ESSENTIAL PSYCHOPHARMACOLOGY 2011: MECHANISMS AND TREATMENT OF ANXIETY AND ANXIETY SPECTRUM DISORDERS

Carl Salzman MD

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Mechanisms of Anxiety

• Overactivation of brain neurotransmission and neuronal firing
• Underinhibition of brain neurotransmission and neuronal firing
• Both
Mechanism of Anxiety

Part I: Overactive Neurons

- Anxiety is related to excess:
  - Stimulatory neurotransmitter (glutamate)
  - Calcium influx, pre- or postsynaptic
Neuronal Excitation: *Role of Glutamate*

- Excitatory amino acid neurotransmitter
- Mediates excitatory neurotransmission
- Interacts with most synapses
- Stress activates cortical and limbic glutamate neurotransmission
- Increased neurotransmission is through NMDA receptor
Mechanism of Anxiety
Part II: Underactive Neurons

• Anxiety is related to insufficient:
  – inhibitory neurotransmitter (GABA)
  – $\text{GABA}_A$ receptor function
  – Enhancement of GABA
GABA_A Receptor

GABA_A receptor

Extracellular

Intracellular
BZ Receptor

Normally in “agonist sensitivity” position: enhances $\text{GABA}_A$ opening of $\text{Cl}^-$ channel
ROLE OF OTHER NEUROTRANSMITTERS: NOREPINEPHRINE

- Fear and anxiety can be produced by electrical stimulation of locus ceruleus.
- Anxiety and panic are produced by $\alpha_2$ antagonists.
- $\alpha_2$ agonist clonidine is anxiolytic.
- Idazoxan can inhibit post-synaptic $\alpha_2$ receptors and decrease anxiety.
- Noradrenergic antidepressants are anxiolytic.
ROLE OF SEROTONIN: 5-HT2 (5-HT1C), 5-HT3 RECEPTORS

- 5-HT2 antagonists are effective anxiolytics
- 5HT-3 antagonists are effective anxiolytics
- SSRIs are effective anxiolytics
- Other serotonergic antidepressants are effective anxiolytics
Treatment of Anxiety: Alter Monoamines

• Alter NE neurotransmission
  – Block postsynaptic $\beta$ receptors
  – Stimulate presynaptic $\alpha$ receptors

• Alter 5-HT neurotransmission
  – Block postsynaptic 5-HT$_2$ receptors
  – Stimulate presynaptic 5-HT$_1A$ and 5-HT$_1D$ receptors
TREATMENT OF ANXIETY AND ANXIETY SPECTRUM DISORDERS
Treatment of Anxiety by Treating GABA$_A$ – BZ Dysfunction

• Increase GABA
  – Block GABA reuptake
  – Increase presynaptic GABA release
• Give better BZ receptor agonists or partial agonists
• Block BZ inverse agonists
BENZODIAZEPINES: IN TODAY’S WORLD, A BLESSING OR A CURSE?
BENZODIAZEPINE CLASSIFICATION

- **Short half-life/high potency:**
  - Alprazolam
  - Lorazepam

- **Long half-life/high potency:**
  - Clonazepam

- **Short half-life/low potency:**
  - Oxazepam
  - Temazepam

- **Long half-life/low potency:**
  - Diazepam
  - Chlordiazepoxide
BENZODIAZEPINES: USE FOR TREATMENT OF ACUTE ANXIETY

• Effective, rapid safe medications for appropriate patients
• Commonly over and under prescribed
• Most use is short term (3 weeks) and prescribed by non psychiatrists
• Excellent add-on medications for short-term sedative/hypnotic function in acute stress
CHRONIC USE OF BENZODIAZEPINES

- Widespread use as primary and secondary treatment for panic disorders
- Widespread use as add-on medication for anxiety spectrum disorders (SAD, OCD)
- Widespread use as add-on medication for affective disorders (mania, depression, dysthymia)
- Controversial use as chronic hypnotic
DOES CHRONIC BENZODIAZEPINE USE LEAD TO DOSE ESCALATION?

• Data do not suggest dose escalation over time for most patients who receive therapeutic doses.

• Dose escalation more likely in:
  – Substance abusers
  – Personality disorders
PROBLEMS WITH BENZODIAZEPINES

• Common dependence and withdrawal
• Interact with alcohol
• Common side effects:
  – Sedation
  – Impaired motor speed and coordination
  – Impaired cognition: short term memory (recent recall)
  – Falls (elderly)
BENZODIAZEPINE DEPENDENCE

- Common after 4-6 weeks of continuous use
- Correlates with daily dose
- Risk highest among attendees of self-help groups
- Severity of discontinuation symptoms depends on:
  - Duration of treatment and Dose
  - Prior sedative/hypnotic dependence
  - Rate of discontinuation
BENZODIAZEPINE DISCONTINUANCE

- Depends on half-life:
  - Short half-life produce most intense rebound
- Long half-life drugs still can cause withdrawal (e.g., seizures)
- Long half-life drugs can be substituted for short half-life to diminish withdrawal
- Intensity of withdrawal correlates with dose and duration of use, and speed of discontinuation
- Long lasting withdrawal is rare
MECHANISM OF BZ WITHDRAWAL

- Chronic exogenous BZs shift BZ receptor sensitivity from agonist to inverse agonist position;
- When exogenous BZs are suddenly withdrawn, receptors are left in inverse agonist sensitivity position;
- Takes 1 week for receptors to reset to agonist sensitivity
- BZ antagonist (flumazenil) blocks withdrawal
BENZODIAZEPINE SIDE EFFECTS

- Correlate with dose, duration of treatment, sensitivity of user:
  - Increased side effects in elderly; patients with damaged or dysfunctional CNS
- Sedation
- Impaired motor speed and coordination
- Impaired cognition: short term memory (recent recall)
- Falls (elderly)
  - Occurs with long- and short half-life drugs
BENZODIAZEPINE EFFECT ON COGNITION

• Acute effect:
  – May decrease recent/immediate recall
  – Does not affect long-term storage/retrieval
  – Dose/potency dependent

• Chronic effect:
  – Reversible
  – Decrease short-term recall
LONG-TERM EFFECT OF BENZODIAZEPINES ON COGNITION - II

- Recent data suggest long-term decline in cognition with therapeutic usage
- Is reversible
- Benefit vs. risk: memory vs. reduced anxiety and enhanced sleep
Table 2: Moses illusions: Mean number of Illusions (I) and of detections followed by a correct answer (F) and criterion I/(I+F) for target word impostors

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Lorazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illusion (I)</td>
<td>3.8 (2.2)</td>
<td>8.4 (4.2)</td>
</tr>
<tr>
<td>Detection (F)</td>
<td>15.3 (2.9)</td>
<td>10.6 (3.9)</td>
</tr>
<tr>
<td>I/(I+F)</td>
<td>0.20 (0.12)</td>
<td>0.44 (0.21)</td>
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EFFECT OF DISCONTINUING BENZODIAZEPINES ON COGNITION IN THE ELDERLY

Discontinuers

Continuers

Baseline

2 weeks post discontinuation

WAIS Testing

(Salzman, 1990)
ANTIDEPRESSANTS FOR ANXIETY

• SSRIs, venlafaxine, mirtazapine, are increasingly used for anxiety
• SSRIs approved for panic, social anxiety disorder, OCD, GAD
• Venlafaxine approved for GAD
SUMMARY: MANAGEMENT OF ANXIETY

• Clinical decision: need rapid response but expect potential dependence, cognitive impairment—BENZODIAZEPINES

• Clinical decision: do not need rapid response; no dependence, good effect on co-morbid anxiety/depressive symptoms, but expect sexual side effects, weight gain, emotional blunting—ANTIDEPRESSANTS
CONCLUSIONS ABOUT ANTIDEPRESSANTS

- Not effective for acute treatment of anxiety
- Not superior to benzodiazepines for chronic treatment of generalized anxiety disorder
- Usefulness limited to anxiety-spectrum disorders
- Significant sexual side effects limit usefulness
- Significant drug interactions limit usefulness
GABAPENTIN (NEURONTIN)

- Not a benzodiazepine; does not work at BZ receptor
- Increases nonsynaptic release of GABA from glia
- Useful for decreasing agitation, rage, irritability
- Excellent sleeping pill
- No data on anxiolytic effect; may be helpful for social phobia, rage outbursts
PREGABALIN FOR GAD

- Pregabalin 300 mg/d as effective in treating GAD as alprazolam
- Side effects: somnolence and dizziness
- Also effective at 200, 400, and 450 mg doses
BUSPIRONE

• An azapirone, not a benzodiazepine; effects serotonin, not GABA
• Delayed onset of action; not as effective as benzodiazepines either acutely or chronically
• No dependence or cognitive impairment
• Not popular with psychiatrists; used more by primary care physicians
• Not useful for acute anxiety; more useful for chronic anxiety states
B BLOCKERS FOR ANXIETY

• Not effective for inner subjective experience of dread
• Very effective for autonomic, objective symptoms
LOW DOSE ANTIPSYCHOTICS FOR GAD

• Atypical antipsychotics:
  – Olanzapine (Zyprexa)
  – Risperidone (Risperdal)
  – Quetiapine (Seroquel)

• Conventional antipsychotics
  – Thioridazine
  – Trifluoperazine, perphenazine
ANXIETY SPECTRUM DISORDERS: DSM IV

- Social Anxiety Disorder
- Panic and agoraphobic disorders
- Obsessive-Compulsive Disorder
- Post Traumatic Stress Disorder
- Generalized Anxiety Disorder
SOCIAL ANXIETY DISORDER

• 13% prevalence
• Begins in childhood or early adolescence
• Twice as common in women
• Predominant symptoms: overwhelming and extreme self-consciousness in normal social situations; intense persistent and chronic fear of being observed by other people and of being embarrassed
• Physical symptoms include blushing, profuse sweating, trembling, difficulty talking, nausea, and stomach discomfort
Figure 1. Pharmacotherapy in Social Anxiety Disorder: Meta-Analysis of Efficacy Studies

- Benzodiazepine
- Monoamine Oxidase Inhibitor
- Selective Serotonin Reuptake Inhibitor
- Anticonvulsant
- Reversible Inhibitor of Monoamine Oxidase Type A

\[ \text{Effect Size}^{b} \]

\[ \begin{align*}
\text{Benzodiazepine} & : 1.12 \\
\text{Monoamine Oxidase Inhibitor} & : 1.00 \\
\text{Selective Serotonin Reuptake Inhibitor} & : 0.68 \\
\text{Anticonvulsant} & : 0.46 \\
\text{Reversible Inhibitor of Monoamine Oxidase Type A} & : 0.42
\end{align*} \]

Reprinted with permission from Hidalgo et al.\(^1\)

\(^{b}\)Effect size weighted to balance sample size.
Tricyclic Antidepressants in Social Anxiety Disorder

- Doubtful efficacy
- Poor side-effect profile
  - sedation, tremor, dry mouth
  - effects on cognitive function
  - sexual dysfunction
  - weight gain
  - constipation
MAO Inhibitors in Social Anxiety Disorder

- Irreversible, non-selective (eg, phenelzine)
  - Good effectiveness
  - Poorly tolerated
  - Hazardous

- Reversible, selective (eg, moclobemide, brofaromine)
  - Moderate effectiveness
  - Well tolerated
  - Approved in some countries
  - Not available in US
Beta-Blockers in Social Anxiety Disorder

- Effective for occasional performance anxiety
- Not effective in generalized social anxiety disorder
- Will not treat comorbid conditions (e.g., depression)
BENZODIAZEPINES FOR SOCIAL ANXIETY DISORDER

• Controversy regarding efficacy:
  – Clinicians: not as effective as antidepressants for SAD
  – Data: more effective than antidepressants for SAD

• May be used as adjunctive medication

• May prevent relapse

• Equal drop-out rate for BZ and antidepressant treatment
PANIC DISORDER

• 3% lifetime prevalence
• High anxiety-spectrum comorbidity
  – GAD 16%; MDD 23%
• High substance abuse (10-20%)
• Etiology theories:
  – Dysregulated NE and 5HT autoreceptors
  – Hypersensitive cholecystokinin receptors
  – Suffocation hypothesis: increased sensitivity to CO$_2$ and lactate
BENZODIAZEPINES FOR PANIC DISORDER

• High potency BZs still used to treat panic, alone or as adjunctive medication:
  – Alprazolam
  – Clonazepam

• BZ and antidepressants equally effective

• Combination CBT and BZ used for most severely symptomatic patients

Bruce, 2003; Pollack, 2003; Stahl, 2002; Starcevic, 2004
EARLY USE OF ANTIDEPRESSANTS FOR PANIC DISORDER

• TCAs and MAOIs have robust anti-panic disorder effects:
  – Commonly prescribed with a BZ for rapid response

• Decline in use due to unacceptable side effects and dietary restrictions; highest drop out rates
SSRI TREATMENT OF PANIC DISORDER

• Are the primary drugs for treatment of panic disorder
• Commonly prescribed with benzodiazepines in early, acute phase of treatment
• May lose efficacy over time
• Unacceptable side effects; higher drop out rate than BZs
Table 2. Comparative Benefits of Medications for Panic Disorder

<table>
<thead>
<tr>
<th>Benefit</th>
<th>High-Potency Benzodiazepines</th>
<th>TCAs</th>
<th>SSRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapidity of response</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Decrease panic attacks</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Decrease anticipatory anxiety</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Decrease phobic avoidance</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Antipanic efficacy</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Antidepressant efficacy</td>
<td>0</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

\(^a\)Based on data from Rickels and Schweizer.\(^16\)

Abbreviations: SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant. Symbols: + = mild, ++ = moderate, +++ = marked, 0 = not present.
Figure 1. Obsessive-Compulsive Spectrum Disorders

- Preoccupations with bodily sensations or appearance
  - Body dysmorphic disorder
  - Depersonalization
  - Anorexia nervosa
  - Hypochondriasis

- Impulsive disorders
  - Sexual compulsions
  - Trichotillomania
  - Pathological gambling
  - Kleptomania
  - Self-injurious behavior

- Neurologic disorders
  - Tourette’s syndrome
  - Sydenham’s chorea
  - Torticollis
  - Autism

OCD

*Reprinted with permission from Hollander et al.*
OCD-II: ETIOLOGY THEORIES

• “Stuck” 5HT \(_{1D}\) presynaptic autoreceptor
  – Hypersensitive to 5HT; stays in “on” position which decreases presynaptic 5HT release;
  – Requires high level of synaptic 5HT to desensitize (why high SSRI doses are necessary)

• Hyperactive corticostriatal dopamine circuit
  – Normal cortical inhibition of amygdala is attenuated by high DA in mesolimbic pathway
  – Explains why DA blockers are effective augmenting medications
Treatment of Obsessive Compulsive Disorder

- Delayed onset of response
  - Onset 6 to 10 wk
  - Maximize dose
  - 12 to 30 wk for maximal response
- Partial response is common
  - 25% to 40% improvement
  - Full remission is rare
  - 25% fail clomipramine or SSRIs
Pharmacologic Treatment of Obsessive Compulsive Disorder

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Starting dose (mg/d)</th>
<th>Minimum effective dose (mg/d)</th>
<th>Dose range (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>20</td>
<td>20</td>
<td>20-60</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>25</td>
<td>100</td>
<td>25-250</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20</td>
<td>20</td>
<td>20-80</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>50</td>
<td>100</td>
<td>10-300</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20</td>
<td>40</td>
<td>40-60</td>
</tr>
<tr>
<td>Sertraline</td>
<td>50</td>
<td>50</td>
<td>50-200</td>
</tr>
</tbody>
</table>

Augmenting the Response to SSRIs in Obsessive Compulsive Disorder

- Exposure and response prevention
- Cognitive-behavioral therapy
- If tics or schizotypal PD:
  - Neuroleptic (haloperidol, pimozide, risperidone)
  - Gabapentin 600 mg/day-3600 mg/day
  - Low dose clomipramine 50 mg/day-100 mg/day
  - Buspirone 30 mg/day-60 mg/day
  - Clonazepam 1 mg/day-4 mg/day
  - Trazodone 300 mg/day-600 mg/day

Medications for Treatment of Refractory OCD

- Add risperidone 1 mg/day-6 mg/day (or other atypical)
- Clomipramine + fluvoxamine
- Clomipramine (150 mg/day) + citalopram (40 mg/day)
- Venlafaxine > 225 mg/day
- Add L-tryptophan + pindolol + niacinamide
- Trazodone (500 mg/day-600 mg/day)
ODANSETRON FOR OCD

• (Zofran): Anti-nauseant
  – Is a 5HT$_3$ antagonist
• Augments other dopamine blockers
  – DA blockade helps OCD symptoms
• Dose: 0.25-5mg BID for 6 weeks added to SSRIs and antipsychotics

Pallanti 2009; CNS Drugs 23:1047
Figure 2. Change in Mean Yale-Brown Obsessive-Compulsive Scale (YBOCS) Scores in Patients With Obsessive-Compulsive Disorder Given Risperidone or Placebo in Addition to a Serotonin Reuptake Inhibitor

Reprinted with permission from McDougle et al.¹⁴

* p = .01.
** p = .005.
Lifetime Prevalence of PTSD

Kessler 1995

Breslau 1991

Treatment of PTSD

- Education
- Support
- Lifestyle modification
- Psychosocial
- Pharmacotherapy
Antidepressants

β Blockers

Clonidine

Neuroleptics

Mood Stabilizers: Valproate, Topiramate

Benzodiazepines

Antidepressants
Fluoxetine vs Placebo in Post-traumatic Stress Disorder

- Fluoxetine up to 60mg/day (N=27)
- Placebo (N=26)

Percent (%)

Much improved or very much improved (*score = 1 or 2)

Very much improved (*score = 1)

* Duke Global Rating Scale for PTSD
BENZODIAZEPINES FOR PTSD

• Not used as monotherapy
• Useful as adjunctive treatment in program of multiple drug therapies
Figure 5. Benzodiazepine Monotherapy in Posttraumatic Stress Disorder (PTSD)\textsuperscript{a}

\textsuperscript{a}Data from Gelpin et al.\textsuperscript{16} Alprazolam (N = 3) or clonazepam (N = 10) vs. no treatment (N = 10).
TOPIRAMATE

• Reduces symptoms of PTSD
• Useful in decreasing nightmares
• Effective dose <200mg/d:
  – Usually <100mg
PRAZOSIN (MINIPRESS) FOR TRAUMATIC NIGHTMARES

- Alpha-1 antagonist
- Easily crosses blood-brain barrier
- Decreases traumatic nightmares