Overview of Pain Management Medications

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Target audience
This continuing education activity was designed specifically for pharmacy technicians.

Learning Objectives
At the end of this article, participants should be able to:

1. Explain the differences between nociceptive and neuropathic pain, and acute and chronic pain
2. Identify disease states that cause chronic pain
3. Identify over-the-counter medications used for pain and the risks associated.
4. Recognize side effects and indications for use of the medications discussed.
5. Explain the differences between addiction, pseudoaddiction, tolerance and physical dependence.

Pain management is an expansive but important topic that keeps our communities safe and patients both comfortable and functional. Pharmacy technicians must be aware of the different types of pain and recognize which medications are used to treat pain. While working in a pharmacy, patients commonly ask what condition their medication is treating. Many of the top selling drugs are used to treat pain. In addition to prescription pain medications, there are also several over-the-counter medications that are also used to treat pain. For technicians, it is also necessary for data entry to know if a prescription is a controlled substance and what form of the drug needs to be dispensed. This is a necessary topic of discussion because in 2009 analgesics were the most commonly continued or newly prescribed medication in ambulatory office visits.¹

Physiology of pain

There are two major types of pain that are experienced: nociceptive and neuropathic. They are classified depending on what types of cells are damaged; nociceptive pain is caused when tissue cells are damaged, and neuropathic pain is caused when the nerve cells are damaged.

When referring to pain, nociceptive pain is more commonly referenced as it is the body’s protective mechanism. To feel this pain, nerves must be activated and transmit a signal of pain to the brain. These nerves, called nociceptors, are activated by substances that are released when cells are damaged. Damage can be due to toxic chemicals, extreme temperatures (hot or cold) or mechanical in nature (cuts). Once the nerve is activated, it transmits the signal from the site of damage to the spinal cord, then finally into the brain to be processed and perceived. As the signal travels along the nerve pathway leading to the brain, the signal can be modified causing a change in the chemicals transmitting the signal. Medications can work to decrease pain by altering the signal and chemicals before, during or after transmission.

Nociceptive pain is classified into two categories dependent upon where the pain originates. Somatic pain is felt in bone, joint, muscle, skin or connective tissue and is described as throbbing
and localized in one area. Visceral pain is the other type of nociceptive pain that emanates from organs like the pancreas or stomach, which are referred to as visceral organs. Visceral pain is normally described as aching or cramping in a generalized area of the body.

Neuropathic pain is not as common as nociceptive pain and is due to damaged or abnormal functioning of the nervous systems. This type of pain is normally due to diseases that affect the nervous system throughout the brain and spinal cord (central nervous system) or within the nerves spreading throughout the body (peripheral nervous system). Diseases can have an effect on nerves and cause them to send more signals or incorrect signals of pain to the brain. The brain nerves that modulate the pain signal can also be interrupted or modified by diseases, and as a result, cause pain signals when there should not be any. Any abnormal processing of the nervous system can be described as neuropathic pain. The pain is normally felt as shooting, burning, tingling, shock-like or electric. Some examples of diseases that cause this type of pain are fibromyalgia, irritable bowel syndrome, diabetic neuropathy, arthritis and chronic headaches.

<table>
<thead>
<tr>
<th>STOP AND REFLECT</th>
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<tbody>
<tr>
<td>What kind of words would a patient use to describe neuropathic versus nociceptive pain?</td>
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<tr>
<td>Answer: For neuropathic pain a patient may use words such as shooting, burning, electric, or shock-like. For nociceptive pain they may use aching, throbbing, or cramping.</td>
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Specific pain diseases

Fibromyalgia is a chronic disease in which pain is experienced all over the body and can be present unilaterally or bilaterally, as well as above or below the waist. The pain is caused by an imbalance of the chemicals that transmit signals along neurons. The pain is normally described as stabbing, shooting, throbbing or twitching. Deep muscles aches are also possible in this disease state. Patients with fibromyalgia commonly have problems with mood, exhaustion, poor sleep and concentration.

Post-herpetic pain can be understood by its morphology: post means after and herpetic means herpes. Varicella zoster is the virus that causes chicken pox, and later in life, it can reactivate to become the herpes zoster virus (i.e. shingles). Post-herpetic pain is caused by the herpes zoster virus inflicting damage on nerves during the time a patient has shingles. This nerve damage causes pain signals to become exaggerated and can last chronically. Post-herpetic pain has been described as burning, shooting, shock-like, itching, numbness or aching. A patient’s skin may also become more sensitive to light or touch, which can easily provoke intense pain.

Diabetic neuropathy is nerve damage that is related to the disease diabetes. The cause is a combination of factors that diabetic patients are likely to have, including high blood glucose, low levels of insulin, abnormal lipiddlevels, etc. The pain is commonly in the limbs, but it can also be
experienced in the digestive organs, heart, or sexual organs. The limbs that can be affected include arms, hands, legs, and feet and the nerve damage may cause tingling, numbness or pain. Other organs that are affected can cause symptoms such as nausea, vomiting, constipation or diarrhea, problems urinating or erectile dysfunction.⁴

Arthritic pain can be osteoarthritis or rheumatoid arthritis. Osteoarthritis is caused by long-term use of a joint or an injury to a joint which causes a break down in cartilage. Cartilage protects the bones from touching and rubbing together, and after the break down of the cartilage occurs, the bone on bone friction can cause pain and inflammation. Rheumatoid arthritis, on the other hand, is due to the body’s immune system attacking nerves and joints like it would a harmful bacteria or a virus, ultimately causing inflammation. Over time, the inflammation can cause cartilage to break down. Rheumatoid arthritis attacks the body symmetrically, meaning joints on both sides of the body, while osteoarthritis can occur in just one joint.⁵

**How is pain assessed?**

The intensity of pain can be measured by many different methods, including numeric scales, visual scales and verbal scales, as illustrated below. According to Oldenmenger et al., a score of one to four is mild pain, five through seven is moderate pain and severe pain is eight through ten. These scores are used to determine what level of pain the patient is currently experiencing and how that pain needs to be managed. These scores can change the type of pain regimen and what dose is started.⁶
Verbal Pain Intensity Scale

None  Mild  Moderate  Severe  Very  Worst
severe  possible

The model below is used to see the location of pain. It should be used with one of the scales above as location is not enough to assess pain severity, type of pain and how to manage it.  

Frequency and duration of the pain should also be assessed to classify the variety of pain. 

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**STOP AND REFLECT**

**Why would a visual analog scale or Wong-Baker face scale be better than verbal and numeric?**

*Answer: With the visual analog scale the patient is able to put their mark where they please without seeing that it is being classified as mild or moderate or being restricted to numbering it. The Wong-Baker scale helps patients visualize how they are feeling so they have a reference. With the numeric scale and visual scale it forces them to pick a number or a category. With the verbal scale patients may be more bias due to them wanting to be treated so they over exaggerate or not wanting to seem like they can't handle pain and under exaggerating.*

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**Classification of pain**

Acute pain can last seconds to several months, until the disease or injury resolves. This is a result of the normal physiologic processes that protect the body from actual or impending tissue damage due to injury or disease. Even though it is protective, it should still be treated to decrease the patient’s discomfort and the risk of developing chronic pain.

Chronic pain is defined in the Hooten et al. study as, "pain without biological value that has persisted beyond the normal time and despite the usual customary efforts to diagnose and treat the original condition and injury." Chronic pain can persist for months to years and continues beyond the normal healing time for an injury. With chronic pain, as compared to acute pain, practitioners
have to worry about how this may affect the patient’s functionality. Sleep difficulties, depression, family issues and dependence or tolerance to a medication are issues that commonly arise with chronic pain and should be monitored. Pain also needs to be tracked regularly and medications modified if the pain is not controlled.

Cancer pain includes both chronic and acute pain. Acute pain caused by cancer is called breakthrough pain, which is severe pain that the patient experiences even when they are already being treated for pain. This pain can either be due to the cancer itself, diagnostic procedures or the treatment regimens. Regimens that treat both cancer and pain need to be assessed regularly and changed if the pain is not controlled.

STOP AND REFLECT

Why would someone with chronic disease have depression or sleep issues?

Answer: A patient may have depression because they are in consistent pain and they may not be able to do activities they want to, or used to be able to. This loss of activity can lead to loss of relationships and jobs. They also may have depression because they spend so much time trying to control their pain and all of this leads to stress. Sleep issues can be due to the patient being in pain or due to the stress they are experiencing.

Over-the-counter and non-opioid medications

Acetaminophen (APAP) is a very effective first-line agent for mild to moderate pain and for some disease states like osteoarthritis and lower back pain. Acetaminophen is also known as paracetamol outside of the United States. The exact mechanism of how acetaminophen works is unknown, but it has the same analgesic (reduction of pain) and antipyretic (reduction of fever) effects as non-steroidal anti-inflammatory drugs (NSAIDs). Acetaminophen does not have the anti-inflammatory effects or effects on clotting that NSAIDs elicit. Acetaminophen is better in patients with stomach or heart issues over NSAIDs, but should be used cautiously in patients with kidney or liver damage. Liver or kidney damage should be a concern in alcoholics and the elderly. Acetaminophen has few drug interactions; however, dosages should never exceed 4 grams (4000mg) per 24 hours to avoid liver injury. Concomitant use of combination drugs like hydrocodone-acetaminophen should be taken into account when calculating the daily dosage.

NSAID’s are a class of drugs that are widely used for mild to moderate inflammatory or non-neuropathic pain. NSAID’s reduce pain, fever and inflammation by inhibiting prostaglandin production. Prostaglandins are hormone-like substances that control inflammation and other body functions. All drugs in this class have nearly identical pain relief properties, so choosing the most appropriate agent depends on cost and side effects. The primary adverse effects associated with NSAID use are due to a lack of prostaglandins, which protect the stomach lining and are involved in
forming blood clots among other things. Some common risks to be aware of are stomach bleeding or ulcers, and cardiovascular issues such as increased blood pressure, stroke, or heart attack.\textsuperscript{1} Medications such as misoprostol or omeprazole are commonly used with NSAID’s to protect the stomach lining.\textsuperscript{9} 

<table>
<thead>
<tr>
<th>Examples of NSAIDs</th>
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<tbody>
<tr>
<td>Etodolac</td>
</tr>
<tr>
<td>Ketorolac</td>
</tr>
<tr>
<td>Diclofenac</td>
</tr>
<tr>
<td>Sulindac</td>
</tr>
<tr>
<td>Meloxicam</td>
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</table>

Aspirin is an NSAID that is normally used to protect the heart by preventing clotting and clogging of blood vessels, thus preventing heart attacks. It can be used as an anti-inflammatory but a dose must be used up to 4 grams daily to be effective.\textsuperscript{10} 

Opiates

Opioids bind to the opiate receptors on neurons as their pain control mechanism. There are three kinds of opiate receptors: mu, delta and kappa. Mu receptors emit analgesia when bound. When opiates bind to the receptors, it decreases the chance that the pain signal will reach the brain.\textsuperscript{2}

Opioids should be used for relief of moderate to severe pain as the next step after acetaminophen, NSAIDs or other analgesics have failed. Many times a combination of opioids with acetaminophen or an NSAID is used because they are more effective together and can lower the amount of opioids needed to treat the pain. The combination drugs are shown in the table below, and the acetaminophen maximum daily dose should be considered when dosing.\textsuperscript{1} Opioids are the next step for acute and cancer related pain; however, chronic non-cancer pain treatment with opioids is controversial.\textsuperscript{2}

Opioid medications are manufactured in several different formulations. There are short-acting medications, also known as “immediate-release” or IR on the prescription. These medications usually last about three to four hours for pain relief and are used for pain that happens intermittently. Long-acting medications are also known as “controlled release,” “sustained release” or “extended release;” CR, SR and ER respectively are displayed on the prescription. They provide pain relief for eight to twelve hours, or up to 24-hours in some cases. Because directions will often change with these formulations, ensuring each patient has the correct medication will always be an important step.

The shared side-effects of opioids are sedation, nausea, vomiting, constipation and respiratory depression. Most patients are able to tolerate these side-effects after time, other than constipation.\textsuperscript{2} Constipation can be helped if a patient is willing to take a stool softener and stimulant laxative. Nausea and vomiting are best diminished or resolved with medications like ondansetron (selective serotonin antagonists).\textsuperscript{1}
Both the short-term or long-term use of opioids creates a risk of addiction.\(^4\) Patients may seek medication in anticipation of need rather than being addicted to them, so it is important to understand the differences in these types of behaviors. Tolerance is when there is a reduced effect of the drug over time, so the patient has to take more of the medication in order to control their pain. Physical dependence means if the patient stops taking, or reduces the amount of the medication, they will experience withdrawal effects. Some examples of withdrawal symptoms are anxiety, irritability, sleep difficulties, diarrhea, nausea and vomiting. This can also happen if the patient takes an opioid antagonist which reverses the effects of the drug in the body, like naloxone. Pseudoaddiction is when a patient becomes obsessed and preoccupied with getting a medication because their pain is not being relieved. The difference between these behaviors and addiction is a patient who is addicted will not be in control of their drug use and will not be able to stop even when it is harmful to them.\(^2\)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Route</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>PO, IV, Rectal</td>
<td>Standard for efficacy and side effects comparison.(^2)</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>PO, IV, Rectal</td>
<td></td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>PO, IV, SQ</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>PO</td>
<td>Combined with acetaminophen or Ibuprofen.</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>PO</td>
<td>Combined with acetaminophen or Ibuprofen.</td>
</tr>
<tr>
<td>Codeine</td>
<td>PO</td>
<td>Mild to moderate pain. Combined with acetaminophen.</td>
</tr>
<tr>
<td>Codeine</td>
<td>PO</td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>PO</td>
<td></td>
</tr>
<tr>
<td>Meperidine</td>
<td>PO, IV</td>
<td>Avoid in long term use due to risk of toxicity(^2)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>IV, SL, IN, buccal, transdermal</td>
<td>Very fast acting(^2)</td>
</tr>
<tr>
<td>Methadone</td>
<td>PO, IV</td>
<td>Has serious cardiac side effects that need to be monitored.(^2)</td>
</tr>
<tr>
<td>Methadone</td>
<td>PO, IV</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>PO</td>
<td>Weak SNRI and mu opioid receptor agonist. Schedule IV Use cautiously in patients with seizure.(^1) Combined with acetaminophen.</td>
</tr>
<tr>
<td>Tramadol</td>
<td>PO</td>
<td></td>
</tr>
<tr>
<td>Tapentadol</td>
<td>PO</td>
<td>Inhibits norepinephrine. Same effectiveness as oxycodone with less nausea, vomiting and constipation.(^1)</td>
</tr>
</tbody>
</table>
Adjuvant medications

Adjuvant medications are medications that are added as a supplement to the regimen that is essential for pain. These medications have mechanisms other than analgesic properties that NSAID's, opioids and acetaminophen contain. They are used to manage more specific pain symptoms that exist concurrently with pain or independently.  

Anticonvulsants, also called anti-epileptics, are approved for first-line treatment use in diabetic neuropathy, post-herpetic pain, fibromyalgia and neuropathic pain. Gabapentin and pregabalin are the most common anticonvulsants used for pain, but if first line fails, carbamazepine, oxcarbazepine or lamotrigine are also used. Pregabalin is a schedule V controlled substance so when dispensed it needs to be double counted and the prescription requires more information such as the prescriber’s DEA number in order to be valid. Anticonvulsants decrease pain by inhibiting the neurons from releasing substances that transmit the signal of pain to the brain. Gabapentin and pregabalin have few drug interactions and favorable side effect profiles. The most common side effects include diarrhea (Gabapentin only), dizziness, somnolence, weight gain, dry mouth, blurred vision and edema (swelling).

Antidepressants are used for neuropathic pain and some non-neuropathic pain including fibromyalgia and post-herpetic pain. The mechanism to decrease pain is to increase the body’s regulatory system to control pain. This means increasing the inhibition of pain signals sent to the brain from the periphery and the pain receptors in the brain itself. They can also be used in chronic pain patients to help with depression associated with the functional difficulties that arise. Analgesic effects of these medications can be seen in a day to a week, while antidepressant effects may take up to six to eight weeks to be seen. Effects of analgesia may be seen at lower doses than are needed to get anti-depressive effects and the lowest effective dose should be used.

Tricyclic antidepressants (TCA) and medications that inhibit both serotonin and norepinephrine (SNRI) are preferred over medications that only inhibit serotonin reuptake (SSRI). Tricyclic antidepressants include amitriptyline, desipramine, imipramine and nortriptyline. These medications, however, are less tolerated then other antidepressants; their side effects include sedation, dizziness, weight gain, constipation, dry mouth and urinary retention. TCA’s should be used with caution in the elderly and not used in patients with heart problems like arrhythmias or epilepsy.

SNRI’s include duloxetine and venlafaxine and are effective for diabetic neuropathy, fibromyalgia and neuropathic pain. These agents should be used when TCA’s are intolerable or inappropriate. Venlafaxine should be used with caution in patients with high blood pressure and should not be started in patients who do not have control of their blood pressure. Side effects of SNRI’s include sexual dysfunction, dizziness, drowsiness and sleep difficulties.
SSRI’s are the most common antidepressant for depression but are third line for treatment of chronic pain. A modest benefit in pain has been observed with paroxetine, citalopram, and escitalopram, but no efficacy for fluoxetine. Bupropion is also a third line agent used for neuropathic pain. It affects norepinephrine and dopamine instead of serotonin and norepinephrine. Some common side effects of this drug are dizziness, sleep difficulties, weight loss and increased heart rate (tachycardia).

Topical therapies can be used when pain is localized to a certain area of the skin. Topical agents available are topical NSAIDs, topical lidocaine and capsaicin. These may be preferred over oral medications to decrease the side effects of the drugs because they act locally and less of the drug is absorbed into the body. Diclofenac is an NSAID and is available as a patch, solution or gel and is used for osteoarthritis and minor sprains. Lidocaine patches or gel have shown efficacy in post-herpetic pain that is localized, and because it is topical, the side effects are mild such as a skin rash. Capsaicin is a natural chemical derived from the seasoning cayenne and can be used for arthritis pain and neuropathic pain including diabetic neuropathy and post-herpetic pain. It should be applied for six weeks in order to see the full benefit. The most common side effect is a burning sensation, but the patient may become tolerant to it after a few days.

Corticosteroids act on the same pathway as NSAIDs to decrease inflammatory mediators like prostaglandin but also inhibit more substances that cause inflammation. Examples of corticosteroids are hydrocortisone, prednisone, methylprednisolone, triamcinolone and dexamethasone. Oral therapies are used less than injections and can be used in chronic diseases such as rheumatoid arthritis or cancer pain. The injection site for corticosteroids in these disease states is directly into the affected joint or joints. Other options are injections into the spine or soft tissue. Corticosteroids can be added on with opioid therapy but should be avoided with NSAIDs as they work similarly. Corticosteroids are not used often due to the many side effects, some including increased blood sugar, bladder dysfunction, swelling, dry skin and agitation.
This step ladder image refers specifically to cancer pain, but it can be referenced for any type of pain. Once pain is identified, a nonopioid medication should be started along with possibly an adjuvant agent to help with symptoms. Adjuvant agents and nonopiates can be used at any step in pain management if they are necessary to help manage the pain or symptoms that are associated with chronic pain. Pain frequency, duration, and cause must be assessed to decide if step up therapy is needed or if the pain is controlled. If the pain is consistent or recurring, the pain medication doses may need to be timed around the clock instead of being used only when the patient needs it. Once the max efficacious dose of a drug is used, a step up in therapy should occur if the pain is not managed.

Conclusion

Pain medications are prescribed very commonly and technicians should be able to recognize what the medication is treating. Technicians should also know if it is a controlled medication or not in order to ensure prescriptions are valid. Most data entry is performed by technicians, and because of this, it is important to understand the differences in formulations between prescriptions and what medications are over-the-counter.
References:


