PTSD: From neurobiology to treatment

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Disclosures

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Consulting Relationship (>5,000/yr)
Janssen

Stock Equity (>10,000)
BioHaven Medical Sciences

Patents:
1. Glutamatergic treatments for anxiety disorders (Biohaven Medical Sciences)
2. Intranasal ketamine for depression (Johnson & Johnson)
3. Glutamate receptor modulation for alcoholism (pending)

Paid Editorial Relationship
Biological Psychiatry - Editor

Speaker’s Bureau: None
Crisis in PTSD Drug Development

- 2 FDA-approved SSRIs
- No new drugs in >10 years
- Minimal investment by Pharmaceutical industry
- Major investments in PTSD research overall by NIMH, VA, DoD have produced very few RCTs
- Large scale studies of new medications (risperidone, prazosin) are negative
- Most patients receive medications (or polypharmacy) not supported adequately by RCTs
- Treatment algorithms based largely on clinical opinion
Toward a rational psychopharmacology of PTSD

• Noradrenaline and anti-adrenergics

• Serotonin: antidepressants, MDMA, and antipsychotics

• Neurotrophics: ketamine, DCS

• GABA and cannabinoids
Noradrenergic hyperactivity: Pathological Alarm

- **Dysregulation:** Elevated NE/metabolites in urine, blood, CSF
- **Learning:** Increased NE release with reminders

NE Dysregulation in PTSD Promotes Overstimulation of NE receptors

Consequences of NE Overstimulation

- Cognitive dysfunction
- Insomnia, nightmares?
- Focused attention
- Enhanced w. memory (up to a point)
- Autonomic arousal
- Fear-related learning - reconsolidation

Norepinephrine Neuron

α-2 Feedback Inhibition

α-1

αα-2

β

Krystal & Neumeister Brain Res 2009; Arnsden Nature Neurosci 2015; Debiec et al. Depression and Anxiety 2011;
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!

From Southwick et al. Arch Gen Psychiatry 1993
Treating NE Overstimulation

Norepinephrine Neuron

α-2 Feedback Inhibition

α-1

• Block α-1: PRAZOSIN

β

• Block β: PROPRANOLOL
• Down-regulate β ANTIDEPRESSANTS

α-2

• Stimulate α-2: GUANFACINE, CLONIDINE

NE Transporter (Uptake)

Krystal & Neumeister Brain Res 2009; Arnsten Nature Neurosci 2015; Debiec et al. Depression and Anxiety 2011;
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
  —<20% receiving 6 mg or more
• Side effects: hypotension, tachycardia

Norepinephrine Reuptake Inhibition in PTSD + Alcohol Dependence
Desipramine (DMI) = Paroxetine (± Naltrexone)
Petrakis et al. Neuropsychopharm 2011
Resilience involves turning off the stress response

“Honey, you’re home.”
Could there be problems in a system designed to “turn off” the response to adrenaline?
What is the biology of coping?
Special Forces Training,
(C.A. Morgan III et al.)
Lower post-stress NPY correlates with dissociation during stress stress

Plasma NPY (ng/ml) during Stress

r = .58; p<0.02

Morgan et al. Biol Psychiatry 2000
PTSD Associated with *Reduced* NPY Despite *Increased* NE release in PTSD

(A. Rasmussen et al. *Biol Psychiatry* 2000)
NPY treatments?

- NPY?
- Y1 agonists, Y2 antagonists
Toward a rational psychopharmacology of PTSD

- Noradrenaline and anti-adrenergics
- Serotonin: antidepressants, MDMA, and antipsychotics
Outline

• Noradrenaline and anti-adrenergics

• Serotonin: antidepressants, MDMA, and antipsychotics

Cell bodies:
Feedback inhibition:
Via 5HT1A

Nerve terminals:
Feedback inhibition:
Via 5HT1B

Picture: Courtesy of NIDA
Serotonin (5HT) dysregulation: compensation for excessive inhibition?

Stimulating 5HT2C receptors worsens PTSD

- mCPP – 5HT2C agonist (other actions)
- 8 (31%) panic attacks
- 7 (27%) flashbacks
- Increase PTSD symptoms
- Different patients worsened with yohimbine (NE)

Southwick et al. Arch Gen Psychiatry 1997
5HT2 receptor antagonists and second generation antipsychotics

5HT: 5HT2 blocker (Trazadone-like)
- Risperidone
- Olanzepine

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

DA: D2 blocker (Haloperidol-like)
Adjunctive risperidone ineffective for PTSD over 6 months (n=247) CSP #504

Krystal et al. JAMA 2011

Minimal important change

Tx: $F_{1,253} = 2.30$, $p=0.13$
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."
A Randomized Clinical Trial of Phenelzine and Imipramine for Posttraumatic Stress Disorder

Julia B. Frank, M.D., Thomas R. Kosten, M.D., Earl L. Giller, Jr., M.D., Ph.D., and Elisheva Dan, P.A.

• First double-blind placebo-controlled trial of antidepressants in PTSD (Am J Psychiatry, 1988)
  • n=38
  • Both medications superior to placebo

Earl L. Giller MD PhD
Yale/VA Connecticut
(1943-2014)
Sertraline efficacy emerges slowly
K. Brady et al. *JAMA* 2000;283
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)
Slight advantage for SRI + NRI?
Davidson et al J Clin Psychopharm 2006

- Venlafaxine ER
- 12-week
- Flexible dose
- 538 randomized
- 350 completers
- ~10% difference in remission

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

• Broadly helpful regardless of mechanism (TCA, MAOI, SRI, NRI, SNRI)
• Slow onset of efficacy vs placebo (~10 wks)
• Better for “negative” (avoidance numbing) than “positive” (hyperarousal, reexperiencing)
• Tolerability issues important: slow, flexible titrations
• In chronic populations, low remission rates
MDMA ("Ecstasy")

- A variant of amphetamine that potently releases serotonin (5HT) and dopamine
- Produces euphoria, stimulation
- Distorts the processing of social cues, creating feelings of trust and intimacy
- **Substantial abuse liability**: associated with disturbances of mood and cognition
- Pilot studies suggest it is can be administered safely to patients and doses of 125 mg (± 62.6 mg)
- Augmented the impact of an insight-oriented therapy (reduced CAP scores vs placebo (~n=10/grp) non-significant trends in a replication study.

Outline

• Noradrenaline and anti-adrenergics
• Serotonin: antidepressants, MDMA, and antipsychotics
• Neurotrophics: ketamine
A “connectionist” hypothesis

• Stress-induced loss of synaptic connectivity in PTSD impairs:
  — Adaptive executive deficits (memory, planning)
  — Executive control of emotion
  — Neuroplasticity

• Some treatments for PTSD may work by restoring connectivity:
  — Restore executive control of thought and emotion
  — Enhance plasticity (capacity to respond to treatment)
Neurotrophins (BDNF) promote resilience to stress-related neural atrophy mediated by glucocorticoids.

Antidepressants raise BDNF levels.

Berton et al. Nat Rev Neurosci 2006;7
Generation of new neurons and glia is disrupted by stress and restored by antidepressants.
Hippocampal Volume Deficits in PTSD: Environments or Genes?

- 5-25% Volume Loss
- Childhood and adult trauma
- Now multiple positive studies
- Type of cellular deficit unclear
- Mechanism unclear
- Role of genetics is unclear

Bremner et al. 1995
Paroxetine treatment increases hippocampal volume and improves memory in PTSD over 6 months.

**Hippocampal Volume**

- Pre: [Graph showing change in hippocampal volume before treatment.]
- Post: [Graph showing change in hippocampal volume after treatment.]

**Wechsler: Paragraph, Delayed Recall**

- Pre: [Graph showing change in Wechsler Paragraph, Delayed Recall scores before treatment.]
- Post: [Graph showing change in Wechsler Paragraph, Delayed Recall scores after treatment.]

Vermetten et al. Biol Psychiatry 2003
Antidepressant Actions of Ketamine

- Hamilton Depression Scale: \( p = .0001 \)
- VAS, "High": \( P = .0001 \)
- BPRS, Positive Symptoms of Schizophrenia: \( P = .007 \)

R. Berman Biol Psychiatry 2000
Specificity of ketamine effects: greater and more persistent than midazolam

Depression Severity: MADRAS

Response Rate: 50% Reduction

J.W Murrough AJP 2013
Ketamine for depression

- Many small replications (>8)
- Reduces suicidality
- Unipolar and bipolar
- Benefits extended by repeated dosing (>3 yr)
- High response rates (50% - 75%) for treatment resistant depression symptoms
- Very well tolerated
- Being adopted clinically
- Ketamine alternatives (S-ketamine, etc.) in development
PTSD (n=41)

PTSD Symptoms

(Feder et al. JAMA Psychiatry 2014)

Depression

(Feder et al. JAMA Psychiatry 2014)
Ketamine stimulates rapid regrowth of synaptic connectivity in these regions
Antidepressant effects of ketamine:
Re-growing dendritic spines by enhancing the “go” pathway and reducing the “stop” pathway

Li et al. Science 2010
Autry et al. Nature 2011
Outline

• Noradrenaline and anti-adrenergics
• Serotonin: antidepressants, MDMA, and antipsychotics
• Neurotrophics: ketamine, DCS
• GABA and cannabinoids
GABA deficits impair another layer of stress-dampening.
Lower parietal GABA associated with insomnia (Meyerhoff et al. Sleep 2014)
Reduced Orbital Frontal Cortex

[123]Iomazenil Binding in PTSD

GABA deficits increase risk for dissociation with 5HT activation (mCPP)

D’ Souza et al. Biological Psychiatry 2006
BZD: Wide but Declining Prescription

- **From 1999 to 2009:** 36.7% to 30.6%
- **Chief concerns:**
  - Abuse liability in patients with high rate of substance use
  - Limited evidence of efficacy in pilot study

Alprazolam impairs fear extinction (Rothbaum et al. AJP 2014)
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
Benzodiazepine Summary

• Widely prescribed but not well understood
• Could reduce impact of GABA deficits to treat anxiety and insomnia: **subtype selective agents?**
• Limitations:
  — Tolerance/dependence: **partial agonists?**
  — Impaired neuroplasticity
  — Abuse liability
Medical Marijuana Program

Pursuant to Connecticut General Statutes, Chapter 420f, Section 21a-408, patients who are currently receiving medical treatment for a debilitating medical condition set out in the law may qualify for a registration certificate.

Including...PTSD
**CB1 Density in PTSD [11C]OMAR-PET**
(Neumeister et al. Mol Psychiatry 2013)
The challenge of THC as a treatment

THC in Amygdala
- Anxiolytic
- Promotes Fear Extinction
- Addiction?

THC in Cortex
- Cognition-Impairing
- Paranoia
The cannabis conundrum

• THC to suppress amygdala activation and promote extinction of fear?
  — Small open label adjunctive trial generally supports
  — Risks: cannabis self-medication associated with worse PTSD outcomes; addiction liability
  — Alternative: FAAH inhibitor

• Block CB receptors
  — CB1-R antagonists (CBD, rimonabant)

Summary: The Emerging Biology of PTSD

• A superficial understanding of the neurobiology of PTSD symptoms limits the ability to develop new treatments...but tremendous opportunities.

• Emerging principles:
  — Multiple systems: many not addressed here (cytokines, glucocorticoid (GR, FKBP5), oxytocin, mGluR2, etc.)
  — Multiple layers of disturbances in neural system homeostasis:
    • Somal and terminal autoreceptors (α2, 5HT1A, 5HT1B)
    • Co-localized peptides (NPY)
    • Microcircuit (GABA, CB1)
    • Macro circuit (executive control of emotion)
    • Synaptic connectivity (dendritic spines, dendrites, neurogenesis)
From Molecular Signature to Treatment Target?

First result
From National PTSD Brain Tissue Repository

Decreased SGK1 Expression and Function Contributes to Behavioral Deficits Induced by Traumatic Stress

Pawel Licznerski1,2, Vanja Duric1,3, Mounira Banasr1, Kambiz N. Alavian2,4, Kristie T. Ota1, Hyo Jung Kang1, Elizabeth A. Jonas2, Robert Ursano5, John H. Krystal1,6,7,8, Ronald S. Duman1,6,7,*, Traumatic Stress Brain Study Group3

SGK1 Reduced In PTSD PFC
SGK1 Reduced In Animal Model
Reducing SGK1: Stress vulnerability
Overexpress SGK1: Stress Resilience

2015
Summary: Addressing the Pharmacotherapy Gap

• Very little study of PTSD pharmacotherapy
  — Inadequate support for medications used in clinical practice
  — Even fewer tests of novel therapeutic mechanisms

• Rational “precision” pharmacotherapy may emerge from effort to link mechanisms of PTSD symptoms to novel treatments
Acknowledgements
PTSD Consultation Program
FOR PROVIDERS WHO TREAT VETERANS

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## UPCOMING TOPICS

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

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<td>Treating Anger and Aggression in Populations with PTSD</td>
<td>Leslie Morland, PhD</td>
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<td>November 16</td>
<td>Cannabis and PTSD</td>
<td>Marcel Bonn-Miller, PhD</td>
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