Don't Ask, Don't Tell, but Benzodiazepines Are Still the Leading Treatments for Anxiety Disorder

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Issue: *Despite their limitations, benzodiazepines are still frequently used along with serotonergic antidepressants for the treatment of anxiety disorders. Prescribing both classes of drugs may have not only an empiric basis of therapeutic usefulness derived from clinical observations but also a neurobiological rationale.*

Prescribe Benzodiazepines? Not Me!

Modern guidelines for psychopharmacologic treatment of anxiety disorders have evolved from recommending GABAergic (gamma-aminobutryic acid) benzodiazepines to recommending serotonergic agents for first-line use.[1] This trend, along with adverse publicity about the dependence potential of benzodiazepines, might lead one to suspect that benzodiazepines, once prominent in the 1980s but now generic and often disparaged, must have significantly declined in use. Not so. In fact, benzodiazepines are still more widely prescribed than antidepressants for the treatment of anxiety disorders (Table 1),[2] and alprazolam is the single most commonly prescribed agent for mood and anxiety disorders (Table 2).[3] Should those who treat anxiety be surprised by this fact or even embarrassed about being caught red-handed prescribing benzodiazepines as well as antidepressants? Or is it possible that wise observations from clinical practice have honed the mixing and matching of these 2 major therapeutic classes to actually optimize treatment outcomes? A glimpse at what is now known about the neuroanatomical substrate of fear suggests that it may be clever, not shameful, to combine GABAergic agents with serotonergic agents to get the best outcome from psychopharmacologic treatments of anxiety disorders.[4–6]

The Brain's Panic Button

The amygdala apparently acts as the brain's panic button. Push it hard enough with emotional input from any of several areas of the brain, and it will trigger an alarm of fear via multiple brain pathways connecting to the body.[4,5] Some inputs to the amygdala are fast and precipitate fear reactions that occur like a reflex and without thought. Other inputs are detoured momentarily to the cortex and hippocampus where they are analyzed before the decision is made to hit the panic button. Emotional inputs to the amygdala frequently use the excitatory neurotransmitter glutamate to ring the alarm, but triggering of the alarm by glutamate can be tempered by both GABA and serotonin.[6] GABA interneurons in the cortex and hippocampus inhibit emotional input to the amygdala, as do serotonergic nerve terminals from the raphe. GABA interneurons and serotonergic nerve terminals in the amygdala itself act as potential brakes on amygdala output to the fear response. Thus, agents that boost output from either GABA or serotonin neurons each have at least 2 chances—from both outside and inside the amygdala—to diminish the likelihood of anxiety and fear.

Combining Independent Mechanisms to Enhance Therapeutic Results

Although serotonergic agents may be first-line treatments for anxiety disorders, they do not always work, and of course, they also have their own limitations. For example, at the beginning of treatment, serotonergic agents may have a delayed onset of action and may even activate anxiety symptoms at first, with less than half of all patients experiencing complete

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Take-Home Points

- Although serotonergic antidepressants have largely replaced benzodiazepines as the recommended first-line treatments for anxiety disorders in treatment guidelines, benzodiazepines are in fact still used more frequently.
- The psychopharmacology of fear and its neuroanatomical substrates predict that both pharmacologic classes should have independent therapeutic actions in anxiety disorders.
- If the goal of treatment of anxiety disorders is remission of symptoms, it may be rational to combine both serotonergic and GABAergic agents.

Table 1. Top 10 Drugs Prescribed for Generalized Anxiety Disorder[a]

Drug	%
Benzodiazepine	
Alprazolam (Xanax)	15
Lorazepam (Ativan)	10
Clonazepam (Klonopin)	9
Diazepam (Valium)	4
Antidepressant	
Paroxetine (Paxil)	12
Venlafaxine (Effexor/Effexor XR)	6
Sertraline (Zoloft)	5
Citalopram (Celexa)	4
Nefazodone (Serzone)	4
Buspirone (BuSpar)	9
Total Top 10	78
Benzodiazepine use in top 10	38
SSRI use in top 10	21

[a]Data from the National Disease and Therapeutic Index moving annual totals.[2]

Table 2. Total Prescriptions Written for All Mood and Anxiety Disorders[a]

Drug	Million
Benzodiazepine	
Alprazolam (Xanax)	31
Diazepam (Valium)	13
Clonazepam (Klonopin)	13
Lorazepam (Ativan)	21
All other benzodiazepines	12
Antidepressant	
Sertraline (Zoloft)	28
Fluoxetine (Prozac)	26
Paroxetine (Paxil)	26
Citalopram (Celexa)	17
Amitriptyline (Elavil)	17
Bupropion (Wellbutrin)	14
Venlafaxine (Effexor/Effexor XR)	13
Buspirone (BuSpar)	7
All others (each)	< 6
Total	280

[a]Data from the National Disease and Therapeutic Index moving annual totals.[3]

remission of symptoms and at the cost of long-term side effects such as sexual dysfunction.[7,8] On the other hand, GABAergic benzodiazepines may have a rapid onset of action and boost early efficacy of serotonergic agents (if sedation can be avoided), and then be discontinued after short-term administration, thus serving as a bridge to long-term serotonergic treatments.[9] Benzodiazepines can also serve as emergency relief for breakthrough anxiety over the long term, and in cases where serotonergic agents are unable to relieve all symptoms, can "top up" such treatments to lead to remission of anxiety. Cognitive behavioral treatments may also work as an "endogenous" GABAergic treatment to enhance the inhibitory action of GABA on fear circuits over time and thereby also "top up" treatment with pharmacologic agents to aid remission of anxiety.[4] Finally, new GABAergic agents currently under development have the potential of less sedation and dependence liability and may be even more useful as combination treatments for anxiety in the future.[10]

So, go ahead and feel less guilty about combining GABAergic and serotonergic treatments for anxiety. You have lots of company and a scientific rationale for this practice. ◆

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