PTSD 101
www.ncptsd.va.gov/ptsd101/

COURSE TRANSCRIPT FOR:
Neurobiology & Pharmacotherapy for PTSD
Course Instructor: Matthew Friedman, M.D., Ph.D.

Slide 1: Neurobiology and Pharmacotherapy for PTSD

Hello. My name is Matt Friedman. I'm the Executive Director of the National Center for PTSD and I'm going to talk about pharmacotherapy for PTSD.

Slide 2: The Stress System

So, the 1st slide shows, basically, a brief narrative about the stress system, which is really the biological context in which we can understand both the pathophysiology of PTSD and the target sites for any of the medications that I'm going to discuss in the course of this discussion. Basically, the stress system is a marvelous system that has developed through evolution, and it really has evolved for survival of the species, and I think for that reason, it's very complicated. It has many, many different brain centers, both cortical and subcortical, and many different neurotransmitters and neuromodulators and/or peptides and/or hormones that play a role. The main components of the stress system are the hormonal part of that, which is the HPA system, or hypothalamic-pituitary-adrenocortical system, which is activated by corticotropin-releasing hormone or CRF, as I'll refer to it during the course of this lecture. And as I'll show, CRF also activates the noradrenergic component, the locus coeruleus-norepinephrine sympathetic nervous system action. There's a third important part of the stress system that we won't be discussing today, although maybe some time in the future we will, and that is the immunological system, which is also activated during moments of stress and is activated by CRF, and I think that the mobilization of the immunological system is one reason why PTSD is a risk factor for medical problems. But that is a subject for another talk.

Slide 3: Central and Peripheral Components of the Stress System

The next slide basically begins to show you what the stress system looks like. You'll see on the left-hand side something that says "CRH". That is corticotropin-releasing hormone. CRH and CRF are the same thing and I generally use the term CRF. But as you can see, on the left part of the slide, you can see the hormonal aspect that CRH, as it says in the slide, which is produced in the hypothalamus; look at the arrow that goes directly below that, releases ACTH from the pituitary gland and ACTH, which is adrenocorticotrophic hormone, then releases a glucocorticoid, particularly cortisol, from the adrenal cortex. And as you can see, those dotted lines are a negative-feedback loop so that when a sufficient amount of glucocorticoid is produced

it turns off the release of CRH. Now, in PTSD this system is altered. It is functioning at an abnormal level. Now also, if you look again back at the CRH blue ball, which basically is the hypothalamus amygdala, you can see that there is a direct line over to the right-hand side of the slide that says LCNC, which stands for the locus coeruleus noradrenergic system-the sympathetic nervous system. And one of the marvelous design features of the stress system is that CRH acts both as a hormone, releasing ACTH and cortisol on the one hand, and as a neurotransmitter, releasing norepinephrine from the locus coeruleus on the other hand, the locus coeruleus being that part of the brain that contains most of the noradrenergic neurons. Those neurons go downstream to the sympathetic nervous system and upstream to the many key brain structures, such as mesocortical, mesolimbic systems, as well as subcortical systems such as the amygdala hippocampus, etc. And in the middle of all of these arrows you can see a bunch of different neurotransmitters are mentioned: serotonin, acetylcholine, GABA-benzodiazepine, dynorphin, which is an opiate, etc. So there are many, many different neurotransmitters that are involved in this system.

Slide 4: (no title)

Now the next slide is a simplified version, and you can see on the left part the HPA system; hypothalamus-pituitary-adrenocortical system, producing CRH, ACTH and on the right side the locus coeruleus having noradrenergic neurons. But the main point of the slide is in the upper part, towards the left part of the slide to show you the main brain nuclei involved in the stress system. You can see the amygdala, which is that part of the brain that is developed to process emotional information, threatening information, dangerous information, and the amygdala is activated during traumatic exposure. The hippocampus, which is right next door to the amygdala in the limbic system is that part of the brain that will remember the context, the memory of the context in which a threat, the traumatic situation—you know in prehistoric times where the saber tooth tiger was--so you'll remember not to go to that place again. Now, to the upper left-hand corner you'll see something that's says orbitofrontal inhibition of the amygdala mediates extinction. What this connotes is that the only major way that the amygdala can be brought under control; because in PTSD the amygdala is in hyper drive. It is dysregulated. It is activated to an excessive amount, and that's a major part of the problem. It's the prefrontal cortex-orbitofrontal cortex-all of those structures, anterior cingulate, that are the major part of the brain that can reign in the amygdala. Indeed, cognitive behavioral therapy and other psychotherapies that only are mediated through cortical neurons-the route, by which the can get to the amygdala, is through the prefrontal cortex. So that's a very important part of the circuitry.

Slide 5: (no title)

The next slide is really more of the same, only it emphasizes the more adrenergic part. You can see the locus coeruleus, which as I said earlier, has 2/3 of the noradrenergic neurons. And you can see that it has synapses that go all over the place, particularly to the amygdala, hippocampus, hypothalamus, etc.

Slide 6: HPA/Norepinephrine Pathway

The next slide focuses more on the relationships between the locus coeruleus and the amygdala, and you can see that there are reciprocal interactions. So, whereas the amygdala is basically the ignition switch for the stress response and it goes to the hypothalamus to get CRF involved in both activating noradrenergic neurons from the locus coeruleus and releasing ACTH from the pituitary gland. But part of the purpose of this slide is to show you the various reciprocal relationships of this system. Again, this is on oversimplification, but the bottom line is what you would expect from all that I've shown you so far, is that norepinephrine is a key part of the problem and that there's excessive norepinephrine and that the HPA system is dysregulated as well.

Slide 7: Norepinephrine and PTSD

Now, you know, we have to recognize that, as with any dose response group, whether it's substances that are produced endogenously by the brain or substances that are administered pharmacologically, is that there is an effective dose and there is a toxic dose, and there is also an inadequate dose. So, on the left-hand side, basically what I'm showing you is that you need norepinephrine to survive. The "Fight-flight or freeze response", first described by Walter Cannon in the early part of the 20th century is essentially a sympathetic activation, where mobilizing norepinephrine during dangerous, threatening situations enables you to run to safety, to protect yourself, to have the emotional signal of fear telling you that there's something that you better pay attention to, and consolidating the memory of those events so that you're not going to repeat dangerous behaviors in the future. And that's all adaptive. So we need norepinephrine to survive-to function. But when there's too much norepinephrine that is in play, as the right-hand column shows, you can see that what is an adaptive response becomes maladaptive: The hypervigilance, the autonomic arousal, exaggerated startle response-even flashbacks, which can be produced by increasing noradrenergic activity as well as the intrusive memories. So, the point of the slide is to indicate that, in PTSD, an adaptive response is excessively produced and that is maladaptive. Another piece of this-and it's important in terms of PTSD, is that what may be adaptive for survival, for example hypervigilance-anyone who's returned from Iraq will tell you that you need to be hypervigilant in order to be able to protect yourself and function in a combat zone. But when you're in a safe situation and you're still hypervigilant that's not adaptive, and that's part of the problem that we have in PTSD, and part of that is related to excessive noradrenergic activity.

Slide 8: Serotonin Pathways

Now the next slide shows you some of the serotonergic pathways. So serotonin is an important piece of the puzzle as well, and if you look at the bottom part of this slide, you'll see two little yellow boxes; one says "MR" and one says "DR." That's the median rafae and the dorsal rafae nuclei, which are the parts of the brain where most of the serotonergic neurons live. The point of the slide is, number 1, to show you that these neurons, like the adrenergic neurons emanating from the locus coeruleus, have many, many connections all over the brain, effecting subcortical limbic structures, such as the amygdala, the hippocampus, and also going into the association cortex, etc. Also, there is a direct relationship between serotonin and the yellow ball-the locus coeruleus and adrenergic neurons.

Slide 9: Serotonin and PTSD

As the next slide will show you, whereas we have probably too much norepinephrine in PTSD, we don't seem to have enough serotonin. So, again, the left-hand part of the slide shows you the adaptive types of serotonergic actions that are put in play during stressful or threatening situations: fighting response, aggressive retaliations, self-defense, etc. But again, when there is a deficiency of serotonin, you can see on the right-hand side that people with deficient serotonin may be suicidal, impulsive, aggressive, and violent. They may be depressed, and they may have anxiety and panic. And to kind of anticipate where some of this is going to go is-that's why medications that increase serotonergic activity such as selective serotonin reuptake inhibitors; the SSRIs, are useful, not just in PTSD, but in other panic disorders and in depression.

Slide 10: Summary of Findings in HPA and Monoamine Dysfunction in PTSD

So the next slide is basically a summary of findings regarding HPA dysfunction and monoamine dysfunction. So that one the things that we see in PTSD is that there's too much CRF, and that leads to alterations in the amount of cortisol that's available; too much norepinephrine, so there's increased noradrenergic tone; too little serotonin; and something else that I won't be talking about today, is that there seems to be a neurodegenerative aspect. Too much stress can produce neuronal death or dendritic defoliation, and that may be an important reason why we see reduced hippocampic volume and other reductions in volume of key brain structures such as the anterior cingulate, and in kids the corpus callosum, in PTSD. But we won't be talking about that very much. But it's probably a good place to mention that almost all of the medications that are useful-all effective antidepressants, and most of the medications that work in PTSD are antidepressants, in addition to whatever they're doing at the synapse-adrenergic, or serotonergic, or dopanergic, or what-have-you synapses-they also produce neurogenesis. In other words, they promote the development of new brain cells, and there's one study that people with PTSD were treated with the SSRI Paxil, paroxetine, for about nine months and in addition to their symptoms getting better, their hippocampus increased in volume, again proving the neuroregenerative aspects of some of these medications. This is an important area for future research and some of our National Center scientists, such as Ronald Dumann at our Clinical Neuroscience Division, are doing ground-breaking research in this area.

Slide 11: Monoamines and Amino Acid Neurotransmitters

Now, the next slide basically points out that, you know, most of you are probably familiar with, you've probably heard about norepinephrine and serotonin, and dopamine, etc., because we know a lot more about them because we've been able to measure them in the brain for many decades. But actually they are really mostly modulators. They are relatively slow to act, and the real action are the fast-acting amino acid neurotransmitters: gamma-aminobutyric acid, or GABA, which is the major inhibitory transmitter in the brain, and glutamate, which is the major excitatory neurotransmitter in the brain. We'll be talking a great deal about these. This is really, I think, where the cutting edge research is going on because a number of medications, particularly what we call anticonvulsants or mood stabilizers now either potentiate GABA or diminish glutamate. And I'll discuss this at much greater length as we move forward. It's important to emphasize that no medication-no drug does anything by itself. All a drug can do is

either potentiate a normal activity or prevent it by blocking its actions. And so, in the case of PTSD, we want to basically increase GABA and reduce glutamate types of actions.

Slide 12: GABA and Glutamate Homeostasis

This next slide, which basically shows the yin and yang of fast-acting neurotransmitters--glutamate in red, as I said earlier, is the major activating neurotransmitter and GABA the major inhibitory neurotransmitter, and in normal brain function these two neurotransmitters are in a very good balance. And again, another remarkable design feature is that it's very, very easy to convert one to the other again for rapid change if that balance needs to be corrected.

Slide 13: GABA

So as I said earlier, GABA is the major central nervous system inhibitory transmitter, and it acts at a ligand-gated chloride channel. And benzodiazepines, which I'm sure you're all familiar with, act at the GABA-A receptor. There are also GABA-B receptors and GABA-C receptors that I will not be talking about. I'll be talking mostly about actions at GABA-A receptors today because that's where most of the information is and that's where most of the medications in practice are.

Slide 14: Glutamate

On the next slide is basically, it talks about glutamate, which as I said earlier is the major CNS excitatory neurotransmitter. There are many different kinds of glutamate receptors. There are the ionotropic receptors which basically act at ion channels where both calcium and sodium are involved. And then there are the metabotropic receptors which act through G-protein and other second messengers. I'm going to talk mostly about ionotropic receptors and the most remarkable of these is the NMDA receptor, which stands for N-methyl d-aspartate, and the NMDA receptors are the receptors that mediate learning and extinction. You can actually see under an electron microscope alterations at the NMDA receptor site, in terms of little growths, as learning takes place. Since fear conditioning is a major theory about PTSD, the NMDA receptor is extremely important. There's also evidence that NMDA receptors are important for regeneration of neurons. And as I said earlier, I think that regeneration of neurons is a very, very important aspect of the effectiveness of a number of different medications. And finally, the NMDA receptor also mediates sensitization. Another important model of PTSD is that the, particularly the limbic nuclei, the amygdala and associated areas, become sensitized to traumatic reminders and activating those receptors, those neurons by traumatic reminders can set off a PTSD relapse. Well that is also mediated by NMDA receptors and a number of anticonvulsant/mood stabilizer medications act to inhibit those mechanisms.

Slide 15: GABA and PTSD

So the next slide is sort of like some of the previous ones on serotonin and norepinephrine, basically talking about GABA and PTSD. And as with serotonin, the problem here seems to be not enough GABA for appropriate balance. So again on the left-hand side, GABA is the bodies own anxiolytic if you will. It's involved in neuromodulation, mediates cognition, hormonal

modulation, and actually can oppose the release of CRF. But, too little GABA, as with too little serotonin, is associated with anxiety, re-experiencing "kindling", and kindling is another form of sensitization. Too little GABA can promote sensitization and that is not necessarily a good thing, impulsivity, hyper arousal.

Slide 16: GABA in HPA-Mediated Fear Responses

So the next slide talks about…basically elaborates on what I just said, in that GABA can inhibit CRF release, and there is too much CRF in the brains of people with PTSD. Too much CRF will activate the stress system, as I said earlier. Too little GABA will permit that to happen, and so that what happens in acute stress is that the inhibitory action of GABA is sometimes compromised so that CRF, adrenergic activity, etc., are unopposed. There are a number of medications: Divalproex, which is a mood stabilizer, and benzodiazepines, which are anxiolytics. Both of these can inhibit stress-induced cortisol secretion in humans. And remember, cortisol is the hormonal result of the CRF activating ACTH activating the adrenal cortex. And that benzodiazepine Alprazolam reduces brain CRF. So, basically the argument that I'm making is that we think that the balances are too much norepinephrine, maybe too much glutamate, maybe too much dopamine, maybe too little serotonin, and too little GABA.

Slide 17: Sensory Information About Harmful Stimuli

Now the next slide basically is looking at the amygdala with a higher power and to show you where we think 3 different types of medications might be effective. What the slide shows is, coming from the top there is stressful information, in this particular slide it happens to be auditory information-could be a saber tooth tiger roaring, or an AK-47 firing, or somebody screaming , anyway…auditory information that is emblematic of a dangerous situation. That information goes to the lateral nucleus of the amygdala, which is the sensory area of the amygdala, and as you can see on the left, the lateral nucleus communicates with the central nucleus of the amygdala through a glutamate receptor. So the glutamatergic neuron is basically the conduit through which this frightening information is transmitted to the central nucleus of the amygdala, and the central nucleus of the amygdala really is the part of the amygdala that gets things going. In this particular slide it activates the hypothalamus, which releases CRF, and as I said earlier, CRF can, on the one hand, get the HPA system in motion and, on the other hand, can get the adrenergic system in motion. What the slide also shows is that there is negative feedback. One thing that is true in all brain systems, and in this case, you can see that the negative-feedback-looking cortisol activating the dorsal rafae nucleus, which is where the serotonergic neurons are. So you see a 5-HT serotonergic neuron and then you see a GABA-ergic neuron. The GABA-ergic neuron is inhibitory. So, there are three places where medication might be effective-just inside the amygdala. One is to block the glutamate receptors so that the threatening information is not transmitted to the central nucleus of the amygdala and is unable to get things going. Second is to increase GABA activity, since GABA is inhibitory and more GABA is going to again inhibit the action at that glutamate receptor. And third, is to increase serotonin. Increased serotonin is going to activate GABA, and which is going to produce more inhibitory information. So you can see that the medications that act at a glutamate receptor, that potentiate GABA, or that potentiate serotonin--all of them might reduce amygdala activation. And so those are things that pharmacologists get very excited about. What the slide

doesn't show is that another source of restraint on the amygdala, besides these internal synaptic processes, is restraint coming from the prefrontal cortex.

Slide 18: Treatment Evolution for PTSD

Moving on to the next slide, which basically talks about treatment evolution for PTSD. Going back to the early 1900s when people used barbiturates, the middle part of the 20th century meprobamate, benzodiazepines later on, and towards the end of the 20th century, we discovered that our antidepressants, both our tricyclics and our MAO inhibitors, as well as our SSRIs, in addition to being good antidepressants, were also very, very effective anxiolytics. And in some head-to-head comparisons actually antidepressants did as well as benzodiazepines-- in terms of anxiety reduction. This slide also shows that we now have two medications that have FDA approval, from the Food and Drug Administration, as treatment…as medications for PTSD. We only have two. Unlike depression, where there are many medications, there are only two right now, both SSRIs, selective serotonin reuptake inhibitors. I will show you data about other medications, including other SSRIs, and we'll talk about other medications that should be effective based on the pathophysiology of PTSD that I've just described, and also the antiepileptic drugs, which, as I said earlier, will act either by blocking glutamate or increasing GABA or, in the case of topirimate, doing both simultaneously.

Slide 19: Pharmacologic Treatment of PTSD

The next slide is basically restating what I said, that the pharmacological treatment of PTSD involves drugs that act on key neurotransmitters: tricyclic antidepressants, monoamine oxidase inhibitors act on monoamines. SSRIs act on serotonin. We'll talk about a number of medications that decrease norepinephrine activity, and we'll talk about the GABA/glutamate, the antiepileptic drugs.

Slide 20: Pharmacological Treatment of PTSD

The next slide is the first of several that basically summarize this information, and what I'd like you to do is just focus on the two left-hand columns. Don't pay any attention to the right-hand column for purposes of this lecture. So, the left-hand column basically talks about the abnormality that we think is associated with PTSD, and …rather the left-hand column is the system that is affected and then the middle column is the proposed abnormality. So this is basically a summary slide. So CRF…there's increased CRF in PTSD. The HPA system: There are variable cortisol levels and a number of investigators, particularly Dr. Rachel Yehuda, has data suggesting that the glucocorticoid receptors are suprasensitive or up-regulated in PTSD, which, interestingly, is the opposite of what you see in depression, where they are down-regulated or subsensitive, suggesting there may be some real differences between depression and PTSD, at least with regard to the HPA system, despite the fact that the two disorders often co-occur. We've talked a lot about the adrenergic system, locus coereleus, norepinephrine hyperactivity, and also neuropeptide Y, which is a neuropeptide which opposes the actions of CRF and opposes the actions of norepinephrine. And I think that that may be a very important system for the future.

Slide 21: Pharmacological Treatment of PTSD - 2

The next slide, again there's dysregulation of the serotonergic system, the opioid system. Substance P, which we used to think was a pain modulator, seems to be more intimately involved in the stress system, and substance P antagonists have shown to be as effective antidepressants as Paxil, paroxetine. So a lot of really interesting questions about substance P, but we don't have any research in PTSD.

Slide 22: Pharmacological Treatment of PTSD - 3

And the last slide basically reiterates some of what I said earlier about the glutamatergic system, about sensitization, and about hippocampal atrophy due to cell atrophy or dendritic defoliation or degeneration.

Slide 23: Controlled Trials in PTSD—More Effective Than Placebo

So the next slide basically lists a number of successful trials in which a medication was more effective than a placebo, and every one of the medications listed is an antidepressant with proven efficacy. Most of these medications are SSRIs: Paroxetine, sertraline, fluoxetine. There also are two tricyclic antidepressants on the list: amitriptyline, and imipramine. There is one monamine oxidase inhibitor: Phenelzine. And Brofaromine, a very interesting drug that was never put on the market, had monoamine oxidase inhibitory actions and also worked at monoaminergic synapses. But there is nothing to really think about. Now here's some of the data.

Slide 24: Randomized Trial of Phenelzine, Imipramine and Placebo (N=60)

So the next slide shows you a randomized trial of phenelzine, imipramine, and placebo. This was done at the West Haven VA. It's an 8-week trial. Veterans with PTSD were randomized to either placebo, imipramine, or The MAO inhibitor phenelzine. We're measuring results with the Impact of Events scale, and as you can see, the two medications worked. Phenelzine worked much, much better than imipramine, but imipramine was better than placebo.
This, unfortunately, is the only randomized trial of an MAO inhibitor, and it was published fifteen years ago. And it's really a shame that we haven't had more good research with MAO inhibitors, but that's the way it is. I think that many investigators are more comfortable with drugs that do not have the side effects and dietary restrictions that MAO inhibitors have, but it's important to emphasize at this point that these are good medications, and if you have a person who hasn't responded to other drugs, you might want to consider an MAO inhibitor. Obviously the need to stay off of alcohol, stick to the diet, and you need to get the other drugs out of the system, but don't forget MAO inhibitors.

Slide 25: Amitriptyline vs. Placebo

The next slide is also with veterans. This is about amitriptyline versus placebo, and this was, again, done with veterans; Jonathan Davidson's group. And amitriptyline did better than placebo. What was interesting about this trial was…up until this trial, almost all successful trials with medications reduced the re-experiencing symptoms and the hyperarousal symptoms but didn't touch the avoidance symptoms. In this trial, the amitriptyline did very well on the

avoidance symptoms, and the big difference between amitriptyline and imipramine is that… both drugs are tricyclic antidepressants and both block the reuptake of both norepinephrine and serotonin presynaptically, but amitriptyline blocks a lot more serotonin than does Imipramine. And so this was a first suggestion that maybe increasing serotonin was more important for the avoidant numbing symptoms than it was for the other class of some of the arousal or re-experiencing symptoms.

Slide 26: Sertraline vs. Placebo

Next slide is the 1st of two Sertraline trials. This was done by Kathleen Brady, and this is one of the two trials that led to the FDA's approval of SSRIs for PTSD. The CAPS is the Clinician Administered PTSD Scale. And you can see, that the sertraline group, at the end of 12 weeks-and there's roughly 187 patients that were randomized to one drug or the other, did better than the placebo.

Slide 27: Sertraline vs. Placebo

The next slide is the 1st of 2 sertraline trials. This was done by Kathleen Brady, and this is 1 of the 2 trials that led to the FDA's approval of SSRIs for PTSD. The CAPS is the clinician administered PTSD scale. And you can see that the sertraline group, at the end of 12 weeks-and there's roughly 187 patients that were randomized to one drug or the other, did better than the placebo.

Slide 28: Paroxetine in PTSD

The other drug approved is Paxil, paroxetine and the next slide shows the data from that trial. And here-it's a big trial. Over 500 patients…651 patients were randomized to either placebo, 20 mg of paroxetine, or 40 mg of paroxetine; and you can see that the 2 medicated groups do much, much better than the placebo group. What's interesting is that the 20 mg group just does a tad better than the 40 mg group. It's not statistically significant, but we often see this with the SSRIs, that sometimes you don't need to go to the maximum dose to get the maximum effect.

Slide 29: CAPS-2 Reexperiencing Cluster

The next slide basically shows that the paroxetine-this is from this trial-is a broad-spectrum drug. This shows its effect on the re-experiencing symptom cluster.

Slide 30: CAPS-2 Numbing/Avoidance Cluster

The next slide shows the effect on the numbing/avoidance cluster.

Slide 31: CAPS-2 Hyperarousal Cluster

And the next slide shows on the hyperarousal cluster, and as you can see, there's significant improvement in all three clusters. And so the SSRIs are really the 1st broad-spectrum drug we had for PTSD, in which all three symptom clusters were improved with treatment.

Slide 32: PTSD Remission Analysis

Now the next slide is called the PTSD remission analysis, and this is, I think, one of the most important slides, because, you know, people say, "Well, okay. I'm glad to see that the people got better on the medications, but are they well?" Because what happens often in clinical practice is people are better, but they're not well. So you get a partial response. So, what this slide shows, and this is from the very big paroxetine trials, 651 participants, how many people had complete remission. And by that, it means that their CAPS scores were below 20, which is normal-- and what you can see is that about 30% got better, but 16% of the placebo group got better. So what that means is that 70% of these patients may have improved, but they're not better after 12 weeks. What the breakdown really looks like is maybe 20% will not have responded at all, another 50% will have had a partial response, and the final 30% will have had a complete remission.

Slide 33: Fluoxetine vs. Placebo (N=53)

This is another SSRI: Prozac. Again, good results...

Slide 34: Fluoxetine vs. Placebo

There have been a number of good studies with Prozac—here's another one: Fluoxetine vs. Placebo.

Slide 35: Sertraline Continuation Treatment in PTSD

And now on the sertraline continuation treatment of PTSD, which again is one of the most important slides that I'm showing you. And if you look at this slide, there are two graphs. They both represent two different PTSD scales: The yellow one representing the Impact of Events Scale, and the dark triangle one representing the CAPS score. Now, if you look at the horizontal axis, note this goes up to 36 weeks, so at the 12-week point, that's where the drug trial ends, and you can see the improvement. But in this, the patients who were in the original two trials, were asked to stay on their sertraline for another 24 weeks; another 6 months. And what you can see is that they continue to show improvement over the next 24 weeks. The improvement is not as steep as it was in the first 12 weeks, but it's unmistakable. In point of fact, if you think back to the remission analysis, 55% of people who had not had a remission by 12 weeks did have a remission by 36 weeks. So, the good news is that if your patient has had a partial response after 12 weeks, you should encourage them to stay on the medication for another 6 months. However, you know, most patients are not going to just want to stay on another medication, but are probably going to want to have additional treatment. You might want to try something else, and I think that this is a point where, if you had a partial responder with an SSRI, that you might want to think of different augmentation strategies, whether it's augmentation with CBT, which is a very effective treatment-in fact it's more effective than medication. Whereas we get 30% remission with medication, we get about 50% remission with CBT. Or you might want to augment with another medication: anti adrenergic drugs, are some of the other medications that I'll be talking about. So it's important to remember that people who have a partial response at 12

weeks may continue to go on to full remission but you need to keep the medication on there and you may want to also add something else to the mix.

Slide 36: Controlled Trials in PTSD—Not More Effective Than Placebo

The next slide shows that not all controlled trials have been successful. There was a multi-site trial in VA settings, which was not successful and my own belief is that that's more about the chronicity of these veterans. I mean if you think about a veteran, a Vietnam veteran with PTSD who's still in VA 30 years after the war is over and is still symptomatic, that's a very chronic refractory individual. Most of the veterans who have…would have responded to PTSD treatment have responded and are no longer in our system. But this trial led people to think that you shouldn't use SSRIs for veterans or you shouldn't use them for males. And again, I strongly reject that conclusion. In fact, there is a trial that I don't have a slide for of European and Israeli and South African personnel that were given Prozac or fluoxetine, and not only did they respond very well, but participation in combat and having combat trauma as a source of the PTSD actually predicted a favorable outcome. So I think it's really apples and oranges to compare chronic Vietnam veterans with PTSD 30 years later who don't respond to medication with newer cases of combat trauma form Iraq or Afghanistan or other U.N or NATO deployments. There's every reason to think that these people will respond to SSRI's.

Slide 37: Negative Trials

There have also been negative trials with benzodiazepines, Alprazolam, this was an Israeli study. Don't use benzodiazepines. A lot of people use them. There's no reason to use them, and I'll elaborate on that a little-well, this gets into that. So, benzodiazepines are still widely prescribed because they're good anti-anxiety medications, but they have not proven effective on PTSD core symptoms. They will help people sleep better. They will reduce general anxiety, but they won't touch the re-experiencing or the avoidance symptoms. So, don't use them. Cyproheptadine is a trial we did up here in White River Junction. It is a serotonin blocker, and there had been some letters to the editor and case reports that this was a good drug for PTSD flashbacks or nightmares. So we did a randomized trial and found that not only did cyproheptadine not work, it made people worse. And to me this is a very reassuring finding because if SSRIs, if medications that increase the amount of serotonin make people better, then a drug that blocks serotonin activity should make them worse, and that's what cyproheptadine does. Buspirone is another anxiolytic that has not proven to be effective in PTSD treatment.

Slide 38: Promising Open Trials in PTSD

The next slide is about promising open trials in PTSD and you can see this is a very long list, and it's a list that I find very interesting, and I'll be talking about the mood stabilizers in a little bit. I think that the trials with the anti-adrenergic drugs, clonidine and guanfacine, which are Alpha-2 agonists, which decrease presynaptic release of norepinephrine, are medications that have been used clinically, but there has not been a good randomized trial yet; a couple of reports in the literature, but nothing to bet the farm on. Propranolol is another anti-adrenergic, this one works with beta-blockers. Again, one trial with kids that had promising results. A recent trial with acutely stressed people that looked promising. And finally, Prazosin, which is an Alpha-1

antagonist. Murray Raskin and his group in Seattle have been using Prazosin for PTSD, mostly to reduce nightmares and what they found is that it also reduced global PTSD symptoms. Murray and his group are now testing Prazosin both in veterans and in returnees from Iraq at Fort Lewis, so stay tuned on that one. It's a very exciting possibility, particularly given what we know about the excessive adrenergic activity. Naltrexone is a narcotic antagonist and one trial with dual diagnoses subjects, which was not that conclusive. And I'm going to be talking about mood stabilizers, so let's move forward.

Slide 39: Antiepileptic Drugs in the Treatment of PTSD*

So now we get into the antiepileptic drugs in the treatment of PTSD, and you can see there's a long list. And these have been small studies without control groups, so we really don't have a lot of really good information. There's only been one placebo-controlled study; a very small study with 15 patients given lamotrigine, and I'll show you some of that data.

Slide 40: Antiepileptic Drugs and CNS GABA

The next slide basically shows the rationale for using these medications, given what I said earlier on. And what we're looking at is increased GABA concentrations as a result of treatment with three different antiepileptic drugs: topiramate, gabapentin, and lamotrigine. And you can see that, although topiramate acutely increases GABA to a great extent, after 4 weeks of treatment, there's considerable increase from gabapentin and lamotrigine as well. So the evidence is that these medications will increase GABA in the brain and that may be a partial explanation for any effectiveness that they may prove to have.

Slide 41: Carbamazepine Efficacy in PTSD*

And I'm going to quickly just-just look at the titles here because we don't need to go through all these details, and I want to go back to the slides. Basically, carbamazepine or Tegretol, an open trial, all 8 of 10 patients, vets, did well. In addition to PTSD symptoms, it also decreased impulsivity and some of the violent angry outbursts. Another study, 22 of 28 sexually abused children became better. So that there is evidence that carbamazepine is effective. We don't have any randomized trials, and it's an old drug. It has a lot of side effects, and my guess is we're probably not going to see any randomized trials with this medication.

Slide 42: Lamotrigine Efficacy in PTSD*

Lamotrigine, lamictol, it's an antiepileptic. It also has an indication for use in bipolar disorder. One double-blind trial, 5 on placebo and 10 received the medication, and according to the study, 50% responded, according to the Duke PTSD scale. This data has been re-analyzed and there's some question about it. It was a small study. It's obviously important to repeat this trial. So the results are inconclusive.

Slide 43: Divalproex Efficacy in PTSD*

Divalproex, valproate, again a good drug for bipolar illness, increases GABA levels and has some promising results. The thing to remember about divalproex is, you don't want to give this

to pregnant women, particularly in the 1st trimester; it can result in teratogenic effects, poor outcomes. So that's one reason not to use divalproex. Also weight gain and some sedation. Some people don't like it.

Slide 44: Response to Dicalproex

So here's some of the data from the open-label trial with divalproex looking at reduction in CAP scores at 4 and 8 weeks, and again there's no control group, but there's a significant reduction from the baseline values.

Slide 45: Gabapentin Efficacy in PTSD*

Gabapentin is another promising medication and there has been a retrospective chart review of 30 patients suggesting that this was a very good treatment, although most of them, 83%, also had an antidepressant on board.

Slide 46: Topiramate Efficacy in PTSD*

The next slide is on topiramate. Topiramate is one of my favorite drugs, and I'm hoping that we're going to get more trials, because topiramate does what an ideal antiepileptic drug would do: it not only blocks glutamate, but it increases GABA activity.

Slide 47: Topiramate Efficacy in PTSD

I'll show you a study showing that topiramate not only reduced total PTSD symptoms, but seemed to have broad-spectrum effects on re-experiencing, avoidance, and arousal symptoms. Again, an open- label trial. We need to do a randomized trial, but it is promising. Also, there's been a lot of really interesting research on topiramate in terms of impulsive disorders. And finally, because most of the medications that we use in psychiatry, with the exception of bupropion, Wellbutrin caused weight gain. Topiramate is one medication that doesn't do that. In fact it is also being considered for use in binge-eating disorders and other kinds of things, as well as substance-abuse problems. So, stay tuned. Hopefully, we'll have some better information on topiramate within the next year or so.

Slide 48: Topiramate for PTSD Results

The next slide just basically says, you know, in the topiramate trial, again it was an open trial, there were reductions in nightmares, flashbacks, etc., and it was well-tolerated.

Slide 49: Vigabatrin Efficacy in PTSD*

Vigabatrin, another antiepileptic drug, increases GABA, and in a case series with 5 patients, made people better.

Slide 50: Psychopharmacology

So here's a summary slide. I've talked about the SSRIs and the dosages on here, and why people like the SSRIs, besides their efficacy and their safety is that they improve…global improvement, that's what CGI stands for: Clinical Global Improvement-- that's a scale. They're also good for comorbid disorders. As you know, if you've got PTSD, you've got an 80% chance of having another comorbid disorder, and that's…and among people we see in the VA and in clinical settings, that percentage is higher. And SSRIs are good in major depressive disorder, panic disorder, obsessive/compulsive disorder, social phobia, and associated symptoms such as suicidality, impulsivity, and aggressiveness. So SSRIs are clearly the drug of choice. Two of them have FDA approval. I mentioned two other serotonergic-acting medications: Nefazodone, which is no longer available, at least not available because of its liver toxicity, just to prove the point that drugs that work on the serotonergic system seem to be good for PTSD and also for, in this case, comorbid depressive disorder.

Slide 51: Psychopharmacology (cont.)

The next slide talks about the antiadrenergic drugs and there are three different classes of them, Clonidine and guanfacine being Alpha-2 agonist, which reduce presynaptic release of norepinephrine. In my own experience, and based on some research we did at the National Center, these medications may also be good for reducing dissociative symptoms. Yohimbine, which is an Alpha-2 antagonist however, does the opposite of what clonidine does, can produce dissociation in about 40% of veterans with PTSD, and that's why I've started using clonidine and guanfacine for dissociative symptoms with considerable success, although we don't have a randomized trial to prove that. I've talked about the Propranolol, and what's missing from this slide is Prazosin, which is an Alpha-1 antagonist, which has had good results. Don't forget MAO inhibitors. I showed you the data from the one trial with phenelzine. Another trial with a selective MAO A inhibitor, moclobemide, also had promising results and these are good antidepressants, good for panic disorder. And tricyclic antidepressants are still available and they're inexpensive. Many of your patients cannot afford some of these more expensive drugs, and the tricyclics, we've managed them for years, even though they do have more side effects than SSRIs, and they're good antipanic agents, and they're good for major depressive disorder, as well as being good on the B-cluster symptoms of PTSD.

Slide 52: Psychopharmacology (cont.)

The final slide in the series mentions benzodiazepines, which are not effective in PTSD symptoms. And they're not even good prophylactically. There are two studies now: An Israeli study by Gelpin and Associates and an American study by Tom Melman and his group, where they gave benzodiazepines in the acute aftermath of traumas. The idea was if we could help people get some sleep after exposure to a disaster or traumatic experience, maybe we could prevent the later development of PTSD. The benzos helped people sleep, but it didn't have any prophylactic value. So there's really no good rationale for using benzodiazepines when we have so many other drugs. I've talked at length about anticonvulsants. And finally on this list, I have atypical antipsychotics and there are now about 6 studies with the atypical antipsychotics risperidone, alanzapine, and quetiapine or Seroquel. Not used by themselves but for treatment failures or partial-responders to SSRIs, given additional treatment. Keeping them on the SSRIs for the reasons I stated earlier, because they may continue to improve, but augmenting with an

atypical antipsychotic and there's now 6 studies-small studies indicating that this may be a very good strategy. There's a Cooperative Study-a VA that John Krystal and Bob Rosenheck of the National Center are now doing. It's a 15 site study in VA, which will be looking at augmentation of SSRI partial responders, or non-responders, with atypical antipsychotics. So that's a very, very important study to be looking at.

Slide 53: New Medications for PTSD

A number of new medications, some of them are not available for human use, but theoretically they ought to be important: CRF antagonists, to basically reduce the important activation of the whole stress system by CRF. NPY agonists, which enhance NPY and which opposes the action. We talked about antiadrenergic agents, etc. We talked about glutamatergic anticonvulsants, etc. And the bottom of this slide mentions BDNF promoters and IGF-1 agonists. BDNF is brain derived neurotrophic factor, which is the mechanism through which antidepressants produce neurogenesis, and I mentioned all antidepressants do that. And insulin-type growth factor-1 is another substance that promotes neurogenesis. So this is my list of medications for the future that, hopefully, will be tested.

Slide 54: Psychotherapies Found Effective in Controlled Trials in PTSD

Let's skip the next couple of slides. The whole point of them is just to emphasize that CBT works, in point of fact it even works better than medications, with remission rates of about 50%, as compared to the 30% remission rate. So I'm showing three slides with some data about exposure therapy and cognitive therapy, all of which work. The other advantage of cogno-therapy, and as a pharmacologist I hate to have to admit this, is that after an intense session of CBT, trial people generally maintain their gains for months or years. Whereas with medication, if you stop the medication after there's been a successful treatment, people are probably going to relapse. So if a person has responded to medication, it's like treating a person with depression, you probably need to keep them on the medication. If they've stayed asymptomatic for a year or so, you might want to slowly reduce the medication, see how well they can do without it. But many people who had good medication responses will lose their gains if you stop the medication.

Slide 55: Treatment of PTSD in Rape Victims: A Comparison Between Cognitive-Behavioral Procedures and Counseling

Slide 56: Treatment of PTSD by Exposure and/or Cognitive Restructuring

Slide 57: A Randomized Trial of Cognitive Therapy and Imaginal Exposure in the Treatment of Chronic PTSD

Slide 58: Prolonged Exposure (PE) Therapy, Stress Inoculation Training (SIT) and Their Combination for Female Assault Victims with PTSD (9 Sessions)

Slide 59: Brief Psychotherapy for PTSD

Slide 60: Treatment of Acute Stress

Okay, so I've gone through slides showing the good data on cognitive behavioral therapy, you have other modules in this course that will address that at length, even the one study showing brief psychotherapy for people with PTSD-but we'll skip over that and end this talk with a few slides talking about treatment of acute stress. Again, there's very little research out there. There are about 10 studies now. But the question is, is there a morning-after pill. In other words, if someone comes to your emergency room and he or she has just survived a traumatic episode, whether it's a motor vehicle accident, a rape, an assault, attack by a terrorist as in places like Israel, where we have a lot of the data. What would we want a morning-after pill to look like. I mean, is this something we can give them that's going to reduce their immediate distress and prevent later development of PTSD. Well, I've listed three things that a morning-after pill ought to do: It ought to reduce excessive stress responses. You know, reduce the excessive CRF for example. It should enhance inadequate stress responses if people are unable to meet the challenge psychobiologically. We need to help them. And the other thing that people don't always realize is that to be a doctor is to be able to mobilize the necessary psychobiological responses when the need exists…when there is a threat; fight or flight or freeze-whatever. But when the danger has passed to be able to return to normality. The problem with PTSD is that many people are stuck, sometimes for decades, in a hyperactivated stress responsive-there's no off switch for these people. So having some kind of an off switch when the danger has passed is an important characteristic of a morning-after pill.

Slide 61: Treatment of Acute Stress

So the next slide basically, and this should be clear by now, in terms of the psychobiology of the stress response, is that, you know, what do we want this pill to do? Well some of the things we might want it to do would be reduce CRF activity, to normalize HPA function, to reduce excessive adrenergic activity, and to normalize the immunological function.

Slide 62: Differential Efficacy at 1 Week of Imipramine vs. Chloral Hydrate for Children with Acute Stress Disorder

So let's look at some data. Here's some data from a randomized trial that was done by Robert & Associates on a pediatric burn unit, so these are kids, who had been burned severely enough to require hospitalization, and if any of you have worked on a burn unit, as I have, it's a terrible place. The kids are in pain. The treatment to get rid of the…to debride the tissue makes the pain even worse. So one of the things that the staff want to do is make sure they (burn patients) get a decent nights sleep. And this slide shows a trial where they compared a typical sleeping pill, chloral hydrate, with imipramine, that the imipramine, which is a tricyclic antidepressant, was very, very much more effective than the chloral hydrate in reducing the acute stress disorder symptoms, among these kids. Unfortunately, there's no follow-up, so we really don't know whether this prevented a later development of PTSD. And as you can imagine, any kid that's been burned badly enough to require hospitalization is certainly a very high risk to develop PTSD as a result of his or her traumatic exposure.

Slide 63: Blockade and PTSD Symptoms

The next slide is a very interesting experiment that Roger Pittman did at the Mass General Hospital Emergency Room. Reasoning as I've outlined earlier on, that excessive adrenergic activation may increase the risk for later PTSD, both through the sympathetic arousal, as well as through the potentiation of the encoding of traumatic memories, Roger gave randomized people, who came to the Mass General within several hours of their trauma, either a 10-day course of propanolol, a beta-adrenergic blocking agent, or a placebo. And these are the results: Looking at CAP scores at 1 month and at 3 months after treatment. It's a small study, only about 21 patients in the study, so I have very, very low statistical power to detect differences. If you inspect this data, I mean, it looks like the propanolol group has an edge, but there's tremendous variance, particularly in the placebo group, and although these results were in the right direction, in terms of lower CAP scores for the propanolol group, they were not statistically significant.

Slide 64: Blockade and Physiological Reactivity

However, if you look at the next slide, which says beta-blockade and physiological reactivity, we all know that one of the hallmarks of PTSD is that if you expose people to traumatic reminders, in this case script-driven imagery, where a narrative about the traumatic event is read to the individual by a female if it's a female subject or by a male if it's a male subject, that the PTSD subjects are going to have significantly greater increases in physiological indicators, such as heart rate, skin conductance, or electromyogram. In this slide, the propanolol-treated group is in black and the placebo-treated group is in pink. So you can see, in terms…looking just at the pink slides for these four graphs, that all of the placebo group shows increased hyper-reactivity one month after exposure to the traumatic episode. If you look at the black however, it's less than the pink and, in the case of skin conductance, the upper right-hand corner, is significantly less, and if you look at the lower right-hand corner, the corrugator electromyogram is almost significantly lower. This is a very, very promising trial, suggesting that acute administration of an antiadrenergic drug, in thins case propanolol, which is a beta-adrenergic blocker, may indeed be a prophylactic and preventive treatment for PTSD. This study is now being repeated, a much larger scale study done both here and in France. So stay tuned. It's a very important experiment.

Slide 65: Plasma NPY: Baseline and Acute Stress

And then my final three slides are about studies that the National Center's been doing at Fort Bragg, North Carolina. And we've been doing studies with Special Forces, so SF stands for Special Forces, and Non-SF stands for Non-Special Forces. They have something called the SERE School training, which is a very, very stressful training experience where people are…troops are asked to evade capture for several days, or he is captured and then they're incarcerated, there is a mock interrogation. This is obviously to prepare them for possible capture following dangerous missions in places like Iraq or Afghanistan, or what-have-you. And the situation is so stressful-these are macho men-that, when you measure neurohormones, and we've measured many of them-many more than I'm showing in these slides-testosterone levels disappeared during the course of this. So this is a credible threat, even to Green Berets and Navy SEALS. If you look at the baseline neuropeptide Y levels for the Special Forces and the Non-Special Forces, the yellow boxes-yellow squares-you can see there's no difference. But if you look at the neuropeptide Y levels during the acute stressful situations, you can see that the Special Forces are much more able to mobilize the neuropeptide Y than are the Non-Special

Forces. What this slide also illustrates is what I believe is the difference between PTSD and, say, depression is that PTSD is a disorder of reactivity, rather than of basal state. In order to really unmask the differences between PTSD and non-PTSD, or resilient versus non-resilient people, you really need to provoke them; in this case we're provoking them with the stressful situation of the SERE Training School. And what it looks like is the Special Forces, whatever the criteria by which the military selects its people for Special Forces, are different in some way. They're more able to mobilize neuropeptide Y.

Slide 66: Plasma NPY: Baseline and Recovery

Here's another slide showing recovery period. You can see that the Special Forces people have recovered their baseline neuropeptide Y, whereas the Non-Special Forces are still quite depleted. Again, there's a difference. There is a biological capacity that's different for Special Forces and Non-Special Forces. I should say also that we found similar results with the adrenogluccorticoid DHEA; dehydroepiandrosterone, which opposes the actions of cortisol.

Slide 67: Correlation Between Dissociation Scores and NPY Levels

So here's my final slide. Why should we care abut how much neuropeptide Y is released? Well, the horizontal axis plots the amount of neuropeptide Y that a given individual is released, and the vertical axis is a dissociation scale, which is also equivalent to a functional scale. And as you can see, the greater the neuropeptide Y, the less the dissociation, and the less the dissociation, the greater the function. So what this data suggests to us is that neuropeptide Y may be a biological marker for resilience, and it's one of the reasons that I've been saying throughout this talk that I think we need to look at neuropeptide Y, and it may be drugs that can enhance neuropeptide Y function, particularly in vulnerable or non-resilient people; may be one pharmacological approach to PTS or acute stress problems. So, thank you very much. You've been very patient and I appreciate your attention.