Sedative Use Disorder - Restrepo

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00:00

This presentation is entitled Sedative Use Disorder: Research and Practice. I will now turn it over to Dr. Ricardo Restrepo to begin our presentation.

00:07

Hello, colleagues, how are you doing? I know that always we are taking this course we get anxious but at the same time craving for knowledge. I'm gonna go with the basics with this topic. We covered earlier the alcohol use disorder. And right now we are going to cover a vast amount of information. But I'm sure that together we will make it learnable and hopefully all of us we will share more knowledge together.

00:38

Well, I do not have any financial disclosures, or any- any relevant connection with any industry. What I'm going to talk about here is directly clinically and based on studies and I really hope that you will follow me on the outline.

00:56

It is always good to have like a historical view. Of course, we are going to cover some neurobiology epidemiology. And absolutely later on we will move with the risk benefits of benzodiazepines as well as targeting other non-benzodiazepine- benzodiazepine hypnotic agents.

01:17

We will move with barbiturates, GHB, and conclusions.

01:23

Well, historical view. One important moment to review when we start with these kinds of new step in science. First half of the 20th century, the barbiturates were kind of the most, let's say, prescribed medications regarding anxiety, or insomnia. But as we know, the barbiturates were kind of with some difficulties at the end of the 1950s, and a new wave came with the benzodiazepines were discovered, and the first benzodiazepine in the market was the chlordiazepoxide. What happened was during the 60s, kind of the benzos replaced more or less the barbiturates from the arena, and in the 70s, it became the most commonly prescribed of all the medications around the world.

02:22

Then, during the 80s, we start to see probably what we know already that can cause some physical dependence that can cause some kind of addictive component into it. And we start to see that trend growing, growing, and understanding the drug tolerance and withdrawal that we see these days right now in our population. Then, at the end of let's say, the past 10 years or 20, we start to see how the elderly population, we need to be more cautious when we prescribe the sedative to this group of people.

03:00

Well, this is kind of the three main components that we're going to review and that you should know: the benzo receptor agonist, the barbiturates and others.

03:14

Look how in the past these used to be marketed. Right now talking about genders and equality and possibilities to maintain the core of, let's say, accessibility. This was a promotion that these days probably right now we wouldn't see. "Her world orbits around doctors." "Psychic tension rules her universe" then in the other side, a little child with probably difficulties, who knows, ADHD or tantrums... the "battered parent syndrome." Let's prescribe my problem. You see how probably the language has changed. And right now we are, let's say more cautious and more respectful in terms of to whom we direct the message.

04:07

Then, let's start to see these cases that we review with the alcohol use disorder. This is the same person that I presented to you, but these days this person had been recovered from alcohol, and right now has insomnia and anxiety with other comorbidities. But he arrives to the ER with confusion and diaphoresis.

04:34

The neurobiology of benzodiazepines. Keep in mind we have two main GABA receptors, GABAA receptor and GABAB receptor. The benzodia- benzodiazepines target the GABAA receptor. We are going to see that GHB targets the GABAB receptor and we have five... a pen- it is a pentameter, the

receptor is two A's, two B's and one gamma.

05:06

Look where the GABA receptor site is between the A1 and B2 is there but the benzo side has been between the A1 and gamma. Remember that we are going to review that GABA requires, or benzo require- requires GABA to get into the action of that receptor. And as I was mentioning before, it is a difference between the different sedatives. Benzodiazepine increases the number of time the chloride channel opens- means frequency.

05:46

The barbiturates increase the duration of the opening of the channel. Barbiturates doesn't need GABA to have the effects that it has. And GABA is a primarily neurotransmitter but as you remember from basic science is the main inhibitory neurotransmitter as opposed to the excitatory neurotransmitter that we review also with alcohol use disorder, when we are having alcohol withdrawal that the glutamate activates.

06:21

Well, I know that you know this kind of effect but when we put together GABA and diazepam on the membrane potential. And the influx of chloride, of course, that is a major component of the effect.

06:39

Then, in more detailed slide that I put there, benzodiazepine require the presence of GABA. Barbiturates do not.

06:50

Be aware that as we these days talk about naltrexone, and naloxone as new receptor antagonists, I don't want to confuse you these in the in the world of opioid use disorder, or any type of overdoses, we use the naloxone. In the case of benzodiazepines, some physicians feel comfortable using flumazenil that blocks the effect of benzos. And non benzos called such as zolpidem.

07:26

But doesn't have any mechanism of action in the barbiturates. Be aware later that we're going to read why flumazenil for some people is not kind of the ideal way to go.

07:39

Well, we already talked about this, we already talked about the importance of where the benzos go,

and the importance of why it it increases the affinity of the receptor for GABA with the frequency and how barbiturates increase the duration.

08:01

We reviewed this slide before with the alcohol use disorder. I don't want to repeat this, but it's so important that we understand the mechanism of action and the effects of either sedatives or another substance in our system. We will we will understand the pharmacology of- we reviewed these already.

08:26

This kind of interesting slide that I decided to put in, I don't want to get confused. Imagine yourself in in in the inter neuron area, ventral tegmental area, nucleus accumbens. We have a GABA neuron and then dopaminergic neuron. The GABA regulates the dopaminergic neuron. GABA is on green. Dopaminergic neuron is on red. Pay attention to the GABAA receptor alpha-1 on the GABA interneuron. When benzodiazepines are not there, the GABA is capable to regulate to regulate how the dopamine releases in the dopaminergic system. The opposite- when benzodiazepines are given to us that benzo attaches to the alpha-1 GABAA receptor. And when you get when this attaches to it, it doesn't have the capacity later on to regulate the dopaminergic system and say to the interneuron "hey, slow down, I have control over you, don't worry about it."

09:42

When benzos come across right away the interruption of that communication between the GABA and dopaminergic inter neurons disappears and that's the reason that dopa is released. And that's the reason that we we have a mechanism of benzodiazepine use disorder.

10:06

Well as we know 80% of patients with benzo use disorders use other drugs keep these in mind, because you are going to see that always when we have another substance and we need to ask the questions: "Hey- do you have use or do you use other substances such as sedatives?"

10:27

Be aware that 30-50% of patients with alcohol use disorder has also sedative use disorder- more related with the benzo use disorder. And people with IV drug use, kind of 50% of them also have the possibility to have sedative use disorder. The average benzodiazepine use is: two females, one male, and approximately 5% of adults in US uses benzos. Their use of benzos increases with age and roughly I fully expect, kind of 80 to 90% of prescriptions are coming from primary care because you- primary cares are the first window of opportunity of treatment for disorders that require this treatment.

11:21

11:21

This slide what I want to show you is how as much as you get older, you have the possibility to have more benzo accumulated through time with you. That doesn't mean that you're going to get more new prescriptions. In, in other words, as much older you get the accumulation of a benzo that was started in your 30s, 40 years of age come across, come across until you're 80. That's what this slide shows us and it's so important to keep this in mind.

12:00

As we know, the benzodiazepine visit rates have been increasing in this country and primarily all benzo had increased almost 95% in the past 12 years. As I was mentioning, it's rarely to see just benzo or sedative use disorder without other comorbidity related with another substance use disorder. You always need to ask farther than "Hey, do you use benzos?" You need to ask for other use of other substance abuse. Okay? And healthy patients prefer placebo to benzodiazepines. And this is surprising.

12:46

An important component that I would like to mention here is that alcohol use disorder patients and their offsprings are more likely to experience mood elevation with benzos. And if you hear your patients and you pay attention to your patients, you are going to realize that many of them do not feel sedated. Actually they said by the way, though, with the combination of benzos in my system, I'm capable, capable to function. I am kind of full of energy. And that's something that you don't see on population without these alcohol use disorder on board.

13:28

We know these, we we kind of are aware of the difficulties that opioid use disorder has an alliance with sedative use disorder. As we know, and in a few minutes, we're going to review the death rates due to opioid versus combination with certain use disorders. But most importantly, always when you see the combination of opioids with sedatives. Pay attention, pay attention to the lethality. Believe it or not, benzos by itself do not have such a strong or higher percentage of lethality as it it seems, when you combine it with opioids.

14:14

Another slide confirming what I was trying to describe the entire time Look- the group on the x-axis and the percentage on the y-axis. Meaning that in blue, that's the amount of secondary abuse of benzos. It's not a primary use disorder. Looked at the primary use disorder ranges between 10 and 15%. And just the tip of the corner which is in green, it is kind of the percentage of primary use of benzodiazepine alone.

14:53

We already discussed this, what is important is to really continue paying attention and again, I do not believe that benzos are not complete or should be banished completely from our armamentarium of

believe that benzos are not complete or should be banished completely from our armamentarium of possibilities, but let's handle it appropriately and carefully. We'll check these data these kind of new data related with the benzodiazepine. It is the National Drug overdose- overdose deaths involving benzos. Benzos involved in 70% of opioid-related overdose deaths. And that's what you see with the yellow line that is there. If you track down just the benzos without any opioids, which is the gray line. Look how the difference is, it is an unbelievable difference when you combine benzos with another depressant such as opiates, and we know this, and it's something that we need to kind of pay attention in the way that we're practicing.

16:06

Now, as we know, these are the National Drug Overdose Involving or Overdose Deaths. Around 1000-1100 drug overdoses that report in 2021, just due to the synthetic opioids, primarily fentanyl. Look that in other lectures from my colleagues, you're gonna see that now with psychostimulants and also cocaine, we need to pay attention because these too are being cut with fentanyl. If you see just benzo by itself, it doesn't cause the mortality as probably we would expect. The mortality comes with combination and is something that we need to keep track in how these days stimulants, cocaine and psychostimulants such as methamphetamine, also increase the potential to overdose.

17:13

ED visits- the risk of serious outcomes. This is kind of redundant of what I'm telling you, but the combination of opiates, alcohol and benzos look where that leads us in terms of the pretence-percentage of ED visits.

17:32

Well, this is not a mystery, but the most frequent benzodiazepine that is overused is the alprazolam, followed by clonazepam, lorazepam, diazepam. And remember, after the opioids pay attention to the type of pharmacological way that we're prescribing benzos, because it has the potential to be overused and abused.

18:01

Well, this is kind of something that we already discuss with the prevalence of benzos. In terms of genders, in terms of who is utilizing more benzos. As much as you get older, you have the tendency to accumulate the use of benzos for longer periods of time. And it's so important that we see on the right side from the study of Olfson and collaborators in JAMA Psychiatry 2015, in the oldest group, as I mentioned 65 to 80, almost 30% Or even more of those using benzos are using them long term and long term is more than 120 days almost more than six months, right.

18:54

More data related with the Olfson group, they have benzo use percentage between men and females, this is corresponding to what we already reviewed. And of course, something that I mentioned earlier that the increase of prescriptions are increasing day by day,

19:14

This is an old study but these these are reflection of what we are talking about. The increase of 6... 67% between year 1996 and 2013. Benzodiazepines use accumulate with age. Those arrows is just to show you basically the red arrows that you see is to show you that the misuse is more frequently in younger population they misuse but the accumulation of benzo use is more frequently as older as you get 50-64 in this study, and even in a people group of 65 years and older, that is also a pattern that you see.

20:11

Now, we put in the context that data that we already talked about. Around 30 million people adults use benzos in this country. Who misuses? Around 5 million people misuse. And from that group point-five (.5) million adults had benzodiazepine or sedative use disorder.

20:40

If we continue with a case, this person didn't receive the alprazolam refilled from primary care, and he starts to look around for another possibility. That person approach- ask the psychiatrist in ER to ask if that person can get the benzo prescribing issued. This is a pattern that we see in this population.

21:05

When you examine the person in ER, you found that their heart was racing, the insomnia was worse. And for the past four days, the- the person is having difficulties following conversations, focusing on daily tasks since the person was off alprazolam. You kind of tried to do a cohesive and coherent approach and those were the symptoms that you found.

21:37

The factors associated with prescribing meds or prescribing benzos in this case when you see anxiety, insomnia, be aware that pain these days, many times treatment with pain is combined with benzos and we know that benzo doesn't help pain. It is also related with the gender as we said and with the race. Pay attention to the psychosocial component of this person. If the person is elderly, as we reviewed, has low income, smokes and probably has more than one doctor and gets prescription through telehealth. Pay attention to it.

22:21

Look at these data as we review is sometimes we are not going to see benzos as the primary substance use but when we start benzos, five to 10% patients newly started on it develop a substance use disorder. 50% of patients with substance use disorder history will develop a

benzodiazepine use disorder and between 50 and 100% of patients prescribe with chronic benzo become physically dependent.

22:50

Think about the population and the characteristics that we talked before about. Benefits and risk- of course these medication is important to have it in our radar of possibilities but also assess the risk. Always try to target if the person is on a therapeutical dose and is getting dependent. If it is overusing with higher dose developing a sedative use disorder or if this person is probably using recreationally the benzodiazepines.

23:22

What are the risk factors for benzo use disorder? Longer duration of benzo use, higher benzodiazepine dosage, lower education, insomnia and if you are with antidepressants.

23:38

I don't need to tell you what are the benefits of benzos. But it is an anxiolytic- it is an hypnotic. It can relax you. It has an anticonvulsant effect, and it creates amnesia and we use it in the appropriate wait for the period of time that we need to use. It maybe makes a lot of sense to use it. But be careful to open a box with a population with substance use disorder when they insist and insist on benzodiazepines when you know that probably behind can be a long term problem. Always pay attention to who you're going to prescribe. And kind of review when maybe the Royal College of Psychiatrists recommend no more than four weeks and try to explain ahead why you are going to do this with your patients.

24:37

As we know these four components in different colors that we put there. Falls, hip fractures, sedation, cognitive impairment is something that we see more frequently as time passed by and age comes. Be aware that the am- amnesia that you develop with benzos is anterograde amnesia and more accidents more psychomotor impairment can be seen in the combination of these medications with others as we already reviewed.

25:13

In 2015, the American Geriatric Society recommend avoiding benzodiazepine in this population. But guess what- benzo use is three times more prevalent in older adults compared to younger adults. And roughly one quarter of long term benzo use is in patients as we saw, older, the older or 65 years of age.

25:39

Now, consideration when prescribing benzos. We talked already about examining the risk and benefits. Avoid a non benzo hypnotic in combination with the benzo. Let's say, zolpidem plus clonazepam try to avoid. Inform patients of plan and the duration of therapy.

26:01

Prescribe for a brief period of time, do not give five refills of the medication, try to really prepare the person of why you are going to do random urine toxicology when you prescribe benzos and attempt right away prior you start the benzo to educate the patient that you are going to taper and how you're going to taper. We have access these days to the prescription drug monitoring and of course, try to formalize these agreements in verbal terms or written terms makes the person feel that you are concerned but that may be you will be willing to try to move in this direction.

26:42

Now, the equivalent dosage of benzos and the elimination half lives is important. Nobody knows these by memory. But why I am putting these into your view is because if some day you decide to do a taper, some kind of school goes from short-acting benzo and you translate the dosage of that short-acting benzo into a long-acting benzo and then you start the taper. Many other clinicians that I know also stay with the benzo that the patient is overusing and they do the taper with the same medication. My school and the way that I learned is I switch people to a longer-term benzo and I do the taper and we will review that.

27:33

Now, why put this into a context of the metabolism. The majority of benzos go through oxidation means to the liver microsomal system making the liver work very, very hard. But three benzos kind of jump the phase one which is the oxidation and they go to glucuronidation. Those are the lorazepam, oxazepam, and temazepam- LOT. And as we reviewed before in alcohol use disorder, many times these days we see that alcohol use disorder withdrawal is free with lorazepam because it respects the liver and it doesn't go and force the liver to work.

28:24

I don't want to go to the details of these definitions. But if we divide these in three main groups: long half-lives of the benzos: clonazepam, diazepam, chlordiazepoxide. Intermediate half lives: oxazepam, temazepam, lorazepam means the LOT, and short-intermediate half life, which is basically alprazolam, triazolam. We will have kind of the window to really figure out what we are going to use, how we can respect the liver, and which of those do not have active metabolites, which maybe will be better in elderly and when we have a person with hepatic dysfunction.

29:10

Be aware that the main difference between benzos is related with the pharmacokinetics. Remember, based on lipophilicity and metabolism, pay attention to the route of administration, the absorption, the elimination, but also what we already reviewed- the timeframes and the onset of action. We

the elimination, but also what we already reviewed- the timeframes and the onset of action. We already reviewed these main and basic things related with the groups- something to keep in mind.

29:44

And when we see Mr. RR, he was found tachycardic, hypertensive, and you did a medical workup in detail that was under normal limits.

29:58

Then you found that this person was restless, irritable with twitches in the face and complain about tinnitus, anxious, and dysphoric. No other components of the Mini-Mental Status were observed.

30:15

Pay attention to the symptoms that were described here. Why? Because we're talking about benzo withdrawal and there are no pathognomonic sign or symptoms of benzo withdrawal. You need to be aware that has few concurrently observed hyper-adrenergic signs or vital sign fluctuations. Unlike acute alcohol withdrawal, sometimes you see a drop on the blood pressure. Sometimes you see an increase in the blood pressure different than the alcohol use withdrawal.

30:53

I tried to divide the symptoms of anxiety versus the symptoms related with benzodiazepine withdrawal and pay attention to what happened to Mr. RR: tingling, sensory- hypersensitive, twitches, tinnitus. You don't see that in anxiety state in general, pay attention to this component in case that you see a case not just in your exam, in your daily practice, because this can give you clues of what to do.

31:26

Challenging, of course, that is challenging to do a benzo taper for you as physicians or clinicians and for for, for the patient. But if you don't have a treatment plan, the problem starts. If you clarify to that person, how you're going to do it, why you are going to do it, what was the plan to do it, you need to consider many possibilities and how to approach that person, including the psychological support, the reason, the lifestyles, the personality.

31:59

Take into account the dosage and type of benzos. Taking consideration for how long that person has been taking benzos, and try to prepare a taper when he's not urging to taper demand. So try to educate the person that it's going to take months. You don't need to do it drastically. And sometimes we see in hospitals from let's say, full dosage to half in one week and from half to nothing in the second week, be prepared for rebound episodes of symptomatology.

32:33

Try to individualize the care, try to figure out what benzo the person is using, concerning the pharmacokinetics and what do you want to do and how do you want to do the taper? Remember that sometimes in books, we see the rebound, the recurrence, the withdrawal. But in reality, sometimes we see these exchanged with each other. What is key here is if you know the pharmacokinetic if you know the mechanism of action of benzo you will see results and positive effects of managing the taper more appropriately.

33:12

Be aware and this is something important that with severe withdrawal from benzos you can really see delirium, similar that when we stopped alcohol- it's kind of a similar path. And as we know we talk about the GABA and the glutamatergic components in terms of neurotransmitters that are related with this. Be aware that when you are unsure active benzos may be the same day you can start to have withdrawal when you are using long acting benzos maybe the withdrawal starts two days later, maybe a week later is when you start to see the full blown of the withdrawal.

33:56

The reason that the recommendation is to give just maximum four weeks of benzos to our patients is related to these different components of the timeframe that I mentioned there. Of patients who take a benzo for more than a month, 50% develop dependance. Keep these in mind. And as we know as much time passed by much more difficult will be to taper the benzo and much more withdrawal can be seen in our patients.

34:32

Management and when to taper- when you see over-sedation. When you see cognitive impairment. When you see a combination of multiple CNS depressant medication, you name it- opioid, other hypnotics, alcohol and of course if you see overuse or misuse that concerns you as a physician or if you hear the family member concerned about these.

34:57

This is when you start to do the possibility to explore the taper of the medication. Now, how to do the taper- go slow. If this is a person that has been for a long period of benzos, you don't need to do an abrupt decrease or taper. Be prepared for months or even a year. And let's do maximum by 25% weekly. As you remember, and a school that I'm coming from, we convert to long-acting benzos instead of keeping the person on the same benzodiazepine, but maybe you will feel comfortable keeping the person and following that person with the same benzo when you do the taper.

35:50

Use other possibilities and other medications that can help the transition. Trazadone for insomnia, mirtazapine for anxiety, depression, insomnia, buspirone, etc. And also be aware that some people use anticonvulsants. And I know some other colleagues use the clonidine patches during the process of taper. Be strategic. And be aware that Ashton, Dr. Ashton from England, she was kind of a pioneer in how to address benzo withdrawal and how to really help our patients. I'm not going to repeat these but be aware that when when we have short acting, we are going to see quicker the withdrawal onset. And of course, the duration of acute withdrawal can be even for a month.

36:45

Now, when we have long-acting benzos we will see much later the withdrawal. Even people on the seventh day after they stop let's say the diazepam, they start to have this type of withdrawal. And suddenly, you start to see protracted withdrawal that we also see in alcohol use disorder. Protracted withdrawal, we saw are symptoms, kind of in congruence with withdrawal that people feel months, years later.

37:16

What to do when we don't know the dosage of benzo, when we have multiple sedatives involved in the presentation of the person, and we are really confused from where to start the taper. These are possibilities and you can use the phenobarbital substitution. Now, these are the equivalents of phenobarbital, but the dose recommended for the taper will be to start with 500 milligrams a day and the phenobarbital should be given TID or QID.

37:50

Maybe some of you that are with me today are familiar with phenobarbital, not just for benzo use disorder but also for alcohol use disorder. And many different hospitals around the nation are using it. Be aware that you can measure the phenolbarbital toxicity easily. And their toxicity are based on the stagmus- horizontal nystagmus, sustained ataxia and slurred speech. If you see that, try to decrease the dose and skip one of the TID or QID. If you saw- if you see two signs of toxicity, you can skip two doses during the day and then recalculate the new daily dose.

38:38

What we're looking to start with is stab- stabilizing the patient of course. And remember that you started taper by decreasing the phenobarbital by 30 milligrams per day. In pregnancy it is so important to keep in mind. The effects of the benzos is a relatively contraindicated due to the cross fetal placental barrier that is kind of accessible by the benzo and it is passing to the breast milk. We are aware of the floppy baby syndrome, neonatal withdrawal, and some teratogenic effects as described in the literature.

39:22

Why some people are hesitant to use flumazenil when we see an overdose of benzodiazepine? The simple reason is that you precipitate cardiac arrhythmias, seizures, and of course, the withdrawal that

simple reason is that you precipitate cardiac arrhythmias, seizures, and of course, the withdrawal that we are kind of trying to treat. That's kind of the main component that people are hesitant to use flumazenil. Be aware that flumazenil is using IV presentation. And you need to monitor one milligram and you need to monitor every 30 to 60 minutes.

39:57

Now, let's move to the second component of this vast family of sedative use disorder. I know that is a lot of information, but I'm sure that you're going to navigate really well the components of the lecture. Let's move now with the famous Z-drugs.

40:15

When I was a resident, I don't know if I want to say long time ago or a few years ago, but let's say long time ago, I remember saying, or listening to people saying to me, Ricardo, we have a great medication that now that is non-addictive, that is not gonna cause any problems to our patients. And it's gonna be extremely helpful for sleep. Well, let's guess- guess what? It was completely the opposite. We create a problem with this medication, we can create the dependance, and we can create a pattern similar to benzo use disorder. And of course, be aware that the side effects of these medications is the risk to create the sleep-related behaviors.

41:05

Again, it's not that the medication is for nobody, but be aware to whom you are going to prescribe. Be aware that the Z drug goes to the GABAA receptor, the alpha-1 subunit with which modulates the sleep.

41:25

Now, let's move with the barbiturates. The oldest sedative hypnotic, as we saw at the beginning of the historical pattern of sedatives, classifying three different pharmacokinetic categories. If you're anesthesiology, you are savvy about it. And be aware that the barbiturates have a low therapeutical index. That's the reason that when we increase dosage, we can really see full effects that we didn't expect. That's the reason that we need to be extremely cautious. And barbiturates induce this synthesis of the cytochrome P450. And alter its own metabolism. It's almost like me, playing with myself and I play with others.

42:14

These are the different components of barbiturates. I don't need to go in detail. But many times if the person is not probably getting phenobarbital for seizure disorder that sometimes we see on our urine panel phenobarbital positive or barbiturates positive and we ask the patient and it was because it was under seizure treatment.

42:39

Also, be aware that these days the butalbital which is called fioricet- many times test positive. And if you don't know that the person is taking that medication, you probably will make judgments ahead of time. Important to have this big picture and as anesthesiologists or in our rotation in anesthesia, we are familiar with these barbiturates.

43:03

Important to have. Now, the last episode, an important one is the GHB. The GHB is the gamma-hydroxy-butyrate. This drug was in the club scene, or it is in the club scene, for a long period of time. But be aware that we also have it as an FDA approved medication for narcolepsy. This is the description of a patient describing the use of recreational use of GHB quotes- "When I woke up, I feel completely refreshed in comparison to the other drugs that are supposed to be clean. G really is clean."

43:51

As I mentioned to you for narcolepsy. it's approved for cataplexy and the effects of GHB indeed, like MDMA, but people describe having the greatest sex ever, relaxation, tranquillity, placidity, mild euphoria, disinhibition. It can cause temporary amnesia, and that's the reason that unfortunately GHB has been used as benzo- benzos for as a date rape drug.

44:27

The neurobiology is really interesting. We produce GHB. It's a neurotransmitter. It has a short half life. It is a precursor and a metabolite of GABA. Be aware that the GHB doesn't touch GABAA receptor, it goes to the GABAB receptor as GHB, remember with GABA B, and it attaches to GHB binding sites. Initially when GHB attaches to the GHB, it starts to release dopamine. And that is the pleasant feeling that people have. But as soon as you overpass the dose that is appropriate to have that effect, the dopaminergic neuron gets knocked down. And it comes with an initial phase of inhibition. And that's kind of the reason that at that moment starts to have some effect with the presentation.

45:31

Be aware that also that GHB increases release of endogenous opiates. This is the kind of structure sometimes it's important to know the structure of the different drugs. The intoxication, be aware that the curve is a steep dose response curve. With mild little tiny dosages, you can have full and very difficult effects and intoxication. What are the intoxication symptoms? Ataxia, loss of coordination, respiratory arrest, hypotension, bradycardia, and coma. Overdose is real danger. The LD50 is only five times the recreational dose. Talking about the steep dose response curve and it has a synergistic effect with alcohol and other sedatives.

46:29

We need to treat GHB as a medical emergency with the ABCs. Intensive care unit should be the way

that we admit this population, and atropine can be used for the bradycardia.

46:44

The withdrawal is rare, but severe and it almost behaves as sedative withdrawal, and how we treat this sedative withdrawal- with benzodiazepines. If someday you see a person with GHB withdrawal, you can give them benzos to taper if necessary.

47:09

Long term features, as we know, the physical physiological dependence, and most of the people will recover quick from from the overdose and completely. As we mentioned, it's a non-FDA-approved medication but you can manage with benzos, the withdrawal. Use and be aware that we are not just prescribers of meds, we are clinicians, and as many of my colleagues have been talking, we have multiple non-pharmacological components of our treatment, including CBT and motivational interviewing. I wish you the best. You take care and hope to see you soon. Thank you.