Anxiety Disorders and Benzodiazepines

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Disclosures

Daniel Zigman

- I have received honorarium from Aifred for participating in a clinical trial
- I will be discussing off label use of medications

LEARNING OBJECTIVES

- Describe evidence-based treatment options for Anxiety Disorders
- Understand the role of benzodiazepines

Outline

- Pharmacotherapy for Anxiety Disorders
- Benzodiazepines, risks and benefits

GAD – DSM5 Criteria

- Core feature: 'Excessive, persistent, worrying that is hard to control, causes significant distress or impairment, and occurs on more days than not'
- Accompanied by 3/6:
  - Muscle tension
  - Fatigue
  - Insomnia
  - Impaired concentration
  - Irritability
  - Restlessness or feeling on edge
- At least 6 months

American Psychiatric Association. (2013). Anxiety Disorders, in *DSM*(5th ed.).

Panic Disorder

- Recurrent unexpected panic attacks
- >1 month of:
  - concern or worry about having panic attacks or their consequences
  - Maladaptive behaviours to avoid panic attacks
- Not due to another mental disorder or substance

American Psychiatric Association. (2013). Anxiety Disorders, in *DSM*(5th ed.).

Social Anxiety Disorder

- Marked fear or anxiety about 1 or more social situations in which possible scrutiny by others. (for children, not just adults)
- Fears of being negatively evaluated
- Almost always provoke fear or anxiety
- Avoided or endured with fear or anxiety
- Out of proportion to actual threat

- > 6 months
- Causes impairment

- Specify if **performance only**

American Psychiatric Association. (2013). Anxiety Disorders, in *DSM*(5th ed.).

Initial treatment

Similar for all anxiety disorders

- SSRIs or CBT
- No advantage to starting with combination
- SSRIs may work faster
- CBT has more enduring benefits
- Consider patient preference and other factors in deciding initial treatment
- For medications, "*start low, go slow*"

GAD

Alternative 1st line agents

- pregabalin 150-600 mg divided bid
- buspirone 20-60 mg divided bid
- Silexan 80-160 mg qhs

2nd line agents

- duloxetine 60-120 mg, venlafaxine XR 75-225 mg
- clonazepam 0.5 mg - 3 mg divided bid or tid
- quetiapine XR 50-150 mg
- bupropion XL 150-300 mg
- hydroxyzine 50-100 mg

3rd line – TCAs, MAOIs

Adapted from
- Katzman, *et al. BMC Psychiatry* **14,** S1 (2014).
- Abejuela HR, Osser DN. *Harv Rev Psychiatry*. 2016 Jul-Aug;24(4):243-56

Treatment resistant GAD

A large RCT suggest benefit for SSRI augmentation with

- pregabalin

Small RCTs suggest potential benefit for

- quetiapine, olanzapine, risperidone (conflicting data)

Small open-label studies suggest benefit for augmentation with

- aripiprazole

Risk/Benefit of SGA augmentation seems more beneficial for patients with severe illness

Adapted from
- Katzman, *et al. BMC Psychiatry* **14,** S1 (2014).

Panic Disorder

2nd line options

Clonazepam, alprazolam, TCAs and MAOIs have proven effective in RCT. No comparative studies with SSRIs

Treatment Resistant Panic

- Pindolol 7.5 mg (b-blocker / 5-HT1A agonist) added to SSRI helpful in a small RCT
- Open label studies suggest benefit for aripiprazole, olanzapine, divalproex augmentation
- Increasing doses of SSRIs *not* more effective than placebo dose escalation
- Augmentation with benzos not systematically studied

Chen, *Prog Neuro-Psychopharmacol Biol Psychiatry* 70(3)2016:219-226
Katzman, *et al. BMC Psychiatry* **14,** S1 (2014).
Freire, Rafael C., et al. *Exp opin pharmacother* 17.2 (2016): 159-168.
Simon NM *J Clin Psychiatry*. 2009. 70(11):1563-70.

Social Anxiety

Alternative 1st-line option

- pregabalin 300 mg bid (!!)

2nd-line

- benzos (alprazolam, clonazepam, bromazepam)
- TCAs, MAOIs (phenelzine)

Treatment resistant SAD

- Adding clonazepam to SSRI more effective than switch to venlafaxine

Performance type

- beta-blockers (e.g. propranolol 10-60 mg) and PRN benzos sometimes used without clear evidence for effectiveness

Katzman, *et al. BMC Psychiatry* **14,** S1 (2014)
Steenen SA. *J Psychopharmacol.* 2016 Feb;30(2):128-39

Comorbid bipolar disorder

Certain patients with bipolar II may be treated with SSRI monotherapy, but others will have mood lability or switching to hypomania or mixed states

Bipolar I should never be treated with SSRI/SNRI/TCA monotherapy. Some studies suggest that risk of switching is low in combination with divalproex or lithium

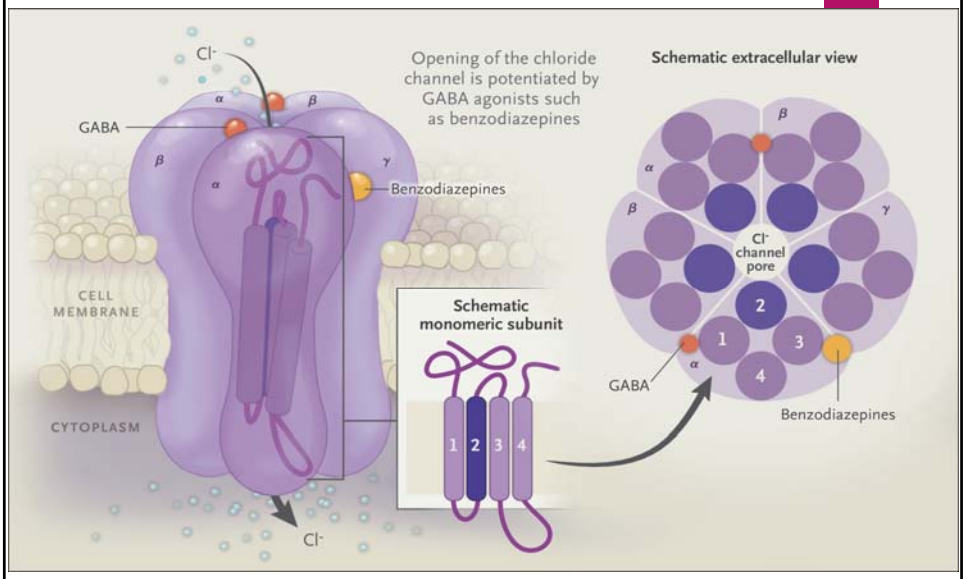
Quetiapine XR, benzodiazepines, pregabalin, divalproex (panic disorder) are reasonable choices for anxiety disorders comorbid with bipolar disorders

Yatham LN, et al. *Bipolar Disord*. 2018;20(2):97-170

Benzodiazepines

- Bind to BZD site of the $GABA_A$ receptor, increasing opening of Cl^- channels
- Voltage sensitive Cl- channels
- 5 subunits
- Multiple receptor subtypes
  - Differences in α subunit determine different pharmacological effects
  - α1- Most closely linked to sedation
  - α2, α3 – Linked to anxiolysis
- BZDs bind non-specifically to different α subunits, Z-drugs specific for α1
- Share pharmacodynamics and differ in their pharmacokinetics
- Activation of $GABA_A$ receptors disinhibits DA release

Rudolph U. (2008) GABAergic System. In: Offermanns S., Rosenthal W. (eds) Encyclopedia of Molecular Pharmacology. Springer, Berlin, Hei
Cheng, Neuropsych Dis Treat, 2018:(14)1351—1361



Soyka, NEJM, 2017; 376:1147-57

Commonly used benzodiazepines

Generic	Brand	Onset (hr)	Duration of action	T1/2 (hr)	Equivalent dose
diazepam	Valium	1	Long	36-200	5-10
Clonazepam	Rivotril (Klonopin)	1	Long	18-50	0.25-0.5
Lorazepam	Ativan	2	Intermed	10-20	1
alprazolam	Xanax	1	Short	6-12	0.5

Adapted from
Guina, J. Clin. Med. **2018**, 7, 20

Indications for BZDs

- 1st line for
  - Acute seizure
  - Rapid tranquilization
  - Procedural sedation
  - Alcohol withdrawal / delirium tremens
  - Acute panic attacks
- 2nd line for
  - GAD
  - Social anxiety
  - Panic disorde

BZDs and Depression

Older studies, mostly with TCAs suggest that the combination of a BZD and antidepressant is more effective in 1st 4 weeks of depression treatment

Older, short-duration (4-6 wk) RCTs have indicated that BZD monotherapy may help anxious-depression or "neurotic depression" with similar benefits as TCAs.

- Alprazolam has most evidence
- Unclear if mediated by effect on anxiety and sleep
- Would not be advised for most patients given lack of longer-term evidence

Benazi, et al. Psychother Psychosom 2018;87:65–74
Ogawa Y, et al. *Coch Data Sys Rev* 2019, Issue 6. Art. No.: CD001026. DOI:
van Marwijk H, et al. Coch Data Sys Rev 2012, Issue 7. Art. No.: CD007139

Relative Contraindications

- Concomitant opioid use
- OSA
- Myasthenia gravis
- Severe COPD

- PTSD or recent trauma (inefficacy, possible increased risk of PTSD)
- Substance use disorders

Guina, J et al. 2015. J Psychiatric Pract. 21(4):281-303

Rational use of benzodiazepines for anxio-depressive disorders

- In first few (e.g. 4) weeks of treatment of severe anxiety disorder (or depression with anxious distress) while waiting for antidepressants to kick-in
- For GAD/panic/SAD that has not improved adequately with SSRIs + CBT
- For GAD/panic/SAD where antidepressants not tolerated
- PRN for infrequently encountered situations (e.g. airplanes)

BZD, Z-drugs and road accidents

- BZDs and Z-drugs linked to 1.3-2x increase risk of road accidents
- Higher doses confer more increased risk

NB. SSRIs and TCAs also increase confer similar increased risk of road accidents

Chang, 2013, Br J Clin Pharm. 75(4):1125-1133

BZDs, Z-drugs and falls in the elderly

- BZDs associated with 1.3-2x increase falls in elderly
- Both short term and longer term linked to increase risk
- Appears more related to dose than T1/2
- NB: Antidepressants and antipsychotics ALSO associated with similar increased fall risk

Huang, 2012. *Drugs and Aging*,29 (5):359-376
Johnell, 2017. *Int J Geri Psychiatry*. 32(4):414-420

BZD and dependence

- Develops in 50% who use BZD > 1 mo
- Physical and psychological dependence can occur in the absence of tolerance
- WD symptoms
  - Physical – muscle tension, weakness, spasms flu-like symptoms
  - Psychological – anxiety, panic, agitation, restlessness, mood swings, sleep prob
  - Serious – seizures, delirium, psychosis

Soyka, NEJM, 2017; 376:1147-57

BZD related cognitive effects

- Short-term: decreased alertness, impaired psychomotor performance, and memory dysfunction
- Long-term: decreased working memory, processing speed, divided attention, visuoconstruction, recent memory and expressive language
  - Conflicting evidence as to whether improvement in cognition is seen with W/D of benzos.

Crowe, *Archives of Clinical Neuropsychology* 2018. 33(7):901–911

BZDs and dementia

- Studies have suggested an association between benzodiazepine use and dementia
- However, this association is NOT believed to be causal
  - Association disappears when comparing benzos to antidepressants active comparator (i.e. controlling for “reverse causation”)
- Studies HAVE linked anticholinergic use and development of dementia

Baek, Yeon-Hee, et al. *J Am Med Dir Assoc* 21.2 (2020): 201-211
Nafti, Mohamed, et al. *Annals of Pharmacotherapy* 54.3 (2020): 219-225.
Grossi, Carlota M., et al. *BMC geriatrics* 19.1 (2019): 1-10.
Osler M, Jørgensen MB *Am J Psychiatry* (2020); 177:497–505

Regularly reassess efficacy and harm

- Efficacy does not *only* mean symptom improvement, but should also lead to an improvement in functioning
- Assess for falls, cognitive impairment, accidents, disinhibition etc.
- Regularly review and discuss risks and benefits of ongoing treatment with patients on chronic BZD therapy

Management of BZD Dependence

- Taper over a period of several weeks (e.g., 4 to 6 weeks or more for diazepam doses >30 mg per day),
  - Recommendations range from reducing the initial benzodiazepine dose by 50% every week or so to reducing the daily dose by between 10% and 25% every 2 weeks.
  - 4-6 or 4 -8 weeks is suitable for most patients.
  - A minority of patients may require very slow titration
- If >1 BZD, convert to only 1 (e.g. diazepam)
- Switching from a drug with a short half-life to one with a longer half-life is not associated with a better outcome.
- Fixed withdrawal schedule with a precise duration of withdrawal treatment is recommended.
- Consider CBT, carbamazepine, non-addictive sleep aids

Soyka, NEJM, 2017; 376:1147-57

Take Home Points

- CBT and SSRIs are first-line treatments for all anxiety disorders.
- Benzodiazepines may be used judiciously for selected patients. The risks and benefits of longer-term use should be reassessed regularly