Alcohol Use Disorder - Restrepo

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SUMMARY KEYWORDS

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00:00

This presentation is entitled alcohol use disorder, neurobiology diagnosis and treatment. I will now turn it over to Dr. Ricardo Restrepo to begin our presentation.

00:09

Hello everyone, colleagues, clinicians, people, I am glad to be in this ASAM review course 2023. And I'm always happy to be part of this community. I know that we are going to cover a lot of information. But I'm going to try to be as much clear as I can be. And of course, with the slides and the material that we send you, I'm sure that you are going to conquer the objective to know these fields better.

00:38

Today is the alcohol use disorder. We're going to review the neurobiology diagnosis and treatment. I don't have any financial disclosures at this moment, meaning that we can talk objectively about these topics.

00:55

This is the outline of of our dialogue. today. We are going to cover from the historical view, some epidemiological data, neurobiology, and of course, what tools do we have in our field, and especially in the alcohol use disorder arena, to differentiate between the detoxes and the relapse prevention aspects. And of course, we are going to conclude with the main objectives of this lecture.

01:24

Well, look what I'm trying to share with you here. Always we are looking for references. I put one from the APA, the practice guideline, very useful tool that you can find for free in the web, and also the ASAM clinical practice guideline for alcohol withdrawal management. I recommend you once in a while when you have questions to reference these two books.

01:55

Well, as I always try to do it, we have the important component that when, and how finally, we turn to instead of keeping the moral component of our view of alcohol or substance use disorders, we move to a real acceptance that these was a real organic disease component in our, in our life.

02:24

Again, I took the book of Genesis in one of the most famous books in the world, the Bible, and if you read the- there, you will see how Noah got drunk, and how well it was this cry when he was drunk. I'm not gonna read it all. But it just is a reference that centuries ago, the alcohol use disorder or alcohol intoxication were described. Then, a Roman ethnobotanist that was in the army of the Roman Empire, here we go, describes perfectly well, when we get drunk.

03:04

What happened for almost 21 centuries that finally we were able to accept that this was a real problem, and that we need to see it as an approachable component of our daily life practice.

03:19

Well, let's take this example, I am just put in a real case. This is a person that I know in the LA area that works in the music theater. And look, he came to be assessed for drinking and depression because his older brother was experiencing difficulties to see where he was going with the alcohol intake. He complains about depression, some irritability and anxiety. And then, in your interview, more than targeting the biological component, you will, of course, open the gate for knowing more about the history. And then you figure out that this person was starting to drink when he was a child, after the parties were over in the house that he lived in.

04:10

Look that as an example, we can see how the amygdala, the hip- hippocampus, the frontal lobe are really close connected with what we are trying to achieve. And remember that when we lose track of our problem, in this case, the alcohol use disorder, the prefrontal lobe will start to have difficulties to really react as the first defensive component to say, "maybe it's not the time to drink, maybe it's the time not to drink more", and the hippocampus and amygdala, with the positive and negative reinforcement, that loop is going to be there.

04:51

Well, as we know, and I'm sure my colleagues during the course are going to repeat this over and over again, but it's really important to differentiate the different neurotransmitter systems, but at the same time how interconnected they are.

05:08

And I'm going to try to simplify or- or simplify during the time of my lecture, certain components of these. But I would like you to keep in mind, the complexity of the addiction field, and also how these neurotransmitters connect with each other. I know that this is pure neurobiology or biology in school, but it's so important that we go back to the essence.

05:35

Let's imagine that I get the stimuli of drinking, even in the glutamatergic system, or the GABAergic system. That message open the calcium channel in the preset- presynaptic neuron. And it released, of course, at that moment, the neurotransmitter that is going to the ion channel that it opens, and then we depolarize. Why we need to understand this? Because that's kind of the essence of what is going to be our target component when we decide to use pharmacological treatments. And in these lectures that I'm going to review with you, which is the alcohol and benzodiazepines or sedatives, pay attention to this slide, because if we understand these, we will understand the rest.

06:24

Well, Mr. RR started to drink at age 12, on weekends, and then he continues escalating, he starts to have that problem. And then he starts to miss work due to hangovers, and driving under the influence. Luckily, he's one of those cases that didn't have DUI, and hopefully, our view and our approach will change that path. Again, when he stops drinking, he develops diarrhea and shakes in the morning. And by the way, some people interpreted this as an anxiety, and he ended up receiving alprazolam to manage that anxiety. For the past decade, he has been getting these benzodiazepine.

07:14

Well, we know alcohol, what it is. We know the components of alcohol, and important sometimes to go back to biochemistry to keep these in mind how it looks- the alcohol molecule.

07:29

Well, let's imagine that you and I, we are celebrating this time of life, this moment of life, we are happy at the end of this course. And then we go and have a few drinks, a glass of wine, a glass of beer. What is the neurotransmitter that is going to be activated: the GABA. And that's when we start to kind of develop this pattern.

07:58

And here we go, again. I'm trying to oversimplify this, but just for the purpose of understanding, then imagine that for not one day, not one week, we ended up drinking six months, one year, every single day, what is going to be the situation? The GABA is going to be downward and suddenly, glutamate starts to wake. And when glutamate, it starts to wake up, is when I woke up in the morning, after six

months drinking, and I have the shakes, and I need to balance my system, drinking again, to put that GABA in order. Here we go- glutamatergic system connection with the withdrawal. And that's the reason that people end [up] drinking or [get] escalated on the drinking.

08:46

New data, and I encourage you to probably look at the SAMHSA website, where you're going to find this information. It is a great slide. I'm not going into the minimum details. But I will like that you have an overview of the alcohol use disorder in the past year among people aged 12 and older. Pay attention: 22.2 million people with alcohol use disorder only. Almost 30 million people with alcohol use disorder.

09:20

Then, if you go to the right side of your screen, it is a middle component that people with alcohol and drug use disorder- that the number of almost 7.5 million. The other side, the yellow one, is related with the people that just use drugs. See the entire picture of this: almost 47 million people aged aged 12 and older with substance use disorder in our country. Big things from this: almost 140,000 people die annually from alcohol-related causes in the US, from 2015 to 2019. It's almost 380 people per day.

10:08

These days, we are paying a lot of attention to our horrible and difficult epidemic with opioids, but alcohol is in our face. Nearly 30 million people aged 12 and older, as we review, had problems with alcohol use disorder. And look: the adolescent population, almost we are hitting the million, we are almost there, aged 12 to 17, with alcohol use disorder in 2021. Important: the fourth leading preventable cause of death in the US is alcohol use disorder.

10:43

More than- important enough here: look that 50% of the liver disease is attribut- attributable to alcohol use disorder. Look, the visits. And of course, let's match the cost of the visit, the cost of the follow up, etc. The most important situation here is of course balance in our society. But at the end it's our patients who are going to benefit from what we do and how we do it.

11:15

AndI look the other piece among people who die by suicide, alcohol use disorder is the second most common mental disorder and is involved in roughly one in four deaths by suicide.

11:28

This is really, really important that... based on Grant, and other studies... Look at in the right side, you

have the severity of alcohol use disorder and the percentage from mild to severe, to any alcohol use disorder between 12 months and a lifetime. What I want that- you graph here is, is kind of the big essence. In US, people have more lifetime percentage with alcohol use disorder, with severe alcohol use disorder, almost 29% compared with the world, and in 12 months, also in US, the numbers are big.

12:13

Well, pay attention to what is happening in our country. And the way that we are kind of accessing these epidemiology components of a big problem in our face. With alcohol use disorders, pay attention to a demographic group in our population, which is the aged 18 to 29 years old. But also, as we know, our indigenous people suffer immensely from this problem and other substance abuse. Pay attention to these ethnicities in our country. We try to kind of divide by groups, by race, by ethnicities. And based on that, we need to kind of get curious about who we have in front of us to understand what we know versus the reality of what we know what we can do.

13:11

And more. Now that we are trying to put in perspective, the quality of our world, the rights of minorities, look what's happening now with the gender component. Women are getting closer in the numbers of drinking. This is not a mystery.

13:32

What I'm trying to show you there is the odds ratio that are related with alcohol use disorder and other mental conditions or other drugs of abuse. When you drink always assess something else.

13:49

More than going back to alcohol use and heavy alcohol use that we are going to define in a minute. But look in age 12 and older in 2020 133 million alcohol users. We, I, you, some of you, can be in that number. Then 60 million binge alcohol users we are going to reviewing that- what is a binge drinking? And by the way, from that group, we take that heavy alcohol user are equal to 16 million average.

14:26

What is heavy drinking? What is binge drinking? And what is an emerging definition that is called high intensity drink? Let's go one by one because I think it's important that we kind of capture the essence. Heavy drinking in women and men: in women it's four or more drinks in a sitting, eight or more per week. In men it's five or more standard drinks in a sitting, 15 or more per week. The high intensity as we are going to see is related with the amount of binge drinking.

14:59

What is it binge drinking? It's a pattern of drinking that brings alcohol levels out of the roof. In women

What is it binge drinking? It's a pattern of drinking that brings alcohol levels out of the roof. In women, it's four or more drinks in two hours and in men it's five or more drinks in the same two hours define.

15:17

We can not forget what we have been going through... the COVID and alcohol use disorder. This is important and is something that we are going to remember forever. And we need to prepare- prepare in the future. But as a broad picture. Some studies show that during COVID, the alcohol consumption increased. But more studies are showing that probably the alcohol use disorder increased in people already with the alcohol use disorder. Just as a big frame. But keep this in mind. More and more data is coming but what- what is most important is to be aware that when we were confined, probably we were drinking excessively. But the problem was most related with people already with the alcohol use disorder.

16:07

As I was trying to tell you look the monthly alcohol use between men and women in our country in the past month. Look, those percentages. Look, those numbers, total of drinking, binge drinking, early drinking. These numbers are growing fast, and the women population degrades, the rates are going from almost increasing: 84 over the past decade- 84% over the past years relatively to 35% in men. And unfortunately, in women, we have more blackouts, liver inflammation, brain atrophy and cognitive deficits, with some cancers related ones.

16:53

We already talked about these important data. Age is a known factor in heavy drinking, and remember that that population that I defined and the young stages, we need to track that population really carefully.

17:08

I'm not going to talk about the DSM-5 criteria. But just to refresh our mind, the DSM-5, unified what it was defined as dependence and abuse, and it put it in one big category. And for the first time, craving was one of the main components of the definition.

17:31

Well, what is important here we we are working with our population that we are seeing clinically, our patients struggling with this. We are the lucky ones that we know what to assess. But in general, just 10% of the population gets the real treatment that they need. We need to really review what is happening in the way that we are practicing- what is happening in our undergraduate, graduate education- related with the substance use component. And when we are in med school, are we getting the right education related with substance use disorder? That's a question but again, it's not the only one related of why we are not kind of treating the people that needs it with the right tools.

18:20

Again, I know that you have seen these slides before from NIDA, from NIAAA, but this is what is this standard drink: it's 14 grams of pure alcohol. And in general, people metabolize about one standard drink per hour. We know when we are intoxicated. We know what are the blood alcohol concentrations as proof. We know that in many states, when you go up that .008 grams per deciliter, their license will be retained. And we know that some people when they are just in the 300 or 4...400 milligrams in the admission to the hospital because let's say they were intoxicated, suddenly they are able to interact with you, they are able to talk with you. When you see big numbers in your alcohol level and people just relating with you on a natural way, you need to consider that that person develops already tolerance.

19:26

The rules of 20s is: in men, each drink adds 20 milligrams per deciliter to the BAL and in women, the the numbers go almost double- 40 milligrams per deciliter. We are going to see these because their metabolism changes. And in terms of genders, what is important is the the metabolism of alcohol goes with the zero order kinetics. It goes kind of inconsequential in resonance with the timeframe

20:02

Let's consider these three important components in women, and of course pregnancy, that we're going to review. The body composition: one of the main main components that in females a greater percentage of the body mass is, is basically with with body mass is, the fat as compared to males, much higher than males are. The concentration of alcohol is increased in the female bloodstream compared to the male body due to body mass that female has most. And also, with the ADH- pay attention to these- females have very little of these inside compared to males in the stomach- means that as soon as we hit the the, the, the body, in women, their blood alcohol concentration goes higher. And in the liver, the ADH also is less active than men. Those are components that I think are important to keep in mind.

21:06

When I'm kind of having a sip of water here. This is really important and something that we can prevent. What is the most common known preventable cause of mental impairment in our young population, and in our babies is this: the fetal alcohol spectrum disorders related with alcohol use disorder. The prevalence average is 50 per 1000. Around you, around us, around 40,000 infants have fetal alcohol spectrum disorder.

21:43

Well, with Mr. RR you do your assessment, you found that he has high blood press- pressure, history of pancreatitis, GERD, and these are the medications. While I will like that you pay attention is to everything, but look, this person ended up with a prescription of alprazolam for the anxiety and with a

prescription of zolpidem, which is a sleep medication that we're going to review on the sedative use disorder component of our lectures, due to insomnia. Pay attention to these combination of meds, the approach that we have with our population.

22:22

Mr. RR had blood pressure high and of course, high pulse. And look what happened: you check the CBC and it was normal except the MCV. And when you checked the liver enzymes, look what you found: elevation on the GGT and elevation on the AST/ALT. Let's say that you have the luxury in your hospital to have the CDT. We are going to review why the CDT and what it means in- in a few minutes, and why this is almost like the h1 AC for diabetes in the component of alcohol use disorder.

23:00

We already defined the SBIRT, but pretty much when you practice SBIRT, you are going to have the big change and high percentage of people involved in the care that they need to.

23:12

What are the screening tools? Well, we are familiar with the CAGE. It's one of the most important ones, but we're going to see that is another one right now used worldwide. But the CAGE questionaire is something that we have been familiar since med school, and two or more positive responses of these are strongly associated with alcohol use disorder.

23:36

Now pay attention to the AUDIT-C questionaire, how simple the brief one is, it can be done by a clinician right away when the patient arrives to your office. And most important, you are able to determine based on the severity, if that person is a candidate for brief intervention for pharmacotherapy, for pharmacotherapy plus patient management. And what a key element it is to have some data and some evidence of the progress of your patient, but also in terms of the identification of the alcohol use disorder.

24:19

The role of biomarkers: don't use biomarkers to punish your patients. I have seen many times almost like we are in the investigation mode. We turn to a patient and I said or we said "I catch you..." No, let's go back to the core of why the biomarkers can be useful. They can promote the change. They can be objective measures to show the patient when you have, let's say high glucose, and you suffer diabetes, and the doctor shows you "hey those numbers are a little bit elevated." Motivation right away. And of course, it involves other contributions for the change, and more than that, can identify the possibility to stop a lapse, that it will turn later on a relapse if we don't identify.

25:09

25:09

Well, types of alcohol biomarkers, we have indirect test; we have direct test. The indirect test are the ones that you are most familiar with- the GGT, the AST/ALT. But also pay attention to carbohydrate-deficient transferrin. It is the only FDA approved alcohol biomarker, very important one, and we're gonna see that is expensive, but when you need to use it, you can use it if necessary, if necessary.

25:39

Direct test, the reflection of alcohol use in the system, the indirect test reflects the damage that you cause. The direct test captures if that person has been drinking before they see you... three or five days before... they are the EtG, EtS, and PEth.

26:01

The windows are: the EtG hours you are able to capture with the EtG. And the practice that I have at the hospital. I use many times the EtG to see if that person is drinking days, or, or is having difficulty with the alcohol before they see us. And as a way to conduct the the session to see we can open the gate to more discussions.

26:29

And here we go. Average, the CDT, the GGT, they are between three and four weeks elevated when you assess them.

26:39

This is a summary of what we review. What I would like to capture here is that between GGT, ASD, ALT that the timeframe is four weeks that you are able to capture the levels high in the lab test. Some of them have false positives. And it's so important that you pay attention to it in case that the person continues denying the drinking. What else is happening when you see the elevation.

27:10

But look, the beauty of CDT that actually captures around five drinks of drinking consecutively for the past two weeks is that it has few sources of false positives, and that's the reason that it is a good marker of relapse.

27:29

Sensitivity and specificity- specificity. We know this from epidemiology. But what I would like that you pay attention is that sensitivity and specificity of the CBT. And also the good tool also have GGT in general and the other ones that we will reach

27:49

We'll continue with it. Mr. RR, his last drink when you saw him was the previous night. He had insomnia, diarrhea, palpitations, shakes, described in the morning, and again, the alprazolam to relieve the anxiety.

28:05

What are the phases of any substance use disorder treatment? And again, I know that this is obvious, but it's so important to say: A- the first step, but not the treatment, is the detoxification. And then what? Am I going to stop there? "Oh, by the way, Doctor, this patient was in a detox he's ready to go back to your program clinic hospital." And and you ask, "By the way, did you start naltrexone on this patient? By the way, did you start any MAT approach to gain some time in these aspects?" That's what is called the relapse prevention stage of treatment.

28:43

Talking about alcohol withdrawal, very important components. We know that the management of alcohol withdrawal, the gold standard is the benzodiazepines. Many of us are using anticonvulsants too but the benzos are kind of the tip of, of let's say, the most important aspect of the treatment for alcohol withdrawal.

29:06

In neurobiology it's so key to understand the kindling component that we're going to review in a minute and be aware that some people can be managed in the inpatient world or in the outpatient and we are going to assess who.

29:19

Well, believe it or not, alcohol withdrawal are not well studied. And I'm using the data there. It is a significance between 13 and 71% of individuals probably are going to need detoxification. And from that 10% will require inpatient medical treatment. Their mortality is around 2%.

29:43

Well, let's review now, what is kindling? Kindling is basically... the definition is...: As much exposure I'm going to have to, in this case, alcohol and the withdrawals are going to be more frequently... I have more the propensity with these episodes of alcohol withdrawal to make those withdrawal getting worse, and that when we have seizures, withdrawal DTS because that theory of the kindling, all right?

30:17

Well, we know how to manage withdrawal. I don't need to go in details about it. But what is key is that it's not in order. And what is crucial here is the importance to always keep in mind why the

that it's not in order. And what is crucial here is the importance to always keep in mind why the supplement vitamins and minerals are a key starting even from ER.

30:36

Important to know and more studies are showing hypomagnesaemia, hypophosphatemia, etc, and disorders in the acid-base components in our system, the electrolyte disorders can change drastically the way that people behave, and react. And be aware that is irrespectively of the social circumstances of that person.

31:00

Be aware of the caloric intake, the needs that that patient has. And remember the thiamine deficiency. Prior you give glucose or IV fluids to a patient, pay attention to the thiamine. Why? Because the thiamine is in the Krebs cycle. And if we don't pay attention and we don't give the thiamine first, we can deplete the few sources that we have still when we arrived to the hospital. And then we will create the Wernicke's and Korsakoff's component of the presentation.

31:36

The Wernicke's is: partial to complete paralysis of the extra ocular muscles, nystagmus, ataxia, remember that the mortality goes higher with these and the treatment is, as we said, thiamine PRIOR dextrose administration.

31:52

In Korsakoff's psychosis: anterograde amnesia with confabulations. This is not the order. We can see first hallucinations, then we see the automatic- autonomic hyperactivity and of course the delirium tremens and the neuronal excite- excitation related with seizures.

32:13

Well, when the autonomic hyperactivity starts at the six hours and peaks at the 24, remember that in alcohol withdrawal, the most common hallucinations are visual, visual hallucinations. And when we have seizures, they are general- generalized tonic-clonic. And they are in the first 48 hours.

32:34

Then when we move to the delirium tremens as the word says delirium tremens, it presents on the third day average with other components and abnormalities in terms of our cardiovascular system. And I'm not going into the details of the CIWA. But these are the symptoms that you tolerate. These are the ranges of the score. And remember that when you have CIWA higher than 8, or in the 15 number, you need to start to pay attention how you're going to treat this population.

33:14

Here we go with what we were talking about. We can divide like this: minimum withdrawal, moderate withdrawal that is already probably the requirement of medication, and the 15 number, which is absolutely "we need to start right away right now" to prevent that this patient either will have seizures, or will have DTs.

33:38

We already reviewed the mechanisms and the importance of GABAergic system as the main inhibitory neurotransmitter in our system, how the glutamate activity pumps up when we are in withdrawal and how that calcium channel and noradrenergic system is related with it.

33:59

Mr. RR you continue pursuing through your motivational interviewing skills. You maintain your open-ended questions, and then you start to share with the person the changes that you saw, they see what you assess, and you said, "Maybe it's time to start your treatment. Mr. RR, what do you think?"

34:21

Here we go. You told him that the elevations of the AST/ALT reflects liver damage and the CDT is related with the high heavy drinking that he had before the surgery. You agreed to start, with the patient of course, an outpatient alcohol treatment program.

34:43

How? You have these tools, and I really hope that you even get more familiar with- these days talking about MAT- medication assisted treatment. Involve the MET, involve the CBT in that process.

34:59

Involve the medical management, and of course, never forget the importance of Alcoholics Anonymous and other 12-Step programs in the core of the treatment of your population.

35:13

Also, individualize the care. Always individualize the care- try to negotiate with the person. What is most important? Why do you think is important and why they think that is not important. It is kind of like a dialogue that we go back and forth.

35:31

Well, we already talked about the importance of benzodiazepines and in the sedative use disorder component, we are going to review more in depth. But key enough, many people use these days lorazepam in terms of the detoxification because it kind of jumps through the conjugation stage instead of oxidation, meaning that with people with hepatic impairment, you can use Lorazepam more than the other ones. But that doesn't mean that you cannot use chlordiazepoxide which is a great benzodiazepine for withdrawal or any other, such as diazepam. Okay.

36:13

What are the indications for outpatient withdrawal treatment? Well, look, when you have a person that doesn't have previous history of seizures or delirium, when they see what numbers are low, or you consider that the person can be managed with your system, with your pharmacological approach in the outpatient setting, no serious medical or psychiatric condition, and has a lot of support and supervision.

36:39

What are the inpatient? Are again, this is overview. Please don't take these as written in stone. Things vary, but it's important that we have big pictures. When do you consider impatient withdrawal: CIWA is high, history of DTs or withdrawal... a person that is pregnant with difficulties with the withdrawal, major medical and psychiatric component that the patient don't even remember how to take the medication, don't follow the instructions, poor social support, active psychosis. Those are parameters and indication for you.

37:17

We talk about mild to moderate alcohol withdrawal. Remember that we were reviewing earlier the long-acting medicines: chlordiazepoxide with the dosages there, diazepam, and short-acting benzos such as lorazepam.

37:33

Remember that diazepam you can use it IV and that's useful in ICU. Lorazepam also is a medication that you can use with moderate to severe liver disease in elderly or confused patients or debilitating patients in different forms: PO, IV or IM.

37:55

I don't want to derail you from the main component, but I will like that we review the importance of anticonvulsants even though they are not FDA approved. But many people these days are using anticonvulsants in the treatment of withdrawal and also relapse prevention strategies. Look, gabapentin, valproic acid, carbamazepine, these are components of the family of anticonvulsants that they can be used. Remember that if you have a person with liver disease, or hematological disease, think twice if the right way to go will be carbamazepine or another anticonvulsant.

38:42

When to consider pharmacotherapy? Always consider pharmacotherapy. Don't hold yourselves in the impatients setting to start naltrexone, or acamprosate, or a non-FDA-approved medication that you consider that can be useful for your patients. Right?

39:01

Remember, and I don't want to derail- this is going to be covered later by my colleague. But methadone maintenance therapy can only be used for treatment of opioid use disorder in a license OTP program.

39:14

Now, pharmacogenetics. We are talking these days about genetics in our field. We are talking about precise methods in our field. We need to be familiar with these. That we are ready to go and use these right- use these right away? No, but I tried to take from studies the different medications that are already with some studies related with genetic variants. And also to see if the heavy drinking or the relapse gets prolonged with these medications.

39:47

And look how important it is. At some point, we thought- we thought that the generic variant OPRM1 with the allele Asn40Asp was related with the predictive value for naltrexone response. That has been reviewed, and it is reviewed right now, but what an intriguing and very important component we are seeing these with pharmacogenetics. Keep in mind.

40:15

Well, we know why the relapse prevention is so important. And right now we have different tools. Use them. And I put there the years that they were approved. And why still, we are not even thinking about to use them, and why we need to start to use them and the reasons related with it.

40:38

Well, talking about naltrexone... naltrexone comes in two presentations PO and injectable form called vivitrol. Why it's important? Because it regulates the dopaminergic system.

40:51

Remember that alcohol release endorphins in the system and alcohol is closely related with the opioid component. If naltrexone is given, that system will be regulated and consequently, as we were reviewing it early, other neurotransmitters will be involved in that. And in this case, the dopaminergic

system will be modulated with the naltrexone.

41:17

There is evidence- mixed evidence, as I was telling you- about the predictive favorable response to naltrexone. And so when it was mentioned: male sex, a positive family history of alcoholism, high levels of craving, and the polymorphism, of the ASP variant of the opioid receptor gene that I mentioned earlier.

41:39

Important we review these. It knocks down the full euphorogenic effect of the alcohol for the reasons that we reviewed. And it prevents that people have a blown- full blown relapse.

41:55

I put there the different studies with meta-analysis, kind of showing you that it reduced the heavy drinking. That is the most important component. And hopefully, you will monitor the compliance. And if compliance is difficult... to monitor the heavy drinking, you know, the binge drinking of the person, you have the option, of course, of the injection.

42:23

Remember that medication comes in 50 milligrams per day. And very important, always before prescribing naltrexone, ask your patients if they are taking opioids or not. Why? Because if you don't ask, next morning, you are going to have a very angry person telling you "What is this medication? It put me in a bad situation I was vomiting and having sweats." "Patient, you said, by the way, do you take other meds? I didn't ask you yesterday." "Oh yes, doctor, I'm taking painkillers." Then you will have the consequences of what we reviewed. Pay attention always and ask.

43:02

Then the regular side effects of this medication are related more- more with the GI system and some sedation exposure. Always keep track of the LFTs, hopefully, or ideally, before you prescribe the medication. And every three to six months, you can check the levels of the LFTs. Why? Because it's very minimum, I don't remember exactly, but I think is 1% by studies that it can create the hepatotoxicity, all right.

43:35

Much the treatment always with the resources that we have, as we reviewed.

43:40

This is the study, the most famous study, done that started or initiated the naltrexone use. As you see the community proportion of no relapses: higher with naltrexone.

43:58

Long-acting naltrexone, one injectable form 3...380 milligrams. Remember that is so important, almost with the clock, to give the naltrexone, IM. Other injectable forms, can stay prolonged period of time your system. Naltrexone as soon as you hit 20 day, 30 day the medication drops down drastically.

44:22

That's the reason that is so important to keep track of these. We reviewed it earlier with naltrexone PO, but keep monitoring the LFTs and in the injection site that is in the gluteal reg- region. Try to monitor how the person responds to it.

44:40

This is another study that shows how the median heavy drinking days was decreased with the dosage of 380 milligrams, and that was the reason that that was the appropriate dose.

44:54

Protracted withdrawal symptoms: remember that the protracted withdrawal symptoms you're gonna see probably with sedatives and alcohol, and maybe all drugs, but in general, those are the two components that you're gonna see protracted withdrawal symptoms.

45:08

Now we are talking about alcohol use disorder. These are the ones that you can see sleep dysregulation, irritability, mood instability, and anxiety.

45:18

How to treat those: with acamprosate. Initially acamprosate and we're gonna see was kind of... always these medication helps... is two tablets three times a day, but studies are showing more and more that is a tool. And I really hope that you consider this tool when it's necessary.

45:35

Remember that acamprosate targets the GABAergic system and the glutamatergic system and restore the balance between both. It is an anticraving medication and reduced the protracted

withdraw- withdrawal and the negative reinforcement. It's really useful when you have liver damage. The patient doesn't want to be on naltrexone. And so you say hey, it is a possibility with these medications.

46:03

As I'm pointing it out, there is more studies, kind of showing the benefits. And of course, the difficulties with these medications. In some point in US, the trial was done in a very diversified population. The first study, on a computer and that was the reason that it was questioned, it was held. Then a more homogeneous component of the provision was done, and the studies start to show that it was more effective compared with the European study that was initially promoting kind of the use of acamprosate eight years ago.

46:42

The dosage, that's the dosage in the tablet is 333 milligrams, is two of them three times a day. Remember that is excreted by the kidneys. Always if you have liver disease, consider acamprosate, but if you- if you have renal disease, pay attention to see if it's better to use other medication, or you need to taper even to half the dose, the acamprosate.

47:11

The mild diarrhea is some side effects that you have. And keep in mind that this medication doesn't have much drug and drug interactions.

47:20

This is another study showing the percentage of abstinence with patients on a acamprosate- Sass and collaborators.

47:30

Let's move along with disulfiram- very fine medication- still used very frequently. It should be the first choice- not always. Consider that we have other strategies. The most important key component here is looked at initially when we were talking about females and why the ADH in the stomach and also the ADH in the liver works with less capacity. Right now we are going to talk about the ALDH- acetaldehyde dehdrogenase that has been- that is inhibited by the disulfiram. The acetaldehyde goes up. And then that flushing, that tachycardia, that vomiting components of the presentation.

48:15

Yes, when I get sick, that's the treatment. That can be an explanation. That aversive reaction is an explanation of a treatment. Absolutely, it can be a tool. But that's the ideal tool? Remember what candidates for this treatment and what can they cannot be.

48:34

I will say repetitively, that probably is the second line treatment. And again, double blind placebo controlled studies were not possible to be done because both the medication, the placebo tablets results in fear of drinking. But in general, the studies show more that the person taking disulfiram with supportive people, you name it, partner, people around, reminding him about these were more successful.

49:06

The dosage is between 250 and 500 milligrams. You can take this medication but please keep up, keep up the awareness of liver toxicity. Keep your awareness of contraindication when you have cardiovascular problems, if you have psychosis, if you have pregnancy, if you have varices. If the person has these aversive reactions, these can really turn the situation of that patient even much more difficult. And remember that this medication also has a lot of drug and drug interaction with inhibiting hepatic enzymes. And I put the family of medication that can have bad interactions or- or difficult interactions with disulfiram.

49:56

Of course side effects are related with acne- acne, drowsiness, headache, metallic taste that is described by patient and loss of libido.

50:05

This is the study done at the VA, showing you the dosage and showing you the people that were complying, with the percentage of remaining options that they achieved.

50:19

These are big summary of the MAT and FDA approved. We kind of review these slowly and gradually during this process, but I would like that you keep this slide for your reference and for your kind of summary, but really helpful to have it in front of you.

50:37

Combinations: of course, you can combine naltrexone and acamprosate. Some studies are showing that this is possible. And these two combinations can be extremely helpful. Some other studies are not in favor of them. But hey, we are talking about clinical strategies. We talk about genetic components, we talk about precise medicine in some point, maybe we will see who responds better to one or two medications at the same time.

51:03

Project MATCH, it has been one of the most important studies in the arena now of substance use disorder, in this case, alcohol use disorder. They try to compare treatments, and including 12-step programs, CBT, and motivational enhancement therapy. Guess what? All of them respond really well. However, outpatients who received the 12-step program were more likely to remain abstinent after one year following the treatment. Very interesting. There were a few matching effects and they were weak.

51:43

The COMBINE study is another important study comparing medications with combined behavioral interventions defined as CBI and medical management. Patients received either one or two medication or none. And pretty much half of the patients received psych- psychotherapy in addition to medical management.

52:01

Guess what? From the COMBINE study, pay attention who responds better to the treatment. All treatment groups had an increasing percentage days of abstinence. Overall effect was from 25% to 73%.

52:29

And if we go in to the details, for the COMBINE study for patients receiving medication management, naltrexone or CBI improved outcomes over placebo plus medication management. In other words, naltrexone plus medication management had a little bit of the best outcome in these different groups of the COMBINE study.

52:51

This was one of the studies that showed that acamprosate didn't benefit much. And again, taking tablets in summary, and seeing that health professional was more effective than receiving CBI based on the study. Remember, we need to individualize the care. But in general, there was no significant difference between the groups.

53:11

Just to finalize, these are the big overview of pharmacological agents these days. Some of them, I'm sure that you are familiar with. In our dialogue, probably we will review uses of clonidine, phenobarbital, anticonvulsants, but for the purpose of this lecture now, I will like that you take the big picture of what is FDA approved, and it starts to consolidate with these conclusions.

53:43

33:43

Don't stop treating people after the detox. It is a continuing relapse prevention. Use the tools that we have. Challenge the system when you have restrictions to prescribe MAT approaches in your setting, and try to use as much as you can. The combination of evidence based medicine, psychotherapy modalities, your motivational skills, plus your pharmacological tools, and all what you do. We really appreciate your presence. Thank you so much for navigating with me this important topic with a lot of information, but I hope that it will be useful for you now and in the future. Take care