

Pharmacotherapy Treatment of PTSD and Comorbid Disorders

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**PHARMACOLOGICAL
TREATMENT OF PTSD AND
COMORBID DISORDERS**

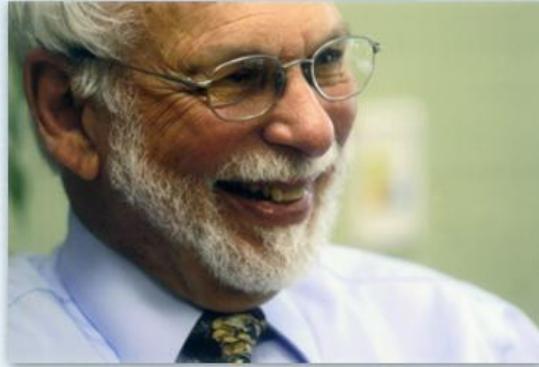
Presented by
National Center
for PTSD
U.S. Department of
Veterans Affairs

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 National
Center for
PTSD
Posttraumatic
Stress Disorder

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Hello, I'm Matt Friedman I'm the Executive Director of the National Center for Posttraumatic Stress Disorder (PTSD) of the US Department of Veterans Affairs, and I'm a professor of psychiatry and pharmacology and toxicology at Dartmouth Medical School. And for the next hour or so I'll be talking to you about medications for treatment of PTSD. I'm a little prejudiced but I think this is a very important topic because so many people who suffer from PTSD do receive medications and it's important for practitioners to know what the latest developments are.

In the interest of full disclosure, I've received an honorarium from AstraZeneca during the past year.

Introduction

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INTRODUCTION

- ▶ Treatments for PTSD have undergone tremendous growth in the past decade, including studies of psychotherapy and medication trials.
- ▶ Cognitive Behavioral Treatment (CBT) is more effective than medication.

Treatments for PTSD have undergone tremendous growth; in the past decade there's been lots of treatment research on both psychotherapy and on medication. The best treatments are not medication, frankly. There's psychotherapy trials especially for CBT (Cognitive Behavioral Treatments), and the two CBT treatments that have emerged as the strongest are prolonged exposure (PE) and cognitive processing therapy (CPT).

Medications are Effective

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MEDICATIONS ARE EFFECTIVE

Medication remains a clinical option for these reasons:

- ▶ Useful for treating comorbid depression and anxiety
- ▶ Generally accepted by patients
- ▶ May be obtained from any prescriber whereas qualified cognitive behavioral treatment therapists are not readily found

Medications are also effective, however, and that's why we'll be talking about them today.

Learning Objectives

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LEARNING OBJECTIVES

1. Understand how the human stress system is altered in PTSD
2. Understand how such alterations indicate the usefulness of certain medications
3. Understand the current evidence regarding the effectiveness of different medications for patients with PTSD

So after viewing this presentation my hope is that you'll have a much better understanding of how the human stress system is altered in PTSD, that you'll understand how such neurobiological alterations indicate the usefulness of certain medications and that you'll become familiar with the current evidence favoring the effectiveness of specific medications for PTSD.

The Stress System

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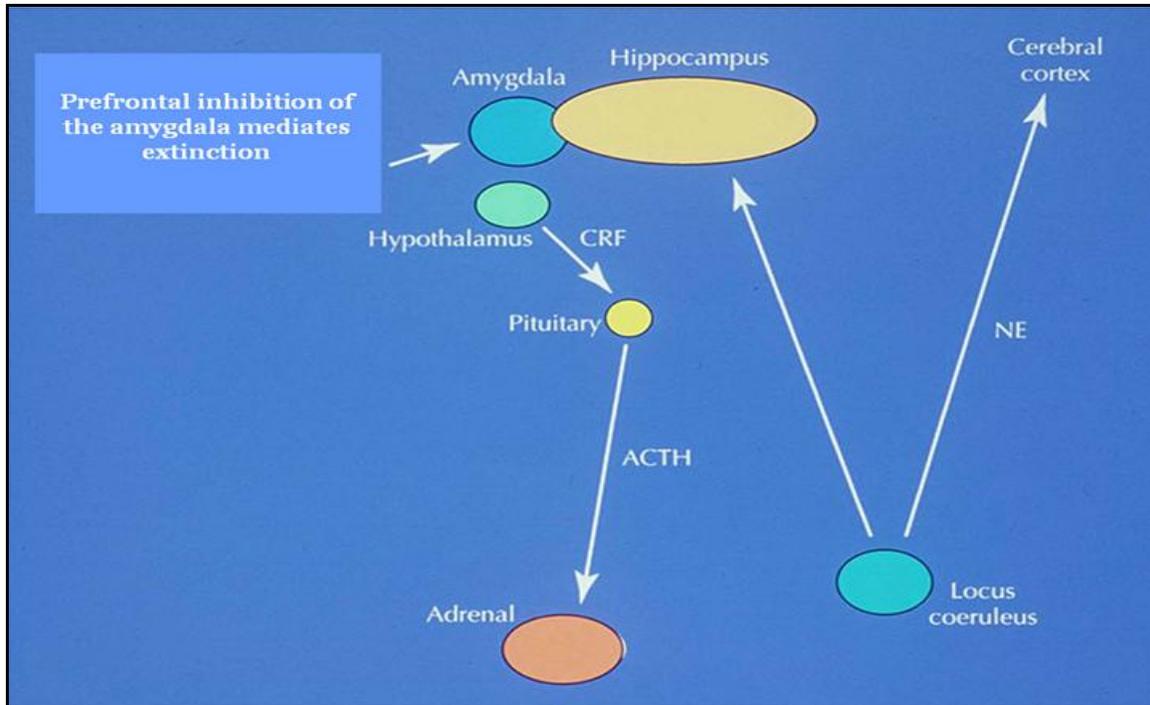
THE STRESS SYSTEM

- ▶ The stress system coordinates the generalized stress response, which takes place when a stressor of any kind exceeds a threshold.
- ▶ Three primary components:
 - Hypothalamic-pituitary-adrenal cortical (HPA) system
 - Norepinephrine/autonomic nervous system
 - Immunological system

In order to understand the neurobiological alterations to the path of physiology of PTSD, it's important to understand the human stress system because that is the neurobiological context in which all medications that we'll be discussing operate. The stress system has evolved to meet demands placed on the organism--both physical and psychological demands--and it has three components: One component is the hypothalamic-pituitary-adrenal cortical system, the second component is the norepinephrine/autonomic nervous system, and the third component is the immunological system.

The Stress System Graphic

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This is a very simplified diagram of the stress system. What you can see is the amygdala, which is the part of the brain that processes strong emotional content or threatening, traumatic information, and the hippocampus, which is the brain structure next to the amygdala which sets that information in context so people can remember where they were almost killed or what other stressful situation happened.

On the left side of the screen going from top to bottom you can see the HPA system--the hypothalamic-pituitary-adrenal system. So the amygdala activates the hypothalamus, which releases CRF, corticotropin-releasing factor, which releases from the pituitary gland ACTH, adrenocorticotropic hormone, which then goes down to the adrenal cortex which releases cortisol and other glucocorticoids.

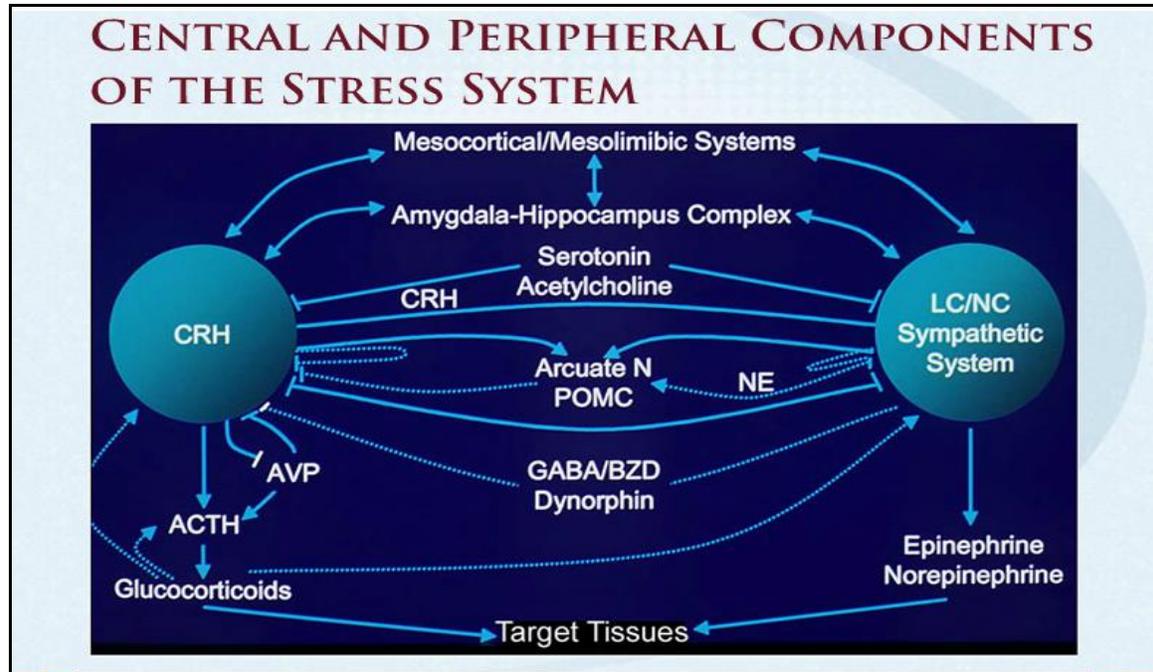
The other component of the stress system shown in this diagram is the noradrenergic sympathetic nervous system which is based in the locus coeruleus. Again, the amygdala activates the locus coeruleus which releases norepinephrine downstream through the sympathetic nervous system--the classic fight, flight or freeze response--and upstream is shown in the diagram into many brain structures including the cerebral cortex.

Now the box on the upper left hand corner of this diagram is extremely important. This represents the prefrontal cortex because the prefrontal cortex is the part of the brain, of the higher centers of the brain, that can actually rein in the amygdala. So in PTSD what

you have is the worst of two situations. You have an amygdala that is in hyperdrive and you have a prefrontal cortex that is deficient in its ability to rein in the amygdala. So the goals of treatment, whether we're talking psychotherapy or medication, is to reduce the amygdala activity and to fortify the prefrontal cortex so that it can do that within the brain itself.

Central and Peripheral Components of the Stress System

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So this is a more complicated diagram which is an elaboration of what I just showed you.

In this slide it's important to know that CRH, which is corticotropin-releasing hormone is the same thing as CRF (corticotropin-releasing factor): it's called by both names. And what you can see is that CRH on the left hand side, looking at the HPA system, so that CRH releases ACTH from the pituitary gland which releases glucocorticoids from the adrenal cortex so that's the classic stress system.

But CRH, in addition to acting as a hormone, also acts as a neurotransmitter. So as you can see in the middle of the screen, CRH actually activates the locus coeruleus norepinephrine sympathetic nervous system, which then releases norepinephrine downstream in terms of the fight or flight response or upstream as I mentioned earlier.

Now in the top, middle part of the slide, this shows you the different brain structures that are affected by either the release of the HPA system, on the left hand side or the locus coeruleus system on the right hand side. You have cortical brain structure the mesocortical / mesolimbic system, you have the limbic system, the amygdala, the hippocampal cortex and the rest of the slide really shows a number of neuro-transmitters, neuro-peptides and neuro-hormones that make this possible, serotonin, acetylcholine, GABA, dynorphin, etc.

And when you're talking about medications this is extremely important because medications don't do anything by themselves all they do is either increase ongoing activity, say increase in serotonin activity, or block that activity. So all the medications we'll be talking about either enhance or diminish different neuro-transmitters and neuro-peptides working at the places where they have to work in order to activate the stress system and other adaptive systems.

Norepinephrine and PTSD

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NOREPINEPHRINE AND PTSD

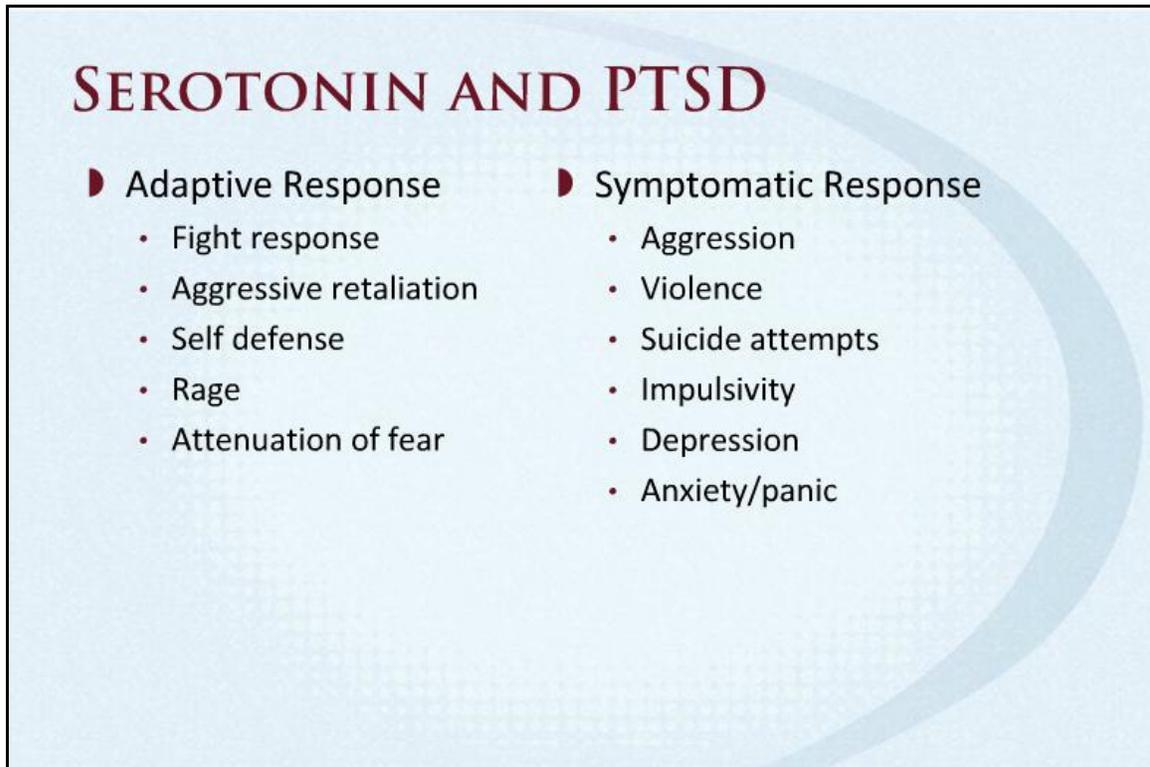
<ul style="list-style-type: none">• Adaptive Response<ul style="list-style-type: none">• Flight response• Fear• Sympathetic activation• Conditioning• Consolidating memory	<ul style="list-style-type: none">• Symptomatic Response<ul style="list-style-type: none">• Hypervigilance• Autonomic arousal• Fear• Exaggerated startle response• Flashbacks• Intrusive memories
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So one of the main neurotransmitters that we talk about when we're talking about the response to stress is norepinephrine. And norepinephrine is extremely important for survival of the species. And the left hand column of this slide basically shows the kind of adaptive reactions that norepinephrine mediates in response to a stressful situation: the fight or flight response, fear, sympathetic activation, conditioning (so if something is going to harm you, you can learn about that and avoid it in the future). And you can remember that, so norepinephrine also facilitates consolidation.

The problem is that too much of a good thing isn't so good, so in PTSD there is excessive norepinephrine activating different brain structures and systems. As you can see from the right hand column, many of the symptoms of PTSD seem in part related to too much norepinephrine: hypervigilance, autonomic arousal, the fearful responses, the exaggerated startle response, flashbacks--which we can actually produce in a laboratory with noradrenergic agents--and intrusive memories. So you want to remember, but you don't want to have those memories haunt you night and day.

Serotonin and PTSD

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SEROTONIN AND PTSD

<ul style="list-style-type: none">• Adaptive Response• Fight response• Aggressive retaliation• Self defense• Rage• Attenuation of fear	<ul style="list-style-type: none">• Symptomatic Response• Aggression• Violence• Suicide attempts• Impulsivity• Depression• Anxiety/panic
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Well, serotonin is another key neurotransmitter that's involved in the human stress response and is altered in PTSD. And again the left hand column shows all the important functions that serotonin does for normal functioning people. It helps to mediate the fight response or to protect yourself, self-defense, and to attenuate fear responses--so serotonin is a key part of the stress response.

Now whereas we have too much norepinephrine in PTSD we have too little serotonin. And when there's too little serotonin a number of changes occur; people become aggressive, even violent. Suicidality is related to too little serotonin, impulsivity, depression and other anxiety and panic reactions.

Monoamines and Amino Acid Neurotransmitters

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MONOAMINES AND AMINO ACID NEUROTRANSMITTERS



- ▶ Glutamate is the major fast-acting neurotransmitter
- ▶ GABA is the main inhibitory neurotransmitter

So actually, although we talk a lot about norepinephrine and serotonin, glutamate is the major, fast-acting neurotransmitter and GABA is the main inhibitory transmitter. And through a marvelous design feature they are rapidly converted one into the other. And really when we think about PTSD and we think of the neurobiology we really have to think about glutamate and GABA and as I'll show you later, certain medications, particularly the mood stabilizers or anti-epileptic drugs, act primarily on GABA and glutamate; they don't act on serotonin or norepinephrine.

GABA and PTSD

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GABA AND PTSD

<p>▶ Adaptive Response</p> <ul style="list-style-type: none">• Anxiolytic• Neuromodulation• Cognitive function• Hormonal modulation• Decreased release of CRF	<p>▶ Symptomatic Response</p> <ul style="list-style-type: none">• Anxiety• Reexperiencing• Impulsivity• Hyperarousal
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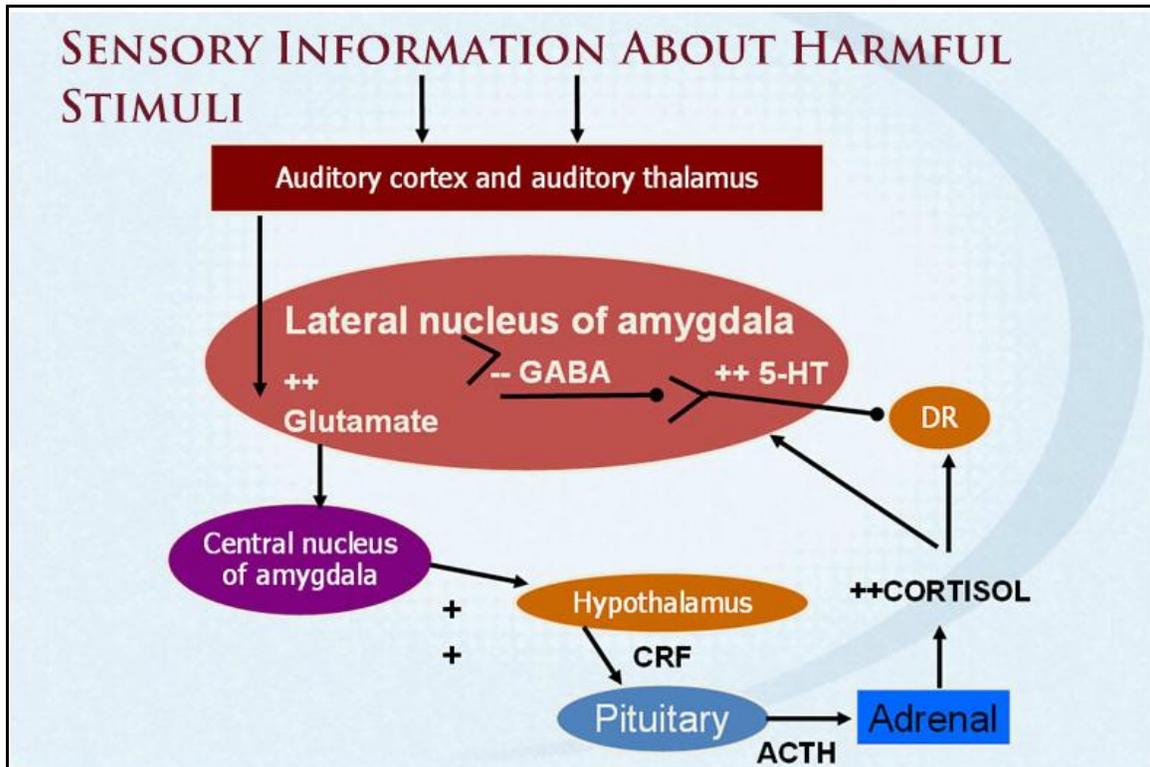
So again, GABA is good for you when it's functioning in the proper amount; it helps people calm themselves, sort of a body's ingrown anxiolytic. It can modulate different neurons, it helps to facilitate cognitive functioning, it can modulate hormones, and it can decrease the release of CRF, corticotropin-releasing factor. Remember, CRF is what the amygdala sets in motion at the beginning of the stress response, and too much CRF can activate too much norepinephrine, etc., so that's an important function that GABA serves.

As with serotonin, too little GABA is not a good thing and when there is a GABA deficiency people tend to feel anxious, they may have re-experiencing symptoms, they may be impulsive, and they may be hyperaroused.

So as you can see what this really is about is trying to restore the proper balance of neuromodulators and neuro-hormones into the system; that's true of all psychopharmacology and we're going to focus on that balance in terms of PTSD.

Sensory Information About Harmful Stimuli

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So in this slide we're showing that there is some threatening information. In this case auditory information comes into the lateral nucleus of the amygdala. It activates a glutamatergic neuron, glutamate is released to the central nucleus of the amygdala, which then activates the hypothalamus, and the hypothalamus releases CRF to the pituitary, but in addition the adrenal gland is activated. There is feedback from the dorsal raphe (DR), which is where many of the serotonin neurons are located. Serotonin, or 5-HT, then is an inhibitory transmitter within the amygdala which activates another inhibitory neuron, GABA.

What this slide basically shows is our current model about the amygdala from a neuropharmacological perspective and as you can see there are three different neurons in the lateral nucleus of the amygdala where a medication might make a difference in reducing PTSD symptoms. On the one hand (the far left) a glutamate inhibitor might block the information going from the lateral nucleus to the central nucleus of the amygdala and setting things in motion. In the middle of the slide, GABA, a medication that enhances GABA activity because GABA is an inhibitory neuron, so that's another way of reducing the glutamate release by inhibiting it through GABA. And finally on the far right of the lateral nucleus you can see a serotonergic neuron, 5-HT, now serotonin

basically serves as a secondary negative neurotransmitter because it activates the GABA neuron. So again, we could block this response with the medication that blocks glutamate, with a medication that enhances GABA, and with a medication that enhances serotonin. And as we'll see later, the most effective medications so far in PTSD treatment are those that activate serotonin, so this is the model.

Now before leaving this slide it's also important to remember that another way of reducing amygdala activity is from the pre-frontal cortex as I said earlier.

Review of Controlled Trials in PTSD

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REVIEW OF CONTROLLED TRIALS IN PTSD

SSRI'S MORE EFFECTIVE THAN PLACEBO:

- Paroxetine for civilians and Veterans (N=551)
- Sertraline for mostly civilians (N=208)
- Sertraline for mostly civilians (N=187)
- Fluoxetine for civilians (N=53)
- Fluoxetine for recent Veterans (N=131)
- Fluoxetine for civilians and Veterans (N=64)
- Fluoxetine for Veterans (N=301)

There have been a number of randomized clinical trials testing different medications for PTSD. The first slide summarizes studies done with SSRI's, selective serotonin re-uptake inhibitors and, as you can see, many of these were very large studies with hundreds of participants and, in all of these studies, the SSRI was significantly more effective than placebo. The medications mentioned are paroxetine (Paxil), sertraline (Zoloft), and fluoxetine (Prozac). And, two of these drugs, paroxetine and sertraline have FDA approval as treatments for PTSD.

Review of Controlled Trials in PTSD

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REVIEW OF CONTROLLED TRIALS IN PTSD

OTHER DRUGS MORE EFFECTIVE THAN PLACEBO:

- ▶ Amitriptyline for Veterans (N=46)
- ▶ Imiprimine for Veterans (N=41)
- ▶ Phenelzyne for Veterans (N=37)
- ▶ Venlafaxine for civilians (N=531)
- ▶ Venlafaxine for civilians (N=329)
- ▶ Prazosin for Veterans (N = 10)
- ▶ Mirtazapine for civilians (N=100)
- ▶ Nefazadone for civilians (N=54); (N=26)
- ▶ Nefazadone for Veterans (N=41)

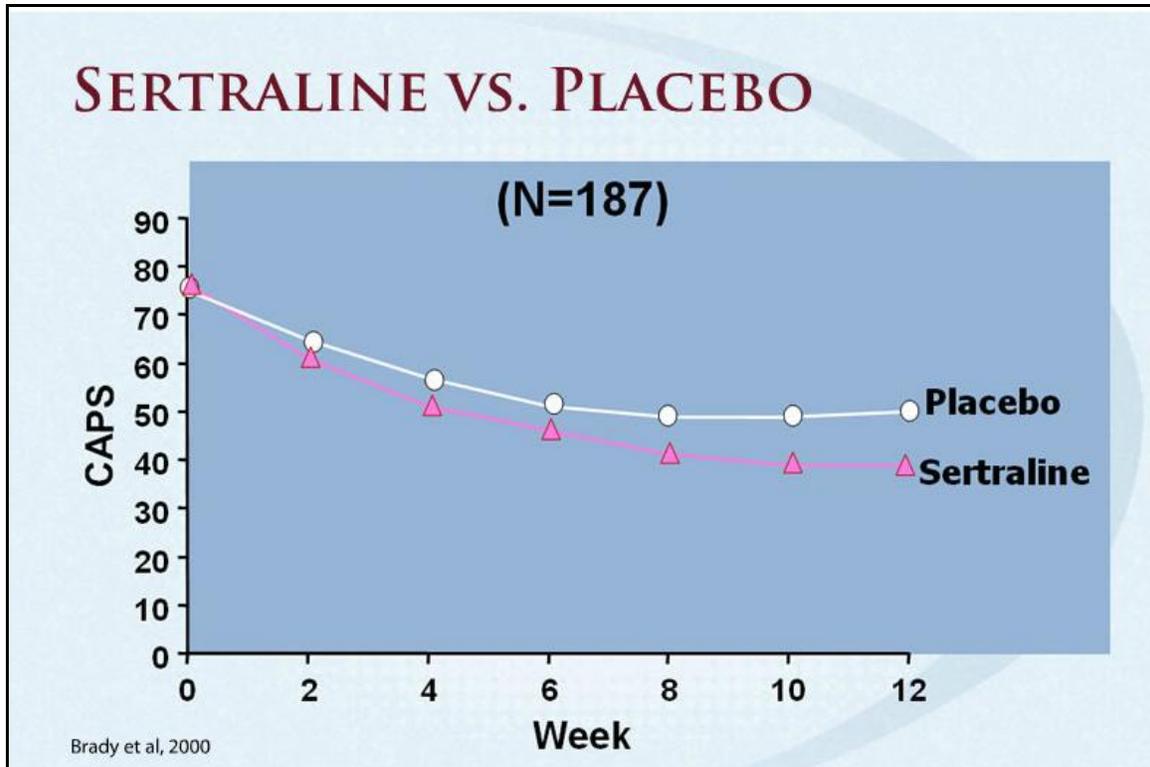
In the next slide, we look at a number of trials for other medications. I want to call your attention specifically to around the middle of the list the two studies with Venlafaxine which collectively involved about 900 patients, and Venlafaxine was extremely effective. In one study it was also compared to an SSRI and did just as well. Other trials, smaller ones, older ones, with tricyclic antidepressants, namely Amitriptyline and Imiprimine. Phenelzyne, a Monoamine Oxidase Inhibitor – it is the only study with an MAO inhibitor that's been done.

Prazosin: there has been only one study with Prazosin for Veterans that has been positive; another study with Prazosin has been negative. As far as PTSD, Prazosin works for nightmares for both of the studies, which is why Prazosin is not recommended at the moment as a first rank treatment for PTSD; although it is a good treatment for nightmares. Mirtazapine (Remeron) is another effective medication.

And finally, Nefazadone, a couple of trials with civilians, and one with Veterans, a very effective drug; of course, the problem with Nefazadone is it also has liver toxicity, which is why it has been removed from the market by its manufacturer although, you can still get it generically.

Sertraline vs. Placebo

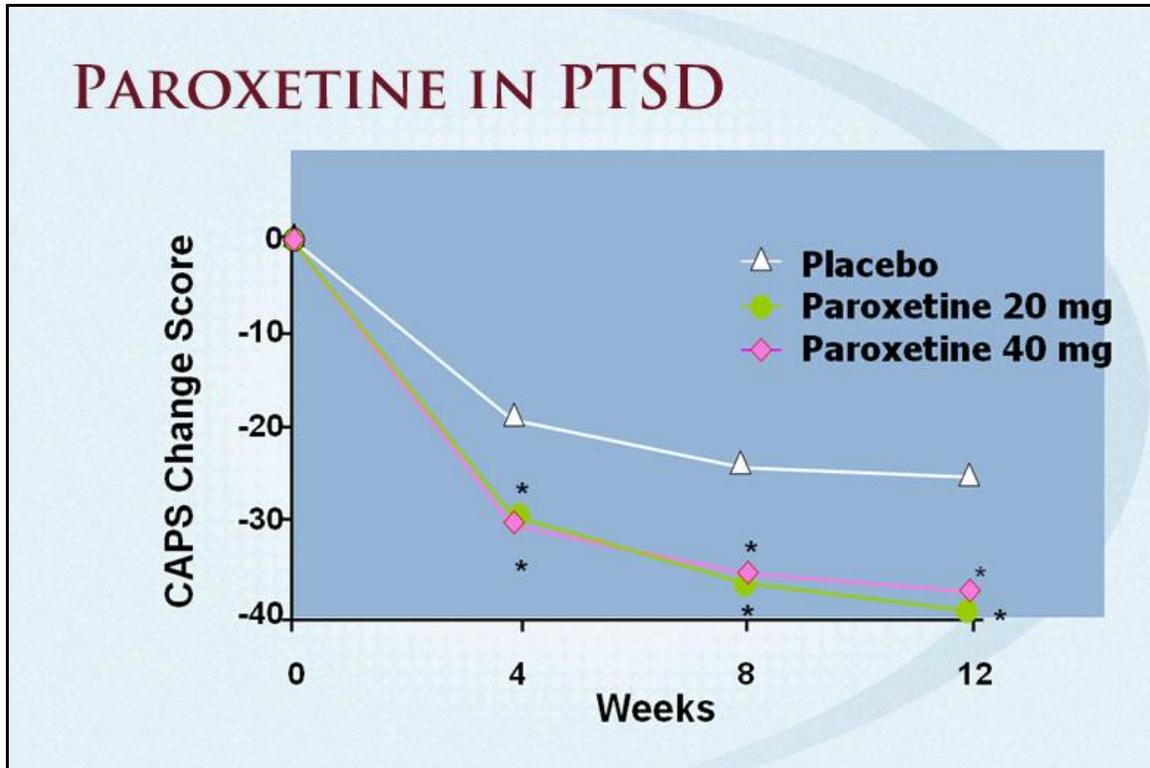
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So, this slide shows data from one of the studies that led to FDA approval for sertraline. We are comparing sertraline versus placebo. There were 187 subjects randomized to both treatments. On the vertical axis, we are measuring CAPS scores, which is a PTSD severity score, and on the horizontal axis, we are measuring time. And, as you can see, it is a 12 week trial and, what the slide shows is that, at the end of 12 weeks, sertraline produced much greater reduction in PTSD symptom severity than did the placebo.

Paroxetine in PTSD

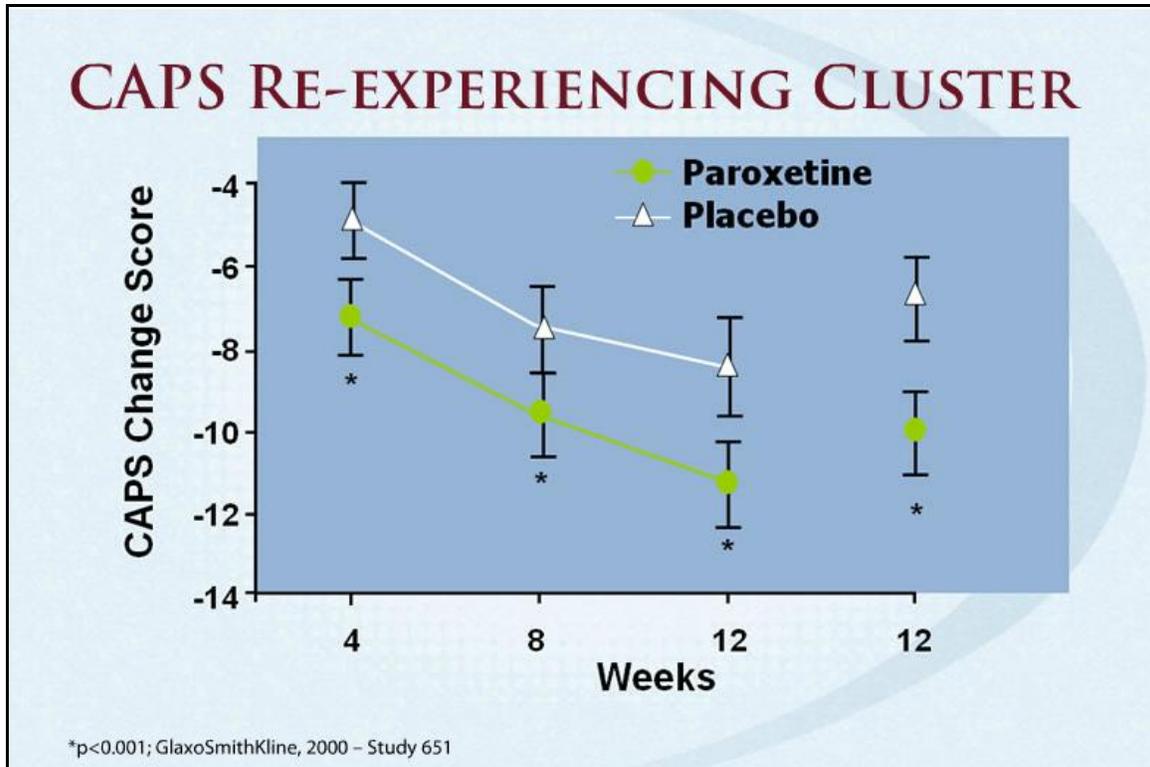
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Next slide shows a similar layout only here we are looking at a paroxetine study. We are looking at two doses of paroxetine, 20 and 40 milligrams, compared to placebo. Here we are measuring CAPS change score on the vertical axis so, that the more the scores are reduced, the better the drug. And again, it is a 12 week trial and again, you can see, both doses of paroxetine were significantly better than placebo.

CAPS Re-Experiencing Cluster

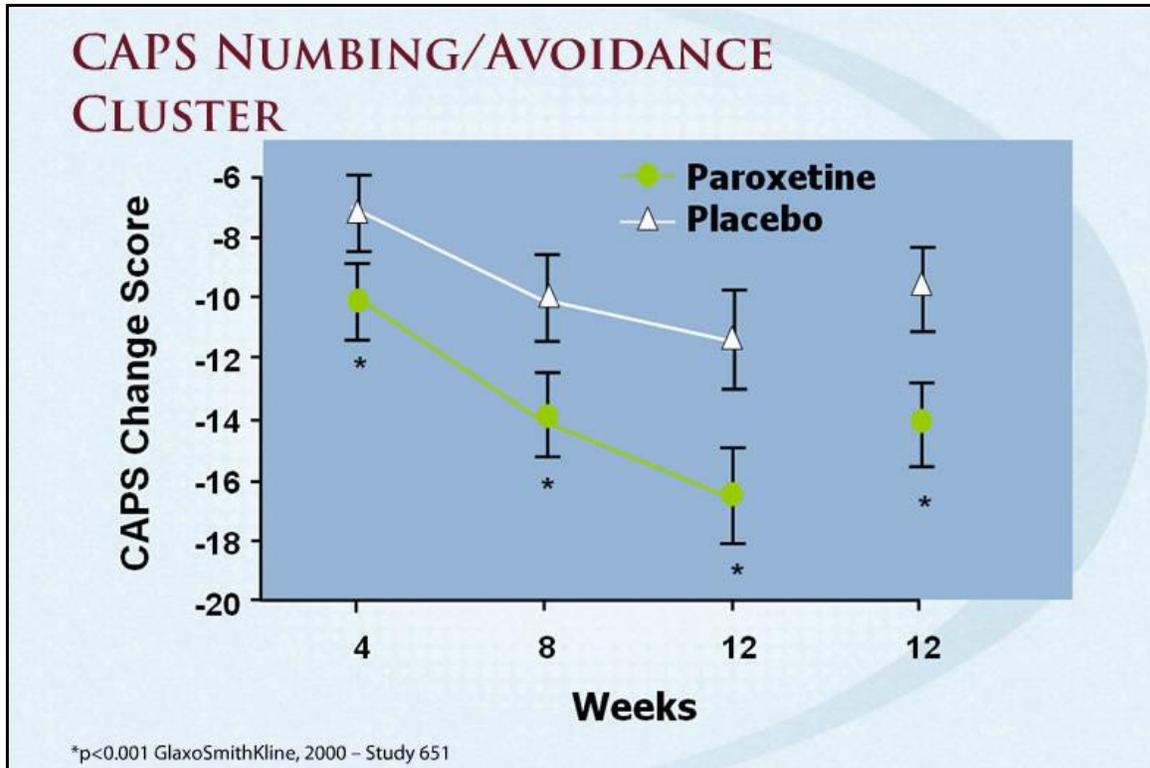
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The next 3 slides break out this paroxetine trial and look at the specific PTSD symptom clusters. The first slide looks at the re-experiencing B cluster and again, looking at reduction in CAPS severity over a 12 week period, you can see that the paroxetine group had significantly greater reduction in re-experiencing symptoms than did the placebo group.

CAPS Numbing/Avoidance Cluster

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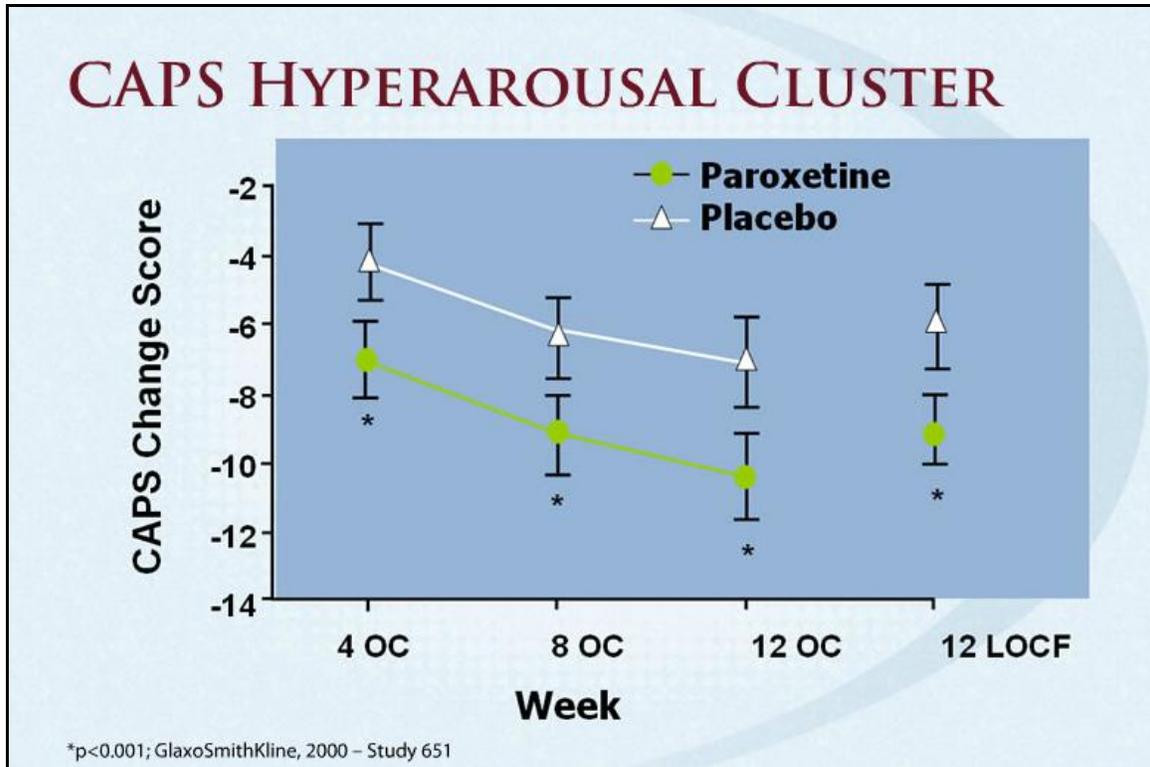


The next slide, same format, reduction in CAPS scores, 12-week period, we are looking at paroxetine reduction of avoidant/numbing symptoms over a 12-week period. And, once again, the paroxetine is significantly better than placebo.

And, I should add that, one of the excitements about the SSRI category, is that this was the first category of drugs to really reduce the avoidant/numbing cluster. Other medications were very good at reducing re-experiencing and arousal symptoms, but the SSRI's were the first group to really show a reduction in avoidance/numbing.

CAPS Hyperarousal Cluster

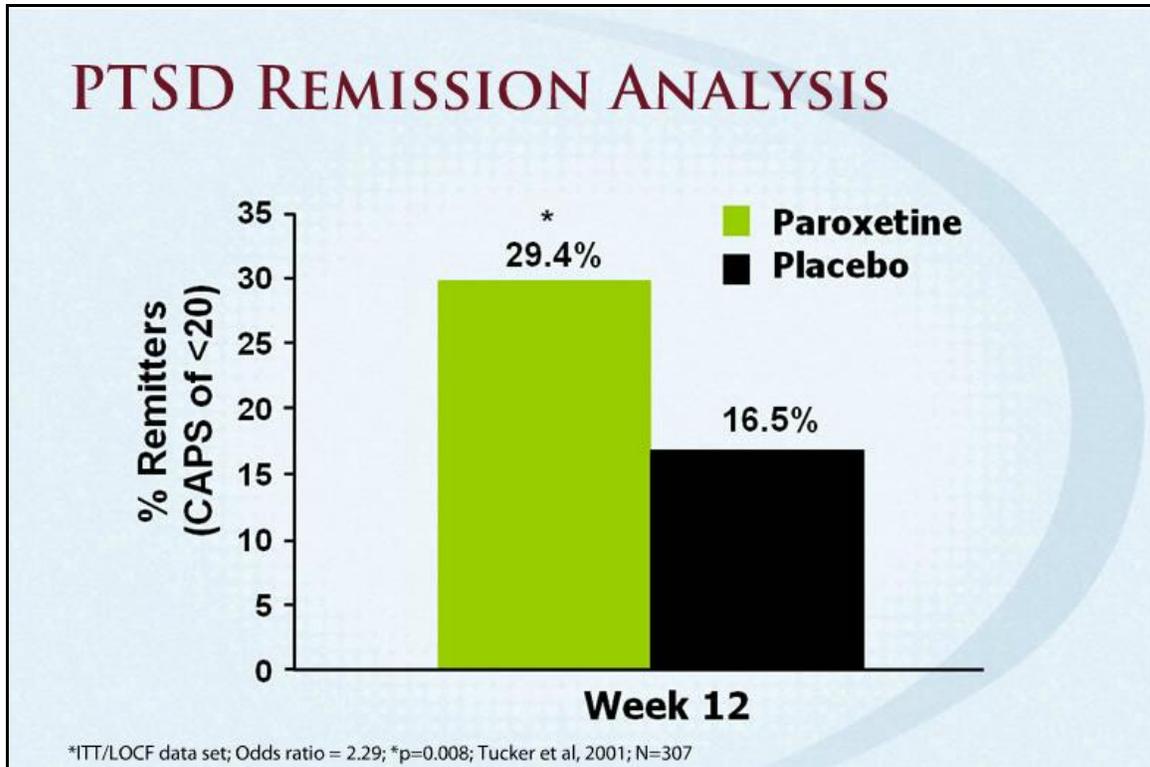
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And, the third slide in the series, again, looks at the D cluster-the hyperarousal cluster. And again, you can see over a twelve week period, reduction in CAPS scores is much greater for the paroxetine group than for the placebo group.

PTSD Remission Analysis

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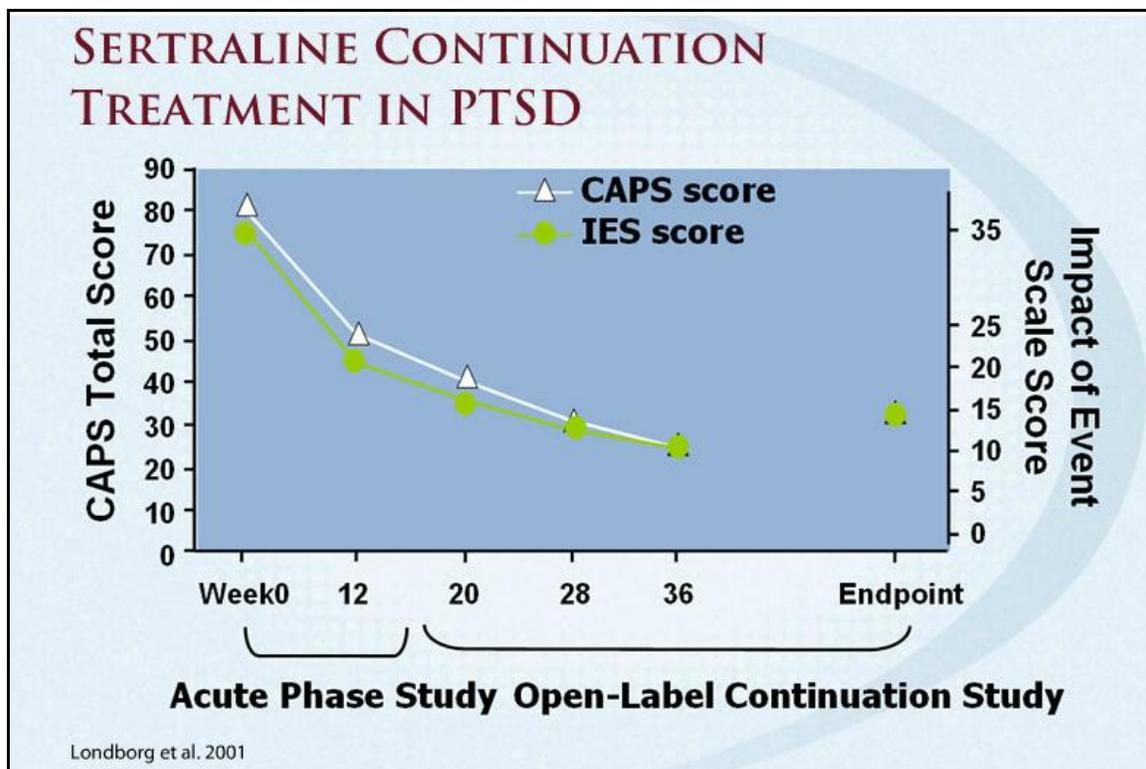


The next slide, in my opinion, is one of most important slides in this series because, you know, it's one thing for a medication to reduce symptom severity but, from a clinical perspective, we really want to know whether we achieved remission, whether the patient really is free of symptoms after they have had a course of medication.

And, here again, from the paroxetine trial, we're comparing, we're showing that 30%, almost a third of all patients who received paroxetine, had complete remission at the end of twelve weeks as compared to the placebo group, which only had about 15%. I should add that a similar analysis from Sertraline trials showed about the same thing, that about 30% of the Sertraline patients had complete remissions, compared to 15% of the placebo group.

Sertraline Continuation Treatment in PTSD

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The next slide really gets into some of the practical issues in treatment. And, here what we're seeing is a Sertraline continuation trial. So, there were two different randomized trials of Sertraline. Twelve week trials, like the data I've just shown you, where at the end of twelve weeks, the patients on Sertraline had much better reduction in PTSD symptoms severity than did the placebo group. And, as you can see on this slide, that twelve week end of the clinical trial shown is pretty close to the left part of the graph.

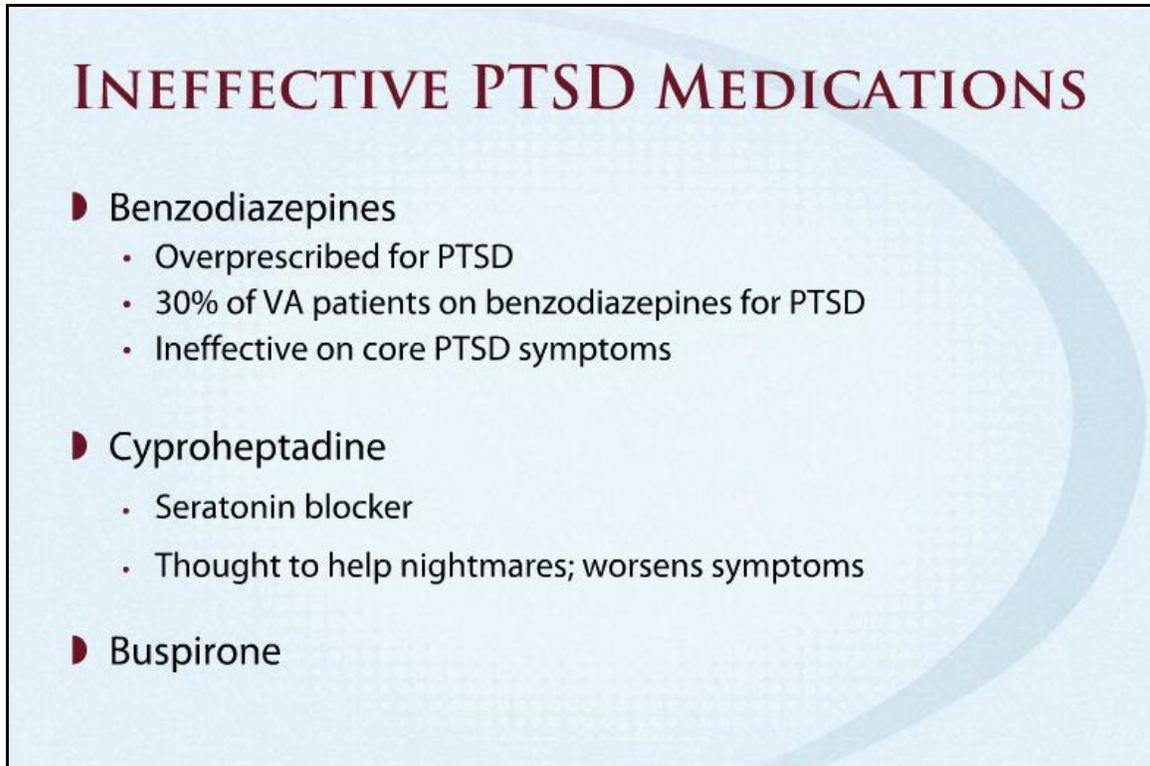
But, these patients were kept on their Sertraline for an additional 24 weeks, so that the actual slide goes out to 36 weeks. And, we're measuring actually two different measures of PTSD symptoms severity; the CAPS total on the left and the impact of event total on the right. But, both curves essentially show the same thing. And, what it shows is that, if you keep a person on the medication after twelve weeks, they continue to show improvement. And, point in fact, whereas only 30%, as I've told you previously, had shown complete remission at the end of 12 weeks, by the end of 36 weeks, more than half, 55% had shown clinical remission.

So, what this means clinically is, if you have a patient whose had a good response at the end of 12 weeks, but they haven't had complete remission, keep them on the medication. You may want to add other medications, or other treatments, such as Cognitive

Behavioral Therapy but, keep them on the medication because it's going to continue to show increased effects as time wears on.

Ineffective PTSD Medications

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INEFFECTIVE PTSD MEDICATIONS

- ▶ Benzodiazepines
 - Overprescribed for PTSD
 - 30% of VA patients on benzodiazepines for PTSD
 - Ineffective on core PTSD symptoms
- ▶ Cyproheptadine
 - Serotonin blocker
 - Thought to help nightmares; worsens symptoms
- ▶ Buspirone

The next slide, unlike the previous of group where I've shown success stories, shows drugs that are ineffective. And, at top of the list of events are the Benzodiazepines. And unfortunately, over 30% of VA patients with PTSD are still getting these medications. There's really no good reason to do this.

First of all, the medications don't work. Secondly, there is, in susceptible individuals, a risk of addiction and dependence. And third, there's some emerging evidence that these medications may actually interfere with Prolonged Exposure treatment, which is one of our most effective treatments. So, just say no. Don't put people on Benzodiazepines because, once you do, it's hard to get them off.

The other two bullets, one is about Cyproheptadine, a Serotonin blocking agent that's used for skin problems. There was some letters and some articles early on suggesting these medications were really good for PTSD flashbacks and nightmares. In a randomized trial that actually I was a part of, we showed that, not only did Cyproheptadine not work, but it made people worse. Which actually, is reassuring because, if drugs that enhance serotonin, like SSRIs make them better, then a drug that blocks serotonin 5HT 2 receptors should make them worse; and, Cyproheptadine does that. And, Buspirone is an anxiolytic, which also has not been shown to be effective for PTSD.

Important Medication Developments

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IMPORTANT MEDICATION DEVELOPMENTS

- Venlafaxine (SNRI)
 - At least as effective as SSRIs in civilian trials
- Prazosin (alpha₁ adrenergic antagonist)
 - Cooperative Study underway; effective in treating nightmares, allows improved sleep
- Augmentation with atypical antipsychotics
 - Negative Cooperative Study with risperidone
- Clonidine, guanfacine (alpha₂ agonists)
- Naltrexone, nalmefene (opiate antagonists)

The next two slides basically summarize what I consider some of the important medication developments in pharmacotherapy for PTSD. The first bullet, I've already addressed, that Venlafaxine, which is a serotonin norepinephrine reuptake inhibitor is at least as effective as SSRIs in civilian trials, and might even be a little better. Prazosin, as I said earlier, which is an alpha₁ adrenergic antagonist, is an excellent drug for blocking PTSD traumatic nightmares. But, the jury is still out on whether it's a good drug for PTSD as a whole. There's a big VA cooperative study that is currently in progress that should give us that answer and we're all looking forward to those results.

The third bullet is about a very important question. There, again, have been some small trials suggesting that for patients who have a partial response to a one of the medications I mentioned earlier, SSRIs or other antidepressants, that if you added an atypical antipsychotic drug, they would have a greater improvement. And, in earlier versions of the clinical practice guidelines, we actually recommended the use of antipsychotics for that purpose.

There was a very large VA cooperative multi-site trial which tested whether or not augmentation with Risperidone, an atypical antipsychotic, would enhance the effectiveness of partial responders to SSRIs and other antidepressants. And, the resounding answer is that Risperidone was ineffective. As a result of that, the practice

guidelines have been revised so that Risperidone is no longer recommended as an adjunctive agent for treating PTSD. The other atypical antipsychotics are now in the “Insufficient Evidence-We Don’t Know” category. In other words, we cannot make a recommendation one way or the other. But, given the side effect profile of these atypicals, which is not insignificant, I would not recommend using them for treating PTSD, unless there are comorbid problems that might warrant their usefulness.

Clonidine and guanfacine are two alpha2 agonists. They work presynaptically, they reduce the release of norepinephrine, they’re good drugs for hypertension. There’s a lot of theoretical reasons why you might expect them to work in PTSD. There’ve been two randomized trials with guanfacine; they’ve both been negative. Frankly, it’s been a disappointment, but at the moment, we cannot recommend that either of these medications in PTSD.

And finally, opiate antagonists have been used in treating people with PTSD and comorbid substance abuse disorder. They seem to work with the substance abuse disorder, they don’t make the PTSD any worse. So, it’s something to consider if you’re looking at comorbid PTSD and substance abuse disorder.

Important Medication Developments

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IMPORTANT MEDICATION DEVELOPMENTS

- ▶ Propranolol (beta adrenergic antagonist)
 - Has not proven to be an effective preventative agent, but reduces arousal
- ▶ Mirtazapine (alpha₂ agonist/5-HT blocker)
 - Positive Randomized Controlled Trials
- ▶ Bupropion (blocks presynaptic NE/DA uptake)
 - No evidence for efficacy in PTSD

Some of the other important developments on the next slide, Propranolol, which is an adrenergic beta antagonist, there have been a fair amount of excitement that these drugs might be good prophylactic agents. So, a typical experiment might be someone who has been in a car wreck, or rape, or domestic violence, comes into an emergency room, their blood pressure is high, they've got PTSD symptoms, you give them Propranolol. Maybe you can prevent the later development of PTSD – doesn't seem to work. Another disappointment, but that's why we do the research to find out whether things work, whether our best ideas really work out in practice.

As stated earlier, Mirtazapine, a very good antidepressant with actions of both alpha 2 receptors, as an agonist and a 5-HT blocker, seems to be a very effective drug for PTSD. And finally, Bupropion (Wellbutrin), which is a good antidepressant, it is a pre-synaptic, norepinephrine dopamine reuptake inhibitor. And, it's getting a lot of use in PTSD, there is no evidence that it works; so, please be careful out there. And, that's again, why we do the research, there was no evidence that it works.

D-Cycloserine Developments

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D-CYCLOSERINE: PROLONGED EXPOSURE AUGMENTATION

► How it works

- NMDA receptors enhanced
- Mediates learning and memory

► Current research

- Shown to be effective for other anxiety disorders
- Faster extinction than exposure alone
- Research with PTSD patients underway

Next slide is on what I consider one of the most exciting developments in PTSD, D-cycloserine. D-cycloserine has been around long time. It was originally developed for treating tuberculosis. It works at NMDA receptors and it mediates learning and memory. And, it has been used in conjunction with prolonged exposure as an augmenting agent.

Unlike most medications that you prescribe every day, the D-cycloserine is only given an hour before the trials. So, you might only need ten or twelve of these for a full course prolonged exposure. And, it works. It seems to accelerate the effectiveness of the prolonged exposure. So, whereas a patient is getting a prolonged exposure, either in a virtual reality, or in a face to face prolonged exposure format, may show remission at the end of ten or twelve weeks, if they've received D-cycloserine, they may achieve remission and five or six weeks. So, that's very, very exciting.

Also, D-cycloserine has been shown to be effective in cognitive behavioral treatments for agoraphobia, and social phobias. So, this is a very, very exciting development, and there's more research underway.

Antiepileptic Drugs in the Treatment of PTSD

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ANTIEPILEPTIC DRUGS IN THE TREATMENT OF PTSD

- ▶ Antiepileptic drugs promising but currently not approved for PTSD
- ▶ Promising open label but negative RCT results:
 - Divalproex
 - Topiramate
 - Carbamazepine
- ▶ An equivocal finding: Lamotrigine
- ▶ Negative findings:
 - Vigabatrin
 - Tiagabine

The next slide is bad news; that Antiepileptic drugs which work at both glutamate and GABA receptors, which again, theoretically, we might expect them to be very effective in PTSD, so far have been very disappointing. There have been some large, negative, randomized clinical trials with Divalproex, Topiramate, and Carbamazepine and it doesn't work; they have not been effective.

A very small, frankly, poorly designed study with Lamotrigine, also was not effective. And, negative findings for other antiepileptic drugs, such as Vigabatrin and Tiagabine. So, at the moment, we cannot recommend any antiepileptic drug in the treatment of PTSD.

Atypical Antipsychotics in the Treatment of PTSD

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ATYPICAL ANTIPSYCHOTICS NOT RECOMMENDED FOR ADJUNCTIVE TREATMENT OF PTSD

- ▶ 4 small positive trials:
 - Risperidone – 3 (mostly in Veterans)
 - Olanzapine
- ▶ 1 small negative trial:
 - Olanzapine
- ▶ 1 large negative multisite trial of Risperidone (N=247)

Bartzokis et al 2005; Hamner et al 2003; Monnelly et al 2003; Stein et al 2002; Krystal et al., 2011; Butterfield et al 2001

The next slide summarizes something I said earlier, but it's important because it's a new development. And, this is basically summarizing the research on atypical antipsychotics as adjunctive agents with SSRIs or other medications. So, at the top of the slide we summarize some small positive trials Risperidone and Olanzapine.

And, it was this research, frankly, that led us earlier on to recommend Atypicals as a good adjunctive agents for partial responders to SSRIs. But, in the last few months, a large, negative, multi-site VA cooperative study with 247 Veterans was published in which, patients who were partial responders to SSRIs and other antidepressant were randomized either to Risperidone or to placebo. And, what we found was Risperidone doesn't work, it doesn't make things any better. Contrary to what was indicated from the smaller trials shown at the top of the slide.

So, as I said earlier, as a result of that we no longer recommend Risperidone as an adjunctive agent for PTSD and, it really has cast doubt on the efficacy of all the other Atypicals. So, no Atypicals are now recommended as adjunctive agents for PTSD.

Strength of Recommendation from VA/DoD 2010 Guideline

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Pharmacotherapy Interventions for Treatment of PTSD: Balance of Benefit and Harm				
SR (Strength of Recommendation Rating)				
A Strong Recommendation	B Fair Evidence	C No Recommendation	D Ineffective or Harmful	E Insufficient Evidence
Significant Benefit <ul style="list-style-type: none"> • SSRIs — • Fluoxetine • Sertraline • Paroxetine • SNRI — • Venlafaxine 	Some Benefit <ul style="list-style-type: none"> • Mirtazapine • Prazosin (Use for sleep/nightmares) • TCAs • Nefazodone (Use caution) • MAOIs (Phenelzine – attention to drug-drug and dietary interactions) 	Some Benefit <ul style="list-style-type: none"> • Citalopram Unknown <ul style="list-style-type: none"> • Prazosin (For global PTSD) 	No Benefit <ul style="list-style-type: none"> • Benzodiazepines [Harm] • Tiagabine • Guanfacine • Valproate • Topiramate • Risperidone 	Unknown <ul style="list-style-type: none"> • Olanzapine and Quetiapine • Conventional Antipsychotics • Buspirone • Non-Benzodiazepine sedative/hypnotics • Bupropion • Trazodone (Adjunctive) • Gabapentin • Lamotrigine • Propranolol • Clonidine

The next slide basically summarizes all of the empirical data from the practice guideline. And, you can see it's divided into five different columns. Column A is the strongly recommended group of medications, and that includes the SSRIs and the SNRI Venlafaxine. The second column, the B level recommendations are some good drugs, Mirtazapine, Nefazodone, with the caution about liver toxicity, some of the older antidepressants, Phenelzine, and Tricyclics, and Prazosin for use in nightmares, but not in use for PTSD in general.

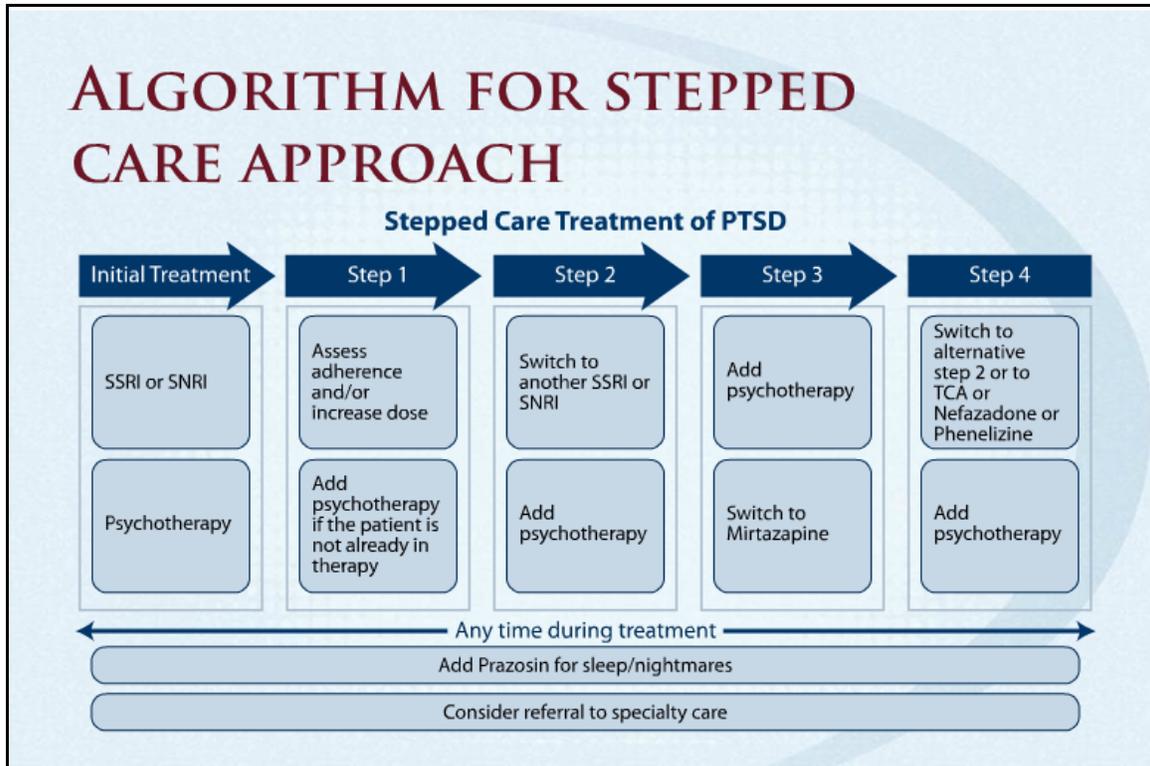
The next column basically has medication for which we have no recommendation, although there is some indications that they might work, but we can't make a recommendation; that includes Citalopram and Prazosin. And finally, in the D column, where we're recommending against their use. So, this is well founded research suggesting that these drugs, right now, don't work. And, that includes Benzodiazepines, Tiagabine, and other antiepileptic drugs, like Valproate and Topiramate, Guanfacine (an alpha2 agonist) and Risperidone, as I mentioned earlier.

And then the final column, the insufficient evidence column, is the biggest column of all. It shows you all the medications, that frankly, some people are prescribing, for which we

really don't have any evidence to justify their use in PTSD. There are atypical antipsychotics on this list, there's Bupropion, Trazodone, some antiepileptic drugs, etc.

Algorithm for stepped care approach

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The next slide basically shows how we recommend using this evidence. It basically is an algorithm for a step care approach. So initially, you want to start with an A-level drug, which is an SSRI or an SNRI, or one of our very effective psychotherapies, such as Prolonged Exposure or Cognitive Processing Therapy.

If the patient doesn't have a good response, than you might want to assess whether or not they are taking the drug as prescribed. And, if they are, you might want to add psychotherapy to the medication, if the patient isn't already in therapy. If you are still not having a good response, you might want to switch to another SSRI or SNRI, or add psychotherapy.

And then at Step 3, if we are still not having a good response, you might want to add a good B-level drug, like Mirtazapine, and on and on. Step 4, you would switch to other medications. If there's a specific problem like nightmares, you might want to consider Prazosin. If there is a problem with sleep, you might want to consider Trazodone, or Cognitive Behavioral Therapy for insomnia.

So, it's basically an algorithm for step care approach where you start with the drugs or treatments that have the strongest evidence and, if they don't work, then you move down the road to those that for which there is some evidence, but it is not as good.

New Medications for PTSD

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NEW MEDICATIONS FOR PTSD

- ▶ CRF antagonists
- ▶ Neuropeptide Y agonists
- ▶ Antiadrenergic agents
- ▶ Selective serotonergic agents
- ▶ Selective opioid agents
- ▶ Substance P antagonists
- ▶ D-cycloserine
- ▶ NMDA/non-NMDA/metabotropic glutamatergic modulators
- ▶ Anticonvulsants
- ▶ BDNF promoters

And finally, to close out this section of my talk, I just, on my list of medications that I think that we'd just want to keep a close watch on trials with these drugs in the future: Antagonist of Corticotropin-releasing factor (CRF Antagonist), Neuropeptide Y agonist. I really think we need to do more work with drugs that work on adrenergic system, more specific serotonergic drugs working on the opioid system. Substance P works on the stress system.

I've talked about D-cycloserine and other medications. The bottom bullet, the very interesting work from Ronald Duman and his colleagues in the National Center, that BDNF brain derived neurotrophic factor promoters, drugs that promote neurogenesis may be very, very good drugs not just for depression but for PTSD as well.

PTSD Treatment Options

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This is a slide which basically summarizes the two different classes of treatment. On the right we have pharmacotherapy and I've spent all this time telling you about pharmacotherapy, but on the left are psychotherapies and I said earlier psychotherapies are more effective than drugs right now. Among the psychotherapies we want to consider are exposure therapy, cognitive therapy, anxiety management, and eye movement desensitization and reprocessing (EMDR).

VA/DoD Clinical Practice Guidelines

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VA/DoD CLINICAL PRACTICE GUIDELINES

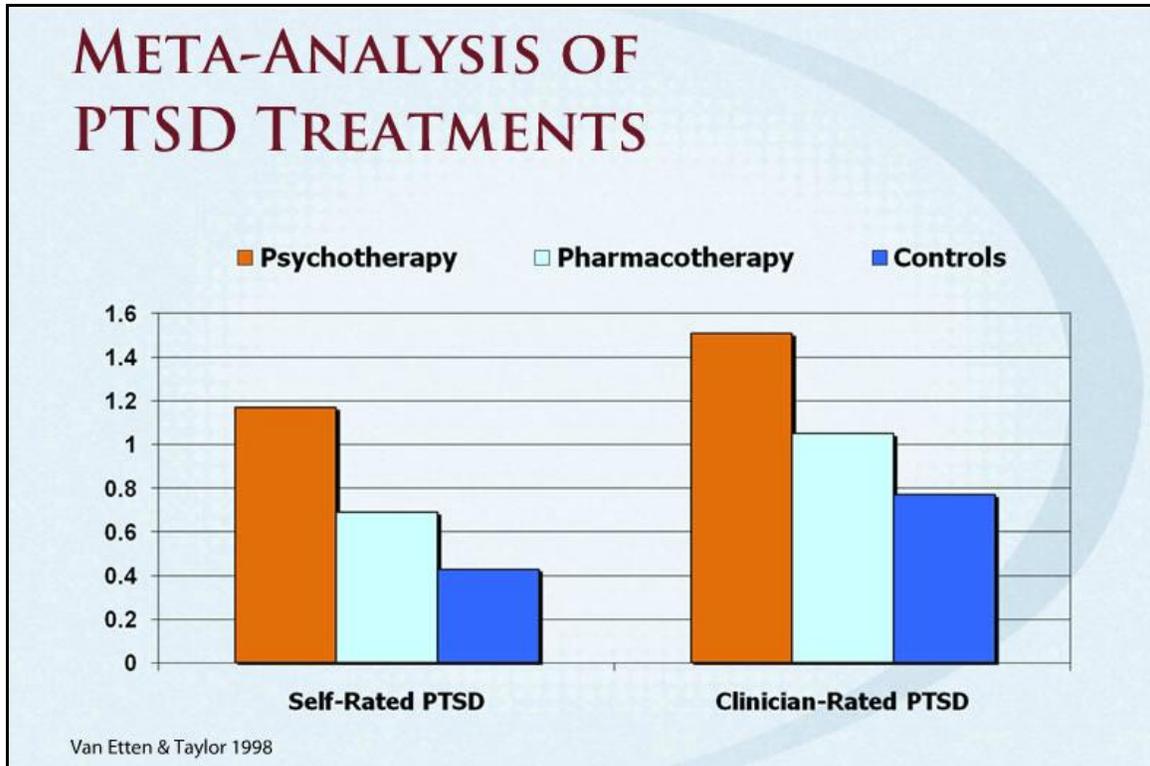
- ▶ **First Line Treatments: Psychotherapy**
 - Cognitive-Behavioral Therapy
 - Cognitive Processing Therapy
 - Prolonged Exposure
 - Eye Movement Desensitization and Reprocessing

- ▶ **Pharmacotherapy Treatments**
 - Selective Serotonin Reuptake Inhibitors
 - Venlafaxine

In a nutshell, if we look at the VA/DoD Clinical Practice Guidelines and other Practice Guidelines, we see that they have come to similar conclusions. First line treatments for PTSD are cognitive behavioral treatments, cognitive processing therapy, prolonged exposure, and eye movement desensitization and reprocessing (EMDR). In terms of medications the SSRIs—the selective serotonin reuptake inhibitors. But I would add to that the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine.

Meta-Analysis of PTSD Treatments

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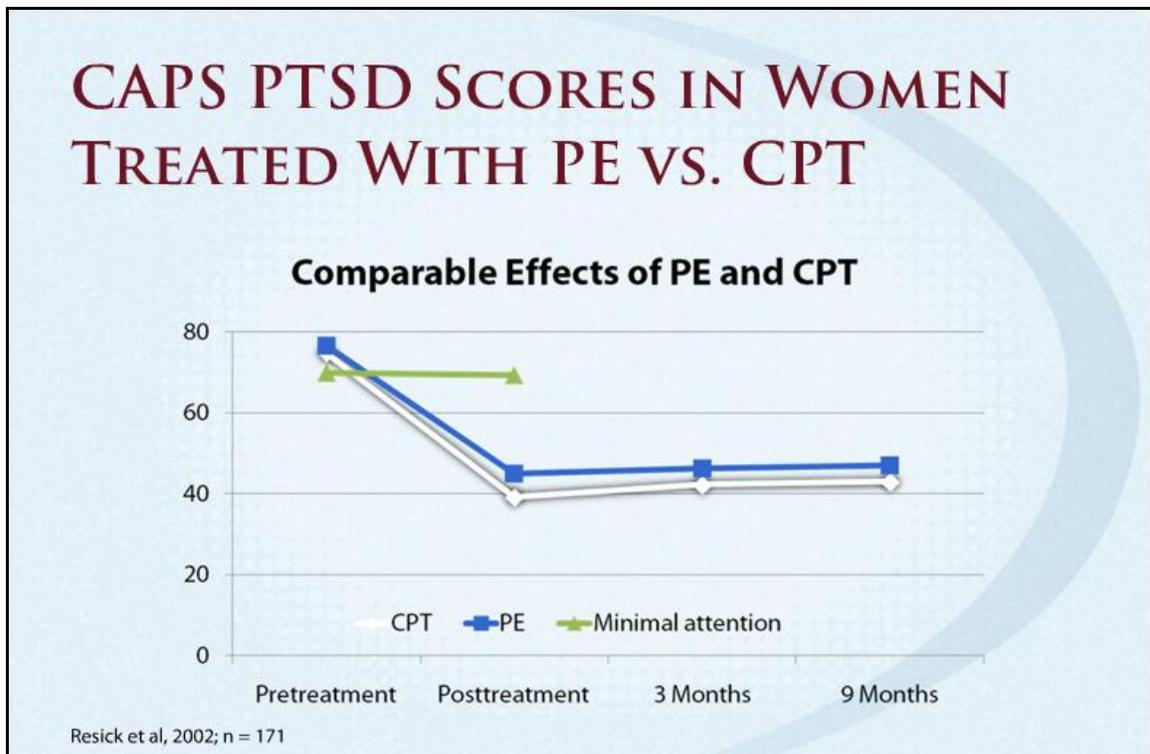


This slide summarizes a great deal of information and what we're looking at are effect sizes. An effect size of one or greater is very good, so if you have a treatment that can produce an effect size of one, that's one standard deviation, you've got a good treatment. And what we're showing here are the results of outcomes, clinical outcomes from psychotherapy, pharmacotherapy, and control patients.

On the left we have self-rating symptoms by patients and on the right we have clinician ratings, but as you can see the pattern is the same, as shown by the orange bars, the psychotherapy clinical trials are the best. The light blue bars show that the pharmacotherapy trials are certainly better than the controls (dark blue), but they're significantly less effective than psychotherapy.

CAPS PTSD Scores in Women Treated With PE vs. CPT

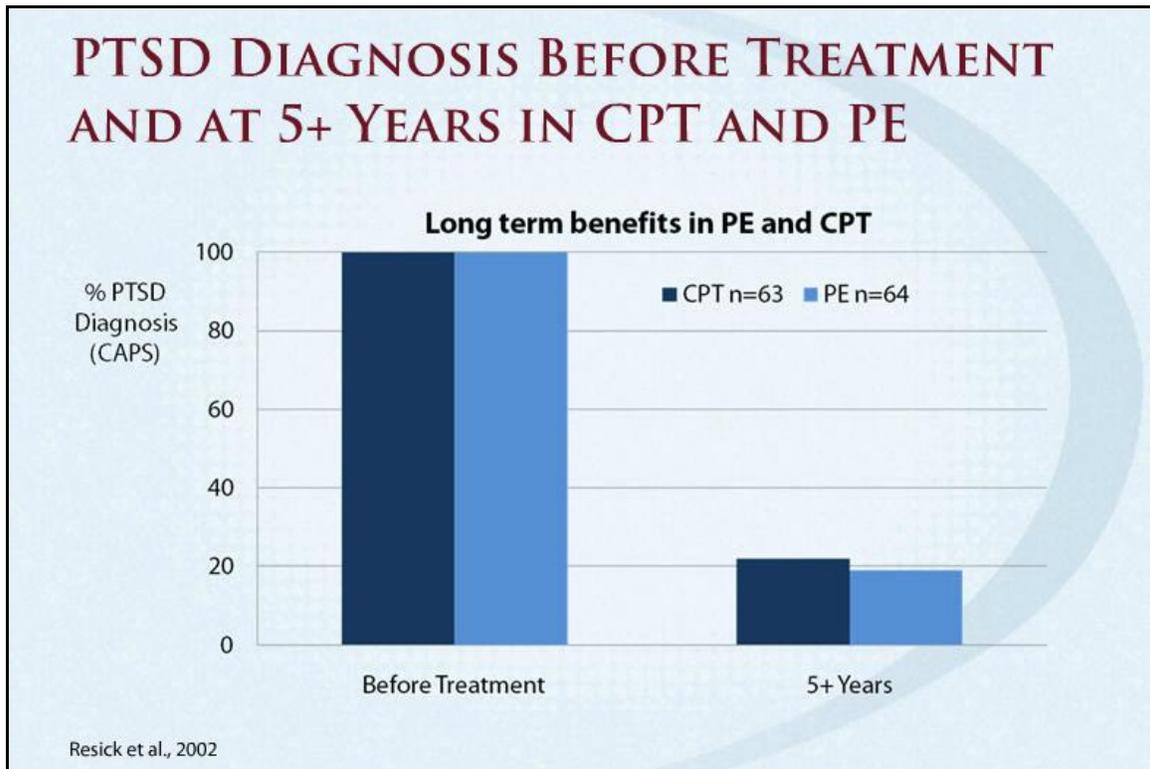
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In this slide we're comparing the two best treatments for PTSD. We're comparing prolonged exposure in blue with cognitive processing therapy in white, with a minimal attention group in green. This is about a ten-treatment trial; 170 women were in this particular trial. You can see that both treatments performed extremely well and that the treatments are sustained not just for three months but for nine months. This is quite dramatic.

PTSD Diagnosis Before Treatment and at 5+ Years in CPT and PE

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And this slide shows what happens in five-year follow up. This is a continuation of the research shown in the previous slide. We're looking at CAPS scores and you can see that five years later most of the patients are in complete remission; it's really quite remarkable. You know in cancer a five-year survival rate is considered a cure; I think we can talk about our cures in PTSD.

I also should emphasize that these women benefitted from their brief ten- to twelve-week course of cognitive behavioral treatment, and then they went on to sustain their improvement up to five years. Whereas with medication, if you have an improvement with medication—this is not just about PTSD but also about depression or other anxiety disorders—if you stop the medications, the likelihood is the patient will relapse. So if a person has a good response to medication you really need to keep them on the medication.

What I generally do is after a year or so I'll see if they can get by without it, slowly try to taper them off, but very often they cannot continue to do well without their medication. So that's another important advantage of the cognitive behavioral treatments over medication at this point in time. Perhaps we'll come up with a drug that will cure people once and for all and they won't have to keep taking it, but we don't have such a medication right now.

CBT over Medication

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CBT OVER MEDICATION

There is some emerging evidence that, given a choice, patients would rather have CBT than medication.

There have been a couple of recent trials, one in Israel, one in the United States, that wanted to determine whether, if patients had a choice, they'd rather have medication or CBT. And in most cases, given a choice, they'd rather have CBT. So I think it's important to be aware that even though you've got good medications that will work for many people, a number of your clients will refuse to take them, at least until they've had a trial of CBT.

Key Questions About Treatment

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KEY QUESTIONS ABOUT TREATMENT

- ▶ How should one choose among treatment modalities?
- ▶ What can one expect from treatment and how does one define realistic goals?
- ▶ How can one combine various treatment techniques?
- ▶ How does one approach complex clinical pictures and comorbid conditions?
- ▶ How long should a treatment be followed?
- ▶ How does one make sense of clinical difficulties and assess failure?

I've listed here six key questions about treatment.

What treatment should you choose?

What are reasonable expectations?

How do you combine different treatments (because most of our patients are on more than one)?

What do you do if a patient has more than one problem?—which is usually the case; if you have PTSD you've got an 80% likelihood that you're going to have at least one other problem

How long should you keep people on different treatments?

And how do you assess failure and what do you do about it?

Criteria For Choosing Treatment For PTSD

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CRITERIA FOR CHOOSING TREATMENT FOR PTSD

- ▶ Expected efficacy for amelioration of PTSD severity
- ▶ Associated disorders and problems
- ▶ Difficulties, side effects, negative effects
- ▶ Acceptability and consent
- ▶ Cultural appropriateness
- ▶ Length, cost, and availability of resources
- ▶ Legal, administrative, and forensic implications
- ▶ Accessibility and acceptability to the family

So, the major reason for choosing one treatment rather than another is the clinical data, and that's why I've spent so much time going over that with you. Those treatments that have the strongest evidence in their favor are the ones that ought to be selected first.

Another reason might be an associated disorder, so for example if you've got a person that has PTSD and depression you might think about an antidepressant and maybe you can kill two birds with one stone. Sometimes people just can't tolerate certain treatments, they have side effects from medications, or they don't want to participate in an exposure therapy, so that obviously is going to be something that drives your decision.

What we're trying to do as clinicians is a goodness-of-fit assessment—we want to find treatment that our patients are going to accept and are going to stay on. Cultural appropriateness—in some cultures taking medication is something that people don't want to do, or contrariwise, don't want to do psychotherapy to talk about emotions, or don't want to talk about their problems in a group format. So cultural appropriateness is always something to keep in mind.

We also have to be realistic, the length and cost of and coverage for different treatments is going to drive some of these decisions. Sometimes people are involved in disability

claims process, or they're in lawsuits for reasons why they got their PTSD. And obviously, if the family isn't going to support the treatment, you're really in an uphill struggle.

Realistic Goals

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REALISTIC GOALS

- ▶ Remission is always the goal, unless proven otherwise
- ▶ Many chronic patients who have failed to respond to other therapies have benefited significantly from CBT or new medications
- ▶ If remission is not a realistic goal, maintenance of optimal function is the desired endpoint (e.g., recovery)

The goal of treatment, at least at the outset, is always complete remission. We always have the hope that our patients are going to benefit from our treatment and are going to be symptom free at the end of it.

Frankly, there are many patients who have had PTSD for decades who still may be excellent candidates for treatment because they've never had an effective treatment. They may have had some medications, or some psychotherapy that really was not a cognitive behavioral treatment, so don't rule out patients as candidates for remission just because of the duration of their PTSD.

On the other hand, there are some patients for whom remission is not a realistic goal, and so in that case the goal is to maintain them as well as possible, to reduce their symptoms as much as possible, to keep them out of the hospital, and to keep them at the optimal functional level.

Combining Treatments

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COMBINING TREATMENTS

- ▶ Introduce treatments one at a time
 - Take into account: treatment efficacy, patient's choices, and clinician's experience
- ▶ Conduct adequate clinical trial to determine effectiveness
- ▶ Discontinue if ineffective or intolerable side effects
- ▶ For partial response: introduce second treatment (Rx or CBT) without discontinuing first (e.g., prazosin, atypicals, mirtazapine)
- ▶ If response is adequate, try to discontinue first treatment
 - Try to eliminate all unnecessary medications

As I said earlier, many of our patients are on more than one treatment. And sometimes it gets confusing, particularly if they're not doing well—how are you going to know which treatment is working and which treatment isn't. So, what I like to do is to introduce treatments one at a time—and that goes for treatments or medications, one at a time.

So I think what you want to do is have a sensible sequence that takes into account the effectiveness of the treatment, that patient's choices and your own experience. If you're more familiar with one treatment than another, obviously that's the one that you're going to want to use.

You want to conduct an adequate clinical trial if possible. So, for medication, two, if not three, months of a trial before giving up on its efficacy. If, however, the treatment is completely ineffective or intolerable side effects occur, then you've got to stop the treatment and try something else.

What is often the case, particularly with medications, is that patients are better but they're not well. You get a partial response but they're not in complete remission. So, what I would do for example, is with the SSRI slide I showed you earlier where only 30 percent have complete remission at 12 weeks, keep them on that medication and then add

something else with the understanding that maybe another half of them will have complete remission just from the SSRI, but something else may accelerate that process.

If you get an adequate response after you've added one or two additional treatments, it's always a good idea to make sure that the patient needs to have all of those treatments. Polypharmacy is something we want to avoid, and so I think if you have a patient who finally after two or three treatments has a good response, it's good to take stock and see whether or not some of the initial treatments are no longer necessary and to eliminate them if at all possible.

Polypharmacy

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POLYPHARMACY

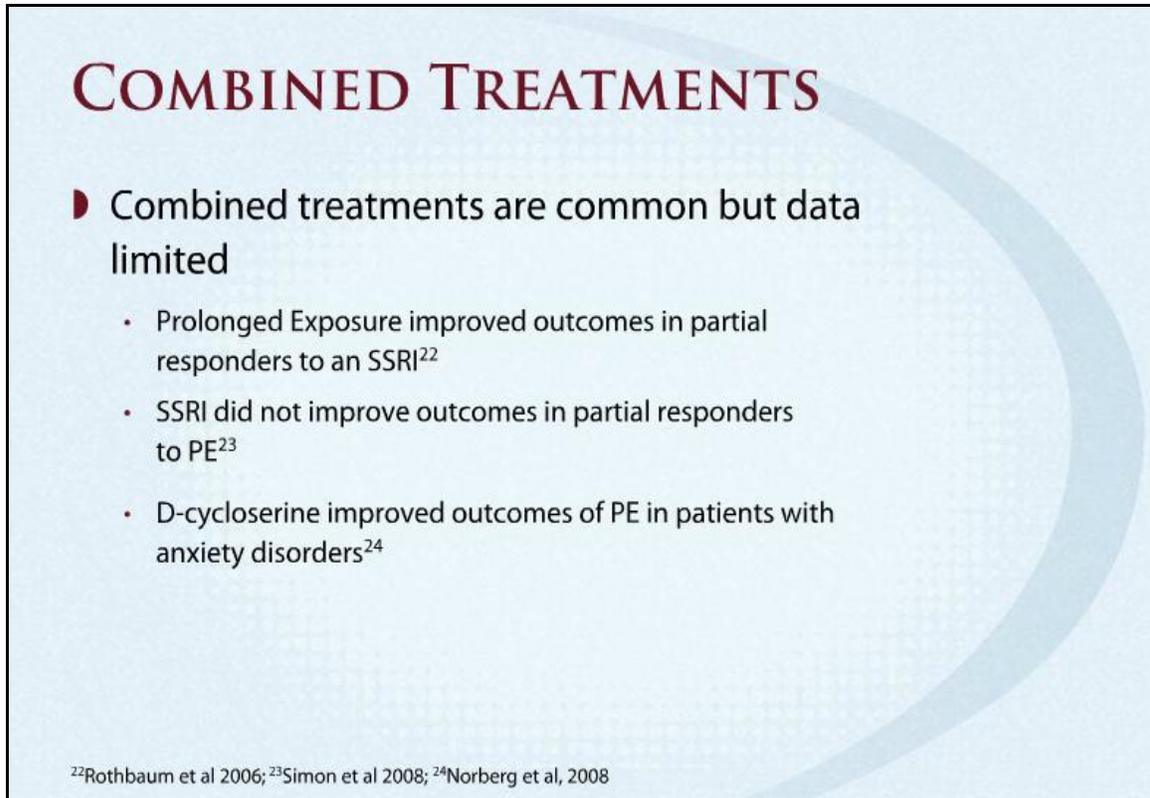
- ▶ The usual reason for polypharmacy is a partial response
- ▶ A clinical tendency is to add additional medications when one or more medications are only partially effective
- ▶ Because of compliance, side effects, and drug interactions, one should always strive to eliminate ineffective medications whenever possible

The usual reason for polypharmacy is a partial response; the patient is better but not well. So you add medications...and this isn't just true in psychiatry or in PTSD treatment; the same thing happens with our colleagues treating cardiac patients, etc. But the clinical tendency is to add additional medications and not to take away medications.

If you've added one medication or two medications, or one treatment or two treatments, and finally the patient is better, then it's best to back and see whether or not all of the treatments on board are still necessary or whether you can eliminate one or two.

Combined Treatments

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COMBINED TREATMENTS

- ▶ Combined treatments are common but data limited
 - Prolonged Exposure improved outcomes in partial responders to an SSRI²²
 - SSRI did not improve outcomes in partial responders to PE²³
 - D-cycloserine improved outcomes of PE in patients with anxiety disorders²⁴

²²Rothbaum et al 2006; ²³Simon et al 2008; ²⁴Norberg et al, 2008

Combined treatments are very common, but we don't have very much data about this.

There are actually three areas we have a little bit of data and I'll tell you about it. We have some data on sertraline and prolonged exposure, where patients who had only a partial response to sertraline showed much better response when prolonged exposure was added to the mix.

I've talked about adding atypical antipsychotics to SSRI partial responders, and I've talked about adding D-cycloserine to CBT, especially to prolonged exposure paradigms.

Treating Comorbid Conditions

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TREATING COMORBID CONDITIONS

- ▶ Vast majority of patients will have >1 comorbid disorder
- ▶ Crises and urgent conditions must be treated first
 - Suicidal/homicidal behavior
 - Severe alcohol/chemical dependency
 - Incapacitating depression
 - Marital/family/vocational crisis

Most PTSD patients will have something else that also requires treatment. And when you're deciding what to do about this, sometimes PTSD is not the first order of business. One always must attend to a crisis and urgent conditions if the PTSD is relatively stable. So obviously suicidal, homicidal behavior needs to be addressed, severe alcohol/chemical dependency may need to be addressed, an incapacitating depression may need to be addressed initially, and finally a marital, family, or vocational crisis.

Treating Comorbid Conditions

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TREATING COMORBID CONDITIONS

Few Randomized Clinical Trials:

- ▶ PTSD and SUD
 - Seeking Safety-5 RCT²⁵⁻²⁹
 - Sertraline-1 RCT³⁰
 - Naltrexone/disulfiram-1 RCT³¹
- ▶ PTSD and psychotic symptoms
 - Risperidone- 1 RCT³²

²⁵Najavits et al 2006; ²⁶Najavits et al 2005; ²⁷Hein et al 2004; ²⁸Zlotnick et al 2003; ²⁹Cohen et al 2006;
³⁰Brady et al 2000; ³¹Petrakis et al 2006; ³²Hamner et al 2003

There have been a few randomized clinical trials for treating a comorbid condition.

There's a fair amount of data now on treating PTSD and comorbid substance use disorder (SUD).

There have been five randomized trials with Seeking Safety which have been successful. There's been one trial with sertraline, a randomized trial on an alcohol ward where the alcohol dependency got better and the PTSD also got better.

There was a trial with chronic substance use disorder in which many patients had PTSD, this was a trial of naltrexone and disulfiram, both medications were effective in treating the chronic substance use disorder and the patients with the milder PTSD seemed to do reasonably well also.

And finally, when PTSD is associated with psychotic symptoms, and it does happen, use of an atypical antipsychotic medication that has shown effectiveness in one randomized trial.

Evidence-Informed Strategies for Comorbid Conditions

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EVIDENCE-INFORMED STRATEGIES FOR COMORBID CONDITIONS

- ▶ PTSD and Depression or Anxiety
 - FIRST LINE - SSRI/SNRI-good for both
 - Augment with mirtazapine, TCA
 - Augment with prazosin/atypicals

- ▶ PTSD and insomnia
 - FIRST LINE - Prazosin
 - Augment with SSRI/SNRI (can add trazodone)

- ▶ PTSD and Hyperarousal/Dissociation/Aggression
 - FIRST LINE - Consider prazosin
 - SSRI/SNRI
 - clonidine/guanfacine, propranolol

So let's talk about some of the common comorbid conditions that occur with PTSD; recognizing that we don't have the randomized, clinical trials but we've got a lot of evidence that we can draw on and I like to call this "evidence-informed information" because you want to do something and you want to do something that makes the most sense at the present time, knowing that further research may change these decisions.

So if you have a person who has PTSD and depression or some other anxiety disorder such as panic disorder (PD), social phobia, or obsessive-compulsive disorder (OCD), it's really a good idea to start with an SSRI or an SNRI because the SSRIs and the SNRIs are good for both. If you only have a partial response I would add then maybe mirtazapine, which is a good antidepressant and anti-PTSD agent which has a slightly different mechanism of action. Or an older antidepressant such as a tricyclic antidepressant (TCA). If the depression has gotten better but the PTSD hasn't, time to reach for the prazosin or an atypical antipsychotic.

Here's another scenario, PTSD and insomnia, not an unusual scenario at all. And here I would really start with prazosin; it's good for traumatic nightmares, it's good for insomnia. If you only have a partial response, I might consider an SSRI or SNRI,

recognizing, however, that sometimes these drugs themselves might produce insomnia; then you might want to add some trazodone into the mix.

A third scenario, PTSD and hyperarousal. A hypersympathetic individual; might be aggressive, might be dissociative. Again, I would go with prazosin. If that didn't work I would consider an SSRI or SNRI, but I frankly would be thinking about other antiadrenergic agents, such as clonidine and guanfacine to activate the alpha-2 pre-synaptic inhibitory receptor, or propranolol at the post-synaptic receptor.

Again, these are not clinical trials, this is evidence informed, based on guesses, based on some good evidence.

Evidence-Informed Strategies for Comorbid Conditions

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EVIDENCE-INFORMED STRATEGIES FOR COMORBID CONDITIONS

- ▶ PTSD and Psychotic/Hypervigilance
 - SSRI/SNRI and atypical antipsychotics
- ▶ PTSD and Bipolar Disorder
 - SSRI/SNRI and mood stabilizer
- ▶ PTSD and SUD
 - Concurrent treatment
- ▶ PTSD and Cognitive Impairment (mTBI) and Dementia
 - Start low, go slow
 - Avoid anticholinergics/benzodiazepines
 - Consider CBT (for mTBI)

So here if we have PTSD and psychotic disorders or excessive hypervigilance, and as you know sometime the hypervigilance can look like frank paranoia; you know it's time to consider a combination of an SSRI or an SNRI plus an atypical anti-psychotic.

Another scenario, PTSD and bipolar disorder; bipolars are not immune from PTSD and here you'd want to have a mood stabilizer along with your SSRI and your SNRI.

As far as PTSD and substance use disorder (SUD), I think that one of the problems that we often encounter is treatment is sequential. They'll enter a drug rehab and then they'll get their PTSD treated later or vice-versa, they'll start on PTSD and then get their drug. And in my experience this is not a very good idea. I think that the treatments need to be concurrent and they need to get their PTSD and their SUD treated at the same time. Because, let's face it, the alcohol or the drugs were one of the maladaptive coping mechanisms that were used for the PTSD. So if you just take away the alcohol or the drugs and don't give them something to replace it, don't give them the clinical tools that they need, they're going to relapse back on their drugs or their alcohol. So they need to be treated concurrently.

And finally, and this is a really important area to consider, is concurrent PTSD and cognitive impairment caused by mild traumatic brain injury (mTBI) in our newer

veterans or by dementia in many of our older patients. So I think that a rule of thumb is “start low, go slow.” These patients have damaged brain tissue; their capacity to tolerate different medications may be limited. So you want to start at low doses and go slowly to make sure that you’re not going to create side-effects and they can’t tolerate the medication.

When you’re worried about cognitive function as in TBI or dementia you want to avoid anticholinergic drugs and you want to avoid benzodiazepines. And frankly, I think one of the things we don’t have the data on right now but we’re trying to get it, is whether or not some of our mTBI patients can benefit from some of our cognitive behavioral treatments. Obviously, if they can then we won’t run into the problems with different medications.

How Long Should a Treatment be Continued?

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HOW LONG SHOULD A TREATMENT BE CONTINUED?

- ▶ Most published follow-up < 1 year
- ▶ Discontinuation of successful pharmacotherapy usually (but not always) followed by relapse
- ▶ Need to periodically assess necessity for continuing medication
- ▶ Since PTSD patients are vulnerable to relapse following complete remission, it would be good to investigate the utility of maintenance prophylaxis

As I've shown you, we have five-year follow up in some CBT studies. Most published follow-up is a year or less.

We need to be aware of the fact that if we stop a medication that has been successful, the likelihood of relapse is high. So we want to discontinue medications very slowly with titration to make sure that the patient is going to do all right.

On the other hand, we don't want to keep people on medications indefinitely. So what I do is every year or so, I try to titrate down; see if the patient can tolerate a smaller dose or stopping his medication. What you'll find after a while is some patients can go off medications and many cannot.

I think that one of the questions that has never been explored is whether patients who have PTSD and are now in remission, whether a small dose of medication or a small dose of cognitive behavioral treatment can prevent future PTSD? It's an important question; it's something we just don't know anything about right now.

How To Understand Treatment Resistance

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HOW TO UNDERSTAND TREATMENT RESISTANCE

- ▶ Inadequate dosage
- ▶ Side effects
- ▶ Drug interactions
- ▶ Poor compliance
- ▶ Adverse life events
- ▶ Ongoing or retraumatization
- ▶ Loss of social support

So if a patient has been on a treatment, let's say medication, and just isn't doing well after an adequate clinical trial, what are the questions we should ask ourselves?

One of the things we want to know is has the dose been adequate? And very often it hasn't been. Secondly, are there side effects that are making the individual not want to take the medication? Are there drug interactions; is there some other drug that they're taking that is metabolizing this anti-PTSD medication so that they're really not getting an effective dose? Are they following the medication regimen just fine, but something else has happened in their lives? As you know PTSD can be re-activated when people are re-traumatized or exposed to traumatic reminders. Is there loss of social support? Because social support has been found to be far and away the greatest protective factor for PTSD.

Conclusions

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CONCLUSIONS

- ▶ Cognitive-behavioral treatments are most effective for PTSD
- ▶ Medications remain a clinical option
- ▶ SSRIs have received the most attention with sertraline and paroxetine approved as treatments for PTSD
- ▶ Research is moving beyond SSRIs and considering medications that may improve psychobiological abnormalities associated with PTSD

So to conclude, it's clear that cognitive behavioral treatments are the proven, evidence-based treatments for PTSD.

However, medication is an important clinical option: it's effective, it's available, and it often works.

SSRIs have received the most attention with sertraline and paroxetine approved by the U.S. Food and Drug Administration (FDA) as a proven treatment for PTSD.

The good news is that research is moving beyond the SSRIs and considering medications that might be expected to improve the psychobiological abnormalities associated with PTSD. It's my hope that we will find more effective drugs in the future. Stay tuned and hopefully next time we talk about this I'll have something better to tell you about. Thank you very much.