Opioid Use Disorder - Polydorou

Fri, Jul 21, 2023 10:33AM 49:58

SUMMARY KEYWORDS

opioid, buprenorphine, methadone, opioid use disorder, terms, overdose, patients, effects, medications, naltrexone, treatment, opium, milligrams, fentanyl, dose, full agonist, mindful, increase, related, naloxone

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00:00

This presentation is entitled: Opioid Use Disorder: Science, History and Clinical Implications. I will now pass it over to Dr. Soteri Polydorou to begin our presentation

00:11

Welcome to the Opioid Use Disorder session of our 2023 ASAM Addiction Medicine Board Review Course. My name is Soteri Polydorou. I'm an associate professor at the Department of Medicine and the Department of Psychiatry at the Zucker School of Medicine at Hofstra/Northwell. I have no financial disclosures.

00:32

And as an outline to our conversation, we will review the current opioid use trends. We'll know important historical and regulatory factors that have impacted care. We'll provide a neurologic and biologic overview, particularly focusing on the opioid receptors. We'll know clinical assessment and management of intoxication and acute withdrawal. And finally, we'll provide an overview of medications for the treatment of opioid use disorder.

01:09

The National Survey on Drug Use and Health is a survey of nearly 70,000 people aged 12 and older, conducted annually by SAMSA. The survey provides critical insight on drug use throughout the US each year. But there are potential gaps affecting substance use disorder related estimates. Specifically, the survey includes residents of households, but it does exclude those without a fixed address, such as those in correctional facilities or homeless without shelter addresses, and mental health facilities. So even with those exclusions, they estimate nearly 3 million people have a current opiate use disorder with over 2 million using prescription opioids and nearly 700,000 using heroin. The RAND Corporation previously attempted to conduct an assessment of the prevalence of opioid

use disorder by including estimates from homeless, incarcerated and other populations. Now they estimated over 2 million people are using heroin, that's about three times the NSDUH estimate. So that implies rates that are higher than HIV and type one diabetes.

02:21

What we also understand is that irrespective of these estimates, we tend to see about a 15 year reduction in life expectancy for opioid use disorder. On the right of this slide, you'll note the leading causes of death in the US. Drug overdoses are incorporated into the fourth item on the list- within unintentional injuries. If we consider drug overdoses as a separate component. At over 100,000 alone, it would still be a top 10 cause of death. If we look into this a little bit more fully, over 80% of all drug overdoses are secondary to opioids. So lethal opioid overdoses alone would still be on this list of the top 10 leading causes of death. A high majority, over 90% of all opioid overdoses are secondary to synthetic opioids, largely fentanyl. So if we were to separate even further, those lethal drug overdoses from opioids, and specifically those from synthetic opioids, again, predominantly fentanyl, would still be one of the top 10 causes of death in the US.

03:32

Over the past seven years, again, opioids and specifically fentanyl has been a leading cause in the rise of overdose deaths. And what you see here, the black line is the total number of opioid related overdoses nationally, and the brown line is overdoses related to synthetic opioids. And as you can see, the significant increase in opioid related overdoses is largely related to synthetic opioids again, predominantly fentanyl.

04:04

But if we take a somewhat longer term perspective, over the past 20 years or so, we appreciate three distinct factors leading to the rise in opioid overdoses. These three waves- starting in the very early 2000s, predominantly driven by prescription opioids, followed in early 2010 by escalating heroin overdoses, and then more recently, beginning around 2013 and very much continuing to this day, the rapid rise of fentanyl-related overdoses. And it's important to note that even prior to 2013-2014 period, fentanyl overdoses were comparatively so uncommon that it wasn't even routinely tested for by medical examiners, including in New York City.

04:54

From a national perspective, drug overdoses from the December 2021 to December 2022 period have increased by less than 1%. And even though that overall increase by percentage levels hasn't been as great as we've seen in recent previous years, we continue to see areas with both large percentage increases, such as Washington and Wyoming, of over 20%. As well as absolute numbers of fatal drug overdoses in urban areas such as New York City of nearly 14% increase, so over 3000 deaths from 2021 to 2022.

05:36

And as we look to understand the overdose risk from illicit opioid use, here's data from primarily non-treatment-seeking heroin users, indicating the high personal risk of experiencing and witnessing an overdose. With roughly half of people personally experiencing a- an overdose in their lifetime, as well as a high percentage witnessing a non-fatal or fatal overdose in their lifetime. Additionally, something to keep in mind, about one out of 20 of those who are seen in the ED or hospitalized related to an opioid overdose will have a one-year mortality again of about 5%.

06:35

And so what can we do? What opportunities do we have? Well, a number of opportunities to really intervene in this crisis. So when did this all start? You know, that's a hard question to answer, but we know it was certainly before the 1990s. It was before the 1970s. It was even before the 1800s. We have evidence from over 5000 years ago of the purposeful cultivation of the opium poppy Papaver somniferum, which contains four naturally occurring alkaloids, including morphine and codeine. The opium trade began in the Middle East and rapidly spread throughout the world. It became very lucrative, and as opium grew in commercial importance, it eventually led to conflict. By the late 1700s, the opium trade was an established business continuously in search of new markets. China served as a very large new market with increasing opium use. The Chinese emperor resisted expanding opium imports after recognizing a growing addiction problem, ultimately ordering ordering an embargo against all opium importation, and confiscated and destroyed all bound supplies.

07:51

The British charged the destruction of their commercial property, leading to the first Opium War. It concluded in 1841, with China paying a large indemnity and ceding Hong Kong to the British for over 150 years. Interestingly, diacetylmorphine is developed in the late 1800s, and soon becomes commercially available and sold by the Bayer company. Diacetylmorphine was quickly identified to have more potent analgesic effects than morphine and codeine, and was marketed as an aid for a whole host of ailments. Also, interestingly, early study participants testing diacetylmorphine reportedly described the drug as making them feel heroic, and well... that stuck- and heroin was introduced. In the early 1900s public health hospitals are established in Fort Worth, Texas, and in Lexington, Kentucky, and they began exploring both the clinical effects of various addictive substances including opioids, and potential treatment models.

08:58

And so in reaction to the US' own domestic rise in opium addiction in the 1800s and early 1900s, the government begins to respond. A number of laws and regulations are intrude- that are introduced. Opium is banned in 1905, and soon thereafter labeling all medications by pharmaceutical companies is required. In 1914, the Harrison Narcotics Act regulates and oversees any manufacturing or distribution of all opioid products as well as coca products. It strictly limits their use and treatment by physicians, and it's described as: in the course of their professional practice only. Now, the reason why this stipulation is important is because that's how opioids continued to be used in medicine at that time- as an analgesic. However, the treatment of opioid- opium addiction was also commonly being addressed by physicians as part of their routine practice of medicine.

09:59

After the Harrison Narcotics Act, that all changes. Physicians soon discovered that using opioids in an attempt to treat addicted patients, even focusing on their withdrawal symptoms, could not continue. Physicians began to be arrested because of- because addiction at the time was not considered a disease, and so a physician could not justify using an opioid in treating addicted patients. Between 1919 and 1935. about 25,000 physicians were indicted, and roughly 10% were imprisoned. The US Supreme Court eventually strikes down arresting physicians for treating addicted patients saying the federal government had overstepped its authority to regulate the practice of medicine. But really by that time, the damage was done. Ultimately, in many ways, we are still working to remedy the effects from that early sudden separation of addiction treatment from the general health care system.

10:59

And so as the years progressed, a number of other regulations and laws were passed. In 1970, the Controlled Substances Act was passed. In 1974, the Narcotic Addict Treatment Act is passed. And that's the the law that allows and allow the use of methadone as a maintenance treatment in an outpatient environment. So the traditional methadone maintenance program currently- the opioid treatment programs are formally recognized in statute in 1974. Even though research had begun on methadone, about a decade prior in terms of its role for as a maintenance medication.

11:41

In 2000, the Drug Addiction Treatment Act is passed and that allows the treatment of opioid dependence or opioid use disorder with narcotic scheduled- scheduled medications three, four and five. And that's really what allowed the use of buprenorphine which was designated as a schedule three controlled substance, with the FDA approving it specifically for the indication of opioid use disorder. It also allowed the prescribing of buprenorphine if you have the capacity to refer patients for counseling.

12:20

But the DATA 2000 required specific training, required a specific waiver, commonly referred to as the X waiver from the traditional DEA license. And that continued for a number of years, with some changes. The- over time the expansion of the number of patients that could be prescribed buprenorphine by any provider with an X waiver expanded from 30 to 100, to more, and then eventually- initially limited to physicians- and then expanded to other health care providers, other ACPs, PAs, so forth.

13:07

And then in 2023, just the early part of this year, as part of the Consolidated Appropriations Act, and a section of it, the Mainstreaming Addiction Treatment Act, or the MAT Act, eliminated and formally eliminated the buprenorphine DATA-waiver. And this allowed and specifically changed the regulations so that a DATA waiver was no longer required to treat patients with buprenorphine for opioid use disorder. Prescriptions for buprenorphine only would now only currently require a standard DEA

registration number. There are no caps on the number of patients that a prescriber may treat for opioid use disorder with buprenorphine. So that traditionally required an eight-hour and for some providers 24-hour educational sessions to be able to qualify for a DATA-waiver is no longer needed. And so for that reason, we've been able to greatly expand the number of providers of buprenorphine to those that have a DEA license.

14:29

And as we begin to start talking about the neurobiology of opioids, important to keep in mind that there are a number of similarities that were reviewed in the neurobiology session of the- of the board review, but specific to opioids, the endorphin and opioid receptor binding results in an increase in dopamine that's released in the mesolimbic and mesocortical pathways, but differently than exogenous opioid... opioid receptor binding, the effect is less robust and naturally does not result in habituation.

15:10

In terms of terminology, so "endorphins" is a term that refers to the whole class of endogenous opioid ligands. So examples would be beta-endorphin, enkephalin, dynorphin.

15:25

"Opioid" describes an entire class of both non-endogenous, so natural and synthetic or synthetic and endogenous compounds that bind to one or more types of opioid receptors. So examples here would be methadone, fentanyl, oxycodone.

15:47

"Opiate" refers to compounds, naturally derived from the poppy plant. So here examples would be morphine and codeine. In 1806, morphine is isolated from opium by Serturner, and its chemical formula is identified in 1847.

16:13

It is important to note though, that the alkaloid content of opium includes substances other than morphine and codeine, some of which do not even have morphine-like effects. So again, in terms of test-taking material, you know, compounds to be aware of in terms of the opium poppy or Papaver somniferum. There are multiple alkaloids listed here on the slide. And it is true that someone who ingests high amount of poppy seeds can test positive for opiates on a urine drug screen. However, it's really dependent on what the cut-off of that test is. But it's important to be aware of.

17:04

And then in terms of endogenous opioids and opioid receptor types. So, in terms of the mu opioid

receptor, it is bound by beta-endorphin and endomorphin. Dynorphin binds the kappa opioid receptor, enkephalin binds to the delta opioid receptor, and orphanin or nociception bind to the nociception/orphanin FQ receptor or the opioid receptor like-1.

17:42

So, what are the commonalities between all different opioid receptors? Well, they all have seven transmembrane domains. They're all G protein-coupled. They're all also primarily inhibitory pathways.

17:58

So again, beta-endorphin primarily binds to the mu opioid receptor, and as a result, it reduces cyclic ANP. And that inhibits the release of GABA, glycine, and glutamate. As an effect, it results in intoxication and the effects that we see in terms of withdrawal.

18:25

Dynorphin A binds to the Kappa opioid receptor and the Kappa opioid receptor mediates dysphoric activities, is related both to opioids as well as cannabinoid binding, and therefore in some ways, it opposes mu receptors in regulating its hedonic tone and modulating stress-induced relapse.

18:50

Enkephalin binds to the delta opioid receptor and the delta opioid receptor has more anxiolytic activity and is somewhat distinct from the mu and kappa receptors. It also may play a role in benefiting in situations of analgesia that is resulting from an inflammatory states but again, in terms of the delta opioid receptor, important to be mindful of, of its anxiolytic effects.

19:23

And so the the broader role of endorphins in normal physiologic functions... So there's many effects beyond the kind of initial thoughts about pain, but effects on neuroendocrine functions, immune function, GI function, cardiovascular function, pulmonary as well as the mood and cognition effects.

19:48

Some specific items to be mindful of, so the sedation, analgesia and euphoria, constipation, and potentially nausea, reduced testosterone levels, increased prolactin and decreased FSH and LH, urinary retention, effects on vaso- vasodilation and for some opioids, increases in QT, which we'll get to you later on in the talk, as well as miosis. But do know that tolerance does vary not only from opiate to opiate, but from person to person.

20:31

20:31

So a couple items to note in terms of specific opioids. So fentanyl- just as a reminder for transdermal patches- if somebody has a fever, the absorption of fentanyl will increase.

20:45

For meperidine, concerns around neuroexcitation as well as serotonin serotonin- syndrome. For tramadol, seizures, as well as serotonin syndrome. Kratom at low doses has more of a stimulant effects similar to caffeine; in high doses has more of an opioid like effect. We do see that that effect is reversed by naloxone. And there is some evidence associating kratom with potentially hepatic cholestasis, which seems to be dose-dependent.

21:21

Tianeptine is an antidepressant more commonly available in Europe. Structurally, it's- it's similar to TCAs. But there are some both mu and delta opioid receptor agonist effects, and also some anticholinergic effects.

21:44

In terms of opioid potency, if we compare synthetic opioids like fentanyl, or carfentanil- much more potent than morphine. Fentanyl, 100 times more potent. Carfentanil 10,000 times more potent. You compare morphine to diacetylmorphine or heroin, it is- diacetylmorphine is twice as potent.

22:13

And as we start to think about interventions, both for overdose, as well as acute withdrawal, and long term treatment of opioid use disorder, it's important to keep those three groups somewhat distinct in your mind. So the role and type of intervention that we need to provide acute relief for an overdose, the type of interventions to address acute withdrawal symptoms and address early stabilization, as well as the role, benefit and long term outcome improvement of maintenance therapy.

22:57

In terms of opioid overdose, the classic tria- triad is miosis, decreased level of consciousness and respiratory depression. Obviously, in terms of test-taking incredibly important. Pulmonary edema we do sometimes see as well as seizures- to be mindful again of meperidine or tramadol.

23:20

In terms of acute response, largely supportive with the use of naloxone. Here's some data in terms of how to bolus naloxone, clinical parameters to be mindful of.

23:35

And then in the community, the benefit of expanded access on naloxone overdose prevention kits with a very clear data showing its effectiveness in terms of training, as well as widespread access to overdose prevention kits associated with reduced rates of overdoses.

24:04

But some items to keep in mind, particular real- particularly related to the increasing frequency of fully synthetic opioids that we see particularly related to overdoses, is that we've tended to need particularly in community naloxone overdose prevention kits, higher concentrations of the of naloxone early on. Two milligrams is now four milligrams intranasal as well as you know, early recommendations of using a single dose, assessing for response and then using the second dose. So going from first dose assessing response then the second dose. Now, recommendations is- are using- for a clinically concerning evidence of an overdose to use the initial dose of four milligram intranasal dose, and then quickly begin and prepare to use the next dose.

25:09

Again, as noted earlier, you do want to be mindful of potential use of fentanyl patches. To be mindful clinically, of a, of a medical emergency that's related to fentanyl. It's called chest wall or skeletal muscle rigidity. It tends to be more common in related use of IV administration, but it's not necessarily dose-related. And this is an absolute acute emergency that requires aggressive intervention with ventilation, naloxone and neuromuscular blocking agent. So important to recognize acute chest rigidity or rapidly impacting respiration and the type of intervention that's necessary.

26:05

Again related to fentanyl. Xylazine is not an opioid but really important to know because we are seeing it being increasingly identified with illicit fentanyl. Xylazine is not opioid. It is a sedative however. It has alpha-2 adrenergic agonist properties, and we tend to see it most commonly related with complex or severe, very severe wounds. Wounds may have an infectious etiology, may have an autoimmune etiology. We're still learning very much about the role of xylazine wound care. But what is important to also know is not only its relationship potentially to opioid overdoses, but also in terms of the wounds, xylazine-associated wounds can be related both to IV use, but also non-IV-use of xylazine.

27:11

And then, you know, as always to be mindful of other substances, not only xylazine but also acetaminophen or other substances related to to a person's opioid use. But as it could potentially be related to overdose.

27:26

Just some general thoughts on intensity of withdrawal symptoms and duration of acute withdrawal

just some general thoughts on intensity of withdrawal symptoms and duration of acute withdrawal. We obviously understand that post acute withdrawal can last much longer, but in terms of acute withdrawal symptoms, to be mindful that diacetylmorphine- really the first few days but can extend longer. Buprenorphine, we tend to think about it as less intense than diacetylmorphine. And methadone again, less intense than diacetylmorphine a bit longer

28:05

You know, one tool of a number of tools to assess and quantify opiate withdrawal symptoms is the Clinical Opioid Withdrawal Scale, sometimes referred to as the COW scale. I list here, the different items that are related. Again, it allows quantification of withdrawal symptoms into kind of a numerical value. That's helpful with both monitoring the intensity of withdrawal over time, as well as introducing medications, particularly buprenorphine, to address withdrawal symptoms.

28:39

And then in terms of addressing acute withdrawal- commonly methadone, buprenorphine, and then also to be mindful of the potential adjuvant role of non-opioid medications as needed, so medications like clonidine and loflexadine, so forth.

29:00

And then as we move on to discuss the medications for opioid use disorder. Let's start by noting that the pharmacotherapy for opioid use disorder treatment compares very favorably to other medications we commonly use. They, as with other medications, share an extensive evidence base of improved outcomes, and over 1 million people are currently benefiting. We have evidence in terms of reduced use of illicit opioids, longer periods of abstinence, retention and treatment, decreased medical and psychiatric symptoms, improved health, reduced risk of HIV and hepatitis C, along with, you know, a number of social improvements such as maintaining or obtaining employment, for family relations, and decreased criminal justice involvement.

29:50

And just to highlight one more additional thing, we have very clear evidence that methadone and buprenorphine treatment reduces the risk of overdose. In this study from the University of Maryland, we looked at the association between the expansion of methadone and buprenorphine treatment, and the prevalence of heroin overdoses in Baltimore from 1995 to 2009. So even though heroin purity during that time increased, the expansion of access to buprenorphine was associated with almost a 40% annual decline in heroin overdose deaths.

30:36

In this retrospective comparative effectiveness study of over 40,000 adults with opioid use disorder, comparing six different treatment pathways, only treatment that buprenorphine or methadone was associated with reduced risk of overdose and serious opioid related acute care use at three months

and 12 months.

31:02

This next study is a retrospective cohort study of little over 17,000 opioid overdose survivors, and we know that these patients are at significantly elevated risk of death. This study looked at whether the use of medications for opioid use disorder after an overdose would be associated with reduced mortality in the 12 months after a non-fatal overdose compared to no use for- no medication use. Both methadone and buprenorphine were associated with decreased all close- all cause mortality, and opioid related mortality. Note a point of concern though, just to be mindful of that in this study, only about 30% of opioid overdose survivors received any methadone or buprenorphine or naltrexone. So again, opportunities to ensure that these life-saving medications are as widely available to patients who would benefit from them as possible.

32:09

And as we begin to now talk about the specific medications, you know, buprenorphine: onset of action is about 30 to 60 minutes. Peak effect at about 90 minutes. Half life is a little over 24 hours; it is metabolized by CYP 3A4. So to be mindful of inhibitors and inducers. There is some evidence that it can alter liver enzymes. So regular assessment and consideration of risk and then labs to to further assess can be- can be done. In terms of pregnancy, buprenorphine safe during pregnancy. One of the early studies identifying reduced morphine use, reduced neonatal abstinence syndrome, severity, and hospitalization stay was the MOTHER study. So something to keep in mind.

33:08

There are a number of different FDA approved formulations for opioid use disorder. So sublingual film, tablet and monthly sub-cu injection. Buprenorphine is a partial agonist of the mu opioid receptor, and it's an antagonist of the kappa opioid receptor. And so it has a high affinity and a slow dissociation from the mu opioid receptor. Therefore, at low doses, it acts as an opioid agonist. But for those with physical dependence and recent opioid use, sudden initiation will result in clinical antagonist effect and potentially an iatrogenic opioid withdrawal if the buprenorphine is dosed at a high enough dose, where, again, it's it's partial agonist effects do not match the patient's tolerance of a highly potent, full agonist in a very short period of time. And we'll go into clinically how we, we address that issue.

34:31

In terms of initiation of buprenorphine, here, there are a number of strategies when inducting patients onto buprenorphine. This slide includes a well-established process. There are however, a number of other protocols that use more rapid dose increases. There are other protocols that use very low initial doses. And so here at the top of the slide. For the traditional induction process, a person needs to begin experiencing mild to moderate withdrawal with the COWS of generally eight or above. Usually that takes roughly six hours or longer, sometimes eight or 12 when using a person's using short-acting opioids. Or 24 or 48 hours or even longer for long acting opioids, particularly methadone, and

sometimes fentanyl, as well. And so common initial dose again, for someone who is going through mild to moderate withdrawal, COWS of eight or above, you start with two to four milligrams, and titration to address withdrawal symptoms.

35:54

A couple items just to note that titration generally can increase to eight to 12 milligrams on day one. But there is a formal FDA approval of eight milligrams on day one and so titration beyond eight on day one should just include some notation that the titration process is being done for persistent withdrawal symptoms.

36:21

Day Two- again further titration to address withdrawal symptoms. Here's a list of some adjuvant medications as well to consider. In terms of low dose or micro dose inductions, this is a tool that has starting to be utilized more and more, particularly for those who are on a full agonist opioid and are unable to quickly transition off the full agonist, discontinue the the full agonist and experience mild to moderate withdrawal. And so in some cases for those who are being prescribed opioids for pain, there is the ability to start buprenorphine at low doses, while a person continues on the full agonist medication, generally at doses of a half a milligram buprenorphine, very slow titration over about a week time, followed by discontinuation of the full agonist.

37:34

Again, in terms of traditional induction protocols, buprenorphine inductions can happen at home with physician instructions, during hospitalizations, and during ED assessments.

37:46

In addition to the sublingual formulation, there is a once a month formulation that has been FDA approved since 2017. Here we begin patients who have been tolerating buprenorphine of eight to 24 milligrams for about a week time seven to 10 days, and then transitioned on to monthly buprenorphine initial dose of 300 milligrams for the first two months followed by a maintenance dose of 100 milligrams monthly.

38:24

Naltrexone: long acting, competitive, non-selective opioid antagonist that has a high affinity to mu opioid receptors. Naltrexone is metabolized by CYP450. And at high doses, there is some evidence that is associated with hepatic toxicity. And so again, mindfulness around potential acute liver disease for a patient or elevated transaminases. And the potential contraindication for the role of naltrexone in such patients.

39:09

39:09

Because it's a mu opioid antagonist, you know, those with current physical dependence on opioids need to first receive withdrawal treatment. So in general, that commonly takes about one to two weeks prior to starting naltrexone. The oral formulation is taken daily- can also be taken three times a week at higher doses, so 50 milligrams daily, or 100 milligrams, 100 milligrams, 150 milligrams taking three times a week. However, low adherence rates with oral formulations from a number of studies frequently limits use to really only those that are highly motivated, that also have some support for adherence. Long acting IM formulation is therefore preferred.

40:00

Medication is administered monthly. Generally in office. A number of studies have supported its use for opioid use disorder with evidence finding it is more effective than placebo, not in- non inferior to buprenorphine. And when ram- when randomization occurred after opiate withdrawal treatment and those that are successfully inducted onto extended release naltrexone.

40:27

One additional item to comment on regarding the antagonist formulations. While it is reported that overdoses in a number of these studies are very low, it is still important to be mindful of the overdose risk concerns from interrupted antagonist treatment in patients who would then also have no physical tolerance to opioids. So as compared to methadone or buprenorphine, which maintains a person's tolerance to opioids. You know naltrexone, the person who's on naltrexone will have no tolerance, and so sudden discontinuation of naltrexone either as an oral form or as a once a month injection, a patient who may be at risk of relapse, will at that point, have no tolerance to opioids. So you want to be mindful of that.

41:22

And then, in terms of initial assessment and transitioning someone onto extended release naltrexone, a couple of clinical items to be mindful of in assessment and generally, transitioning. A patient has not used opioids for about two weeks. You know, two to three weeks, no opioid use, no evidence of withdrawal and an opioid negative toxicology can generally start the extended release naltrexone injection. If there's concern and want to assess further for any potential withdrawal risks, you can begin by a low dose oral naltrexone- 12 and a half milligrams and then following that administration the next day initiating the extended release naltrexone. There are other methods of introducing extended release naltrexone in an attempt to reduce that duration from two to three weeks to one to two weeks or a shorter period of time as possible. And so there are some included slides that we won't discuss during- during this talk. That will be available later, as part of the course to review in more specific detail.

42:37

Methadone was approved by the FDA in 1972 for opioid use disorder. It is both a mu opioid receptor agonist and an NMDA antagonist. We believe that the NMDA antagonist effects is related to the reduced development of tolerance for those on methadone. It's, it's available in 2 enantiomers which

are generally mixed in equal amounts. The "I" or "R" is the active formulation. It's absorbed rapidly, orally in 30 minutes, but its onset of action is delayed, with peak levels in two to four hours and sustained levels for 24 hours or longer. It's metabolized by CYP450. There are several isoforms, which may impact why some patients need higher doses than others. It is excreted in both urine and feces, and this avoids accumulation and reduces the risk of toxicity for those with renal disease, or liver dysfunction. The half life of methadone is 24 to 36 hours, but can be a highly variable. And that's really important to know, particularly in considering the need to very slowly titrate the methadone dose changes over multiple days, as opposed to hours, as well as the importance in recognizing opioid conversion tables.

44:25

Noting that the ratio of methadone to morphine equivalents changes as the dose of methadone increases. So really important to be mindful of how to convert onto methadone and, you know, always prudent to initiate at low doses and slowly titrate out. In 2006, there was a Black Box Warning, noting the dose related risk of QTc prolongation. Its safety profile during in pregnancy is well established for many years.

45:09

And in terms of initial dosing- 10 to 20 milligrams orally or half that dose by IM, 20 milligrams, eliminate severe withdrawal. General first 24 hour dosing for those to treat withdrawal symptoms is generally 20 milligrams up to 30 milligrams again, total- it's a total daily dose. But it is not recommended to exceed 40 milligrams in the first 24 hours. Cravings are addressed by slow titration of methadone, generally five to 10 milligrams over a number of days. And the the long term clinical benefit of methadone and again, in terms of you know, noting the factors that we identified earlier, we tend to see at least 80 milligrams of the daily dose and up- there is no you know, absolute ceiling, you know, recommended ceiling dose for methadone, but we do see that patients tend to tend to need to be on at least 80 milligrams, if not higher. And again, that dose can continue to be titrated to provide the clinical benefit needed for the patient. And after stabilization, both methadone and buprenorphine do not produce euphoria or sedation.

46:38

In terms of opioid treatment programs, in which methadone is available in an ambulatory environment. There are comprehensive assessments available in all OTPs. There are generally multidisciplinary treatment plans, routine toxicology testing, well established diversion control protocols.

46:59

OTPs tend to incorporate not only methadone treatment, but also buprenorphine and potentially other MAT treatment as well. There is an attendance schedule for medication dispensing. There is the ability to provide guest medication for a person as they travel to other areas with with OTPs. And there's a you know, as a structured regulatory oversight as well as confidentiality.

47:29

So when treating patients with fentanyl-related opioid use disorder, you know, it's helpful to consider a few other items in terms of the duration it may take to initiate medications, as well as withdrawal risk, time to reach full therapeutic dosing, as well as its effects on craving reduction. Here's an outline of different considerations that are specific to fentanyl. In terms of initiation after last use of buprenorphine, again for traditional initiation strategies that can take one or a few days before initiating buprenorphine withdrawal for the patient to experience adequate withdrawal symptoms. For low dose buprenorphine, to get the LDB type the initiation can happen same day and then for high dose buprenorphine, it could take a number of days a few days before initiating.

48:29

For naltrexone generally, generally two weeks. Can be done in a shorter period of time, depending on the acute withdrawal protocol. And then for methadone, methadone can be initiated same day.

48:50

And as we consider which medication in which treatment setting may be the optimal fit for your patient, now we do want to consider, you know, patient goals around abstinence to harm reduction as a continuum. The role of chronic pain and the potential, potential for the need for opioid analgesia. A person is pregnant or planning to become pregnant, recent overdose or high risk use, medical and psychiatric comorbidities, diversion risks, as well as additional substance use disorders and what medications and interventions are available in the community.

49:32

Again, thank you so much for taking the time to go through this session. I've enjoyed discussing the topic and sharing all this information with everyone who was able to join in. If you have any questions, please feel free to reach out any questions concerns in the chat box and we will be able to address them. Thank you so much, and good luck on the test.