Psychopharmacology and PTSD 5
Written Video Transcript

That's the antidepressants. Now, we've kind of more move into open label territory, unknown territory. There's not as much in the way of double blind data for the other agents, but we use them. So, we do have data from other disorders that we can carry over to PTSD. Mood stabilizing [00:00.20.00] anticonvulsants being the next class. These are the agents that were shown to be effective for acute mania, being valproic acid was and are thought to be effective for impulsive anger, effective instability and possibly anxiety in general. The agents that we're talking about here are valproic acid or Depakote, [00:00.40.00] carbamazepine or Tegretol, gabapentin or Neurotin, [00:46] or [00:47] and [00:48] or [00:49]. The mechanism of actions of these agents are uncertain but they seem to be influencing those amino acid transmitters by at least some of them potentiating or increasing the effects [00:01.00.00] of the inhibitory GABA and decreasing or attenuating the effects of the excitatory glutamate transmitter as well as probably some of them having effects on just nerve conduction in general. So, overall kind of inhibitory effect on at least parts of the brain. Valproic acid or Depakote this is about ten years ago I know [00:01.20.00] received FDA approval for the treatment of in acute mania and it has been rapidly over taking lithium as a primary, you know, first line therapy. In addition to that, you know, it's been thought to be effective for impulsive anger as well. There's only there's one published trial of any of these agents in PTSD, as I'll describe it in a minute, although [00:01.40.00] there are a number of trials ongoing including one of our own with (topyramate). The one published study was in 1999 by Hertzburg and colleagues with (lamotagene). It's just (lamatogene) versus placebo. They looked at 15 subjects, so a small study. They reported 50% of them [00:02.00.00] responded to the drug whereas 25% responded to placebo. So, you know, it's a small study but preliminary evidence that these agents may very well be effective for PTSD. As I said, a number of ongoing trials going with—I know with Depakote, our own and a couple of other places looking at (topyramate). [00:02.20.00] So, in the next few years we should have a lot more information about these agents. In addition to their effects that I've already stated at least a couple of them have additional effects that often clinically become useful to try to kill two birds with one stone, if you will. Gabapentin [00:02.40.00] there is double blind randomized trial that it is an effective agent in treating neuropathic pain. So if you have patient with impulsive anger or anxiety and neuropathic pain you may be able to, you know, kill two clinical birds with one drug, which again decreasing polypharmacy. Likewise valproic acid has been shown [00:03.00.00] in the double blind manner, in randomized trials, has FDA approval for preventing migraines. Again you may be able to combine those uses. Okay, the next class of agents are the hypnotics, so agents used to the treatment of insomnia which certainly in our male veteran [00:03.20.00] combat population is extremely high. Some of them say that, you know, this is the primary—if you treat this symptom then you're going to do—you'll have a great improvement. Trizadone is our first line agent in that it's being a sedating

antidepressant that's non addicting [00:03.40.00] and effective for the majority of patients. Fourth class are the (anxiolytics). What I'm talking about here are the benzodiazepines primarily that have been used to treat, you know, since the 1960s for treating generalized anxiety, panic, other anxiety symptoms. [00:04.00.00] When you look at the data in PTSD there were—there's three reports that I've been able to find. One in 1990, a very small, crossover designed study. What the means is that at one phase in the study you're on placebo and in another you're on drug. You don't which [00:04.20.00] or at what time. It's a way of kind of maximizing your patients. It can only work for a drug that wears off after a period of time. You couldn't do it with the antidepressants. So, anyway crossover design. They showed modest improvement in anxiety symptoms. The patients said, "Yeah, I'm feeling better," but their PTSD symptoms remained the same. [00:04.40.00] A study in 1996 asked the interesting question—and I think we're going to have studies like this coming out in the next few years—and they were looking at the preventive ability of a benzodiazepine. This was just a naturalistic study though. They looked at 13 trauma survivors—I think these were burn [00:05.00.00] victims, but I'm not sure—matched them up with 13 other trauma survivors who were not getting benzodiazepine. And then they looked at them later on. So, the question being if you were on either clonazepam or (prazelam) for a period of time, you know, did this affect your chances of getting PTSD. [00:05.20.00] And from this small study they would say no, it did not. A similar study was presented in a poster—I haven't seen this published yet—but with 21 subjects looking at temazepam versus placebo. Similar—okay you treat them acutely and these were burn victims I believe. You look at them for—[00:05.40.00] you treat them for a period of time. They looked at sleep and they looked at PTSD symptoms after they were off the drug. No difference whether or not you're on placebo or benzo. So, you know benzos are probably useful for treating clinically significant anxiety acutely but they probably don't prevent, based on this data, PTSD in the future. [00:06.00.00] The fifth class of agents are a bit more on the theoretical end. And if they work it will be interesting because they're actually based on, you know, a hypothesis. And that are agents that affect (neuroangeneurgic) neurons. [00:06.20.00] Either through blocking their effect, blocking the receptors—those would be the beta antagonists or the alpha 1 antagonist that block the actual affects of the noreprinephrine—or by shutting down or slowing down the activity of the neuron—and that would be the alpha 2 (agonist). So, they all kind of potentially have a similar [00:06.40.00] effect. And the idea here has been—this is an old one—that noreprinephrine neurons may be altered in PTSD. In fact I saw reports going back to the Civil War that they were talking about this even though they really didn't know what was going on at this point. A report from I think it was 1910 in which they were actually looking at [00:07.00.00] administering epinephrine to patients with war trauma. This shows my basic research bias, this is actually a rat brain. But the idea being here these are noreprinephrine neurons. They're interesting in that there's a small number of neurons can go from the base of the brain, a compact area called the (locus arealious) and they project up to a wide area, have lot of [00:07.20.00] effects. They have effects on attention, mood, concentration we think. We know a lot about them from rats because you can stick an electrode right there and measure them because they're in a compact area. Anyway, because they're involved in stress we thought—there's been a

lot of thinking that maybe they're altered in PTSD. This was a study from last year, for instance, in which [00:07.40.00] the researchers were looking at, just measuring the noreprinephrine in the CSF around the brain. These were combat veterans or control subjects and these were highly controlled patients off drugs in a clinical research unit. And what they found were the patients with PTSD had higher levels of noreprinephrine in the [00:08.00.00] CSF than the patients that did not. Now, so there is interest of maybe if you attenuate this effect or block it could you treat some of the symptoms? I've already gone over the classes of these agents but the alpha 2 agonist, the ones that would shut down the neurons, would be [8:18] and [8:19]. [00:08.20.00] Beta blocker [8:22] being one that gets into the CSF. And that should be an alpha one antagonist, not an alpha 2 antagonist but (crezasine) would be an example of that. So, we're looking at whether or not by inhibiting neuronanergic output you start affecting possibly [00:08.40.00] the hyperarousal symptoms in PTSD. Also, question about whether or not you could prevent PTSD from happening, that by administering a beta blocker for instance could you prevent the progression after a trauma to PTSD. And I know there's a double blind trial that's going on [00:09.00.00] looking at this question. All that being said, we actually don't have any randomized data. We're participating in two studies, one with (guanfasine), one with (clonadine). And I know there's a couple of others going on. So, in the next few years we should have data. These are all generic drugs [00:09.20.00] at this point too so they're not getting funded by drug companies but by researchers. And then finally there was some question about whether or not—there's some evidence that maybe one of these drug, (prazasine) in particular, some researchers up in Seattle had discovered clinically that it seemed to affecting [00:09.40.00] nightmares. They did recently—this is a very small double blind trial in another crossover design in which they showed improvement when patients were on (prazasine) in their dream item on the CAP score [00:10.00.00] but not when on placebo. Overall, their clinical global impression they said they were moderately improved when they were on drug but not when they were on placebo. Again, these were veterans with PTSD. So, they're following this up I believe with a large, larger double blind trial. So, moving on then, sixth class of agent. [00:10.20.00] Again, this one not being specific to PTSD. But possible uses include substance abuse disorders, alcohol and other substance abuse disorders and self-mutilation behaviors that can occur in PTSD. And these are the (opiate antagonists), naltrexone being the primary [00:10.40.00] one. Which has been shown, again, in a double blind randomized fashion to be effective for decreasing alcohol urges and decreasing the chance of relapsing. Likewise, the seventh one on the list (disulfaram) [00:11.00.00] or (antibuse) is still around. We still use it within our residential program often—often from the patients. The patients know more about this and they're the ones that come forward to us and say, "You know I would really like to give this a try." For those of you who don't know (antibuse) is a drug that blocks one step in the metabolism of alcohol. And what you get [00:11.20.00] if you take alcohol is you get an accumulation of a toxic metabolite, causes people to feel sick and they throw up and they have hypertension and headaches. And for most people it can be pretty noxious. Some people of course can take the full dose and drink on (antibuse), so—[00:11.40.00] and then obviously you have to be motivated or it's not going to work. But I think it still does have a use particularly when patients are coming out of residential programs like ours at

least to give them a little bit of a crutch, if you will, for the acute phases of abstinence. [00:12.00.00] Okay, the final class of drugs that I'm going to talk about are the antipsychotics. Their proposed mechanism of action includes delusional guilt or paranoia. So, the delusional symptoms that I referred to earlier that can occur in a subset of patients with PTSD. [00:12.20.00] Micropsychosis, what I mean—you know it's a term that I pulled from the borderline personality literature and that this refers to when certain patient, [12:28] patients or patients who have been, you know, likewise traumatized and have (characterlogical) disturbances under severe stress break down, they lose touch with reality. They start to become delusional, you know, start accusing [00:12.40.00] the staff of doing things that goes beyond rational thinking. Antipsychotics, the older ones particularly, have been shown to be effective for that in the past. And then there's been proposed uses for antipsychcotics for treating impulsive anger and nightmares. Representatives of these agents that we're talking [00:13.00.00] about here for those who don't know, (Haldol) being kind of one of the typical older antipsychotics and then (resperadone, patiapene and lamanzepene) being the class of the newer atypical antipsychotics. Now from—and they all work through one—[00:13.20.00] to one degree or another by affecting the neurotransmission of dopamine in various parts of the brain, the atypical ones in a somewhat more selective manner. Now from talking to our Vietnam veterans these agents seem to have been overused in the past, at least by patient report. That a lot of people say, you know, they were shoved full of thorazine and tried to kept [00:13.40.00] quiet in certain settings. And there was a lot of resistance to this. Actually, I just ran into somebody this weekend at a booth someplace who was going on and on about this and why he would never return to the VA because this was his experience in the past. You know, whether that's true or not [00:14.00.00] I don't really know. But anyway, that being said, these atypical agents are different in the fact that they have a lot less in the way of side effects. You can use them—most of the proposed uses that we're talking about here are at small doses that can affect what I've already gone through effectively, [14:19] impulsive anger, [00:14.20.00] comorbid psychotic thinking as well as possibly, again, some of the (characterological) symptoms associated with severe dissociation, flashbacks or micropsychoses as well as severe insomnia and nightmares that are refractory to our other attempts. You know the patient not responding to (trazadone [00:14.40.00] or denadryl) sometimes. And they're having nightmares and they're getting up at night and they're agitated, (desperadone) can be—seems to be a good agent. Now, that being said, to date there's no published double blind data. I did see a reference to a (resperadone) trial that I believe was done in veterans in North Carolina [00:15.00.00] but I've never seen that published yet. It did show efficacy of (resperadone). I know there are people who have done a number of open label trials (showing infact). But I was just asking around recently and I don't know of any ongoing double blind trials but hopefully there will be in the future, shortly in the future. Okay. So, those are the eight classes of medications. [00:15.20.00] Now, moving into the last section here in our remaining time in the lecture would be my recommendations. Well, you could probably guess this one yourself based on the data that we have now that the SSRIs would be you know your first line of treatment. That's what we have the most data on. [00:15.40.00] We know that these work. So, and I would again based on my bias that I think some of what—my bias that I think that if

veterans were not responding in these studies it was probably due to this compensation issue, in which case you would want to still try this. I mean you would still want this to be your first agent. They tend to have less [00:16.00.00] in the way of side effects, sexual dysfunction being probably the biggest problem. That can be a problem in our male population as well but anyway they're still probably the first way to go. If patients don't respond to those, it probably makes most sense, just like in depression, to switch to another class of antidepressant rather than stay with it [00:16.20.00] —another SSRI unless you have a reason to. You know, so theoretically you're working on different neurotransmitters or different processes so that would be probably the way you'd want to go. Okay. (Trazidone) like we do in depression, so adding (trazidone) for insomnia, I've already referred to that. We talked about the mood stabilizers [00:16.40.00] for impulsive anger and [16:42]. Now, again, we really don't have the data done about that yet. I guess I'll just mention in passing there was a large multicenter study that was done with trying to measure impulsive anger and the effects of valproic acid. But unfortunately it's not the easiest thing to measure, particularly in outpatients, [00:17.00.00] trying to figure out how do you measure impulsive anger? So, it didn't work too well because of that I think. Okay. Again although there's hopefully we'll have some data in the next couple of years if patients are not responding to these other agents and they have a lot of hyperarousal or [00:17.20.00] anxiety symptoms it's probably still worth a try to look at these, you know, (adrenergic) agents like the alpha 2 agonist pro refractory symptoms. I mentioned [17:33] for acute anxiety and I'm thinking more of, you know, shortly after a trauma. But again, every now and then they may be necessary for [00:17.40.00] severe refractory symptoms, particularly in patients with a high suicide potential. You know, we shouldn't—just because they're potentially addicting and have problems with short term memory we shouldn't totally restrict them. [00:18.00.00] Addition of (gabapentin) when neuropathic pain is also an issue, it would probably make sense. Now I know the VA probably has a different view on this because (gabapentin) is being prescribed at a phenomenal rate at the VA last time I looked. And there actually isn't any data yet that it works, as I just said, in any psychiatric disorder [00:18.20.00] and yet we're prescribing it at a phenomenal rate. And it's not a cheap drug, so. But that being the case we do know it works for neuropathic pain. So, again it's the idea of killing two birds with one stone, makes sense. We talked about the treatment for alcohol dependence or abuse. [00:18.40.00] Buproprion or Welbutrin I did not mention. But as most of you know its been shown to be effective for the treatment of nicotine addiction, when sold in the name of (Ziban). Therefore, when patients are making—wanting to stop smoking and they're on an antidepressant it often makes sense then to try—[00:19.00.00] again, killing two birds with one stone. You can get them stabilized on buproprion instead of the SSRI that they're on and help their nicotine addiction at the same time. And finally, I mentioned a low dose atypical antipsychotics for either delusional symptoms [00:19.20.00] or these refractory impulsive anger [19:23] symptoms. Okay, we did not nor do we have much time to talk about the combination of psychotherapy and pharmacology. As I said, there's only been 15, you know, 16 studies of any drug treatment in PTSD so [00:19.40.00] we have not got to the level yet of trying to look at the combination of psychotherapy and pharmacotherapy. But from what we know from depression where there's been a recent study showing an additive effect of

antidepressant and CVT treatment that you would expect that there would [00:20.00.00] be a similar additive effect in PTSD as well. Future treatments, just in passing I mentioned treatment for acute trauma a lot of people talking about this idea can you prevent the development of PTSD by a drug therapy. I believe that there are a number [00:20.20.00] of naturalistic studies that are being done post 9/11 in New York in which they're trying to see, you know, depending what patients got for medication-wise was there any difference in whether they get PTSD or not. It's not the best—it won't be the most definitive but it could provide some evidence along this way. [00:20.40.00] I didn't talk about—I mention this (glutacortacoid) stuff there that refers to cortisol which is a stress hormone that can affect central nervous system function. The idea being that too much of it for a prolonged period of time may have adverse affects so if you could partially block this effect [00:21.00.00] during a trauma maybe you could prevent some of the changes in brain function. I mentioned the CRF antagonists, for instance. I'm just giving that as an example of these, you know, neuropeptides that we know about that we've just started to developing drugs for. And then finally that the majority of neuromodulators, when we look at genes being expressed [00:21.20.00] in the brain we can take a good guess at them. The majority of the things we haven't even—we haven't identified yet. So we, we don't even know what they are yet so we haven't developed a drug against them yet, so—interacting with them yet. So, there definitely is a lot of room for investigating different types of agents in the future that may be effective [00:21.40.00] for psychiatry in general and PTSD in particular. With that I'd like to open it up for questions and that includes questions from our TV audience out there. Apparently, if you look on your screen you can see the number that you're supposed to phone into.

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