

Generalized Anxiety Disorder

by

Frank Minirth, M.D., Ph.D.

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- Introduction
- Bible verses
 - Genesis 45:5 – Now therefore be not grieved, nor angry with yourselves, that ye sold me hither: for God did send me before you to preserve life.
 - Numbers 12:1 – And Miriam and Aaron spake against Moses.....
 - Numbers 12:9 – And the anger of the Lord was kindled against them.....
 - I Kings 19:12 – And after the earthquake a fire; but the Lord was not in the fire: and after the fire a still small voice.
- generalized anxiety disorder (GAD)

GAD is a professional diagnosis from the *Diagnostic and Statistical Manual of Mental Disorders*. It pertains to a specific set of symptoms that have gone on for at least six months. The symptoms may include worry, restlessness, fatigue, irritability, muscle tension, sleep disturbance, and difficulty concentrating.

 - anxiety disorder is number one in mental health today.
 - anxiety disorders are comorbid of depression, bipolar, substance abuse and self harm issues.
- generalized anxiety disorder (GAD)—two new treatment options

Tigabine (Gabitril), an anticonvulsant that blocks the reuptake of GABA, and pregabalin (Lyrica), a drug approved for neuroleptic pain and an anticonvulsant that possibly enhances GABA have both been used off-label in GAD. If tigabine is increased too rapidly, it can cause seizures rather than decrease them.
- antianxiety drugs: nuances of interest
 - The first antianxiety drug were barbiturates and meprobamate in the 1930's
 - TCAs were used in anxiety disorders in the early 1960's
 - MAOIs were also found to be effective in anxiety disorders in the early 1960's
 - The benzodiazepines were found to be effective in anxiety disorders in the 1960's
 - In the 1980's buspirone (BuSpar, an azopyrone) was used in GAD
 - SSRIs (the most popular antianxiety agents today) were used in the 1980's and beyond
 - SNRIs were used in the 1990's and 2000's
 - Anticovulsants, beta-blockers, and antipsychotics have been used off-label for anxiety
 - To treat anxiety disorders with SSRI or SNRI the general rule is to start lower and go higher than in treatment of depressive disorders
 - TCAs used for anxiety can be lethal in overdose
 - Benzodiazepines increase the effects of GABA (the most calming neurotransmitter of the brain) through allosteric receptors; when GABA interacts on the postreceptor site and results in an increased passage of chloride ions

- Some benzodiazepines increase both GABA_A and GABA_B (diazepam/Valium); most benzodiazepine increase GABA_A.
- Buspirone (BuSpar) is approved for GAD; it is a partial agonist at 5HT_{1A}; its metabolite, 1-phenyl-piperazine, has an anxiolytic effect by action on alpha-2-adrenergic
- Betaadrenergic blockers are used off-label for their antianxiety effects; they antagonize epinephrine and norepinephrine; they act primarily on a peripheral basis; beta-blockers include: propranolol (Inderal), timolol (Istalol), nadolol (Corgard), atenolol (Tenormin), betaxolol (Kerlone), metoprolol (Toprol XL, Lopressor), penbutolol (Levatol), acebutolol (Sectral), and esmolol (Brevibloc)
- Gabapentin (Neurontin) and pregabalin (Lyrica) have been used off-label for anxiety; they increase GABA in a nonaddicting way
- Tigabine (Gabrilitril) has been used off-label for anxiety; it blocks the reuptake of GABA by transport inhibition
- GAD drugs include: benzodiazepines, buspirone (BuSpar), paroxetine (Paxil), venlafaxine (Effexor)
- Fluoxetine (Prozac), paroxetine (Paxil), and sertraline (Zoloft) are approved for PMDD
- SAD drugs include: sertraline (Zoloft), venlafaxine (Effaxor), paroxetine (Paxil), benzodiazepines
- Panic disorder drugs include: sertraline (Zoloft), paroxetine (Paxil), venlafaxine (Effaxor), benzodiazepines
- PTSD drugs include: paroxetine (Paxil), sertraline (Zoloft)
- OCD drugs include: fluoxetine (Prozac), fluvoxamine (Luvox), sertraline (Zoloft), paroxetine/Paxil, clomipramine (Anafranil); citalopram (Celexa) has been used for treatment of refractory OCD; drugs with FDA approval in pediatric OCD include: sertraline (Zoloft), fluoxetine (Prozac), and fluvoxamine (Luvox)
- SNRIs have been used for GAD, SAD, PTSD, PD, and OCD; the most common side effects include somnolence, dry mouth, and nausea
- TCAs have been used for GAD, PTSD, PD, and OCD; they do not seem very effective against SAD; TCAs with more of a serotonergic effect [amitriptyline (Elavil), imipramine (Tofranil)] have been used more in PD
- Trazadone (Desyrel) seems effective in GAD
- Other nuances of interest in antianxiety drugs are:
 - Benzodiazepines have at times paradoxically worsen the course of PTSD by inducing depression
 - The benzodiazepines, alprazolam (Xanax), and clonazepam (Klonopin), are often effective in PD
 - While buspirone (BuSpar) is effective in GAD, it seems ineffective many times in OCD, SAD, and PD
 - Beta-blockers have been used off-label in performance anxiety, but seems ineffective many times in SAD, PD, and OCD; beta-blockers have been used with somatic symptoms of anxiety; beta-blockers can block traumatic memories in PTSD

- Anticonvulsants [gabapentin (Neurontin), valproic acid (Depakote), and tigabine (Gabrilitril)] have been used off-label in PD
- Topiramate (Topamax) has been used off-label to decrease intrusive thoughts in PTSD
- Sertraline (Zoloft) has been started at 25 mg/day or higher for week 1 in GAD; venlafaxine (Effexor) is often started at 75 mg/day for week 1 in GAD
- Common side effects of SSRIs include GI (nausea, diarrhea) and headaches
- The most common side effects of benzodiazepines is drowsiness; rare side effects of benzodiazepines include anterograde amnesia, rash, and memory problems
- The sedative effects of benzodiazepines are increased with alcohol, analgesis, and barbiturates
- The absorption of benzodiazepines is decreased by food; the plasma levels are decreased by barbiturates, carbamazepines, steroids, and rifampin; the plasma levels are increased by antifungals, contraceptives, cimetidine (Tagamet), disulfiram (Anatabuse), erythromycin, fluvoxamine (Luvox), isoniazid, and nefazodone (Serzone)
- Benzodiazepines can be teratogenic; they can cause withdrawal symptoms in neonates; they can cause problems in those with COPD and sleep apnea; up to 50% of patients may have withdrawal symptoms upon discontinuation of benzodiazepines; alprazolam (Xanax) is one of the most problematic in regard to withdrawal syndrome; abuse potential may be the highest with certain benzodiazepines including: alprazolam (Xanax), diazepam (Valium), and lorazepam (Ativan)
- Benzodiazepines vary in their half-lives from long to short—examples include:

	<u>hours</u>
clorazepate (Tranxene)	60
diazepam (Valium)	40 (60 with metabolite)
chlordiazepoxide (Librium)	20 (60 with metabolite)
prazepam	60
clonazepam (Klonopin)	30-40
halazepam (Paxipam)	26-72
flurazepam (Dalmane)	48-72
triazolam (Halcion)	3
temazepam (Restoril)	15
midazolam (Versed)	2.5
alprazolam (Xanax)	14
lorazepam (Ativan)	14
oxazepam (Serax)	9

- Benzodiazepines vary in rate of onset from fast to slow:
 - clorazepate (Tranxene)—fast
 - diazepam (Valium)—fast
 - chlordiazepoxide (Librium)—intermediate
 - alprazolam (Xanax)—intermediate
 - lorazepam (Ativan)—intermediate
 - oxazepam (Serax)—slow
 - prazepam—slow
- SSRIs and SNRIs are often the first-line pharmacological intervention for anxiety in older adults
- The antianxiety drugs target the core symptoms of the anxiety disorders—anxiety and worry involving the cortico-striatal-thalmo-cortical (CSTC) circuits. Connections between the orbitofrontal cortex, the anterior cingulate cortex, the amygdala, the hypothalamus (HPA axis, cortisol level, endocrine response, ANS) and the periaqueductal gray area of the brainstem. GABA is one of the most important neurotransmitters in anxiety reduction. Benzodiazepine sensitive GABA-A receptors have two beta units plus a gamma unit (2 or 3) plus two alpha units (1, 2, or 3) on the postreceptor side. GABA-A alpha 2, 3 are important in anxiety; GABA-A alpha 1 in insomnia. NE is an important neurotransmitter in anxiety arousal. Certain GABA-A receptors are benzodiazepine—insensitive; those with alpha 4, alpha 6, gamma1, and delta subunits are insensitive. They do bind to other drugs such as alcohol, certain general anesthetics, neurosteroids, and some of the new hypnotics.
- Lyrica (pregabalin) and Neurontin (gabapentin) are alpha 2 delta calcium channel ligands that decrease anxiety.
- SSRI increase 5HT in the amygdala and this decreases anxiety.
- SNRI also decrease anxiety.
- Buspirone (Buspar), a partial 5HT1A agonist (SPA) decreases anxiety.
- Gepirone ER, a partial 5HT1A agonist (SPA) is being tried for antidepressant effects. It may have antianxiety effects.
- Beta blockers have been used in PTSD anxiety.
- Conclusion
- Bible verses
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