The pharmacotherapy of PTSD

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The pharmacotherapy of PTSD

Anti-depressants

Anti-adrenergics

PRO-GABA

Anti-serotonergics

The Future
Antidepressants superior to placebo (Frank et al. AJP 1988)

A Randomized Clinical Trial of Phenelzine and Imipramine for Posttraumatic Stress Disorder

Julia B. Frank, M.D., Thomas R. Kosten, M.D.,
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Several studies (1–5) have used antidepressants to treat more than 60 patients with posttraumatic stress disorder (PTSD) and found that tricyclic antidepressants and monoamine oxidase (MAO) inhibitors are helpful in 67%–82% of cases. Here we report the preliminary results of what we believe to be the first placebo-controlled, double-blind clinical trial of both types of antidepressants in the treatment of PTSD.
Findings

- IMI and MAOI both effective (MAOI > IMI)
- Intrusion (hyper-arousal and reexperiencing) better than avoidance (avoidance, numbing)
- Depression did not improve much
Sertraline efficacy emerges slowly
K. Brady et al. JAMA 2000;283

![Graph showing mean change in CAPS-2 score over time for Placebo (n=90) and Sertraline (n=93).](image)
FDA-Approved SSRI’s: Sertraline and Paroxetine

- Better for some symptoms?
  - Sertraline: avoidance/numbing ≥ hyperarousal > reexperiencing? (Brady JAMA 2000; Davidson Arch Gen Psychiatry 2001)

- Profile of best response:
  - Positive studies: 10% - 20% bigger reduction from baseline than placebo
  - single trauma, acute, female, no substance abuse

- Veterans: A negative sertraline study (Friedman J Clin Psychiatry 2007)
Do SSRI’s Compromise Resilience?  
Shalev et al. Arch Gen Psychiatry 2012  
12-week study follow-up

**PLA**: Placebo  
**SSRI**: S-citalopram 10 mg  
**WL**: Wait list control  
**CBT**: Cog.-Behav Therapy  
**PE**: Progressive Exposure

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Figure 2. Prevalence of posttraumatic stress disorder (PTSD) at 5 and 9 months, by study group. CT indicates cognitive therapy; PE, prolonged exposure; SSRI, selective serotonin reuptake inhibitor; WL, waiting list (participants received delayed PE).
Norepinephrine Reuptake Inhibition: Desipramine (DMI) = Paroxetine (± Naltrexone)
Petrakis et al. Neuropsychopharm 2011

![Graph showing the comparison of Norepinephrine Reuptake Inhibition between Desipramine (DMI), Paroxetine, Naltrexone, and Placebo over time.](Image)
Slight advantage for SRI + NRI?
Davidson et al J Clin Psychopharm 2006

- Venlafaxine ER
- 12-week
- Flexible dose
- 538 randomized
- 350 completers
- Vs PLA: 10%
- Vs SSRI: 5%

**FIGURE 2.** $P$ value for the treatment differences are based on the Pearson $\chi^2$ test. Remission = CAPS-SX$_{17}$ total score $\leq$ 20.
* $P<0.05$ venlafaxine ER vs placebo; † $P<0.01$ venlafaxine vs. sertraline; ‡ $P<0.001$ venlafaxine ER vs. placebo; ‡‡ $P<0.05$ venlafaxine ER vs. sertraline.
Antidepressant summary

- All helpful (TCA, MAOI, SRI, NRI, SNRI)
- Slow onset of efficacy (~10 wks)
- SSRI’s better for “negative” (avoidance numbing) than “positive” (hyperarousal, reexperiencing)?
- Tolerability an issue: slow, flexible titrations
- In chronic populations, low remission rates
The pharmacotherapy of PTSD

- Anti-depressants
- Anti-adrenergics
Noradrenergic hyperactivity: Pathological Alarm

• **NE:** FIGHT or FLIGHT

• **Dysregulation:** NE hyperactivity at rest

• **Learning:** Reminders activate NE systems

Yohimbine-Induced Flashback: Combat Veteran with PTSD

Patient: (Appears agitated)

Dr. Krystal: What’s happening?

Patient: The helicopter is going down! I saw the flash of light and the smoke trail! It’s crashing! I can hear it! I can smell smoke!
Reduced Norepinephrine Uptake May Increase Synaptic NE in PTSD

Norepinephrine Neuron Based in Locus Coeruleus

NET: Norepinephrine Transporter

Pietrzak RH, et al. JAMA Psychiatry 2013
Decrease NE Tone

Norepinephrine Neuron

α-2

NE

NE

NE

NET

α-1

PRAZOSIN

Block α-1

Enhance α-2

Guanfacine, Clonidine

Block β

Propranolol

Prazosin

• Reduced nightmares, awakenings
• 1 mg at bedtime: “first dose effect”
• Increase by 1 mg every 3-7 days
• Usual dose: 3-4, Usual max dose: 6-10
• Side effects: hypotension, tachycardia

Clonidine-Guanfacine

- Clonidine: α2 + imidazoline agonist
  - 0.05 mg gradually increasing to 0.1-0.2 t.i.d.
  - Sleep, nightmare, hyperarousal
  - Adjunctive to antidepressants
  - Side effects: sedation, hypotension

- Guanfacine: more selective α2
  - Inconsistent efficacy across studies

β-Blockers

- Limited direct efficacy
- Interference with fear consolidation in animal models
- Prophylactic efficacy not holding up
- Reactivation of memories “reconsolidates” fear...role for β-blockers?

The pharmacotherapy of PTSD

- Anti-depressants
- Anti-adrenergics
- Anti-serotonergics
5HT Activation in PTSD?

- Stimulation of 5HT receptors with mCPP worsens symptoms (Southwick et al. AJP 1996)
- Reduced 5HTT and 5HT1B receptors may increase 5HT release (Neumeister Biol Psych 2011; Murrough et al. AGP 2011; Pietrzak et al. Mol Psych 2013)
Reduced serotonin (5HT) uptake (SERT) and feedback inhibition (5HT1B) may increase 5HT levels in PTSD.
Trazodone and Nefazodone

- 5HT2-R antagonist (NEF also SRI)
- Trazodone
  - most commonly prescribed medication for PTSD in VA in 2010
  - No placebo-controlled trials
  - 25-50 mg commonly increased to up to 200 mg for sleep
  - Concerns include daytime sedation, headache, priapism
- Nefazodone start at 100 mg qhs increase to 200-300 mg BID; pilot studies positive

Second Generation Antipsychotics

DA: D2 blocker (Haloperidol-like)
- Risperidone
- Olanzepine

NE - α-1 blocker (Prazosin-like)
- Quetiapine
- Ziprasidone

5HT: 5HT2 blocker (Trazadone-like)
- Clozapine
- Aripiprazole
Adjunctive Risperidone for SRI resistant PTSD symptoms: VA Cooperative Study 504

- SRI-resistant chronic military-related PTSD
- 6-month trial
- 247 patients in the ITT

No significant effect of risperidone on CAPS total score

Study#504: Risperidone Treatment for Military Service Related Chronic Post-Traumatic Stress Disorder

Figure-1: LSmeans of CAPS Scores


Tx: $F_{1,253} = 2.30, p=0.13$

Minimal important change
Significant but small effect on Reexperiencing Symptoms

Least Square Means for CAPS Reexperiencing Symptoms

Treatment: Placebo
Risperidone

\( F_{1,253} = 8.16, p = 0.0046 \)
Effect size: \( d = 0.298 \)
Side effects associated with risperidone

• Adverse events:
  – Somnolence: 9.9% vs. 1.5% (p=.001)
  – Hypersalivation: 9.9% vs. 0.8% (p=.001)
  – Weight gain: 15.3% vs. 2.3% (p=.001)
  – Decreased libido: 6.1% vs. 0.0% (p=.001)
  – Dyspnea: 6.1% vs. 0.0% (p=.001)

• Measured side effects not significant
  – EPS, akathisia, weight gain

• No difference in “added” medications during trial
VA Spent $717 Million on a Drug Deemed as Effective as a Placebo

By Bob Brewin, Nextgov.com
Updated: August 23, 2011 | 12:24 p.m.
August 23, 2011 | 12:25 p.m.

EDITOR'S NOTE: This is the 13th story in an ongoing Nextgov series that examines the invisible wounds of war.

Over the past decade, the Veterans Affairs Department spent $717 million for an antipsychotic drug to treat post-traumatic stress disorder that a recent study shows is no more effective than a placebo.

Data provided by the department in response to a Nextgov query showed that VA doctors wrote more than 5 million prescriptions for risperidone from October 2000, the beginning of fiscal year 2001, through June 2010. Risperidone is the generic name for Risperdal, a second-generation antipsychotic drug originally developed by the Janssen Pharmaceuticals division of Johnson & Johnson to treat severe mental conditions such as schizophrenia and bipolar disorder.

But a paper by VA researchers published on August 2 in the Journal of the American Medical Association concluded, "Treatment with risperidone compared with placebo did not reduce PTSD symptoms."
Caveats

• Beneficial for paranoia/psychosis
• Might have greater effects in less severe population on fewer other medications
Other SGA’s

• Quetiapine (Seroquel)
  — Most commonly prescribed SGA
  — Start: 25 mg, commonly increased to 100-200 mg
  — Encouraging preliminary data
  — Concerns: Daytime Sedation, Weight gain

• Others: Olanzapine, Aripiprazole

The pharmacotherapy of PTSD

Anti-depressants

- Anti-adrenergics
- PRO-GABA
- Anti-serotonergics
BZD: Wide but Declining Prescription

- From 1999 to 2009: 36.7% to 30.6%
- Chief concerns:
  - Abuse liability (esp. with substance use history)
  - Limited evidence of efficacy in pilot study

GABA: Another Layer of Stress-Dampening Deficit in PTSD?
Reduced Orbital Frontal Cortex
[123]lomazenil Binding in PTSD
GABA deficits increase risk for dissociation with 5HT activation (mCPP)

D’ Souza et al.  
Biological Psychiatry  
2006
S-Zopiclone (Lunesta): relatively high affinity for α2/3 GABA-A receptors

- Improved sleep and reduced PTSD symptoms
- Starting dose: 2-3 mg; Max: 4 mg

J Clin Psychiatry 2011
Other GABA modulators?

- **TIAGABINE**: Large negative trial (Davidson et al. J Clin Psychopharm 2007)
- **VALPROATE**: Small negative trial (Hamner et al. Ann Clin Psychiatry 2009)
- **TOPIRAMATE**: Small (12-14/group in completer analysis) encouraging study (Yeh et al. CNS Neurosci Ther 2010)

Anticonvulsant medications
Toward the future!

- Promoting neuroplasticity (extinction)
- Rapid-acting antidepressants
- Anti-inflammatory agents
- Promoting resilience
Traumatic Memories Activate Amygdala
(Rausch et al. Arch Gen Psychiatry 1996)

Regions Activating During Trauma Scripts: [15O] PET
Fear Extinction is dependent upon NMDA receptors

- Extinction might reduce amygdala output
  - LTP of GABA neuron that inhibits amygdala output

After M. Davis
D-cycloserine (DCS) facilitates NMDA-R function with half of the efficacy of glycine
DCS Findings

- Helpful for other anxiety disorders (phobia)
- PTSD studies: modest benefit or even worsening

Toward the future!

- Promoting neuroplasticity (extinction)
- Rapid-acting antidepressants
Stress reduces dendritic spines and causes dendrite atrophy

Contribute to reduced structural and functional connectivity in PTSD?

Duman and Aghajanian Science 2012
Antidepressant Actions of Ketamine

Hamilton Depression Scale: \( p = 0.0001 \)

VAS, “High”
\( P = 0.0001 \)

BPRS, Positive Symptoms of Schizophrenia
\( P = 0.007 \)

R. Berman Biol Psychiatry 2000
Toward the future!

- Promoting neuroplasticity (extinction)
- Rapid-acting antidepressants
- Anti-inflammatory agents
Stress and TBI promotes neuro-inflammation

Anti-inflammatory strategies:

- Cytokine receptor antagonists (TNFα; infliximab)
- Drugs that promote glutamate uptake (minocycline, riluzole)
- Raise glutathione levels (N-acetyl-cysteine)
Toward the future!

- Promoting neuroplasticity (extinction)
- Rapid-acting antidepressants
- Anti-inflammatory agents
- Promoting resilience
Promoting resilience?

- Glucocorticoids
- Opiate receptor agonist/partial agonist
  - Experience with burn patients
- Neuropeptide Y
Summary

• SRI’s: validated, but limited, efficacy
• Other medications: only preliminary support
• Open questions: Relative efficacy, adjunctive treatment, personalized treatment?
• Exciting possibilities for the future
Its More than PTSD

Pre-Stress

Genotypes

Prior Stress Preparation

Stress

Neural-Subjective Responses

Extreme Stress

Post-Stress

PTSD

Alcohol/Drug

Depression

TBI

Chronic Pain

Other Psych.
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