinoids exhibit their respective mechanism of action on the same channel as which of the following medication classes?

A) Benzodiazepines  
B) Muscle Relaxants  
C) Sedative Hypnotics  
D) All the above  
E) A & C

19) Which of the following medications are classified as mixed action opioids?

A) Methadone  
B) Tapentadol  
C) oxymorphone  
D) All the above  
E) A & B  
F) A & C

20) Which of the following medications are classified as controlled substance class three?

A) Buprenorphine for pain management  
B) Tapentadol  
C) Dihydrocodeine containing products  
D) All the above  
E) A & B  
F) A & C