So on behalf of the national regional team initiative, my name is Dr. Abili and I am the pain pharmacist and provider and square meter here at Walter Reed. Thank you so much for joining us. Before we talk about ecology, I have to read some disclaimers.

So this certifies that I had not has my spouse or partner or any immediate family member have had in the past 12 months or expect to have in the upcoming 12 month any financial relationship or gift in kind industry. This certifies that the views expressed in this presentation are those of mine and do not reflect the official policy of the Department of Army, Navy, Air Force, Department of Defense or U.S. government. So as Mister Spencer said, pharmacology and pain is all we will discuss today. I will present you with some goals to get some feedback, and just to discuss the scenarios that may occur. The learning objectives are to discuss the definition of pain, to describe the types of pain, to describe a social approach to pain management and to discuss available therapy for management of pain.

Before we go further, I want to let you know that we may take a break in about an hour, maybe a 50 minute break and take another break may be around the two hour mark depending on how everything goes. Just to give you an overview for historical background as it relates to pain, pain is derived from Latin. Greek and Roman mythology used to describe pain as an inflection by the gods. Perhaps retribution or punishment for something, so in Latin, the Roman god punishment was called away. It has been changed to the French for pain and then pain is suffering. The Romans also had demigods and one of them was called the lower and in Spanish, that means to pain. They were born from the union of air and land. That is where pain came from. In the Greek thought of the goddess of revenge.

She also had algae and they were demigods of strife and grief and suffering and they were the personification of pain, grief, and stress. So historically people associated pain with some sort of punishment that came from a God. Around 4000 BC this relates to treatment for pain management, the experience is to cultivate the opium poppy. That's called the plant of joy. The Egyptians were also cultivating at themselves and there was an opium trade. And 4000 BC, the Seminarians and Egyptians use robots for [Indiscernible] around 300 BC, Hippocrates was on to prescribe willow bark. Methods of herbals to try to manage pain.

According to the international Association for the study of pain, pain is defined as an emotional experience associated with the potential tissue damage. So the definition itself does carry some implication. Because first of all, it is implied that pain is subjective because it aligns pain as part of an emotional experience, so pain is subjective. So two individuals could have potentially the same injury. Everything could be the same, but you could talk to patient one and ask patient one on a scale of 1 to 10 where would you say your pain is, and patient one would say three, and then you can ask patient 2 on a scale of 1 to 10 where would you describe your pain and patient 2 would say [Indiscernible] it is subjective and it is an emotional experience. It also says it could be actual or potential, but it is associated with an emotional experience.

So it also implies pain and nociception are different. Pain implies it may be impacted by social and the psychological well-being of the individual.

Just to say a few things about nociception because I said pain and nociception. They are not the same thing. Nociception is the signaling of tissue damage, and that is usually transmitted by nerve cells called nociceptors, those are pain neurons. The actual message has been transmitted saying I have a paper cup, now because pain and nociception are not the same, you can have nociception without pain, but for example, you hear about soldiers in a war zone that may have been shot a number of times, but because of the environment, they are in and their adrenaline, they are running to rescue this person and you may hear a soldier recalled a story and say I did not even know I was shot. After the fact, when they are taken away from that environment, they notice the reality that they were shot three times and didn't know.

Nociception can be had without pain. For example with a small child, when my children were very young and they had to get there first demonization, if the nurse was about to give them the shot and I distracted them and would make sounds to make them smile, when the nurse administered it, they saw something, but they would still pay attention to any and I am laughing with them and they would laugh and smile as well, but I personally do not like injections, so there have been occasions when I had babies and I would take them and I would forget, I would be smiling with them and playing with them and as the nurse gives the shot, I would look at them and I would maybe have a sad look on my face and the child would burst out crying, so sometimes you can have nociception without pain with a child who gets a shot, so the child is not reacting, or they also have pain without nociception.

Another example of nociception without pain would be under general anesthesia, so they cut the skin to do whatever procedure or surgery is required because the individual is on anesthesia, then they will not feel the pain until they wake up. Of course you can have incidents of pain without nociception. For example, may be in a scenario where the individual is expecting whatever is going to happen is going to hurt or be painful. They may feel a heightened sense of pain. I read about a study in which individuals, I think they keep up a mental bar.

Beforehand, they told the individuals that they made it as hot as it was going to be and to be careful, so they touched it attends their skin and they told them they had made it as hot as possible and they said it was painful. When they would tell the individuals that the metal bar had been made as cold as it needed to be for a massage, the individuals would express pleasure as opposed to pain. The irony was the temperature was exactly the same in the study, so it was not necessarily different temperatures, it was the same temperature, but unfortunately because of the expectations of harm or pleasure or the association with the metal bar with pleasure or harm, they were reported having pain.

There are also times when you have incidents with patients who have pain without nociception whereby an individual or parts having pain in some particular area, but no matter how much you do, you really can't

find what the cause of the issue is. So pain is subjective. Basically that is the definition of subjective. It varies from one individual to the next.

The way we treat pain really is by looking at the hole individually, looking at it holistically and we do that by the form of a pain model. This pain model implies that it requires us to use a model of pain. It basically gives us an idea that pain has a biological component, a psychological component and a sociological component. Let me -- there we go. Okay. It was described by Doctor Engel in 1977 and the overall perspective of the psychosocial pain model is that our belief impacts our perception of pain. So our pain can be impacted by our mood, our social support, our prior experiences, and all those things have to be taken into consideration when one is trying to manage an individual's pain.

So for example, a biological component, your age, somebody who is 20 years old versus somebody who is 77 years old is more likely going to experience pain a little bit differently, and they are more likely because of the age difference, the younger individual is more likely to heal faster. Than an individual that is 77 years old. Even our psychological aspect, our beliefs built into managing our pain. If you have an individual who says you know I am -- this injury changed everything and I'm not going to recover from it, or the only medication that will work for me is XYZ, that belief already impacts the outcome of how you manage the pain and the outcome of how they feel the pain.

Also with the psychological aspect, anxiety and depression, they also contribute to pain and a lot of individuals who have chronic pain tend to have depression and anxiety, and they feed on each other and attends to be cyclical. The depression gets bad and then it makes the chronic pain bad. It kind of goes around and around. Also the sociological aspect with pain.

For example, studies have demonstrated that individuals who tend to have more education, lower socio- economic status seem to be more likely to experience chronic pain, and also if you have chronic pain, what is your social support like? If you have family to support you and encourage you, are you from a background where when you are in pain, you have some kind of illness, it is best not to talk about it and suffer in silence. Or do you have a culture or are you amongst individuals, you can talk about it and have that societal support around you.

Also psychologically and sociologically, what happens if you are suffering from pain, do you end up becoming attachment is a do something for you. It allows you to play the victim and not to say that individuals who have pain perceive themselves as a victim, but [Indiscernible] or is it giving you something of some sort? So overall, there are different aspects that contribute to how individuals experience pain and also contribute to the overall management of pain.

So bio model of pain, you do want to approach it in a multimodal fashion. You want to use integrative care. That would mean trying to use cognitive behavioral therapy, trying to use exercise, not necessarily approaching the management of pain from a purely biological standpoint,

whereby we need to give the person medication. That may not be the best way to approach the individual's pain. That maybe what the individual desires, but that may not be the best way to go, so typically we want to try treatments, acupuncture, physical therapy and we also want to try non-opioid medication.

Then we also want to have a comprehensive history, and it should include an individual's psychiatric morbidities. You want to discuss functional status as well as their goals. On a scale of 1 to 10, if an individual's pain is a 10 and their goal is I want to get down to zero, then you need to be able to manage the person's expectations because that may not be realistic. Oftentimes with pain, the individual may still end up having pain, but what you are trying to do long-term is to improve their ability to function, so their activities of daily living, being able to, maybe the individual used to work full-time and now because of the pandemic, they are not able to. Part of it may not necessarily be to take away the pain completely, but help them so they can go for a walk here or be able to drive their car to this location without having severe back pain.

So, you do want to manage the individual's expectations. You also want to disk us potential treatments options for an individual so it is not just medication, not just opioids necessarily because individuals have their own opinions of what they believe will work best for their pain, and you need to keep that in mind as you discuss available treatments for them, but you also want to try to give them appropriate recommendations based on guidelines that would be more effective for whatever pain they are dealing with.

In addition to psychiatric comorbidities and history, you went to find out has this person in the past had substance abuse histories over maybe they are misusing, so you want to try to get a complete history or maybe the patient may be adverse to using certain types of medications because maybe their family member had used such and such medication and had become addicted in that forever impacted them. So have a comprehensive discussion to process the individual.

This page simply strobes what I discussed in the previous page, which is cognitive behavioral therapy. If one is approaching pain, cognitive behavioral therapy is a psychological aspect, exercise, physical therapy, acupuncture, and then he would consider non-opioids. Acetaminophen, ibuprofen, Celebrex and then [Indiscernible] first. So pain can be classified based on time, so classification of pain would be acute pain versus chronic pain.

Acute pain is usually caused by an injury or maybe I was playing a game and I feel and broke my ankle, or maybe the person was in a car accident and suffered trauma or maybe the individual had a C-section and is recovering from the C-section. Acute pain usually have the start and end, and usually is resolved when the underlying condition is resolved. Maybe in a woman who has a C-section, when the incision heals in the tissue heals completely, then the pain goes away. It's typically some disease or illness, but also has a protective role in the sense that for example if I am exercising frequently, maybe I don't stretch and I start

to feel the pain, okay stop, maybe I need to slow down a little or maybe stretch a little bit more.

Maybe you are working out too much. And has a protective role to warn us of something we are doing or have done. However, chronic pain, defined as three months or longer is considered to be a dysfunction cannot really biologically protective, and chronic pain is something existing beyond the normal course of healing. So in the case of the woman who has a C-section and after the incision has healed and two years later she is still feeling pain, that would be chronic pain because it is beyond the normal course of healing it is estimated by the CDC that in 2019, more than 20% of adults in America were suffering from chronic pain. The incidence of chronic pain increase with age for adults 65 years and older.

So there are different types of pain, and to be honest, there are so many different categories, so depending on which society I look at, they have various categories. I'm going to simplify this and we are going to look at the different kinds of pain as neuropathic pain, inflammatory, nociceptive and mixed. Neuropathic pain is usually due to an injury or disease of the nervous system, and for example now diabetic neuropathy or maybe pain leads to spinal damage, and it is typically described as stabbing or burning. Or even tingling or numbness. Intends to respond best to antidepressants and anticonvulsants as well as local anesthetics.

It is also inflammatory pain, and that usually occurs due to [Indiscernible] Anna whole host of [Indiscernible] and it is typically dude to some sort of nociception, maybe a stimuli in that area. It can also be caused by infection as well. And individuals who have inflammatory pain tend to have increased sensitivity to a normal level of touch. So individuals who have inflammatory pain and he touch that particular area, touch it lightly, but it is very tender to them.

An example could be infection, you injure your arm and have it swell up, and they tend to respond. Nociceptive pain is due to injury. It is usually do some kind of painful stimuli and it could also be something like maybe a vibration or due to some kind of inflammation or force. Maybe a cut or breaking a bone. It is typically sharp and achy and throbbing.

With nociceptive pain, you could divide it into pain that is in the receptors that they feel and think internal organs. This pain is typically not localized. It tends to be more-vague. Sometimes it could be pressure or ache. Within the nociceptive group, you can have active pain that would be pain in the tissue like the skin and the muscles in the skeleton and connective tissue and it could be described as sharp. So I think how about if we do the first poll question here before we go into medications.

So we are going to bring out a poll question. So Mrs. Smith is a 53-year-old patient who has had multiple back surgeries. She describes her pain as shooting and burning and radiating. What type of pain as she most likely experiencing? Inflammatory, neuropathic, nociceptive, she doesn't really have any pain, she is just making it up. Okay. So yes.

Everybody seemed to put nociceptive. And neuropathic, I apologize. That is because she said it is shooting and burning and radiating. Okay. Thank you. So let's go ahead and talk about the class of medications.

First, can I ask if anybody has any questions? You can either type your question or let me see. I am not sure how to bring up the question box. Thanks. Okay. Thanks. I will keep on going on and I will stop and see if anyone has questions. So we are going to talk about acetaminophen. We are going to talk about NSAIDs, anticonvulsants, opioids and topicals.

So acetaminophen is popular worldwide. In some countries, it is Panadol. It was discovered in the lead 1800s. But it really was not used in the U.S. until the 1950s. That is when it was approved by the FDA. It is thought that its mechanism of action is through maybe [Indiscernible] maybe there is an alternate site for acetaminophen or maybe it binds on Cox three because individuals are not quite sure of the mechanism of action, but these are the theories they are having proposed.

It is believed that it inhabits the intermediary [Indiscernible] it inhabits the intermediates, but it is not very effective in the system and that is because in the peripheral nervous system, typically what happens acetaminophen may reduce that intermediate somehow, but because the peripheral nervous system, they we oxidize them back, so acetaminophen may not have as much of an impact peripherally, but it is able to work quite well.

Are you there?

Hello? Hello? Hello?

We can hear you.

Sorry you could not hear me.

Where did I leave off?

We were back maybe a slide. I just noticed you stopped talking.

I'm sorry.

Someone says the beginning of acetaminophen. Okay. We are right here.

Okay. Thank you so much. I was still talking. Okay.

You can continue.

You know I just thought you guys were awesome and listening quietly. Thank you so much. So acetaminophen, sorry. The mechanism is unknown. There are some theories, two primary theories that are discussed. One is that it inhibits Cox three. It is believed it inhabits the same enzyme that NSAIDS inhibits, but it is believed that well, it is believed that it inhibits that enzyme, but in a different binding site or it binds to Cox three incentive 2. Let me go back. It may bind to Cox

three, so Cox one and Cox to. Truly, the mechanism of action is not known.

What is believed is that the intermediate perfect Landon that is made from our asset before the final end product and other derivatives are formed, not intermediate. It is believed perhaps it is reduces and when it reduces that intermediate, because it is doing that in the periphery, the proxy sitting will we oxidize the intermediate reduced, so that in the periphery it does not really help with information, but essentially it still helps with the pain. Acetaminophen is for nociceptive pain, it is available over-the-counter, in other countries like the UK, it is behind the counter because individuals have overused it and ended up with liver damage or used it to commit suicide, so it is usually available as a prescription in the UK, but in the U.S., it was not even really approved to be used until the 1950s.

It was discovered in the 1800s, but it was not approved until the 1950s by the FDA to be used for pain. So we know it has properties, but when individuals are taking it, I try to encourage individuals to take four grams or less, and the elderly should take two grams or less and you want to be especially cautious with individuals with dysfunction. So NSAIDS are also more appropriate for inflammatory pain, and the anti-inflammatory drug and the anti-inflammatory examples that we know every day like ibuprofen and naproxen, you know.

NSAIDS are made of different chemical classes. For example NSAIDS may be made of acetyl acid derivatives as naproxen or they could be made from propionic accident derivatives like ibuprofen or naproxen or piroxicam.

NSAIDS tend to be categorized sometimes as nonselective or maybe Cox to selective and for NSAIDS for Cox one, Cox one is G.I. protective and it helps to increase mucus secretion in the stomach, in the G.I. system. And also increase bicarbonate secretion and causes the decrease of acid production. So let's say you take a nonselective NSAIDS, you may have a higher incidence of gastric ulcers because it is inhibiting Cox one, which is G.I. protective.

Also, Cox is found in platelets, so Cox stimulates nasal constriction and a psyllium does the opposite. Cox is also in the kidneys, so it also impacts the renal function because it helps with renal blood flow and distribution, so that is part of why when individuals take NSAIDS, they could potentially impact their kidney if they overuse it because it is so important for the renal function. So with Cox one and Cox to, they have an influence on the inhibition of kidney regulation. So that is what caused peripheral edema and retention.

Cox 2 is primarily the one that mediates pain and inflammation. So that is why it may be a good idea to give individuals Cox 2's electives NSAIDS so that you don't have as much of an impact on the G.I. system and as much on the renal system, but NSAIDS are available in multiple forms, in topical forms, oral and IV.

This next chart breaks it down by chemical class. We talked about how they could be derived from appropriate asset, and the second bar shows how selective it is to Cox 2, so locks at 10, Celebrex, those seem to be more selective for Cox 2, but true Cox 2 selective NSAIDS, the mechanism by which the other NSAIDS are slightly different. The last chart shows a half-life of various NSAIDS.

So the mechanism of action that you can see here, if you focus on the right side, it starts with arachidonic acid and oxygen is and it inhibits oxygenase and we see IBM from boxing and prostacyclin. That should have been made with NSAIDS. It inhibits Cox one and Cox 2 conversion. To the prostaglandin and intermediate H2 intermediate, so by stopping the conversion, it stops the formation of propoxyphene important for platelet aggregation. It also stops other derivatives like PG too. It is written PGF2. Which are on the G.I. systems, but also cause pain, fever and inflammation and then it also stops the formation of proxy cycle and proxy cycle and counters from box and, so proxy cycle and creates dilation and prevents platelet aggregation.

So with NSAIDs, we want to be especially cautious because as we discussed, Cox has an impact on the renal function, so we want to be careful with that, and also NSAIDS can increase the risk of cardiovascular events and that seems to be particularly on initiation. But it can happen throughout.

There have been studies that have shown the doses of NSAIDS have a height incidence of cardiovascular Bostic events. So one does have to be careful when initiating someone on NSAIDS and on NSAIDS long-term. Contract indications include allergy or hypersensitivity to the NSAIDS or salicylates. Coronary artery graft surgery or third trimester pregnancy.

I think the next topic would be another set of medications, so maybe I wonder if we could just take maybe a 10 minute break here and then come back and in the meantime before we go, Mister Spencer, would you mind resetting my screen for me.

Does anybody have questions? I wanted to find out if anybody has questions. Then maybe we can take a 10 minute break and start again around 2:05. Does anyone have questions first? Then we will go to another topic. Another class of medication. So if -- okay. Okay.

I don't see any questions, so how about we take a 10 minute break and start back at 2:05. With that be okay?

Okay. We will see everyone back at 2:05.

Okay. Welcome back. Hopefully everyone can hear me. I am going to go ahead and continue on anticonvulsants.

Anticonvulsants are another method of medications to manage pain. They would typically be for neuropathic pain, so I am first going to talk about grab up and anoints. Currently we have gabapentin. Gabapentinoids work in subunits which inhibit the transmission of transmittance signals. Gabapentin can be used. Those individuals with gabapentin need

immediately relief and you could go up to 3600 milligrams. However, it is nonlinear, so the higher the dose, it is not necessarily the higher the ability. With gabapentin, when you give somebody 900 milligrams, 60% are available. When you give somebody a 3600, only about 33% is available, so it is nonlinear and absorption.

With gabapentin, studies have shown there is no additional benefit in going about 1800 milligrams. With pregabalin, the dose of the 600 milligrams and it is absorbed in a linear fashion. Such that at least 90% of whatever is given is made available regardless of the dose. Both medications have adverse-affects. Weight gain, memory or concentration issues. In the medication, so even if you have a lower dose of opioids, somehow it helps it to be more effective. However they can be abused. They are objects of abuse, unfortunately. So you still have to be cautious. Pregabalin is controlled.

In Maryland, gabapentin is not. In Virginia, if I do a search for gabapentin, if I look at somebody's prescription drug monitoring profile in Virginia, I know I will see gabapentin because they collect gabapentin, it can also be abused. For these medications, the dose will need to be adjusted based on the renal function. For example with gabapentin, you could give individual, maybe you started with 300 and then slowly increase it over time, make it three time dose and if the individual is struggling with staying awake during the day because of gabapentin making them sleepy, then you may want to decrease the night dose while reducing the daytime dose, or you could use extended-release gabapentin. If you also have an individual struggling with pain. They have been unable to sleep at night, you could potentially have them take it at bedtime to help them with sleep and pain.

Topiramate is another consultant used for headaches. Perhaps it works by inhibiting the sodium channels and it has inhibitory effects of gamma and by blocking the effects [Indiscernible] typically you give an individual 25 milligrams twice daily and then [Indiscernible] the maximum dose you want to give an individual is 200 milligrams. If you do go up to 200 milligrams per day even though you can go up to 400, you want to be careful.

I apologize. The maximum you can give somebody is 400, but for pain, I see individuals taking 200 milligrams in divided doses. When you go above 200, you had to be careful about potential drug interactions with oral contraceptives, because above those doses, it decreases the efficacy of all contraceptives and it seems to increase the concentration of meta-foreman, so there was a study where individuals who are healthy are given meta-foreman and then they were given paramedics and the meta-foreman concentration increased by 1825%.

You doing to be aware of that. With lithium, it seems to increase the concentration as well. If you have individuals on lithium, you are going to be doing labs, but you want to be extra careful. Because [Indiscernible] paramedic may impact the concentration. Typically with the parapet, you don't really need to address the dose unless the occurrences below 70. You and to give them half the adult dose. The tie traits with prepare [Inaudible] is when people are taking prepare it for pain, some of the same patients have concern with confusion, individuals

will say I was confused. I was out of it. I couldn't speak, I couldn't remember things. So it does have an impact on your memory, on your speech, and also it may make you tired and dizzy and so to permit they also cause weight loss. It is given in combination with weight loss.

Are you there?

Yes, I am. Can you hear me?

We can hear your reception going out a little bit. Maybe you are not in the right space. Sometimes you go in and out. Not really sure if you are pausing or if we just can't hear you.

Can you hear me now?

We can hear you.

Okay. Please let me know if it happens again. Thanks.

Okay. So next I'm going to talk about carbamazepine. Carbamazepine, the mechanism of action is through inhibition of the channel that inhibits propagation of action potential. Before you initiate carbamazepine, you want to make sure you do HLA B-52, specifically for individuals because it is negligible and Caucasians are people of African descent. You want to do that because of Stephen Johnson and likewise when you are also going to be similarly for the next medication, you want to do that before hand before initiating it. Before you start, if you want to make sure individuals on MAOIs have been off it for at least 14 days also, individuals are allergic, you want to avoid this medication.

You went to get a baseline CDC LST before initiation because it can cause anemia. Typically you also want to be cautious about individuals already on three or four inhibitors. For example verapamil, grapefruit. You also want to be careful with individuals who may be taking medications that are 384 inducers because the inducers will reduce the concentration whereas the inhibitors will increase the concentration, so if individuals are also on scene of ours, you want to be careful and four inducers, you want to potentially increase the dose, and four inhibitors, you may want to either avoid it or decrease the dose substantially.

Carbamazepine for substrates. Warfarin, level thyroxine, Cal blocker, when it is administered with those, it may decrease the concentration of those medications. Carbamazepine could be used sorry for neuralgia. The dose is can range from 600-800 milligrams. You also could have drowsiness, dizziness and Milo suppression.

Also, oxcarbazepine, he went to get ABC 02 tests for advanced because of Stephen Johnson and toxic necrosis. It works similarly by blocking the channel and it affects the coxswain channel. Thereby stopping propagation as well. It can be used for diabetic neuropathy in neuralgia and it is typically given around 600 milligrams in divided doses from maximum of 1800 milligrams. Side effects include headaches, dizziness, nausea and vomiting, fatigue, diplo via, ataxia.

When it is given concurrently with two 319 substrate, you want to be careful because it may increase the concentration of the substrates. For example Karas of Bernal. Diazepam. It may increase concentration of those medications, and then it may impact oral contraceptives as well and reduce the concentration when given concurrently and also with channel blockers like so little pain. It may also decrease their concentration, so you want to be mindful of concurrently with those and just monitor those medications.

LaMacchia game inhibits calcium channels in the release of glutamate it can also be used for neuralgia. You would use it slowly over a number of weeks and increase every two weeks for a maximum of 400 milligrams. If it is given concurrently with valproic acid, you are going to want to use half of the dose, half the normal dose you would give when given concurrently. You also want to be careful when it is given with other inducers such as revamp and because those in-turn will decrease the motor gene, the concentration in the system and also with this, all contraceptives will reduce its concentration in the body.

So if an individual is taking this and is taking oral contraceptives, you would want to increase the dose you are given. Side effects like dizziness and nausea and vomiting, diplopia, blurred vision, rhinitis. Into commotions like Lamotrigine the carbamazepine, those typically I have seen more so for trigeminal neuralgia and that's because it is seems headaches and other neuropathic types of pain gabapentin tends to be the go to. More so than these other anticonvulsants for the treatment of neuropathic pain.[Indiscernible] not so much for diabetic neuropathy or other kinds of neuropathies.

Move on to antidepressants. Antidepressants are also neuropathic pain as well. I do have to say as I go through this, I went to say I think there was a meta-analysis and I think it was published this year that really said antidepressants, those are effective very minimally. I think that speaks to how pain is subjective because

With people taking medication for diabetes, you can usually say this medication may reduce A1c from eight to 7.8 or 7.7. It is that effective. Or we can say this blood pressure medication will bring the blood pressure down by, from 150 over 120 to 120/90 or something of that major. With pain, because of how subjective it is, it is very hard to categorize. I think even though we use tools to measure the pain, the reality is subjective. The same person you may ask about pain over a couple visits. Sometimes it is different and maybe perhaps you have not really done that much to change pain, but it is very subjective, so I just want to provide that information.

So typically for pain, neuropathic pain, we tend to use SNR I and PCA. For SNR I, the primary ones we are going to talk about is the loxapine and Manasseh Brandon. Antidepressant in Europe. In the U.S. it is not approved as an antidepressant. In the U.S. it is only approved for fibromyalgia. First you want to avoid with other drugs similarly like amphetamines, you want to avoid it because of the risk of serotonin syndrome. You also want to avoid using it within 14 days of MAR I. At the NRA typically works with an uptake of serotonin. We are going to discuss

venlafaxine first and venlafaxine, typically he would start around 75 milligrams per day and before [Indiscernible] common side effects could be nausea, anorexia and with the loxapine is approved for chronic pain syndrome. The loxapine is approved. And has multiple approvals for skeletal pain, fibromyalgia and diabetic neuropathy. It has several indications.

You may start by starting with 30 milligrams once a week. Maximum of 120. Typically doses above 90 have not necessarily been shown to be more clinically significant, so you may want this around 90 or so. Side effects are similar. Dry mouth, weight loss especially in children and teens and fatigue and diarrhea. Alexa teen, all of them tends to impact blood pressure. All of them have an impact on elevating blood pressure. I think there are incidents. The blood pressure may have increased by more than 10 millimeters, so you want to be cautious when you are getting it to individuals. Increase incidence of perspiration. I don't like it, it is making me sweat so much, or I don't like it because

I am feeling palpitations. So you do want to be cautious about who you are giving it to. Melissa paren, it is not approved for depression in the U.S. Both are generics. Melissa paren is not available as a generic. It's only approved for fibromyalgia here in this country and you would start it slowly from 12.5 milligrams over several days, you would [Indiscernible] you could do a maximum of 200 milligrams. Hopefully for the 200 milligrams, the individual may get some kind of improvement with Manasseh paren. The bigger issue where that 30% or 40% of individuals that quit the study because of the side effects, because of the palpitations and constipation, headaches, dizziness, so a lot of people would drop out of the studies because of the side effects or adverse effects of medication.

The other thing you want to be cautious with his the enzymes. Some of them show there was elevation [Indiscernible] unit to care for individuals who have some kind of dysfunction and the medication causes urinary retention for some individuals, so you may want to be very careful in prescribing it for men who have some kind of urinary disorder maybe urinary retention.

You want to be cautious before prescribing it to them because it may make it worse. You also don't want to administer it with concurrent administration. One thing I think that is positive about this unlike Manila vaccine in the loxapine, it is not metabolized. So that is something to consider if the patient is on a medication metabolized by C6 and you don't want to have any reaction related to that. We will talk about PCA. PCAs are antidepressants. It is also somewhat similar in that they block the reuptake of serotonin. However it is not as selective as FRA and two types on the market, secondary and tertiary. The tertiary blocks serotonin morsels than the secondary.

Tertiary amine would be medications like a nipper mean our aunt to trip or doxepin whereas secondary would be medications like nortriptyline or desipramine. So that tertiary amines block the uptake of serotonin and the secondary amines more so block the reuptake of more epinephrine, but the secondary, when you take the tertiary amine amitriptyline and you

take that, it is metabolized to a secondary amine and my trip to lean. It ends up locking both. When you take a tertiary amine you are blocking the serotonin and reuptake and also norepinephrine uptake, but secondary amines tend to be preferred because they are more tolerable because they are side effects and not as bad as a tertiary amine.

Part of that is because the tertiary amine have more acidity for certain receptors. So they have more receptors and by [Indiscernible] when they antagonize them, they cause sedation. Is for the receptor, we get those effects like dry merit, constipation, blood vision. So you want to be careful about recommending them for older individuals. You know could also increase the cardiac arrhythmia.

Between SNR ATCA, SNR I might be a better choice because of how pronounced the side effects tend to be for the PCA. The last antidepressant I want to talk about would be SSRI. To be honest, regarding SSRI, they are used a lot in the UK and other European countries. Here they are not used so much. Studies with pain management, it basically says the SSRIs, there was not much support for them being effective for pain management. So I will not touch on them, but I am giving you a list of SSRIs because they are used here in the U.S. I didn't find studies to support them.

So I think here, I'm going to go ahead and maybe ask Mister Spencer to please bring up poll number five. Okay. Thank you. I'm going to read number five. Mister Smith is 50 years old. He suffers from depression. He describes has pain as a key. He states he is doing better with depression and pain. He sleeps well, but he is often tired and drowsy in the morning. What changes would you make regarding [Indiscernible]? Acetaminophen two grams, ibuprofen, 800 milligrams. So I see here there is BNC in the next one is, the second one of A. You know for me if he is doing well with his depression and he is doing fine, and at the same time he is finding he is tired and drowsy in the morning, I would not necessarily change his medication. There's nothing else to say he's having significant issues because it is PCE. IA would probably go ahead and consider changing his gabapentin and I would tell him to take amitriptyline earlier. You can change it, which is fine, but then you have to start to give me appropriate to manage his depression.

Mister Spencer, would you mind bringing up question number six?

Number six, same Mister Smith has chronic back pain and suffers from depression. He describes his pain as radiating, burning, achy and dull. He states he is doing better with his pain, but not his depression. Here is his current medication list. What changes would you make regarding his depression? Gabapentin, a trip to Maine, 150 milligrams and acetaminophen two grams in divided doses. Ibuprofen 800 milligrams TR in. Just a few more moments. Okay. I see people adding comments in the box. I'm sorry I can't see the box because someone is blocking my box view. I would -- sorry.

I see a comment, but I can't read it completely. Mister Spencer, would you mind potentially removing the guest entry box because I see lots of comments. In the meantime, what I will talk about here for

number six, but I probably would do based on the options you have is I would go ahead and I would change his amitriptyline. He is saying his depression is not well controlled and it is already on one 50 milligrams. Actually, I think amitriptyline you can go to 300 milligrams. We are assuming he is outpatient, so I probably would go ahead and I would recommend his medication be changed and refer him to behavioral health.

The same patient, would you mind bringing up case seven Mister Spencer.

One moment. I am having issues.

No problem. I am having issues with the screen. We can both have issues.

I will get it.

No problem. Okay. Thank you. Mister Smith, 50 years old has chronic back pain and suffers from depression. He describes his pain as birding, achy and dull. He states he is doing better with his pain and depression. Here is his current medication list. What other changes would you make? Gabapentin 600 milligrams TID. Two loxapine 60 milligrams. Acetaminophen two grams PRM. Ibuprofen 800 milligrams PRM. I see he is not complaining for adjusted meds.

I would recommend they change to Bella pox and TID. The higher the dose of certain NSAIDS, the higher the incidence of the party of vascular accident. So I would do B or C, change his Vermont pharmacological intervention and I would recommend he be changed to CIV. Now I can read. Thanks so much. Now I read the comments. I'm sorry. I see Doctor Koller. Increase the dose.

The max of 300, but I think you have to be inpatient. Sorry. Just looking at the comments, a recent case of JAS 22 motivation. You are recommending people be very careful, basically. I apologize. Due to providers not knowing the regimen, I think we want to be very careful.

Thank you so much. I'm going to continue with opioids and I may be able to finish sooner if that is okay. Maybe if everyone is okay with it, if you are hungry or thirsty, we can take a break. Maybe step out for five minutes and come back, that would be okay. I continue with opioids and perhaps maybe finish it.

Let me talk about opioids for now. Thank you Mister Spencer. Let me talk about opioids for now. With opioids, best practice would be only for a short duration. Just use it acutely also when you start individuals on opioids, you don't want to start them on a high dose because the higher the dose, the longer they are going to be on it. It will take that much longer.

You want to try to only take individuals down, so you don't want to for example, let's say somebody is on 100 milligrams of oxycodone, went to perhaps taper them down 5-50%, you don't want to try to trap them down to 50 milligrams, see how that works and a person comes back and says to

you I know you have to bring them back on. Try to wean them down in one direction. Try to take them down and don't go back up. You may need to go slowly. You want to make sure the patient is okay with that. If you are weaning them down to 100 milligrams of oxycodone, you're going to take 20 milligrams twice daily, take 10 in the afternoon to help you and the person is not on board and that is not going to work because part of it also, the individual has to feel ready and not be fearful, especially with opioids, people tend to have a fear of withdrawal, so the individual has to be on board before you do that.

Whenever prescribing opioids, you want to use informed consent in the contract. Because part of it is to let the individual know the potential of what opioids can do, and then it lets them know the other options that are available, and then it tells them typically, so VHA has one, and I can't remember the specific form, but I think it is 622 something. I don't recall the number, but there is one, and it also tells them very specifically here are other options for you to get treatment.

You can do physical therapy, you may be better off going to a chiropractor, having a CDT. It spells out other options and stipulates in the contract if you get opioids from another provider, we have the right to maybe discontinue service. We have the right, we are going to pull regularly to see how you are using medications, if you are using opioids from other providers and have you do urine drug screens. As part of a best practice, it would be advisable to have a patient sign for consent. Of course you want to do randoms.

Minimally, you at least want to screen annually. That is because the guidelines recommend that at minimum. It would be wise to do random because sometimes what you find is it is not surprising because you meet Mister Smith who is 75 years old and he has been taking opiates for the last 10 years, but you a urine screen and it is not positive for opioids. You do a confirmatory test, so if you do a test and it is negative, you can also ask them to do a confirmatory test because sometimes depending on where it is done, they may do something like a test whereby there binding something in the test, but if you do something, they can go one step further with that same sample and confirm it is actually negative for opiates.

So, sometimes people may feel uncomfortable. Maybe it makes him feel like you are not trusting them or you are the provider. They feel I have a good relationship, that she has come for the last five or 10 years, and now she is doing one, and she may feel offended, but it is part of best practice, and he sometimes will be shocked at a result, or maybe Ms. Smith takes it and instead of the opioids, something else and other things, so it is just important to do that, to make sure the patient is taking what they are supposed to be taking, what you are prescribing them. On top of this, as soon as you give her the oxycodone, she's using other medication that combines oxycodone could lead to respiratory depression and potentially death. So you also want to be careful in doing that because it is for her safety and also would help you better manage prescribing her the opiates. Now she is using it appropriately.

The other thing to consider, coming back to Ms. Smith, one other thing is sometimes it is important to do the random. But it is also important, especially for individuals who have chronic pain and if you have a spouse who also has chronic pain and maybe they are sharing medications and you are not aware, or maybe the spouse is prescribing medication for chronic pain, but so maybe Ms. Smith is getting chronic pain medication, but Mister Smith has not really even seen a doctor for chronic pain, but he takes Ms. Smith's medication and she's calling you all the time at the clinic to get a refill, but she should not have run out, or sometimes Ms. Smith may call you and explain to them it fell down the toilet. She flushed it down the toilet or it fell over the floor so she needs a new one, so that is where I think having a contract and doing the random drug screen is important and also checking the prescription drug monitoring program.

I know NHS has a policy, now they have a policy whereby all providers need to register with PMP and MHS PMP.

I think it has almost all the space. It may not have every single one, but it has almost all the space. It is similar to the Virginia PMP format wise, the look is very similar. It is especially important to check PMP because there are occasions when I will go to the PMP and check for a particular patient, maybe I want to see the patient of a full writer program because of abuse by the patient is already in the pool provider program and I will see the patient received more from an outside provider five days ago and came to Walter Reed and received a 30 day supply and the supply they received five days ago was also 35 days, so it is important to check because not everybody is taking it appropriately.

That is something you can do to help the patient into helping with liabilities because the PMP is available. I see the individual has a 30 day supply of opiates and you are prescribing the same one to them. That is problematic. So it is good to check the PDMP, whether you are checking NHS or your estate version. The NHS has numerous states. Also, for risk mitigation, you went to provide my locks and as well because Ms. Smith may be taking that medication and maybe she received a phone call from someone and forgets that she is taking that medication and comes back and takes it again, or maybe Ms. Smith is feeling especially bad today and instead of taking it the way it was described, she maybe double that and Mister Smith comes and finds her not as responsive as she normally would be. She is now sluggish and tired and dragging herself. So as a risk mitigation factor, we would prescribe Naloxone.

Studies show that prescribing Naloxone with opioid prescriptions decreased the incidence of ER visits. Due to opioid abuse or overdose, so it would be a good idea to co-prescribe Naloxone. Also, you don't want to prescribe opioids if the individual has an untreated substance use disorder history, so that is where getting a complete comprehensive history is valuable. You also don't want to prescribe it with benzos because we know it increases the incidence of depression, so we want to be careful when we are prescribing opiates to individuals and the human house as a policy.

Prayer that policy, you had to have a face-to-face appointment with the patient every time, when you are prescribing medications, especially

if you are giving them opiates. You want to at least see them every 90 days and evaluate [Indiscernible] before you prescribe it, you want to keep on prescribing it to Ms. Smith because Ms. Smith has been coming to you for the last 10 years or five years and she has been on a and that is the only thing that works for her. You want to evaluate her on a regular basis. So going into opiates, opioids tend to agonize and you, the Delta receptor and the neuro- sector in particular produces euphoria and causes respiratory depression, nausea, vomiting, decreased gas and tolerance. So there are two types of receptors. M1 and M2.

Delta produces an energy field and in general will give, it is helpful for pain and helpful for informant Terry Payne, and [Indiscernible]. Also inflammatory pain as well. Opiates, the Delta helps with inflammatory pain. But it causes this for you. R will produce an analgesic and be useful for inflammatory pain. Neuropathic pain, yes, but not so much. Neuropathic pain I would [Indiscernible] and antidepressants. Kappa also is analgesic as well.

So opioids can be capitalized as protagonist. This is just a list of potential protagonist. Tramadol is a very [Indiscernible]. The no receptor it is very strong and morphine for methadone. They can be classified as other ways. They can be classified as [Indiscernible] and of course antagonist. [Indiscernible] it will be put in combination with my locks and for management of pain and also sleep disorders. Just to talk about opioids morphine, activity Kappa and Delta.

With morphine you want to adjust the dose. And when it is less than 60, avoid use, or reduced dose to 50 percent to 75 percent. 15 to 50, use or reduced dose to 25 percent to 50 percent. I am so sorry, it is 60. Between 15 percent you want to reduce it by 35 percent. You want to avoid it. The frequency is going to be determined by whether you're using a unique combination. Morphine equivalents daily dose.

This is the standard we look at for opiates. Typically people convert them by a factor mixed with morphine. Going from oxycodone to see morphine we want to use some kind of conversion practice that will help us comfort. For example, if somebody's using methadone and you want to change them to morphine, you would look at methadone, just as just a small example because you can get a much bigger list of conversion factors. You can go to a [Indiscernible].

Methadone has a [Indiscernible] from 1 to 20 the conversion factor would be number four. Someone is either 20 milligrams of methadone you would multiply that by four. Morphine is the standard we need to convert all opiates. They recommend that we don't go above 19 milligrams. And in fact, it implies that there is no good does, individuals who are taking 20 of morphine we see respiratory respiration and death. Especially when it is mixed with the presence, you want to be careful. Another medication methadone somebody you typically 2.5 milligrams dosage tort, you don't have to adjust the dose until it is the correct [Indiscernible].

There's no adjustments for hepatic dysfunction but we want to be careful about you to prologue good navigation. Individuals that take

[Indiscernible], can impact the concentration of methadone. The next one is oxycodone. 5 to 10 milligrams 46 hours as needed. In the past, maybe the last 10 years ago, oxycodone opioids were prescribed regularly for pain medication to we would put an individual on a long standing medication. However, the CDC guidelines no longer recommend necessarily opioids for chronic pain.

The DOD guidelines recommend if individuals take opioids [Indiscernible]. That is an aside, but with oxycodone company would start them from 4 to 6 hours and based on the renal function go ahead and reduce the dose. Or you could do an observation. We do want to reduce it as well. You want to avoid the extended release. And you want to decrease the duration immediately. As well as reduce the dose.

Hepatic dysfunction, if it is mild, reduced dose to 33 percent to 50 percent usual dose for mild hepatic impairment for immediate and extended release. For severe hepatic dysfunction, also extend the dosing interval. I see questions about informed consent, I cannot see the comments. I apologize that I cannot see the comments. The one thing I see is informed consent is something everybody should do. The form I was referring to is a [Indiscernible] form. It is an official form that would make that specifically opioid consent, I cannot tell you the number because I do not have the form. It has a specific type on it. I am struggling to find it. Maybe I can find it and pass it on. Will this PowerPoint uploaded somewhere for people to access in the future?

Yes, they can download it now or at any time. [Indiscernible]

Okay, great.

If you want to send that to me an email, I can't get that out to anyone.

That is the right number, I can look it up and send it to you to send to upper wanted. That is the official form and I recommend you use it. It is so clear and spells everything out for the patient. And let them know the options they have, and potential side effects from the opiates. It spells out the fact that you will be checking the PDM P and also a urine drug screen. There is a concern individuals [Indiscernible]. I would recommend that, and I looked it up and send it to you. Let's talk about fentanyl. Do not use on opioid naïve.

Various formulations are spray intranasal and sublingual. Lozenge, pickle, sublingual tablet. Adjust those space on kidney function. Reduced dose by 75 percent, if it is between 10 to 50 milliliters minimum. Reduced dose by 50 percent if 10 milliliters minimum. Adjusters based on hepatic function. Reduced dose by 50 percent of mild or moderate hepatic dysfunction. Not recommended in severe hepatic dysfunction. [Indiscernible].

If there is an issue with individual hepatic function, you want to reduce the dose by 50 percent. Trauma though is a binding [Indiscernible]. Tramadol binds to and you opioid receptor inhibits pain pathway. Also inhibits reuptake of North Center for a serotonin. Read on

hepatic dysfunction adjusters if CRC all is 30 milliliters minimum 2Q 12 hours max of 200 milligrams a day. Now dose adjustment for mild to moderate hepatic dysfunction.

For severe hepatic dysfunction, just those 250 milligrams every 12 hours. Caution for serotonin syndrome. As I said, just like with tramadol, more so with tramadol, less than they intend Penta doll, it does binds to and you receptor inhibits ascending pain pathway. Inhibits nor any different reuptake. It is four times higher morphine milligram equivalents than tramadol.

Approved for neuropathic pain associated with diabetic peripheral neuropathy. 50 to 100 milligrams every four hours to six hours max 600 milligrams. ER dosing is every 12 hours. Renal and hepatic dysfunction, now dose adjustment for CRC all 30 milliliter minimum not recommended before, below 30 milliliter minimum. For moderate hepatic impairment 50 milligrams every eight hours for IR ER 50 milligrams Q 24 hours max 100 milligrams don't use for severe hepatic dysfunction. With tramadol versus cat Penta doll, more potent than tramadol. Metabolism then tramadol is less. More constipation, respiratory depression than tramadol. If one has to choose between the two, if they have an issue with metabolism, you could decide between the two. I'm going to ask would you mind bringing out case number two.

Ms. Smith was recently in a car accident, she is struggling with aches and pain. She is already on gabapentin 300 milligrams. She is hoping you can prescribe some oxycodone for short time to help with the new onset aches and pains due to the accident. The options are on your screen. I will wait to see if anyone else wants to add anything. With this one, it is kind of a tricky question. If you did B or D both would be okay. Sometimes a patient will say to me, my husband has chronic pain, and he said, the jockey uses I don't know what it is called. It starts with AP. I guess they want me to take Percocet, I don't want to call it that. What do you think about that medication?

Typically I will tell in patients who asked me that the VA DOD guidelines do not recommend using opioids for chronic pain long-term. Because they may do more harm than good long-term. An unexplained to them why, but I would be careful about the patient calling and saying can you give me this particular job. Especially when you have not had a chance to assess them. It makes sense to increase it and they are already on gabapentin, and on a daily basis [Indiscernible]. I would not necessarily give them oxycodone right now. It is better to see the person and assess them and then decide.

Here is case number three. Take a look at your screen for the information.

What would you recommend? Most people recommend all of the above. I would talk to her about use and abuse. We are not necessarily [Indiscernible]. You want to excite to her the potential for harm and what can happen as a result of taking the medication. Maybe she needs to have other modalities to help her like acupuncture. I would say all of the above.

Bring a case number four please. Take a look at your screen for the information. Thank you. Morphine is a receptor antagonist. It is available for [Indiscernible]. Use cautiously in moderate hepatic dysfunction, do not use with severe hepatic dysfunction.

Transdermal patch and Google film approved for pain management. Often in combination with naloxone to prevent misuse and abuse. It prevents misuse. Sometimes with no locks or somebody tries to shoot it up, it will cause withdrawal. That's why it is given in combination. There is no need to adjust the dose. You do want to use it cautiously.

This chart is a simple chart to show you the available formulations. Take a look at your screen for the information.

Here is a simple conversion for individuals. There is no issue about the taste. Some people think it is an unpleasant taste, and with both of these drugs, one is more pleasant. You have to keep your mouth closed until it actually dissolves. Some people may find it difficult to use it because they have to wait up to 30 minutes. The one that is approved for pain is Belbuca. Titrate down to 30 before conversion.

Google film dissolves in 30 minutes. Every 12 hour administration. 600 micrograms, 750 micrograms and 900 micrograms for those already titrated on the medication. Now you wouldn't change them over to the drug but you can give it to them [Indiscernible]. Unless they have another medication [Indiscernible]. It is not recommended. It doesn't have any locks on inside. The only other formulation that's been approved is the patch. The patch based on the morphine equivalent you would do up to 20. You want to apply it to an area that is hairless. Change the patch every seven days. May return to original site after 21 days. If the patch falls off, apply a new one to a different area. If you have to apply more than one, you would apply them on the opposite sides of your body. You would do it at the same time.

For lidocaine topical which is the last topic. Lidocaine and capsaicin is what we are going to talk about. Lidocaine is available over the counter. I'm going to pick up a patch because it is absorbed 3 to 5 percent better. Take a look at your screen for the information.

Using more than 12 hours at a time, in multiple studies have not produced toxics effects. Now dose adjustment and renal dysfunction. Primarily metabolized by liver, caution with liver dysfunction. Be aware of that. And then capsaicin is available over the counter. It is made from chili peppers. Desensitizes receptors and deplete substance. Now dose adjustment for renal or hepatic impairment. Available is patching topical. Wear gloves when applying any formulation. A percent patch must be applied by healthcare professional, apply topical anesthetic first. A percent patch for up to 30 minutes for theory 60 minutes everywhere else. Every three months. It can cause burns and irritation.

It works by desensitizing neuro- receptors. The prescription version is a patch that has to be applied by a healthcare professional. And you have to apply a non-aesthetic to that area as well. It can be

left on for 30 minutes. It can be done every three months. Usually the healthcare professional needs to where PPE when applying. Here are the citations.

Any questions? I am looking, would you mind bringing back the box and see if there are any questions.

Do I need to address any comments? [Indiscernible]. Any other questions? [Indiscernible].

If you wanted anyone to unmute your phone, they can do that.

If you have a specific question, they can unmute their phones. We do have time. Otherwise, if no one does, then I guess whatever information you need to get to them to get the credit.

Ladies and gentlemen, if you want to unmute your phone, I ask you go one at a time.

If there are no other questions, would you mind telling people how to get their credit?

Mr. Spencer? Would you mind people how to get their credit. Is there anything they need to do before they go?

If you would like to download anything from the pod, you can do that. Make sure you fill out the sign out sheet. Fill out all of the information and get it back to my email. I will put that in the chat box. Don't forget your registration and take the surveys. You will find that at the Navy website. If there any other questions, you can unmute yourself, and I will leave the workshop open until 4 PM. Thank you.

Thank you.

Thank you for joining us.