Psychopharmacology and PTSD 3
Written Video Transcript

Okay. So that's it on the neurochemical review. Now, moving on to the heart of the talk and that is the evidence for the what works and doesn't work in the treatment of PTSD. Before I go into that though I'm just going to give [00:00.20.00] a few bits of information about an overview about pharmacological treatment of PTSD. And despite what I said in the beginning of the talk we're still kind of at the—getting the basic information here. There's definitely less objective information available for PTSD than for other psychiatric disorders. There's approximately 15 or 16 [00:00.40.00] published double blind randomized trials of any agent in the literature over history. So, we're talking of actually a fairly small number of trials. And therefore some of what we still know is based on other disorders. And therefore we're often using co-morbid symptoms as the [00:01.00.00] target of our treatment. So, again, if the patient has panic disorder we're often focusing on the panic as the primary target of our treatment. Because each patient, as you've learned through this series, has a variable collection of these symptoms and co-morbid disorders the treatment can be very individualized. So, one patient's [00:01.20.00] treatment may be very different from the next patient's treatment. And sometimes multiple medications or polypharmacy is necessary but is should always be minimized. A lot of what we do within our residential program is take the opportunity of residential treatment to take people off medications [00:01.40.00] rather than put them on new ones. We're often, more often, simplifying than adding medications. The classes of agents, starting with the one that we know the most about, that's the antidepressants. Okay, this is in that same web site that I showed you before [00:02.00.00] again showing an axon terminal, neurotransmitters being released and a postsynaptic cell. What this is supposed to be showing, you actually have to look at it for a little while, is what happens when you give antidepressant that's either blocking reuptake of the neurotransmitter or inhibiting metabolism. And what you end up with is [00:02.20.00] more neurotransmitter out in that synapse for a longer period of time. So, it has a longer—a better ability to interact with the post-synaptic cell. Okay and this is the first, probably just the first step in line of how these drugs work. But it's the one that we know, you know, we know is the first step. [00:02.40.00] Now, the first drugs in this class to be discovered were the tricyclid antidepressants and then the (monomine oxidase) inhibitors. The tricyclids work by blocking either serotonin or noreprinephrine or a little bit of both. (Monoamine oxidation) inhibitors [00:03.00.00] inhibit the metabolism of serotonin, noreprinephrine and dopamine. And these were developed in the '50s and '60s. As far as PTSD concerned now the reports date back, the first one being in 1988. So again, a fairly long (way) from when we knew these medications were working until it [00:03.20.00] was applied to PTSD. There's three controlled trials using the tricyclids and four with (monoamine oxidation) inhibitor. One of those trials actually uses both so there's actually a total of six trials. So, one was comparing a tricyclid with MAO1. [00:03.40.00] The summary, I'm not going to go over those, that's the old news. But the summary of those

was that they were mostly small studies. Overall, you could probably they were showing efficacy for these agents. These were mainly in combat veterans with PTSD that these studies were done. And there was one study that suggested that [00:04.00.00] the (MAO1) inhibitor was actually better than the tricyclid. Those types of studies actually normally don't get done, so it's—comparisons like that—so that's a little bit of interesting data. But these medications is mostly (don't) have a lot of side effects. They're very dangerous in overdose so, you know, they're definitely not our first (line of) treatment any more. [00:04.20.00] So, where the bulk of the research has been done to date is with the selective serotonin reuptake inhibitors. Now, these were, you know, working through a very similar mechanism as these older agents, like the tricyclids. [00:04.40.00] Basically they're cleaner, they have a lot less in the way of other effects on the brain, in the body. So, they have a lot less side affects, much better tolerated. The drugs I'm talking about are, you know, (sertrilene) or Zoloft, Fluoxitine or Prozac, Proxitene or Paxil, Flumoximine or Luvox [00:05.00.00] and [5:00] or Selexa. As I said they already have less in the way of side effects. You know, for a variety of reasons one in which some of these patents are running out on these drugs, the pharmacological companies turn their interests towards PTSD but to the benefit of us because they can fund these multimillion dollar huge studies that an individual [00:05.20.00] investigator never could. So, the trouble is that we don't always see the data for all of them which is what I'll describe in a second actually. So. in the literature there are published double blind trials now with Prozac, Zoloft and Paxil. And I'll go over those now in that order. For [00:05.40.00] Floroxitene there are three double blind trials. Actually there's three reports, there are two trials one of which was published in two separate reports which I'll describe in a second. The first one was in 1994, (Vander Colpin), co workers, 64 subjects, 22, men, 42 women. There were 31 veterans [00:06.00.00] and 33 non-veterans. This was a five week randomized double blind trial. And what they found was Floximine, Prozac was better than placebo. In fact, it showed a significant reduction in PTSD symptoms by the criteria whereas placebo did not. But one piece of data was that the [00:06.20.00] VA patients responded better—the non-VA patients responded better than the VA patients. As a matter of fact, the VA patients did not have a statistical, you know, improvement with Prozac. Okay, and I'll get back to that point here in a few minutes because we have some more data that's along that line. [00:06.40.00] The next study, now we're jumping up to 1999, (Connor) and co-workers, there were 54 subjects at the beginning of this study with 36 at the end. There was more dropout of the patients on placebo than the drug which is kind of what you would like to see if you're trying to show these drugs work. [00:07.00.00] And the data shown here, so the white bars are placebo, the black bars are the Prozac and what you have here on the Y-axis is the percentage of patients that met the criteria are very much improved. This is just using what's known as a clinician global assessment scale. Basically it's what it sounds like, [00:07.20.00] they're either slightly better, much better or very much better. So, we're saying that these patients are very much better. And what you can see is at four weeks, eight weeks and 12 weeks there was a statistically greater percentage of patients who met this criteria on Prozac than on the placebo, with at [00:07.40.00] the end 59% of the patients met this criteria on Prozac with 19% meeting that criteria on placebo. So, pretty strong evidence from a small study that Prozac was probably helpful in this population

with PTSD. Like I said [00:08.00.00] this—I think I've already mentioned this—this is mostly in female patients, outpatients, in which the study was done. Now the same researchers did a parallel study, the same design, that they published the year after. Had a very small number but 12 veterans [00:08.20.00] that they ran through the same design and reported that there was no significant difference, there was no significant effect. Actually I think it was both the placebo and the Floximine that the veterans did not show the same level of improvement and they certainly did not show the difference between drug treatment and placebo treatment. Again, I'll get back to that again in a few minutes [00:08.40.00] because there's yet one other piece of data that's consistent with that, that I think we should discuss and that is with (the Certraline) trials. Now, (Certraline) apparently made a concerted effort that they were going to be the first ones to get the FDA approval for PTSD because they went all out. They had four very large randomized [00:09.00.00] double blind trials that they did kind of one—actually parallel a couple of them. I think they were all done more or less at the same time. Very similar design in these studies. Two of them showed efficacy, two did not as I'll describe in a few minutes. The two that did are the two that we have the data for that have [00:09.20.00] been published recently that I'll show in a minute. If you look at those two trials 76% of the patients were female with a mean duration of symptoms of 12 years. So, you know, it's pretty—this is chronic PTSD. Forty four percent of them met the criteria for a secondary depressive disorder. [00:09.40.00] The first trial there was published [9:44] wrote this up a few months ago. It was published which is showing here on the Y axis there's a mean change in the CAP scores. I think they started out like around a 75 and you see natural drop in points over the [00:10.00.00] 12 weeks of the study. The orange line are the placebo patients. The blue lines are the (Certraline) patients. And as you can see there was a significantly greater change, decrease in the severity of their PTSD symptoms with the (Certraline) than with the placebo. Now, [00:10.20.00] any questions about this or this design because this is kind of what you're going to see a lot more of this here. Yeah.

[10:28] of the dose?

(Up) the dose, actually I should—I think it would be—both of these were flexible dose studies. So, they went [00:10.40.00] between 50 and 200 milligrams a day. And the mean dose was greater than—it was like 175 or something. So, most of the patients got pretty much the maximum dose. Okay. This is a second parallel study that was published in a [00:11.00.00] separate publication and this data is presented a little bit differently. This is with a statistical probability of response plot, statistical correction method that you can use to look at what was your percentage—what was your probability at a given point in time if you're in this study of getting better. Okay, they set up a criteria [00:11.20.00] of so much, I think it was 30% improvement in your CAP scores. And what you can see is that at all time points you had a much better chance of getting better if you were on the drug than if you were on placebo. So, both of these studies pretty strong—strong enough that the FDA which was I understand [00:11.40.00] it was somewhat skeptical that they went ahead and gave approval for (Certraline) for PTSD. They were skeptical because they hadn't actually proved that the wasn't just an

antidepressant effect, which they did. If you take out the depressed patients, the non-depressed patients had just as much improvement with the drug. Okay, as I said, [00:12.00.00] there were four studies. I've been hearing about this data, I didn't really know a great way to get at it. So, I went onto the FDA web site, searched around and sure enough I found the PowerPoint presentation by the drug company that they presented to the panel for the approval of (Certraline) and got the slide [00:12.20.00] off that web site. It's kind of the things that you kind of have to go through when these studies don't get published. So, as I said, there were four studies, they're just numbered differently. And they were fairly identical except for 641 was mainly—and it was done at the VA for the most part. I think it was all the VA with 71% of the patients being combat veterans. [00:12.40.00] As you expect if you look at the gender ratios, those are flipped when it comes to the VA population with more, you know, much more men than women. The mean age is a little bit higher. The mean duration of the PTSD is a bit higher, from 12 years to 18 in their VA population. [00:13.00.00] Other than that the design was similar. Now, I know this slides a little bit difficult to see but these are the four studies. If you just look at the top row there these are the CAP scores, the 641 again is a VA study. And what you can see is that not only was there not a difference between placebo and drug [00:13.20.00] in the VA study but there seemed to be a less of a response overall, less change in their CAP scores than in the two studies that showed efficacy. The third study that did not show efficacy basically they—the patients seemed to respond but they responded as well to the placebo as to drug. [00:13.40.00] So, at this point I'd like to ask you as practitioners of the VA for your ideas as to maybe what could be going on here. If this data, now we've seen you know three different trials that have all indicated that maybe veterans are not responding as well to these SSRIs, what do you think the difference could be?

[End of audio]