Generalized Anxiety Disorder

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Generalized Anxiety Disorder (GAD) Presentation

OUTLINE

- Questions and Learning Points
  - Illness Characteristics
  - Morbidity and Comorbidity
  - Diagnosis and Assessment
    - Treatment
    - Summary
  - Questions and Answers
- Future Treatments (Optional)
Question #1

True or False

Women have a HIGHER Lifetime Prevalence of GAD as compared to Men.
Question #2

Which Psychiatric Illness has the HIGHEST LIFETIME PREVALENCE of COMORBIDITY with GAD?
What Anxiety Assessment Scale is commonly used to Assess Outcomes in GAD? and...

A decrease of ____% or greater on this scale defines **RESPONSE** while a score of ____ or less on this scale defines **REMISSION**.
Question #4

What PHARMACOLOGIC TREATMENTS are Effective in Treating GAD?
Question #5

What Percentage of Patients with GAD Relapse Within the First Year After Stopping Pharmacotherapy?
Teaching Point #1

GAD...

- Is More Likely to Occur in **Women**
- Has a Modal Age of Onset in the **Early 20s**
- Is **Usually Comorbid** with Another Psychiatric Illness
Teaching Point #2

Somatic Symptoms are Prevalent in GAD

HOWEVER,

Medications and Medical Conditions Should be Included in the Differential Diagnosis of a Patient Suspected of Having GAD
Teaching Point #3

Selective Serotonin Reuptake Inhibitors, Serotonin Norepinephrine Reuptake Inhibitors, and Benzodiazepines are commonly used to treat GAD.

Long term treatment may be required.
GAD Diagnostic Criteria

- Excessive anxiety and worry
- More days than not for $\geq 6$ months
- Worry is excessive and difficult to control
- Symptoms impair social, occupational, family role functioning and/or cause significant distress
Diagnostic Criteria for GAD

- Associated with 3 of the following
  - restlessness/keyed-up
  - easily fatigued
  - difficulty concentrating
  - irritability
  - muscle tension
  - sleep disturbance

- Cannot be confined to another Axis 1 diagnosis or the effects of a substance or medical condition

GAD Symptoms

- Psychic symptoms
  - worry
  - "on edge"/unable to relax
  - Impaired concentration-memory
  - *Concern over health*

- Somatic symptoms
  - muscle tension
  - Insomnia
  - Fatigue
  - irritability
  - nausea or diarrhea*
  - Sweating*
  - urinary frequency*
  - Palpitations*
  - Pain*

Lifetime Prevalence of GAD: National Comorbidity Survey

Epidemiology of GAD

- Lifetime prevalence 5.1%
- Women > men 2:1
- Modal age of onset is early 20s
- High comorbidity in clinical and community samples. “Pure” GAD is rare.

Kessler RC et al. Arch Gen Psychiatry. 1994;51:8
Course of GAD

Chronic course (mean > 20 yrs)

- Low rate of spontaneous remission (25% at 2 yrs)
  - For each add’l Axis I disorder 50% lower
  - For each add’l Axis III disorder 19% lower

10-Year Anxiety Disorder and Major Depressive Disorder Remission Rates

Keller, MB, Culpepper L, Data on file; CDS- Collaborative Depression Study
Low Probability of Remission in GAD*
Patients in treatment (HARP)

Relapse Rates in GAD After Full Remission

N = 130.
GAD Patients: Comorbidity

- 90% have another psychiatric disorder
- In patients with GAD
  - 62% have lifetime major depression
  - 40% have dysthymia
- Anxiety disorders predict greatest risk of secondary MDD
- 58% of patients with lifetime MDD have an anxiety disorder

Wittchen H-U et al. Arch Gen Psychiatry. 1994;51:355
Overlapping Symptoms of MDD and GAD

Generalized Anxiety Disorder
- Worry
- Muscle tension
- Palpitations
- Sweating
- Dry mouth
- Nausea

Major Depressive Disorder
- Depressed mood
- Anhedonia
- Appetite disturbance
- Worthlessness
- Suicidal ideation

Common Symptoms:
- Anxiety
- Sleep disturbance
- Psychomotor agitation
- Concentration difficulty
- Irritability
- Fatigue

Lifetime Prevalence of Comorbid Disorders in Patients with GAD

- Any Disorder: 90.4%
- Major Depression: 62.4%
- Panic Disorder: 23.5%
- Social Anxiety Disorder: 34.4%
- Alcohol Abuse and Dependence: 37.6%
- Post-Traumatic Stress Disorder: 22.0%

GAD+MDD: Implications

- Treatment resistance or delayed response
- Increased suicidal behavior
- Antidepressants indicated
- One open-label clinical practice reports effectiveness of venlafaxine in comorbid state
- CBT efficacy for comorbid state less clear, needs study
- Much written, little known

GAD: Complications

Never Marrying
- 27%

Receiving Public Assistance
- 37%

Suicide Attempts
- 13%

GAD Often Perceived as Physical by Patients--High Health Care Utilization and Low Recognition

- Gastrointestinal distress
- Insomnia
- Fatigue
- Musculoskeletal complaints
- Headache
- Cardiovascular complaints
Generalized Anxiety Disorder (GAD)

Under-recognized

Under-treated

Health-care utilization

Disability/impairment

Risk for new psychiatric disorders
Generalized Anxiety Disorder

Services Utilization and Comorbidity

Comorbid GAD  GAD Only  Gad only (N = 395)

Souetre et al, J Psychosom Res 1994;151
GAD in Cardiology

Cardiovascular Evaluation Sought by GAD Patients

- Evaluated: 50%
- Treadmill: 40%
- Echo: 23%

GAD
Differential Diagnosis

- Adjustment disorders
  - With anxiety
  - With depression
  - With mixed symptoms

- Anxiety disorders
  - Generalized anxiety disorder (GAD)
  - Panic disorder
  - Phobias
  - Post-traumatic stress disorder (PTSD)
  - Obsessive-compulsive disorder (OCD)
Patient Assessment

- Establish Diagnosis
- Comorbid diagnosis present?
  - Current or past depression
- Natural History of Illness
- Treatment History
- Family History
- Medical History and exam
  - Review medications, including herbal medicine
Differential Diagnosis

Medications Which Can Cause Anxiety Symptoms

- Stimulants (caffeine)
- Thyroid supplementation
- Antidepressants
- Corticosteroids
- Oral contraceptives
- Bronchodilators
- Decongestants
- Abrupt withdrawal of CNS depressants
  - Alcohol
  - Barbiturates
  - Benzodiazepines
Differential Diagnosis

Medical Conditions with Secondary Anxiety Symptoms

- **Endocrine disorders**
  - Thyroid disease
  - Parathyroid diseases
  - Hypoglycemia
  - Cushings Disease

- **Cardio-respiratory disorders**
  - Angina
  - Pulmonary embolism

- **Autoimmune disorders**
- **Neurological**
  - Seizure disorder

- **Substance-related dependence/ withdrawal**
  - Nicotine
  - Alcohol
  - Benzodiazepines
  - Opioids
Goals of Treatment in GAD

Response

≥ 50% decrease from baseline in HAM-A scores or CGI score of 1 or 2

Remission*

HAM-A score ≤ 7
Patient asymptomatic
Psychosocial/occupational functioning restored

*Peer-reviewed published studies on remission in GAD not yet available.

Outcomes Assessment in GAD

- Hamilton Anxiety Rating Scale
  - Traditionally used in clinical trials

- Hospital and Anxiety Rating Scale
  - Patient rated 14 items
    - 7 items for anxiety
    - 7 items for depression
    - Sensitive to change
    - Equivalence to Hamilton Anxiety Scale shown in large patient sample
Response vs Remission

HAM-A Total Score
Change During Treatment

Placebo (n = 123)
Drug X (n=112)

Response = \( ^3 \) 50% decrease in HAM-A
Remission = Ham-A \( ^2 \) 7
Treating Anxiety Disorder May Reduce Risk of MDD

- National Comorbidity Survey
  - Sept. 1990 - Feb. 1992 (interview and re-interview 2y later)
- Respondents with GAD w/o prior MDE
- ≥4 doses psychotropic medication for GAD
  - Lower risk of depression
    - 5.73% vs. 18.9%, p<0.0001
  - Receiving any medication for GAD or consulting mental health specialist was not.

Treatments for GAD

- Anxiolytic agents and antidepressants are effective in the treatment of GAD
  - BZDs
  - Buspirone
  - TCAs
  - SSRIs
  - SNRIs Venlafaxine XR (extended release)
    - (duloxetine in clinical trials 2006)

- Some forms of psychotherapy are effective in the treatment of GAD
GAD Psychosocial Treatments

– Cognitive-Behavior Therapy*
  – Manualized treatment developed
  – Limited data
  – Behavioral alone (eg relaxation, imaginal exposure) vs Cognitive alone better outcome
  – Combined cognitive and behavioral

– Other Psychotherapy
  – Insight-oriented
  – Family/group

– Support
  *Unclear for comorbid states

– Education

Deacon and Abramowitz J Clin Psychol 2004; 60:429-41
Psychotherapy in GAD

Recovery rates at 6-month follow-up

- Cognitive behavioral therapy: 44 of 87 patients = 51%
- Applied relaxation: 23 of 38 patients = 60%
- Analytical psychotherapy: 1 of 23 patients = 4%
Pharmacotherapy for GAD

- TCAs
- Buspirone
- SSRIs
- BZDs
- SNRI
- Other ADs
- Adjunctive
Traditional Anxiolytics

Limitations

• Poor tolerability (TCAs, MAOIs)
  - *SSRIs*-Less than ideal

• Limited breadth of efficacy (TCAs, BZDs, MAOIs?)

• Lack of antidepressant efficacy (buspirone?, BZDs)

• Safety (TCAs, MAOIs)
Initiating therapy: treatment considerations

Ease of management

- Safety
- Concomitant meds
- Pregnancy
- Age
- Washout

- Compliance
- Ease of switching
- Ease of discontinuation

*
GAD Treatments
SSRIs and SNRIIs+

Advantages
- Effective
- Safety
- Tolerability
- No dependence issues
- Once-daily dosing

Disadvantages
- Delayed onset of action
- Early anxiogenic effect
- Sexual side-effects
- Usually requires dose titration

+venlafaxine
SSRIs: Paroxetine for GAD
Flexible Dosing

Mean HAM-A Total Score

Placebo (n = 163)
Paroxetine (Mean Dose 26.8 mg; n = 161)

Baseline 2 4 6 8 Week

**P < .05 vs placebo.
SSRIs for GAD: Sertraline vs Placebo

ITT sample


![Graph showing Mean HAM-A Change Score over Treatment Week for Placebo (N = 188) and Sertraline (N = 182). The graph demonstrates a significant reduction in HAM-A scores for both groups over time, with Sertraline showing a more pronounced reduction compared to Placebo.](image-url)

**P < .01
***P < .0001

Mean HAM-A Change Score vs Treatment Week

- Base
- 1 2 3 4 5 6 7 8 9 10 11 12 LOCF

Placebo (N = 188)
Sertraline (N = 182)
Venlafaxine Treatment of GAD

Fixed-dose Study

Week

Baseline 1 2 3 4 5 6 7 8

HAM-A Total Score (Mean Change from Baseline)

Placebo (N = 96)
Venlafaxine-XR, 75 mg/Day (n = 86)
Venlafaxine-XR, 150 mg/Day (n = 81)
Venlafaxine-XR, 225 mg/Day (n = 86)

P = .03.

Duloxetine

- SNRI: binds with high affinity to serotonin and norepinephrine transporters
- Mimics physiologic effects of antidepressants
- More potent than fluoxetine as inhibitor of serotonin reuptake
- FDA-approved for MDD
- GAD studies in Phase III now

GAD Treatment
Benzodiazepines

Advantages
- Rapid onset
- Effective
- Well-tolerated
- General anti-anxiety effects
- Safe in overdose
- Generics available

Disadvantages
- Withdrawal reactions
- Sedation
- Multiple daily dosing often required
- Abuse potential in patients w/ Hx abusing
- Poor antidepressant effect
## GAD Treatment

### Benzodiazepines

<table>
<thead>
<tr>
<th>Agent</th>
<th>Daily Dosage Range (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>2-6</td>
</tr>
<tr>
<td>Clonazepam*</td>
<td>1-3</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>4-10</td>
</tr>
<tr>
<td>Diazepam*</td>
<td>15-20</td>
</tr>
</tbody>
</table>

*Slow elimination, longer to steady-state*
**Imipramine, Diazepam, and Trazodone Treatment of GAD**

OC = observed cases; OC dataset.

*P < .05.  **P < .01.

Rickels K et al. *Arch Gen Psychiatry*. 1993;50:884-895.
BZ for GAD-Considerations

- No long-term studies with BZ monotherapy
- GAD
  - Highly comorbid with depression
  - Often requires long-term therapy
- Benzodiazepines
  - Not effective for depression
  - Not considered ideal as *monotherapy* treatment
    - This is based on zero data
  - Useful as adjunctive medication for many patients

*
Buspirone

- Buspirone-Partial 5HT1a agonist
  - Early studies showed efficacy at 15 mg comparable to diazepam 15 mg
  - Limited breadth of efficacy in comorbid patients limits enthusiasm
  - Outcomes of various studies are uneven
  - Higher dose (at least 30 mg daily) probably necessary
Long-Term Treatment of GAD

- Need to treat for long term
- Full relapse in approximately 25% of patients 1 month after stopping treatment
- 60%-80% relapse within 1st year after stopping treatment

Rickels K, Schweizer E. J Clin Psychopharmacol. 1990;10(3 suppl):101S-110S.*
**Paroxetine Long-Term GAD Treatment**

**Remission Takes Time**

- **Placebo (n = 274)**
- **Paroxetine (n = 285)**

**Paroxetine 20-50 mg (n = 599 Responders)**

**Randomization**

- Phase 1: Single Blind PAR
- Phase 2: Double Blind Stay on PAR or switch to PBO

 Patients Remitted (%)

**P < .01 vs placebo. Remission = HAM-A ≤ 7; LOCF dataset. Pollack, M. APA; May 2002**
Paroxetine Long-Term GAD Treatment
Relapse Prevention

*P < .001; N = 286/274; LOCF
6-Month, Placebo-Controlled Trial of Venlafaxine XR in GAD

HAM-A Total—Observed Cases Analysis
(Mean Baseline HAM-A Total Score 25.0, Mean Daily Dose 176 mg)

* P < 0.05 vs. placebo †; P < 0.001 vs. placebo

Remission Takes Time
GAD Pooled Analysis (N=767)

Remission HAM-A ≤7

Time
Wk 1  Wk 2  Wk 4  Wk 6  Wk 8  Mo 3  Mo 5  Mo 6

Remission Rate (%)

Placebo
Venlafaxine XR

*P<0.001 vs. placebo. †P<0.01 vs. placebo.
Placebo-Controlled Trial of Sertraline in the Treatment of Children with GAD

- N = 22
- 2-3 week run-in, 9 weeks of double-blind treatment with sertraline or placebo
- Primary diagnosis of GAD; excluded MDD, OCD, MR, ADD
- Ages 5-17 years (mean 11.7 ± 3.9 years)
- Sertraline dose: 25 mg/d for week 1; 50 mg/day weeks 2-9

Placebo-Controlled Trial of Sertraline in the Treatment of Children with GAD

Mean Total Scores on Hamilton Anxiety Rating Scale at 9 Weeks*

*LOCF. Low and high depression severity indicated by Hamilton Depression Rating Scale scores ≤ 10 and > 10, respectively.
# Summary: GAD Antidepressant Dosing

<table>
<thead>
<tr>
<th>Category</th>
<th>Usual Dosage Range (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRIS</strong></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20-60</td>
</tr>
<tr>
<td>Sertraline*</td>
<td>100-200</td>
</tr>
<tr>
<td>Paroxetine*</td>
<td>20-40</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>100-300</td>
</tr>
<tr>
<td>Citalopram*</td>
<td>20-40</td>
</tr>
<tr>
<td>Escitalopram*</td>
<td>10-20</td>
</tr>
<tr>
<td><strong>SNRIs</strong></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine**</td>
<td>75-225</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>60-120</td>
</tr>
<tr>
<td><strong>Tricyclic Antidepressants</strong></td>
<td></td>
</tr>
<tr>
<td>Imipramine*</td>
<td>100-300</td>
</tr>
<tr>
<td>Clomipramine*</td>
<td>50-100</td>
</tr>
</tbody>
</table>

*Controlled data, **FDA approved*
Anticonvulsants Potentially Useful as Adjunctive GAD Treatment

- **Vigabatrin**
  - Inhibits GABA transaminase

- **Topiramate**
  - Acts at ion-gated channels

- **Tiagabine**
  - Inhibits GABA reuptake

- **Gabapentin**
  - GABAergic anxiolytic, novel mechanism
  - Pilot study evidence of efficacy in PD, SP, EtOH withdrawal

- **Pregabalin**—clearly effective for GAD but not FDA-approved for GAD
Selective GABA Reuptake Inhibitor Tiagabine for GAD:
HAM-A Total Scores--marginal effect possibly due to design--
Phase III in progress in 2006

†Final visit was calculated using last post-baseline observation for each patient.

Pregabalin vs. Alprazolam in GAD

*\( p < 0.05 \)
**\( p < 0.005 \)
***\( p < 0.0005 \)

vs placebo by ANCOVA

Mean baseline HAM-A score (SD): 25.0 (3.4); 4 weeks

Does not have FDA approval

Pollack et al (2001) ACNP
Strategies for Refractory GAD

- Evaluate treatment intensity
  - Dose and duration of antidepressant Rx?
- Switch to a second SSRI/antidepressant
- Add
  - benzodiazepine
  - buspirone
  - GABAergic anticonvulsants
    - Gabapentin, tiagabine, vigabatrin, topiramate,
  - low dose atypical neuroleptics
- Review psychosocial variables for stress management
  - Add CBT

Most suggestions from clinical experience
Coplan et al JCP 154 (supp) 63-74, 1993
Summary

- GAD is common
- Remission is the goal
  - Identification of target symptoms, including physical symptoms
- Careful evaluation, patient education key aspects of treatment
- Medication: start low and go slow
  - Adequate dosages for adequate lengths of time
  - May require long-term treatment
Question #1

True or False

Women have a HIGHER Lifetime Prevalence of GAD as compared to Men.
Answer #1

TRUE!
Question #2

Which Psychiatric Illness has the HIGHEST LIFETIME PREVALENCE of COMORBIDITY with GAD?
Answer #2

Major Depressive Disorder
Question #3

What **Anxiety Assessment Scale** is commonly used to Assess Outcomes in GAD?

and...

A decrease of ____% or greater on this scale defines **RESPONSE** while a score of ____ or less on this scale defines **REMISSION**.
Answer #3

Hamilton Anxiety Rating Scale
A decrease of 50% or greater on this scale defines RESPONSE while a score of 7 or less on this scale defines REMISSION.
Question #4

What PHARMACOLOGIC TREATMENTS are Effective in Treating GAD?
Answer #4

- Benzodiazepines
  - Buspirone
- Tricyclic Antidepressants
- Selective Serotonin Reuptake Inhibitors
- Serotonin Norepinephrine Reuptake Inhibitors
What Percentage of Patients with GAD Relapse Within the First Year After Stopping Pharmacotherapy?
Answer #5

60-80%
Part II-May be used separately or used with Part I
Future Strategies for Anxiety Disorders

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Traditional Anxiolytics

Limitations

• Poor tolerability (TCAs, MAOIs)
  • *SSRIs*-Less than ideal
• Limited breadth of efficacy (TCAs, BZDs, MAOIs?)
• Lack of antidepressant efficacy (buspirone?, BZDs)
• Safety (TCAs, MAOIs)
Anticonvulsants

- Carbamazepine
- Valproic acid
  - *Both have some GABAergic action (VPA > CBZ)*
  - *Marginal antidepressants*
  - *Breadth of efficacy not clear*
Anticonvulsants

- Vigabatrin
  - Inhibits GABA transaminase
- Topiramate
  - Acts at ion-gated channels
- Tiagabine
  - Inhibits GABA reuptake
- Gabapentin
  - GABAergic anxiolytic, novel mechanism
  - Pilot study evidence of efficacy in PD, SP, EtOH withdrawal

*Utility in anxiety disorders not known*
Bad News Peptides

- Corticotropin-releasing factor (CRF)
- Cholecystokinin (CCK)
- Substance P
CRF and Acute Stress

Stressor

ACTH

CRH

Glucocorticoids

Catecholamines

↑ Gluconeogenesis
↑ Lipolysis
↑ Proteolysis
↑ Insulin resistance
↓ Inflammation
↓ Immune function

↑ Blood pressure
↑ Heart rate
↑ Blood sugar
↓ GI blood flow

↓ Eating
↓ Reproduction
↓ SW Sleep
↑ Grooming
↑ Neophobia (novel environ)
↑ Locomotor activity (familiar environ)
↑ Behavioral despair
↑ Seizure/kindling
↑ Locus coeruleus FR
↑ Pyramidal FR
CRF Role in Stress Related Illnesses

CRH

- Pain Perception
- Anxiety Disorder
- Hyperreactivity to Somato/Psych Stimuli
- IBS/Visceral Hyperalgesia
- Victimization/Abuse Psychiatric Disorders
Locus Coeruleus System as a Site of Action for Psychotropics

Stress

CRF

GLUTAMATE

Locus Coeruleus

Reduced Norepinephrine Reactivity and Release

Inhibitory

Stimulatory

SSRIs  TCAs  MAOIs  BZDs

5-HT  GABA
Neurotransmitters—Mechanisms of Action

PRESYNAPTIC CELL

Reuptake transporter

SYNAPTIC CLEFT

Autoreceptor

Neurotransmitter

POSTSYNAPTIC CELL

Neurotransmitter receptor

Nemeroff CB. Scientific Amer. 1998;June:43-49.
Antidepressants: Transductional Targets of Action

- Antidepressants increase NE, 5-HT or both
- Activate transductional cascades
  - Activate or inhibit the synthesis of specific gene products
- Multiple, synergistic mechanisms likely
Hypothesis of Stress, Anxiety and Depression

Normal Survival and Growth

Stress/Anxiety

Antidepressants

- Glucocorticoids
- BDNF
- Serotonin and NE
- BDNF
- Glucocorticoids

Atrophy/death of neurons

Increased survival and growth

Other Neuronal Insults:
- Hypoxia-ischemia
- Hypoglycemia
- Neurotoxins
- Viruses

Genetic factors

Nemeroff CB. Scientific Amer. 1998;June:43-49.
The First 20 Patients: *Effects of the High-Affinity CRF 1 Antagonist* (R121919) *in Major Depression*

Substance P Antagonists

- Substance P ⇒ anxiety, depression, pain
- Three receptors identified in CNS
- MK-869: nonpeptide NK₁ receptor antagonist
- Oral, once-daily formulation

Effect of MK-869 and Paroxetine on Depression

Mean Change in HAM-D21

Placebo (n = 70)
Paroxetine 20 mg (n = 72)
MK-869 300 mg (n = 71)

Glutamatergic System
mGLU Agonists

- Novel presynaptic mechanism
- Decreases excitatory neurotransmitter glutamate release
- May modulate GABA transmission
Glutamatergic-GABAAergic Interactions

Pathology

Hyperexcitability

mGlu Receptors

Physiological Range

mGlu Receptors

Hypoexcitability

Pathology

Glutamate

GABA

HO₂C

O₂H

NH₂

HO₂C

NH₂
LY354740 (mGlu2 agonist) inhibits glutamatergic transmission.
Partial BZD Agonists

- Pagoclone
  - Effective in panic disorder
  - In development
- Abecarnil
  - Some effect in GAD, not sustained?
- Others in pipeline
BZD Receptor Subunit Agonists

- **GABA-A_{1a}**
  - Sedation, anxiolytic

- **GABA-A_{2a}**
  - Anxiolytic

- **GABA-A_{3a}**
  - Muscle relaxation

- **GABA-A_{5a}**
  - Memory, muscle relaxant
Pregabalin Novel Mechanism: $\alpha_2\delta$ Binding Inhibitory Effect

Synapse

Reduces release

NEUROTRANSMITTERS:
- $\downarrow$ Noradrenaline
- $\downarrow$ Glutamate
- $\downarrow$ Substance P

$\alpha_2\delta$ subunit

Voltage-gated $\text{Ca}^{2+}$ channel

Attenuates $\text{Ca}^{2+}$ influx

GABA neurotransmitter transporter enhanced

Noradrenaline Glutamate Substance P

Neurotransmitter binding site
**Pregabalin vs Venlafaxine IR Study in GAD**

**Mean HAM-A Score**

- Placebo (n = 100)
- Venlafaxine 75 mg/day (n = 110)
- Pregabalin 600 mg/day (n = 104)
- Pregabalin 400 mg/day (n = 94)

All medication doses b.i.d.

Data on file, Pfizer Inc.