Anxiety and Related Disorders: Neurobiology and Treatment

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Dr. Ressler is a founding member of Extinction Pharmaceuticals/Therapade Technologies, which exist to develop d-Cycloserine for use to augment the effectiveness of psychotherapy. He has received no equity or income from this relationship within the last 3 years.

Patents: D-cycloserine and psychotherapy, targeting PACAP for extinction, targeting tachykinin 2 for prevention of fear, targeting angiotensin to improve extinction of fear.

Funding: NIMH, HHMI, NARSAD, Burroughs Wellcome Foundation
DSM-5 reorganized Anxiety Cluster

DSM-5 Disorders
Anxiety Disorders

- Separation Anxiety Disorder
- Selective Mutism
- Specific Phobia
- Social Anxiety Disorder (Social Phobia)
- Panic Disorder
- Panic Attack (Specifier)
- Agoraphobia
- Generalized Anxiety Disorder

- Substance/Medication-Induced Anxiety Disorder
- Anxiety Disorder Due to Another Medical Condition
- Other Specified Anxiety Disorder
- Unspecified Anxiety Disorder
DSM-5 reorganized Anxiety Cluster PTSD, etc., now in separate category

**“Trauma- and Stressor-Related Disorders”**

<table>
<thead>
<tr>
<th>Disorder Name</th>
<th>Used To Be In (DSM-IV-TR)</th>
<th>Now In (DSM-5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactive Attachment Disorder</td>
<td>“Disorders Usually First Diagnosed in Infancy, Childhood and Adolescence”</td>
<td>“Trauma and Stressor-Related Disorders”</td>
</tr>
<tr>
<td>Disinhibited Social Engagement Disorder</td>
<td>--</td>
<td>“Trauma and Stressor-Related Disorders”</td>
</tr>
<tr>
<td>PTSD</td>
<td>“Anxiety Disorders”</td>
<td>“Trauma and Stressor-Related Disorders”</td>
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<tr>
<td>Acute Stress Disorder</td>
<td>“Anxiety Disorders”</td>
<td>“Trauma and Stressor-Related Disorders”</td>
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<tr>
<td>Adjustment Disorders</td>
<td>“Adjustment Disorders”</td>
<td>“Trauma and Stressor-Related Disorders”</td>
</tr>
</tbody>
</table>
DSM-5 reorganized Anxiety Cluster

OCD, etc., now in separate category

Specific Changes Per Diagnostic Category in DSM-5

Obsessive-Compulsive and Related Disorders

- OCD is now a stand alone category
- Body Dysmorphic Disorder listed under OCD as F01
- Added Hoarding under category of OCD as F02
- Trichotillomania now called Hair-Pulling Disorder is listed under OCD as F03
- Skin Picking Disorder moved under OCD as F04
However, from research, and often treatment, perspectives, we still see them very similarly

### Human Anxiety Disorders

<table>
<thead>
<tr>
<th>Primarily Fear</th>
<th>Primarily “Anxiety”</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panic Disorder</td>
<td>Generalized Anxiety D.O.</td>
<td>OCD</td>
</tr>
<tr>
<td>Specific Phobia</td>
<td>Anxiety D.O. due to Medical</td>
<td>OCD-related</td>
</tr>
<tr>
<td>Social Phobia</td>
<td>Anxiety D.O. due to Substances</td>
<td></td>
</tr>
<tr>
<td>PTSD</td>
<td>Separation Anxiety D.O.</td>
<td></td>
</tr>
</tbody>
</table>

Krueger (1999) Arch Gen Psych, 56(10): 921-;
Vollengerh et al., (2001) Arch Gen Psych, 58(6): 597-603
Genes + Environment Increase Risk of Anxiety / Fear Disorders and Posttraumatic Stress

GENES

ENVIRONMENT

TRAUMA

Development

Fear-Related Disorders

PTSD
Fear is evolutionarily useful
LeDoux, 1996

but… Dysregulated Fear leads to Phobia, Panic, and PTSD

- Single or repeated exposure to **extremely traumatic** situations

- Characteristic symptoms of PTSD
  - Increased **anxiety** (and hypervigilance)
  - Declarative **memory** alterations
  - Problems in sleep and concentration
  - **Flashbacks**
  - Inability to inhibit **fear**
Neural Circuits Regulating Fear Processing

**Sensorimotor Cortex**
- Function: Coordination of sensory and motor functions
- In PTSD: Symptom provocation results in increased activation

**Thalamus**
- Function: Sensory relay station
- In PTSD: Decreased cerebral blood flow

**Parahippocampal Gyrus**
- Function: Important for memory encoding and retrieval
- In PTSD: Show stronger connectivity with medial prefrontal cortex; decreases in volume

**Fear Response**
- Function: Evolutionary survival
- In PTSD:
  - Stress sensitivity
  - Generalization of fear response
  - Impaired extinction

**Hippocampus**
- Function: Conditioned fear, Associative learning
- In PTSD: Increased responsiveness to traumatic and emotional stimuli

**Prefrontal Cortex**
- Function: Emotional, Regulation
- In PTSD:
  - Decreased gray and white matter density
  - Decreased responsiveness to trauma and emotional stimuli

**Anterior Cingulate Cortex**
- Function: Autonomic functions, cognition
- In PTSD: Reduced volume, higher resting metabolic activity

**Orbitofrontal Cortex**
- Function: Executive function
- In PTSD: Decreases in volume

**Amygdala**
- Function: Conditioned fear, Associative learning
- In PTSD: Increased responsiveness to traumatic and emotional stimuli
The Human Amygdala and Fear

Etkin & Wager, 2007
PANIC ATTACK:
"All of a sudden I felt dizzy, my legs gave out on me, and I couldn't catch a breath. It felt like someone was choking me. I could feel my heart was beating too fast and I was terrified I was dying. I knew I had to get away before I lost it."

Increased heart rate
Chills, hotflushes
Nausea / abdominal distress
Shortness of breath
Expressions of fear

Chest discomfort
Sweating
Lightheadedness / faint
Choking sensation
Fear of dying / losing control

PANIC ATTACK = ‘Fear Attack’ in Fear-related Disorders
Monoamine Dysfunction: Principal Evidence for Noradrenergic and Serotonergic Dysfunction in Anxiety / MDD

**Norepinephrine (NE) dysregulation**

- Evidence suggests possibility of overactivation of NE release or hypersensitivity of receptor systems

**Serotonergic (5HT) dysregulation**

- Overall evidence for decreased activity of serotonin system
Physiology of NE and 5HT Firing

**NE**

- Crucial role in organizing the behavioral state
  - Arousal / Vigilance / Stress response
  - Modulation of emotional memory systems
  - Burst firing with switch from calm wakefulness vigilance / attention


**5HT**

- Most active with quiet, internally directed activity
- Inhibited by orientation

Regulation Of Amygdala By NE
Feed-Forward CRF-NE-CRF Stress System

TH Levels Decrease With Antidepressants or ECT

TH=Tyrosine Hydroxylase

Enhanced 5-HT Release Following Chronic Antidepressant Treatment

*Enhanced 5-HT Release Following Chronic Antidepressant Treatment

Hypothalamus

Hippocampus

Frontal Cortex

*Enhanced 5-HT Release Following Chronic Antidepressant Treatment

*Enhanced 5-HT Release Following Chronic Antidepressant Treatment

*Enhanced 5-HT Release Following Chronic Antidepressant Treatment

*p<.05

Stress and Antidepressant Effects on Hippocampal Neurogenesis and Atrophy

Control | Stress | Antidepressant

The Amygdala In Anxiety

• NE and 5HT modulation of cortical-hippocampal-amygdala pathways likely modulates:
  – attention and vigilance
  – response to aversive experience
    • perceived stress
    • perceived fearful stimuli
NE Release In Amygdala Stimulated By Aversive Events

<table>
<thead>
<tr>
<th>NE Level (% Of Baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>225</td>
</tr>
<tr>
<td>200</td>
</tr>
<tr>
<td>175</td>
</tr>
<tr>
<td>150</td>
</tr>
<tr>
<td>125</td>
</tr>
<tr>
<td>100</td>
</tr>
<tr>
<td>75</td>
</tr>
</tbody>
</table>

** Time (min)**

- No Foot Shock
- Low Intensity (0.3 mA)
- High Intensity (1.2 mA)

* P < .005.
** P < .01.
Regulation Of Amygdala By NE & 5HT

Summary

• NE enhances learning of fearful and other amygdala-dependent events
• NE blockade may ↓ or block fear learning
• 5-HT in some paradigms inhibits fear learning
• This inhibition appears to be due to 5-HT activation of inhibitory interneurons
Anxiety/MDD

- Amygdala
- Locus Coeruleus
- NE
- CRF
- Ventral PFC
- Dorsal PFC
- Hippocamp
- 5-HT
- Locus Coeruleus
- Raphe Nucleus

External sensory
Internal memory

Stress
Fear
Tolerance Resilience

Pathways:
- NE
- CRF
- 5-HT
Treatment of Anxiety / MDD

ECT → Dorsal PFC

Psychotherapy?

Ventral PFC

Benzodiazepines

SNRIs / NRIs

NE → CRF

ECT

SSRIs

Amygdala

Hippocamp

5-HT

Locus Coeruleus

Raphe Nucleus
Phobia

- **Description** - DSMIV- Marked, persistent, and excessive fear of clearly discernable, circumscribed objects or situations....Provoking an immediate anxiety/fear response, which may take the form of a Panic Attack. The fear is recognized as excessive and unreasonable by the patient and significantly interferes with functioning.

- **Specific Phobias**
  - Air travel
  - Closed Spaces
  - Heights
  - Storms
  - Water
  - Animal Phobia
    - Snakes
    - Dogs
    - Spiders
  - Blood / injury

- **Social Phobia**
  - Separate DSM dx from specific phobias
  - Persistent / excessive fear of social or performance situations in which person exposed to unfamiliar people or scrutiny by others. Principally fearing humiliation or embarrassment.
  - Some Specific Performance fears likely related – eating, drinking, or writing in public, or using a public restroom.
Phobia

- **Predisposing factors:** traumatic events (i.e. attacked by animal) during childhood, unexpected panic attacks in to-be-feared situation, observation of others undergoing trauma or experiencing fear, or “informational transmission” (repeated parental warnings about dangers / media reports of airplane crashes, etc.)

- **Course:** Bimodal distribution of Age of Onset – most begin in childhood, with a second peak in mid-20’s. Note: traumatic onset phobia, can occur at any time (i.e. fear of choking after near-choking incident -- ? overlap between phobia / PTSD?)

- Social phobia typically begins in mid-teens, often in an individual with childhood hx of social inhibition or shyness.

- **Epidemiology:**
  - Very Common in general population, but rarely sufficient impairment or distress to meet diagnostic criteria.
  - 1yr prevalence ~9%
  - lifetime prevalence ~10-12%
  - social phobia lifetime 3-13% (one study 20% excessive fear, but only 2% met dx criteria)
Panic Disorder

- **Description**-
  - DSMIV- “Recurrent, unexpected Panic Attacks,” followed by at least 1 month of persistent concern about having another Panic Attack, worry about implications / consequences of Panic Attacks or significant behavioral change.
  - Unexpected (spontaneous, uncued) defined as one that is not associated with a situational trigger. At least 2 unexpected attacks required for dx, but most pts also have numerous situationally pre-disposed panic attacks.”
  - **With Agoraphobia:**
  - anxiety/fear of being in places from which escape might be difficult (or embarrassing), or in which help might not be available if Panic Attacks or symptoms occur (i.e. fear of sudden dizziness or diarrhea). Anxiety leads to pervasive avoidance of a variety of situations which may include being alone outside the home or being home alone, being in a crowd, traveling in an automobile, bus, or airplane, or being on a bridge or in an elevator. Avoidance significantly impairs daily functioning (travel to work, grocery shopping, going to doctor, etc.)
Panic Disorder

• Epidemiology:
  - Lifetime prevalence: 1.5-3.5%, 1 yr prevalence 1-2%.
  - 1/3 to 1/2 of those with P.D. meet criteria for Agoraphobia (community samples)
  - Clinical samples suggest the majority of P.D. occurs with Agoraphobia. (more severe cases)

• Course:
  - typically begins late adolescence to mid-30’s.
  - likely bimodal distribution peak in adolescence, peak in mid-40’s.
  - small # cases begin in childhood and > 45 yrs.
  - Remitting / relapsing – some individuals have episodic periods with years of remission, others with continuously severe symptomatology.
  - Naturalistic f/u 6-10yrs post-tx, 30% well, 40-50% improved but symptomatic, 20-30% continuous sx.

• Risk Factors:
  - Significant familial pattern with 1st degree relatives having 4-7 X risk.
  - monozygotic concordance (14->50%), suggesting some - most variance not genetic
  - early disruptions in parental attachment (early maternal death (<10yrs)) – 7X greater risk of later P.D.
  - Patients also unusually sensitive to perceived or actual threat of separation of primary attachment figures; Having a companion present reduces the likelyhood of panic during CO2 inhalation.
  - traumatic / adverse life events in childhood increases risk.
Post-traumatic Stress Disorder

- **Epidemiology:** not recognized until 1980 DSM-3
- lifetime / current prevalence = 8-13% / 3%
- Lifetime trauma exposure risk = 40-75%
- Lifetime prevalence among those exposed to sign trauma up to 25%
- (diff studies: 15% Vietnam veterans, 24% young urban adults, 39% traffic accident victims)
- **Significant percentage of prisoners have PTSD**

- **Risk factors:** parental separation in childhood, family hx of anxiety, pre-existing anxiety /depression, other psychiatric disorder, acute dissociation with trauma, family hx of antisocial behavior, female, poorer coping strategies.

- **Course:** Often preceded by acute stress disorder. Can begin at any age. Usually sx begin within first 3 mos but may initiate >6 months after the stressor. May improve or disappear within a few months, or may become chronic, relapsing condition.
DRUGS USED FOR ANXIETY

- **Antidepressants**
  - (i) TCA - with sedative effects.
  - (ii) SSRI - Especially good for panic disorder / OCD
  - (iii) SNRI - New group, aimed at mixed anxiety/depressive states

- **5H-T_{1A} receptor agonists** - Buspirone; Ipsapirone; Gepirone.
  - Result in decreased 5H-T activity.
  - Maybe indirect effect via GABA.

- **Direct Noradrenergic agents agonists** – B-blockers e.g. propranolol; alpha-blockers, e.g., prazosin

- **Benzodiazepines** – activate GABA(A) system – decrease overall activity of fear/anxiety circuits

- **Barbiturates** - largely superseded by Benzodiazepines, except for general anaesthesia/epilepsy.
BENZODIAZEPINES

- Anxiolytic activity discovered as a result of routine screen in 1961. Now the most widely prescribed group of drugs.
- All compounds have same basic ring structure but there appears to be some selectivity i.e. some better for anxiolysis, others have more Anticonvulsant activity.
- These drugs may be life saving and IV Diazepam is the standard method for terminating Status Epilepticus.
- Main practical difference is $T_{1/2}$ of compound and metabolites.
- Most important effects on CNS are
  - **Reduction of anxiety and aggression** (“taming” in animal studies) May be element of release of aggressive actions in humans by reduction of inhibition.
  - **Sedation and induction of sleep.** Reduce sleep latency, increase sleep duration if usual time is less that six hours. Effects decline after 1-2 weeks regular use. Reduced REM and SW sleep leads to REM rebound when drug is discontinued.
  - **Reduction of muscle tone and co-ordination** - especially cats. Not same activity as sedation. Can be very useful with muscle spasm.
  - **Anticonvulsant effect** - **All of these drugs show this activity.** More effective with chemically induced convulsions (GABA) than with electrically induced methods (Glycine), thereby suggesting a site of action for benzo’s
BENZODIAZEPINES - MECHANISM OF ACTION

1967 - Schmidt et al - Benzos potentiate effect of GABA on cat spinal cord.

- Benzo binding sites have similar CNS distribution to GABA
  - Most in Cerebral Corte; less in Limbic System; Least in Brain Stem.
- Not direct effect on GABA receptors because effect is abolished if the endogenous GABA is reduced. Implies that Benzo’s modulate inhibitory transmission via GABA.
- Binding to Benzo sites is enhanced in the presence of GABA or a GABA agonist.
  - Suggests an independent relationship between two receptors. Benzos bind to their specific receptor and cause a structural change which enhances the effect of GABA. This indirect facilitatory activity is the mode of action of classical benzodiazepines.
  - Other drugs e.g. alcohol and barbiturates act more directly on sites associated with the chloride ion channel.
  - Different GABA_A isoforms mediate sedative and anxiolytic effects.
- Other drugs e.g. cyclopyrrolone “zopiclone” also act on the same receptor.
- New class of drugs called “Benzodiazopine Receptor Ligands”.
  - Now have Agonists - classical Benzos.
  - Antagonists - block agonists. no inherent action e.g. flumazanil.
  - Partial Agonists - mixture of activities.
  - Inverse Agonists - opposite effect to agonists.
- **Natural ligands - do they exist?** No specific compounds identified but a number of candidates which act as agonists or inverse agonists 
  (a) Diazepam - binding inhibitor (DBI).
  (b) Trihilin (anxiogenic)
- New approach to anxiolytic drug design is to develop drugs which either facilitate endogenous agonists or inhibit inverse agonists at the benzodiazopine site.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Half Life of Drug</th>
<th>Active Half Life</th>
<th>Half Life of Metabolite</th>
<th>Metabolites</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam (Ativan)</td>
<td>12 hours</td>
<td>None</td>
<td></td>
<td></td>
<td>Short</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>8 hours</td>
<td></td>
<td></td>
<td></td>
<td>Short</td>
</tr>
<tr>
<td>Temazepam (Normison)</td>
<td>8 hours</td>
<td>-</td>
<td>None</td>
<td></td>
<td>Short</td>
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<tr>
<td>Diazepam (Valium)</td>
<td>32 hours</td>
<td></td>
<td>Nordiazepam</td>
<td>60 hours</td>
<td>Long</td>
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<tr>
<td>Chlordiazepoxide (Librium)</td>
<td>12 hours</td>
<td></td>
<td>Nordiazepam</td>
<td>60 hours</td>
<td>Long</td>
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<tr>
<td>Nitrazepam (Mogadon)</td>
<td>28 hours</td>
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<td>Long</td>
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<td>Halcion (Triaxolam)</td>
<td>Short Action</td>
<td></td>
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<td></td>
<td>Short</td>
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<tr>
<td>Flurazepam (Dalmane)</td>
<td>1 day</td>
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<td>Desalkyl- flurazepam</td>
<td>60 hours</td>
<td>Long</td>
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<tr>
<td>Bromazepam (Lexotan)</td>
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<td></td>
<td></td>
<td></td>
<td>Intermediate</td>
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<tr>
<td>Alprazolam (Xanax)</td>
<td>6-8 hrs</td>
<td></td>
<td></td>
<td></td>
<td>Short</td>
</tr>
</tbody>
</table>
BENZODIAZEPINES

Unwanted Effects

Toxic effects from acute overdosage
- Less dangerous than other anxiolytic/hypnotic drugs. Antagonist (flumazenil) available
- Lethal dose is 300+ times the therapeutic dose. (TCAs ratio 15-20)

Side effects - occur at normal therapeutic dose (especially with Elderly.)
- Drowsiness; Confusion; Impaired Motor Performance; Interaction with alcohol.
  
  N.B. Such effects may persist into the next day if long acting benzos are used as hypnotics. 16-20% of RTA’s are due to people falling asleep.

Dependency (Defn: Compulsion to repeat dose) Similar risk to other hypnotics.

Physical Addiction: related to the production of “withdrawl effects”
- Occur when stop drug, include nervousness tremor and convulsions.
- Most likely to occur with short acting drugs i.e. low T1/2. NB when prescribing.

Tolerance:
- Two components:-
  (a) Pharmaco-kinetic:-lower blood concentration with prolonged use due to induction of enzymes. Not a big problem with benzos.
  (b) Tissue tolerance i.e. target issues adapt to higher doses. Occurs to degree similar to barbiturates.
BETA ADRENOCEPTOR BLOCKERS

1. Propranolol (Inderal) A & B Blockers
   Anxiety helped particularly
   (a) Cardiac symptoms - rapid pulse; palpitations
   (b) Tremor
3. ? also weaker Central action.
4. Mechanism - Counteract peripheral effects of adrenaline.
5. Low Dosage - e.g. 30-40 mgs daily.
7. May be use in combination with additive benefit.
8. Side effects:- In low doses - few in healthy subjects
   Bradycardia, bronchospasm (in arthritis) cardiac failure.
9. Used by musicians, public speakers, students?.
Fluoxetine Treatment of Panic Disorder

- Open, 12-month study of fluoxetine in 25 patients with panic disorder (with or without agoraphobia)
- Treatment began with low doses (e.g., 5 mg/day); median dose at 6 weeks was 20 mg; dose range 2.5 – 80 mg
- Concomitant benzodiazepines in 19 patients
- Moderate improvement or remission of panic attacks: 76% (19 patients)
- Intolerant to side effects: 16% (4 patients)

Paroxetine Treatment of Panic Disorder

≥50% Reduction

Dose-ranging Study: Reduction in Panic Attacks

Mean change from baseline

Week

Placebo
Paroxetine 10 mg
Paroxetine 20 mg
Paroxetine 40 mg

* p < 0.05 vs placebo

Reduction in frequency of panic attacks

12-week double-blind, fixed-dose study

Mean no. of attacks:
% of baseline

- Pooled sertraline (n=126)
- Placebo (n=43)

Time (weeks)

p<0.05 (sertraline vs placebo at endpoint)

Reduction in panic attacks and anticipatory anxiety

% reduction from baseline to endpoint

- **Sertraline 50-200 mg/day**
  - Mean panic attack frequency: p=0.002
  - Median limited symptom attacks: p=0.006
  - Median anticipatory anxiety: p=0.003

- **Placebo**
  - Mean panic attack frequency
  - Median limited symptom attacks
  - Median anticipatory anxiety

*% time spent worrying

Complete remission at endpoint

No panic attacks, no limited symptom attacks, CGI-I 1 or 2

% patients in complete remission at endpoint

- Sertraline 50-200 mg/day
- Placebo

$p<0.001$ (combined analysis)

Data on file, Pfizer
Percent of Patients Free of Panic During Paroxetine Treatment

105 patients with no relapse during a 3-month maintenance phase of paroxetine 10 mg, 20 mg, or 40 mg were randomized to 3 months of same-dose paroxetine or placebo. Adapted with permission from Burnham et al. Presented at 34th Annual Meeting of the ACNP; December 11-15, 1995; San Juan, Puerto Rico.
Paroxetine vs. Placebo: Liebowitz Social Anxiety Scale (ITT/LOCF)

* $p<0.05$ vs placebo; Adapted from: Stein MB, Liebowitz MR, Lydiard RB, et al. JAMA. 1998(Aug 26);280(8):708-713
Sertraline* Treatment Of Social Anxiety Disorder

* Sertraline is not FDA-approved for treatment of social anxiety disorder.
Response rate is based on the Liebowitz Social Phobic Disorders Rating Form (rating of “moderately” or “markedly” improved).
# Expert Consensus Guidelines

## Recommended Adult Medication Doses (mg/Day)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>25-50</td>
<td>200</td>
</tr>
<tr>
<td>Paroxetine (Paxil)</td>
<td>10-20</td>
<td>50</td>
</tr>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>10-20</td>
<td>50</td>
</tr>
<tr>
<td>Fluvoxamine (Luvox)</td>
<td>50</td>
<td>300</td>
</tr>
<tr>
<td>Citalopram (Celexa)</td>
<td>20</td>
<td>60</td>
</tr>
</tbody>
</table>
Psychosocial Treatment for Anxiety Disorders and PTSD

• Cognitive-behavioral treatments
  – Exposure
  – Anxiety management techniques
• Eye Movement Desensitization and Reprocessing (EMDR)
• Psychodynamic treatments
• Group therapy
Expert Consensus Guidelines

Early Intervention and Prevention

• Immediately after exposure:
  – Normalize distress
  – Educate patient, family and significant others
  – Repeated retelling of the event
  – Provide emotional support
  – Relieve irrational guilt
  – Refer to peer support group or trauma counseling
  – Consider short-term sleep medication for insomnia

Foa, Davidson, Frances, 1999
Expert Consensus Guidelines

Noncomorbid children, adults, geriatric patients

- Mild PTSD: Psychotherapy first
- More severe: Psychotherapy first or combine meds/psychotherapy

Comorbid population

- Combine meds/psychotherapy from start
Modeling Fear Disorders

Pre-existing Sensitivity (gene + environment)

Generalization
Recruitment of Non-associated cues

Sensitization
Increased Fear With repeated exposure

Discrimination
Fear is limited to specific trauma cue

Extinction
Diminished response to cues Over time

Schizophrenia
PGC2 10/2012
25K cases
62 loci
The *current* Genome-wide Landscape for PTSD

<table>
<thead>
<tr>
<th>Study</th>
<th>Ancestry</th>
<th>SNP</th>
<th>Nearest Gene</th>
<th>Sample Size</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logue et al. (2012)</td>
<td>European American, African American</td>
<td>rs8042149</td>
<td>RORA (protein-coding)</td>
<td>Discovery: N = 491 EA Replication: N = 600 AA</td>
<td>2.5 x 10^{-8}</td>
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<tr>
<td>Guffanti et al. (2013)</td>
<td>European American, African American</td>
<td>rs10170218</td>
<td>LINC01090 (noncoding RNA)</td>
<td>Discovery: N = 413 AA Replication: N = 2,541 EA</td>
<td>5.09 x 10^{-8}</td>
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<tr>
<td>Almli et al. (2015)</td>
<td>European American, African American, Latin American, East Asian</td>
<td>rs717947</td>
<td>BC036345 (noncoding RNA)</td>
<td>Discovery: N = 147 (multi) Replication: N = 2,006 AA</td>
<td>1.28 x 10^{-8}</td>
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<tr>
<td>Stein et al. (2016)</td>
<td>European American, African American</td>
<td>rs11085374</td>
<td>ZNF626, ANKRD55 (protein-coding)</td>
<td>N=5,049 EA N=1,312 AA</td>
<td>4.59 x 10^{-8} 2.34 x 10^{-8}</td>
</tr>
</tbody>
</table>
Modeling Fear Disorders

Pre-existing Sensitivity
\((\text{gene} + \text{environment})\)

Learning of Fear
\((\text{Traumatic event})\)

Consolidation of Fear
\((\text{Hours – days following event})\)

Expression of Fear
Memories, Nightmares, Flashbacks
Avoidance, Sympathetic Response, Startle

PTSD

Generalization
Recruitment of Non-associated cues

Sensitization
Increased Fear With repeated exposure

Discrimination
Fear is limited to specific trauma cue

Extinction
Diminished response to cues Over time

Recovery
Enhance Extinction e.g., target plasticity
NMDA blockade prevents extinction, while an NMDA agonist (D-cycloserine – DCS) enhances Extinction


Given systemically or Intra-amygdala

Enhancement of Extinction in Humans
D-Cycloserine and Virtual Reality Exposure:
Barbara Rothbaum, PhD and colleagues
Therapy for Acrophobia

NMDA Receptor Enhancer IMPROVES Psychotherapy (extinction) across Anxiety Disorders

Social Anxiety

Obsessive – Compulsive

PTSD / Panic

Meta-Analysis: D-cycloserine Augmentation of Behavioral Therapy for the Treatment of Anxiety Disorders

Ms. Allyson Bontempo, B.S., Ms. Kaitlyn E. Panza, B.A., and Dr. Michael H. Bloch, M.D., M.S.
Yale University Child Study Center

A Meta-Analysis of D-Cycloserine and the Facilitation of Fear Extinction and Exposure Therapy

Melissa M. Norberg, John H. Krystal, and David F. Tolin

Background: Translational research suggests that D-cycloserine (DCS), a partial N-methyl-D-aspartate (NMDA) receptor agonist, might facilitate fear extinction and exposure therapy by either enhancing NMDA receptor function during extinction or by reducing NMDA receptor function during fear memory consolidation. This article provides a quantitative review of DCS-augmented fear extinction and exposure therapy literature.
Modulating Fear through Circuitry Modulation

Chhatwal et al., *Nature Neurosci*, 2008
Choi et al., *PNAS*, 2010
Gafford et al., *PNAS*, 2012
Andero et al., *Science Transl Med*, 2013
Jasnow et al., *J Neurosci*, 2013
Parsons et al., *Nature Neurosci*, 2013
Rationally Designed Therapies Based on Amygdala Biology
Rationally Designed Therapies Based on Amygdala Biology

Select Neuronal Populations in Amygdala

<table>
<thead>
<tr>
<th>Marker</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRP</td>
<td>?</td>
</tr>
<tr>
<td>Thy1</td>
<td>Fear On</td>
</tr>
<tr>
<td>Parv</td>
<td>Extinction</td>
</tr>
<tr>
<td>SST</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>FoxP2</td>
<td>Extinction</td>
</tr>
<tr>
<td>MOR</td>
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<tr>
<td>CRF</td>
<td>Fear On?</td>
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<tr>
<td>PKCd</td>
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<tr>
<td>Tac2</td>
<td>Fear On</td>
</tr>
<tr>
<td>VP</td>
<td>Excitatory</td>
</tr>
</tbody>
</table>
Switching on and off fear by distinct neuronal circuits

Cyril Herry¹*, Stephane Ciocchi¹*, Verena Senn¹, Lynda Demmou¹, Christian Müller¹ & Andreas Lüthi¹
Optogenetically activating the Thy-1 neurons inhibits CeM output

Jasnow et al., 2013, J. Neurosci
Optogenetically activating the Thy-1 neurons in vivo inhibits fear consolidation

Take home:
If we can target the ‘Fear Off’ neurons specifically, it would create a novel and powerful new way to treat fear-related disorders.

Jasnow, Ehrlich, Rainnie et al., 2013, J. Neurosci
Treatment of Anxiety / MDD

ECT

Future: Circuit-Based Targeted Therapies for Modulating Fear / Anxiety

Dorsal PFC

Ventral PFC

Amygdala

Hippocamp

NE

CRF

Locus Coeruleus

Raphe Nucleus

5-HT

SSRIs

SNRIs / NRIs

Benzodiazepines

ECT

Psychotherapy?

SSRIs

Psychotherapy?