

Effective pharmacotherapy for PTSD



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Disclosure slide



- The author has no conflicts of interest to disclose.
- This presentation reflects the views of the author and does not necessarily reflect the views of the Department of Veterans Affairs, UT Health Science Center San Antonio, or any other affiliated agencies.

Objectives



- Describe elements of collaborative care in treating PTSD patients.
- Explain how differing levels of evidence inform medication choice for treatment of PTSD.
- Identify first-line and second-line medication choices according to the VA/DoD PTSD Clinical Practice Guideline.
- Follow the stepped care approach to prescribing.



Collaborative care may be broadly defined as establishing roles and responsibilities between the prescribing clinician and therapist working toward the common good of the patient.

(Ref:
Psychopharmacology
and Psychotherapy: A
Collaborative Approach
edited by Michelle Riba,
MD and Richard Balon,
MD,1999)



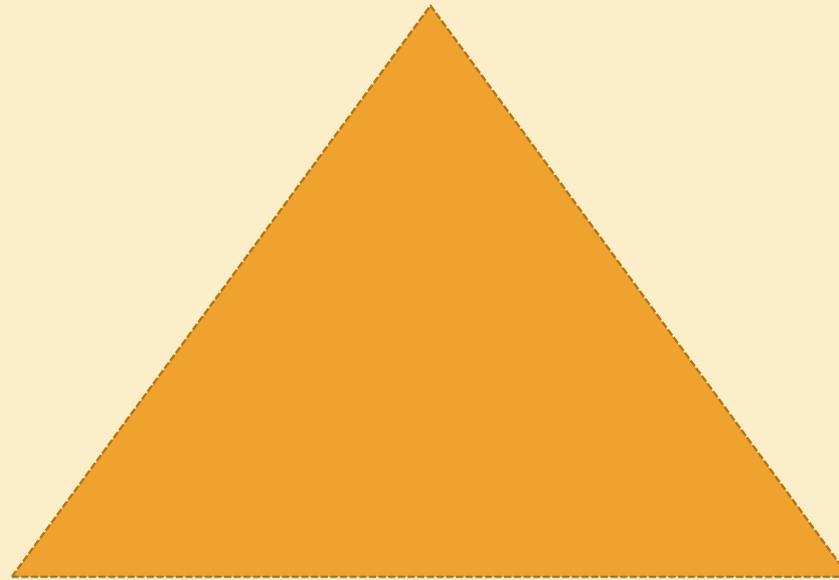
Collaborative Care

The therapeutic triangle



Patient

Therapist



Prescriber

Advantages and disadvantages of collaborative care



Advantages

- More options for the patient
- More cost effective
- Mutual support for the prescribing clinician and therapist

Disadvantages

- Potential for fragmentation of care
- Time needed for proper collaboration
- Conflicts over treatment direction and philosophy

Defining your role



Remember, you will be working with both the patient and the other clinician.

- Consulting clinician
- Supervisor/supervisee
- Colleague

Some questions to ask include

- Do we have similar treatment philosophies?
- Do we have trust in each other's clinical judgment?
- Do we communicate well together?

Overlap and differences in treatment roles



- **Pharmacotherapist:** symptom reduction, monitoring side effects, treatment adherence, therapeutic alliance
- **Psychotherapist:** exploring distressing emotions, distress tolerance to gain symptom reduction, therapeutic alliance, treatment adherence

Common pharmacotherapy barriers disclosed in psychotherapy



- Adherence
- Beliefs about taking medication
- Side effects

Therapeutic contract



Elements of a therapeutic contract may include

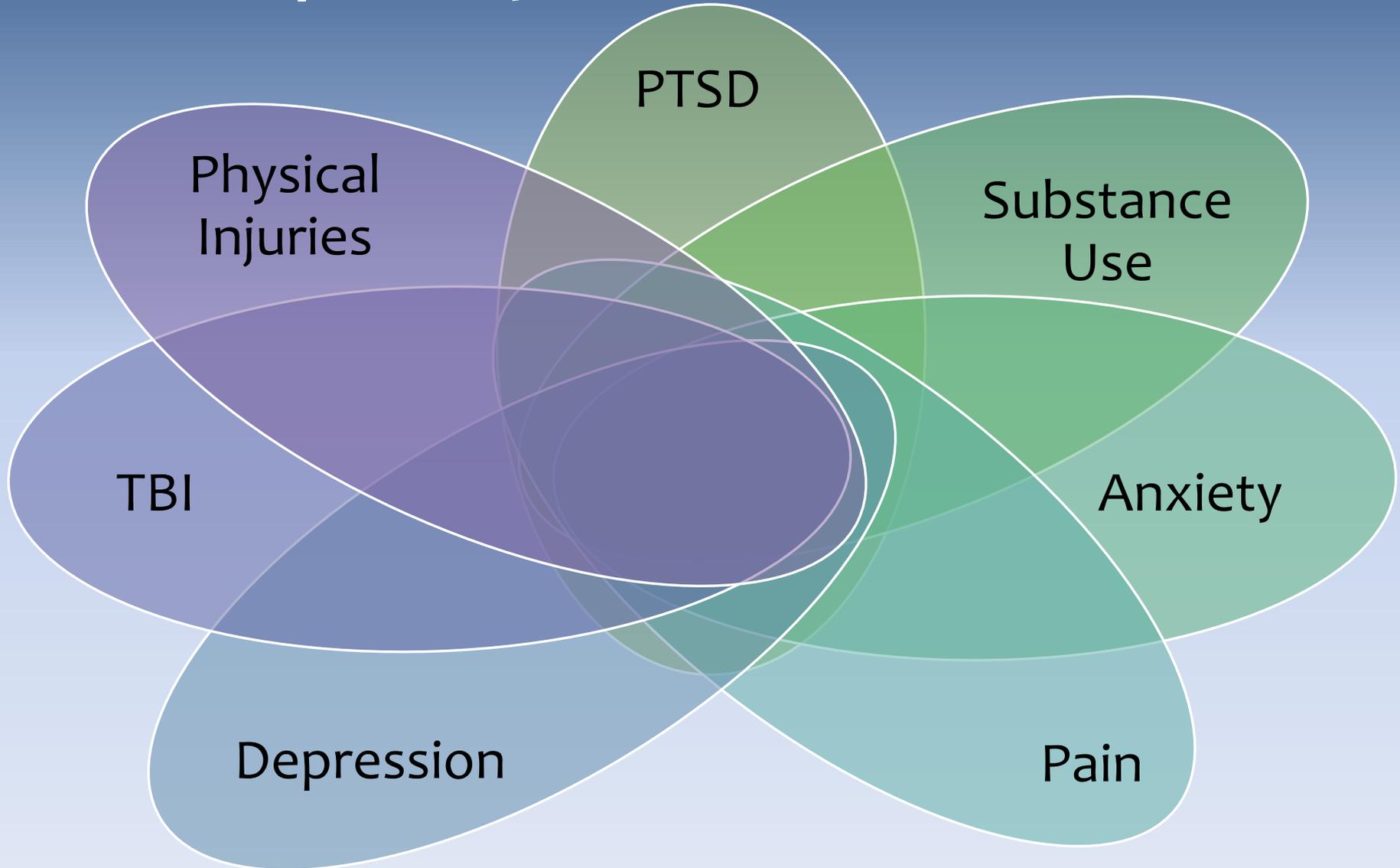
- Roles and responsibilities of the clinicians
- Coverage and access during emergencies
- Initiation and termination of treatment. What happens if the patient decides to terminate with one of the clinicians but would like to continue with the other?

Special considerations

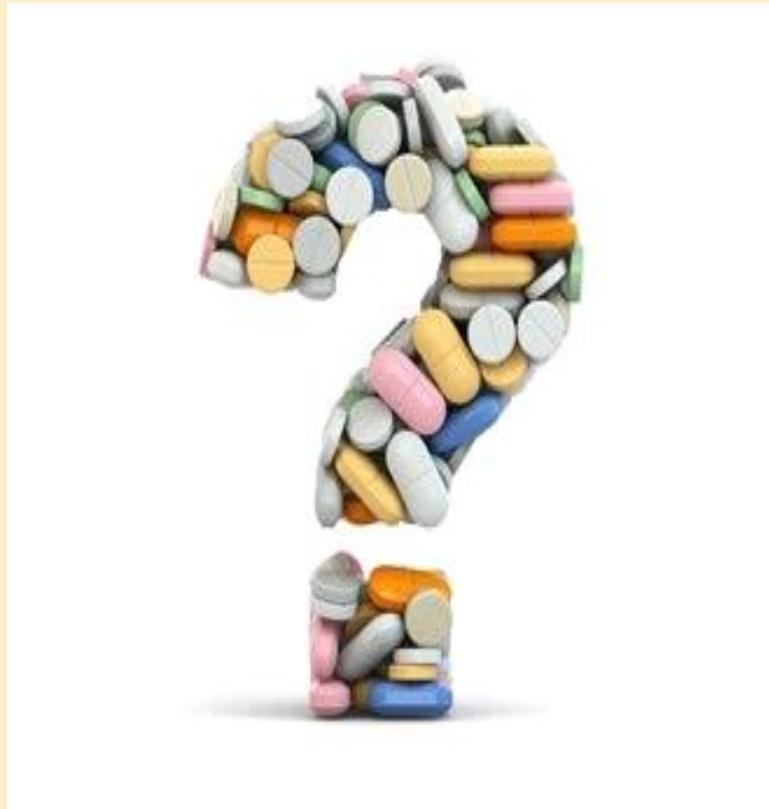


- Emergency access to clinicians and clinician roles in emergencies
- Patient dynamics such as splitting, devaluation and idealization, projective identification

Complexity is the New Normal



Pharmacotherapy



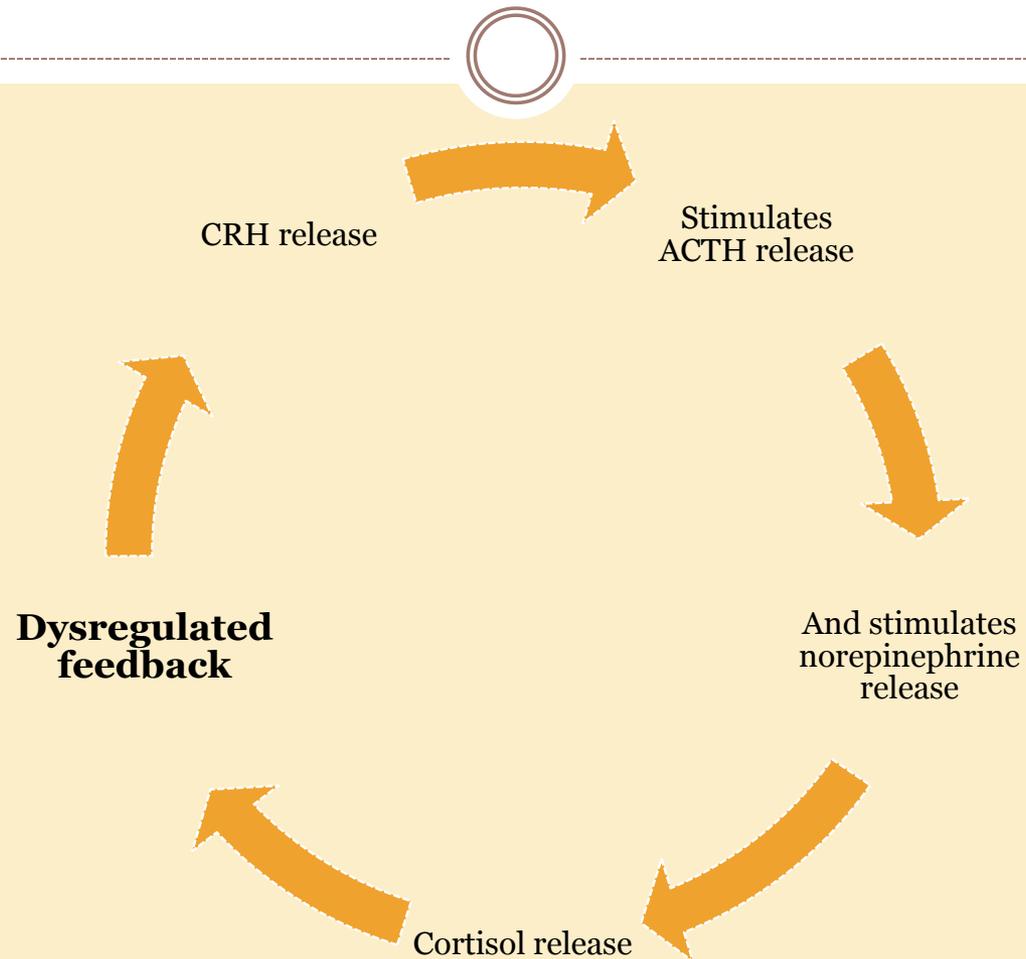
Anxiety circuit dysregulation in PTSD



- Increased noradrenergic sensitivity
- Dysregulated ACTH response
- Decreased inhibition of the prefrontal cortex on amygdala alarm system

Refs: Strawn, Depression and Anxiety, 2008

Dysregulated NE feedback in PTSD



Levels of evidence for PTSD pharmacotherapy



**Meta-
analyses of RCTs**

Randomized
Controlled Trials

Observational Studies

Non Analytical Studies

Expert Opinion

Rating the quality of the evidence



- Quality of Evidence (QE)
 - Good
 - ✦ At least 1 Randomized Controlled Trial (RCT) or 1 well-designed controlled trial *directly* linked to health outcome
 - Fair
 - ✦ At least 1 RCT or 1 well-designed controlled trial directly linked to *intermediate* health outcome **or** well-designed cohort or case-control study **or** multiple time series evidence
 - Poor
 - ✦ Opinion of experts, descriptive studies, case reports **or** no linkage of health outcome
- Net Benefit (NB)
 - Coded as substantial, moderate, small, or none

Strength of recommendations



- **A**
 - **A strong recommendation** that clinicians provide the intervention to eligible patients. Good evidence ... that the intervention improves important health outcomes and ... benefits substantially outweigh harm.
- **B**
 - **A recommendation** that clinicians provide (the service) to eligible patients. At least fair evidence ... that the intervention improves health outcomes and ... benefits outweigh harm.
- **C**
 - **No recommendation** for or against the routine provision of the intervention is made. At least fair evidence ... that the intervention can improve health outcomes but ... the balance of benefits and harms is too close to justify a general recommendation.
- **I**
 - ...evidence is **insufficient to recommend** for or against routinely providing the intervention. Evidence that the intervention is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms can not be determined.
- **D**
 - **Recommendation against** routinely providing the intervention to symptomatic patients. At least fair evidence...that the intervention is ineffective or that the harms outweigh benefits

Pharmacotherapy for PTSD: Summary

Balance = Benefit - Harm				
SR	SUBSTANTIAL	SOMEWHAT	UNKNOWN	NONE or HARM
A	SSRIs, SNRIs			
B		Mirtazapine, TCAs, MAOIs (phenelzine), Prazosin (nightmares), Nefazodone (caution)		
C			Prazosin (PTSD)	
D				Guanfacine, Topiramate, Valproate, Tiagabine Benzodiazepines (harm), Risperidone (adjunct)
I			Buspirone, Bupropion, Non-benzodiazepine Hypnotics, Lamotrigine, Gabapentin, Clonidine, Trazodone (adjunct), Propranolol Atypical antipsychotics (mono), Atypical antipsychotics (besides Risperidone) (adjunct) Conventional antipsychotics	

SR = Strength of recommendation
(Full Guideline, p. 149)

First line agents



- SSRI's
- venlafaxine
- Only the SSRI's sertraline and paroxetine are currently FDA approved for treatment of PTSD. All other medications are off-label use.

SSRI's



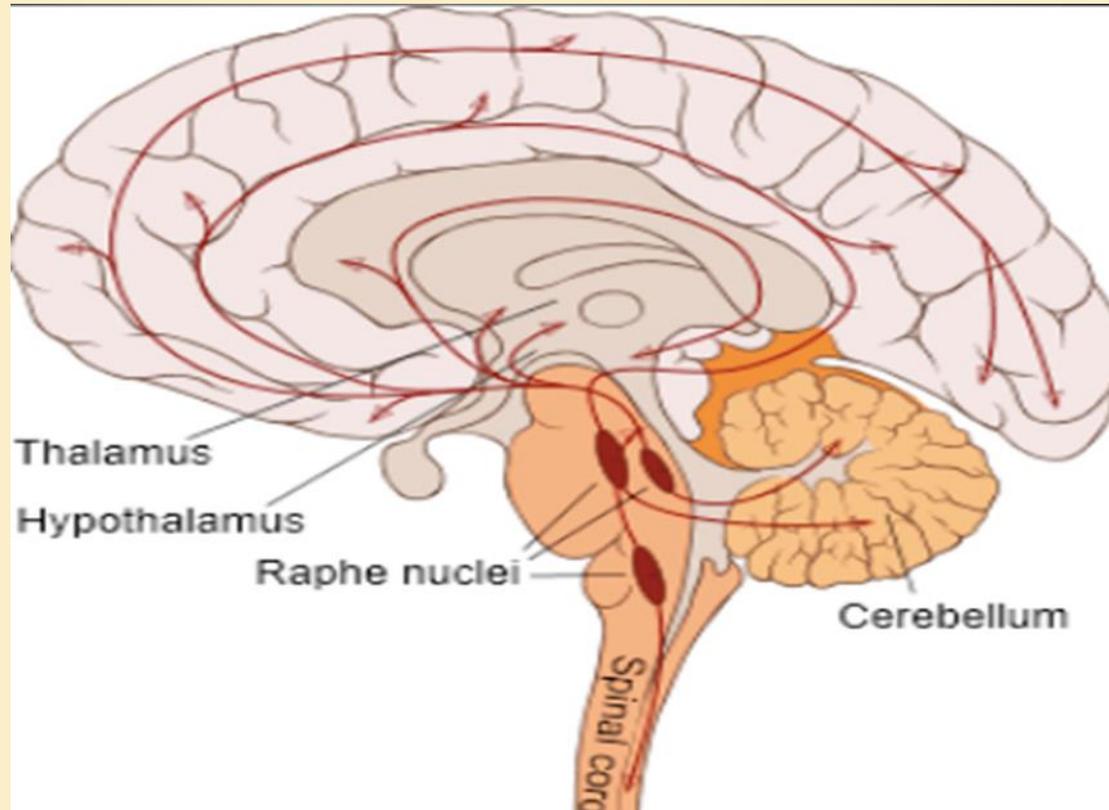
- sertraline (Zoloft)
- paroxetine (Paxil)
- citalopram (Celexa)
- fluoxetine (Prozac)

Common SSRI side effects

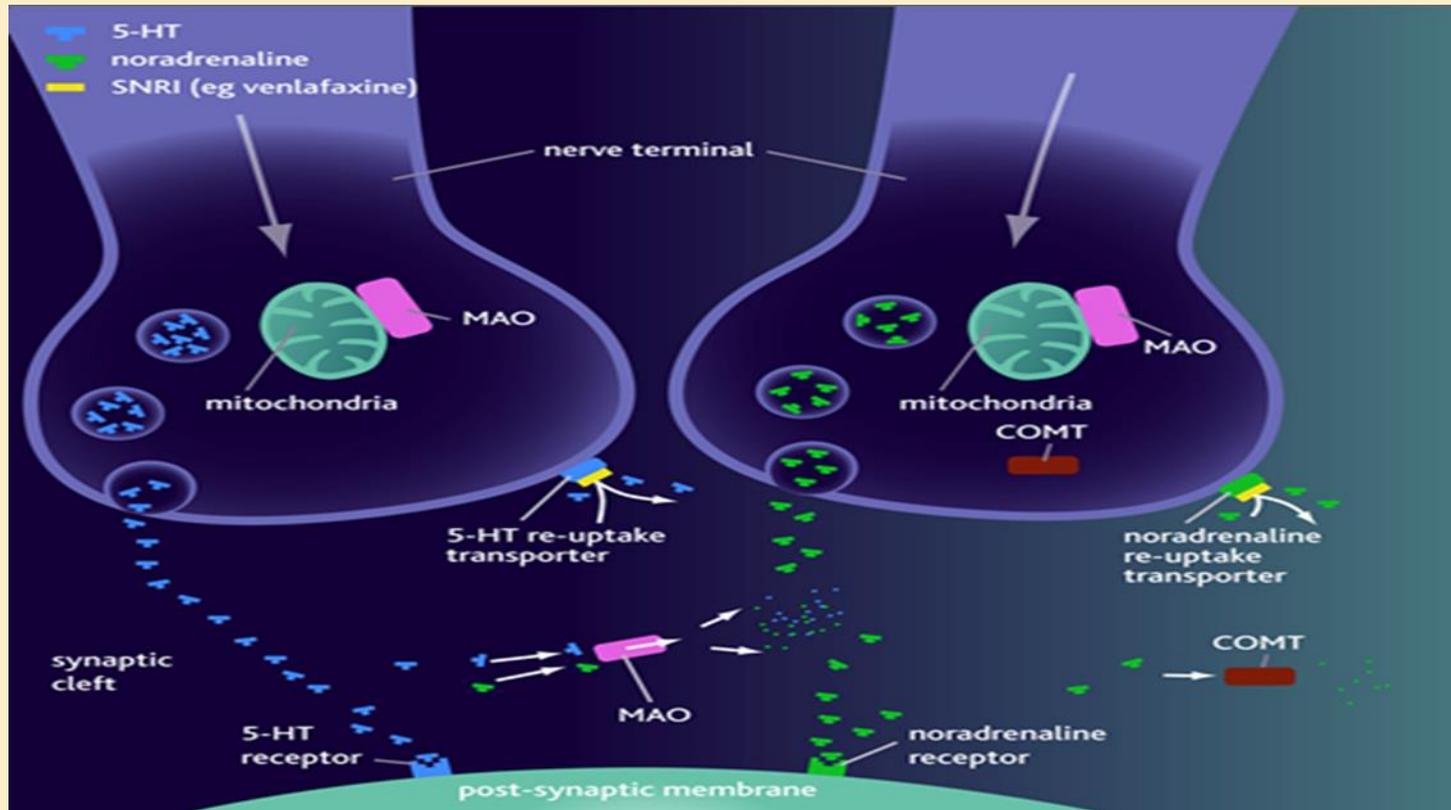


- Gastrointestinal (GI): nausea, vomiting, diarrhea
- Headache
- Sexual side effects: erectile dysfunction, delayed ejaculation, and anorgasmia

Serotonin distribution



Mechanisms of action (serotonin and norepinephrine reuptake inhibition)



Key points in using first line agents



- These medications treat the core symptom clusters of PTSD and not just co-morbid conditions.
- Be sure to provide an adequate trial at an adequate dosage
 - Reduction of anger within two weeks is a positive prognostic sign of good medication response at 12 weeks
 - PTSD symptoms may require up to 12 weeks for an adequate medication response

Sertraline outcome



CAPS-2 Total Score	Sertraline (n-93)	Placebo (n-90)	<i>P</i> value
Baseline	76.6	75.1	
Change	-33.00	-23.2	
Endpoint	43.6	51.9	0.02
	Ref: Brady, JAMA, 2000		

Venlafaxine outcome



CAPS-SX total score	Venlafaxine ER (n-161)	Placebo (n-168)	<i>P</i> value
Baseline	81.0	82.9	
Week 24	29.2	38.1	0.006
	Ref: Davidson, Arch Gen Psychiatry, 2006		

Second line agents



- Nefazodone (black box warning for 1/300k serious liver toxicity)
- Older TCA's (ex amitriptyline or imipramine)
 - potential cardiac side effect
 - can be LETHAL in overdose of >2 grams
- MAOI'S (ex phenelzine)
 - dietary restrictions to avoid hypertensive crisis
 - possible problems with lowered BP

Mechanism of action

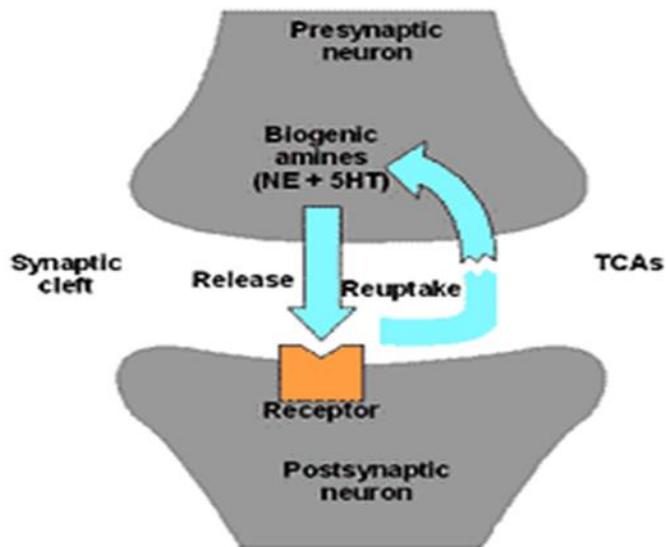


- Nefazodone
- Tricyclic antidepressants (TCA's) block the re-uptake of serotonin, norepinephrine, and other amines.
- Monoamine oxidase inhibitors (MAOI's) block the breakdown of amines through inhibition of the enzyme monoamine oxidase.

TCA's and PTSD



Mechanism of action of tricyclic antidepressants



MAOI's and PTSD



MAO INHIBITORS
Nardil / Parnate / Marplan

No
Popular
Meds

No...

- Barbiturates
- Tricyclic Antidepressants
- Antihistamines
- CNS Depressants
- Antihypertensives
- OTC Cold Meds

• Sweating

• Tremors

• Dizziness

• ↑ BP

• Pounding or Fast Heartbeat

No...

- Cheese
- Wine
- Pickled Foods

1997 xxx

Pickles Tyramine

SMILER

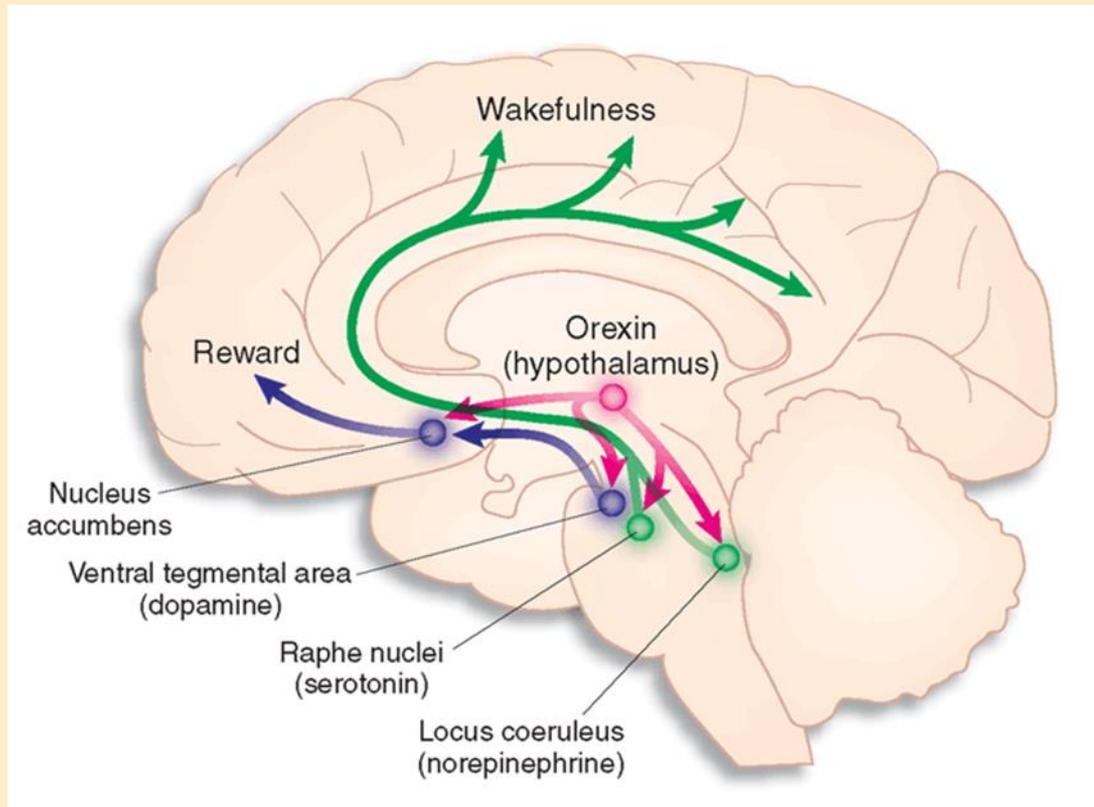
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Adjunctive treatments



- Prazosin titrated gradually up to 10 to 12 mg at bedtime may be helpful for nightmares.
- Mirtazapine 7.5 to 22.5 mg at bedtime may be helpful for sleep. It also has some beneficial effects on daytime PTSD symptoms and may be used as a second line agent.
- Trazodone 50 to 150 mg at bedtime may be helpful for sleep.

Noradrenergic projections



Alpha-1 adrenergic receptor blockade



Medscape® www.medscape.com

α_1 Adrenoceptors

α_1

α_1 antagonists (α_1 blockers) occupy the α_1 adrenoceptor site for norepinephrine -- inhibiting smooth muscle contraction.

α_1 Blocker

WebMD/ Medscape © medscape.com 2002

Medications with insufficient evidence or not effective for PTSD



- Mood stabilizers such as valproate lithium, etc.
--a possible exception is topiramate
- Guanfacine
- Bupropion
- Atypical antipsychotics as monotherapy
- Risperidone as adjunctive or monotherapy
- Benzodiazepines

Valproate and PTSD



- Twenty nine patients randomized to divalproex (n-16) or placebo (n-13) showed no significant differences on CAPS scores after 8 weeks except for significant decrease on avoidance for placebo.
- Eighty-five military Veterans were randomized to divalproex (n-44) or placebo (n-41) and showed no significant differences on the CAPS hyperarousal scale after 8 weeks.

Ref: Hamner, Annals of Clinical Psychiatry, 2009

Davis, Journal of Clinical Psychopharmacology,
2008

Topiramate and PTSD



- A randomized controlled trial of topiramate (n-35) vs. placebo (n-35) demonstrated significant decreases in total CAPS scores for topiramate
- Another trial in 67 combat Veterans randomized to topiramate (n-34) vs. placebo (n-33) demonstrated significant improvement for the topiramate group.
- Topiramate has shown improved sobriety in PTSD.

Ref: Yeh, CNS Neuroscience & Therapeutics, 2010
Akuchekian, Journal of Research in Medical Sciences, 2004
Batki, Alcoholism, clinical and experimental research, 2014

Risperidone and PTSD



- Earlier trials had indicated risperidone might be a helpful adjunctive treatment for PTSD.
- A 6-month randomized controlled trial of risperidone adjunctive therapy (n-147) vs. placebo add-on (n-149) demonstrated no significant differences on total CAPS scores.

Ref: Krystal, Journal of the American Medical Association, 2011

Benzodiazepines and PTSD

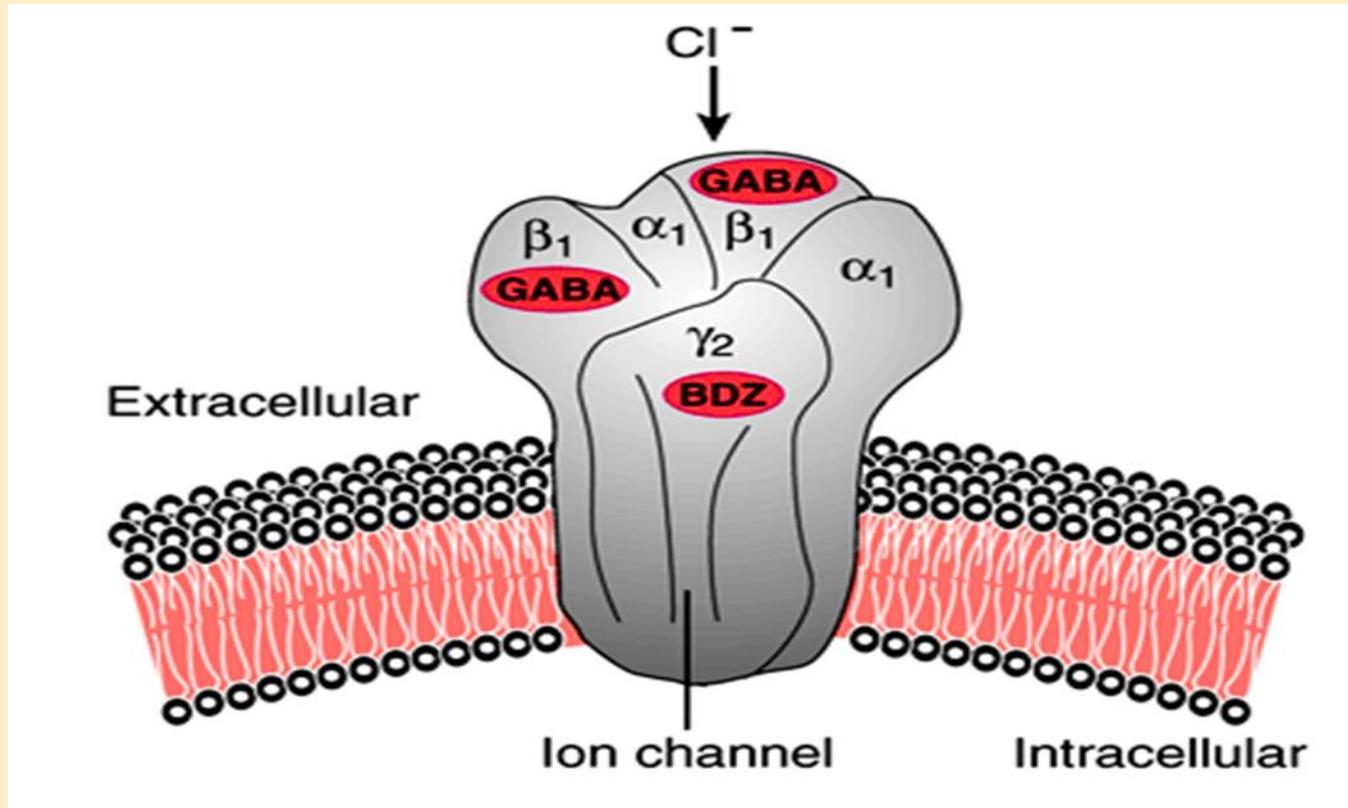


- Trauma survivors given a benzodiazepine (n-13) or no medication (n-13) demonstrated no significant differences on outcome measures for PTSD at 1 and 6 months.
- Patients with PTSD involved in prolonged exposure therapy were randomized to placebo (n-53), d-cycloserine (n-53), or alprazolam (n-50). The alprazolam group did significantly worse than placebo at 3 month follow up.

Ref: Gelpin, Journal of Clinical Psychiatry, 1996

Rothbaum, American Journal of Psychiatry, 2014

Benzodiazepine mechanism of action



Medications to be avoided in PTSD



- Avoid benzodiazepines!!
- The benzodiazepines are not shown to be helpful in PTSD
- Further issues with benzodiazepines
 - May create addiction problems
 - Are relatively contraindicated with Prolonged Exposure

The Problem with Benzodiazepines





Stepped care approach

Abbreviations:

SSRI – serotonin-specific reuptake inhibitors (e.g. paroxetine, sertraline)

SNRI – serotonin-norepinephrine reuptake inhibitors (e.g. venlafaxine)

MIRT – mirtazapine

NFZ – nefazodone

TCA – tricyclic antidepressant (e.g. imipramine, amitriptyline)

Initial TX

- SSRI, SNRI
- Psychotherapy

Step 1

- Switch SSRI or SNRI
- Add psychotherapy

Step 2

- Mirt, NFZ, TCA
- Add psychotherapy

Step 3

- Switch to alternative in Step 2
- TCA or phenelzine
- Add Psychotherapy

Monitoring treatment outcomes



- The PTSD Checklist-5 (PCL-5) in current use is a 20 item self-report scale which provides an objective measure of symptoms
- It is NOT diagnostic of PTSD
- Clinically meaningful cutoff is estimated to be 33

Ref: National Center for PTSD (www.ptsd.va.gov)

PCL-5

Instructions: Below is a list of problems that people sometimes have in response to a very stressful experience. Please read each problem carefully and then circle one of the numbers to the right to indicate how much you have been bothered by that problem in the past month.

In the past month, how much were you bothered by:	Not at all	A little bit	Moderately	Quite a bit	Extremely
1. Repeated, disturbing, and unwanted memories of the stressful experience?	0	1	2	3	4
2. Repeated, disturbing dreams of the stressful experience?	0	1	2	3	4
3. Suddenly feeling or acting as if the stressful experience were actually happening again (as if you were actually back there reliving it)?	0	1	2	3	4
4. Feeling very upset when something reminded you of the stressful experience?	0	1	2	3	4
5. Having strong physical reactions when something reminded you of the stressful experience (for example, heart pounding, trouble breathing, sweating)?	0	1	2	3	4
6. Avoiding memories, thoughts, or feelings related to the stressful experience?	0	1	2	3	4
7. Avoiding external reminders of the stressful experience (for example, people, places, conversations, activities, objects, or situations)?	0	1	2	3	4
8. Trouble remembering important parts of the stressful experience?	0	1	2	3	4
9. Having strong negative beliefs about yourself, other people, or the world (for example, having thoughts such as: I am bad, there is something seriously wrong with me, no one can be trusted, the world is completely dangerous)?	0	1	2	3	4
10. Blaming yourself or someone else for the stressful experience or what happened after it?	0	1	2	3	4
11. Having strong negative feelings such as fear, horror, anger, guilt, or shame?	0	1	2	3	4
12. Loss of interest in activities that you used to enjoy?	0	1	2	3	4
13. Feeling distant or cut off from other people?	0	1	2	3	4
14. Trouble experiencing positive feelings (for example, being unable to feel happiness or have loving feelings for people close to you)?	0	1	2	3	4
15. Irritable behavior, angry outbursts, or acting aggressively?	0	1	2	3	4
16. Taking too many risks or doing things that could cause you harm?	0	1	2	3	4
17. Being "superalert" or watchful or on guard?	0	1	2	3	4
18. Feeling jumpy or easily startled?	0	1	2	3	4
19. Having difficulty concentrating?	0	1	2	3	4
20. Trouble falling or staying asleep?	0	1	2	3	4

Some advantages and disadvantages of using self-report forms



Advantages

- Consistent way to measure symptoms
- Cover many symptoms quickly
- Can be saved in the electronic medical record
- Many are free of charge and in the public domain

Disadvantages

- Patients can over- or under-endorse responses
- Can seem mechanical

Summary



- Lesson 1: Collaborative care can offer many advantages for enhancing PTSD treatment
- Lesson 2: Start with an SSRI or venlafaxine and make sure the patient has an adequate trial and dosage.
- Lesson 3: Remember the stepped care approach following initial medication trials.
- Lesson 4: Avoid benzodiazepines whenever possible.

Additional resources



- VA/DoD PTSD Clinical Practice Guideline (www.healthquality.va.gov)
- National Center for PTSD (www.ptsd.va.gov)
 - Clinician's Guide to Medications for PTSD
 - PTSD Consultation Program



PTSD Consultation Program

FOR PROVIDERS WHO TREAT VETERANS



PTSDconsult@va.gov



(866) 948-7880



www.ptsd.va.gov/consult



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(866) 948-7880 or PTSDconsult@va.gov

UPCOMING TOPICS

SAVE THE DATE: Third Wednesday of the Month from 2-3PM (ET)

July 20 Evidence-Based Couple Therapy for PTSD Candice Monson, PhD

August 17 Shared Decision-Making for PTSD Juliette Harik, PhD

September 21 PTSD: From Neurobiology to Treatment John Krystal, MD

October 19 Treating Anger and Aggression in Populations with PTSD Leslie Morland, PhD

November 16 (To be determined)

December 21 Treating Tobacco Use in Patients with PTSD Andrew Saxon, MD

