

# UVM Project ECHO: Adult Complex Mental Health

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# “Introduction” to ZOOM

- Please mute microphone when not speaking
- Please use camera as much as possible
- Test both audio & video before joining
- Communicate clearly during session:
  - Can use “raise hand” feature to comment
  - Use chat function for questions, comments or technical issues



# RECORDING OF SESSION TO BEGIN

# Series Objectives

**Learning objectives for this ECHO series include the ability to:**

- Enhance diagnostic skills in patients with complex mental health issues
- Incorporate new treatment strategies into management of common but challenging mental health disorders
- Improve the care that patients with mental health issues receive in the primary care setting

# Session Agenda

- Welcome
- Objectives
- Didactic Presentation (30-35 min)
- Case presentation(s)
  - Clarifying questions
  - Participants – then faculty panel
- Discussion
- Recommendations
- Closing Announcements
  - Submission of new cases
  - Completion of evaluations



# CMIE Disclosures

University of Vermont (UVM) Office of Continuing Medical and Interprofessional Education (CMIE) is approved as a provider of Continuing Medical Education (CME) by the ACCME. UVM designates this internet live activity for a maximum of 1.5 AMA PRA Category 1 Credits.

UVM CMIE is accredited by the American Nurses Credentialing Center (ANCC) to provide CE for the healthcare team. This program has been reviewed and is acceptable for up to 1.5 Nursing Contact Hours.

As a Jointly Accredited Organization, The Robert Larner College of Medicine at the University of Vermont is approved to offer social work continuing education by the Association of Social Work Boards (ASWB) Approved Continuing Education (ACE) program. Organizations, not individual courses, are approved under this program. State and provincial regulatory boards have the final authority to determine whether an individual course may be accepted for continuing education credit. The University of Vermont maintains responsibility for this course. Social workers completing this course receive 1.5 continuing education credits.

This activity was planned by and for the healthcare team, and learners will receive 1.5 Interprofessional Continuing Education (IPCE) credit for learning and change.

Participants should claim only the credit commensurate with the extent of their participation in the activity.

# CMIE Disclosures

**Interest Disclosures:** As an organization accredited by the ACCME to sponsor continuing medical education activities, UVMCMIE is required to disclose any real or apparent conflicts of interest (COI) that any speakers may have related to the content of their presentations.

**Meeting Disclaimer:** Regarding materials and information received during this educational event, the views, statements, and recommendations expressed during this activity represent those of the authors and speakers and do not necessarily represent the views of the University of Vermont.

# Treatment-Resistant Anxiety Disorders: Current Pharmacotherapy and Treatment Options



Sara Pawlowski, MD

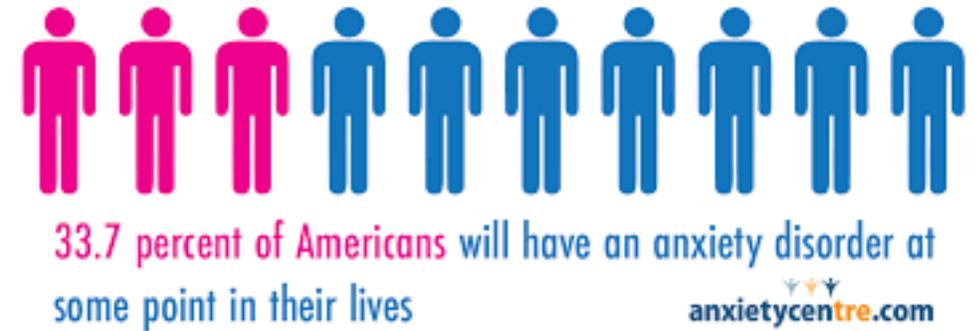
June 22, 2022

# Objectives

To summarize current pharmacological treatments (both approved and off-label) for panic disorder (PD), generalized anxiety disorder (GAD), social anxiety disorder (SAD), and specific phobias (SP) including:

- selective serotonin reuptake inhibitors (SSRIs)
- serotonin norepinephrine reuptake inhibitors (SNRIs)
- azapirones (e.g., buspirone)
- mixed antidepressants (e.g., mirtazapine)
- antipsychotics
- antihistamines (e.g., hydroxyzine)

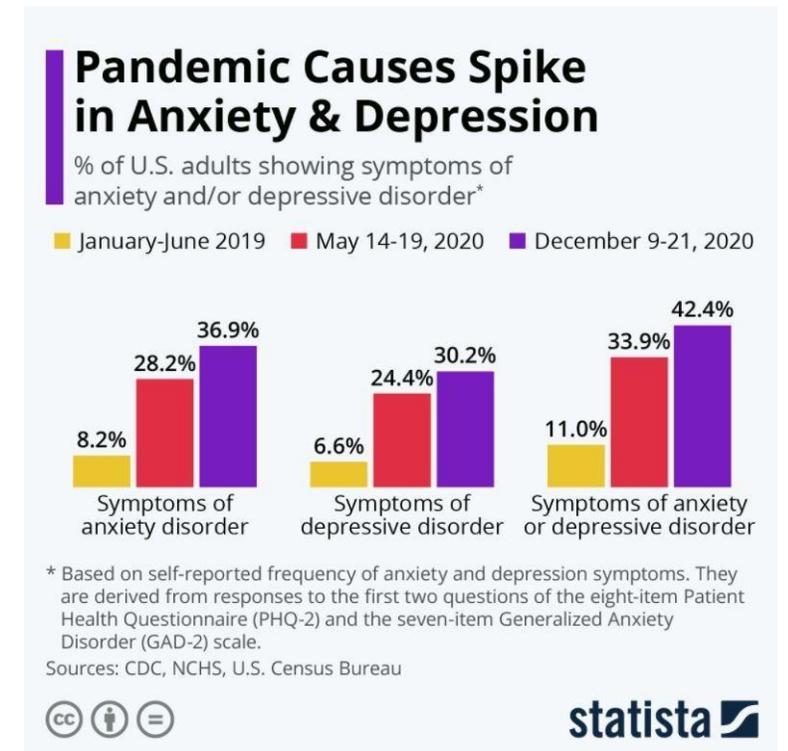
# Introduction



- Anxiety disorders are the most prevalent psychiatric disorders and a leading cause of disability.
- Generalized anxiety disorder is the most common anxiety disorder seen in the primary care setting.
- Lifetime prevalence in the United States of around 33%, according to the National Comorbidity Survey Replication (NCS-R).

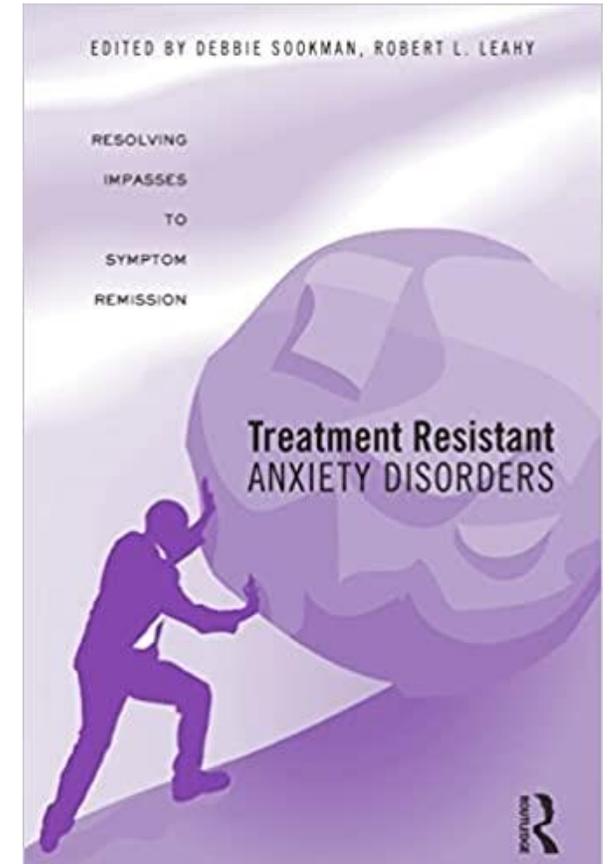
Ref: Craske MG, Stein MB, Eley TC, Milad MR, Holmes A, Rapee RM, et al. Anxiety disorders. *Nat Rev Dis Primers*. (2017) 3:17024. doi: 10.1038/nrdp.2017.100

Ref: . Bystritsky A. Treatment-resistant anxiety disorders. *Mol Psychiatry*. (2006) 11:805–14. doi: 10.1038/sj.mp.4001852



# Introduction, continued

- Anxiety disorders include: panic disorder (PD), generalized anxiety disorder (GAD), social anxiety disorder (SAD), and specific phobias (SP) (DSM-5).
- Posttraumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD) were removed from Anxiety Disorders section and placed into their own diagnostic classes.
- The literature indicates that only 60–85% of patients with anxiety disorders respond (experience at least a 50% improvement) to current biological and psychological treatments.
- Only about half of the responders achieve recovery (defined as minimal anxiety symptoms).



# First-Line Treatment

- SSRIs and SNRIs are both first-line treatments for anxiety disorders.
- A recent meta-analysis reported that most SSRIs and SNRIs are more efficacious than placebo in GAD, with **escitalopram and duloxetine** potentially having the largest effect sizes.
- Nonpharmacologic interventions for treatment of GAD include psychotherapies such as cognitive behavioral therapy or relaxation therapy.
- These psychotherapies can be used as first-line treatment choices or in combination with medication therapy

Ref: He H, Xiang Y, Gao F, Bai L, Gao F, Fan Y, et al. Comparative efficacy and acceptability of first-line drugs for the acute treatment of generalized anxiety disorder in adults: a network meta-analysis. *J Psychiatry Res.* (2019) 118:21–30. doi: 10.1016/j.jpsychires.2019.08.009

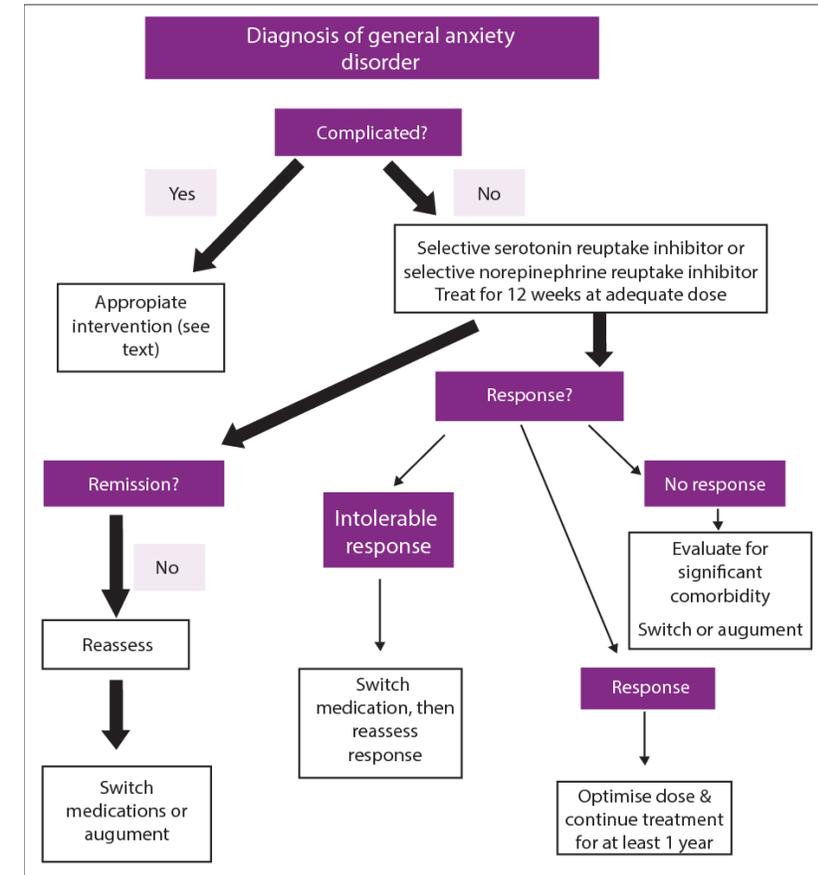


Fig. 1. Algorithm for pharmacotherapy of generalised anxiety disorder.<sup>[6]</sup>

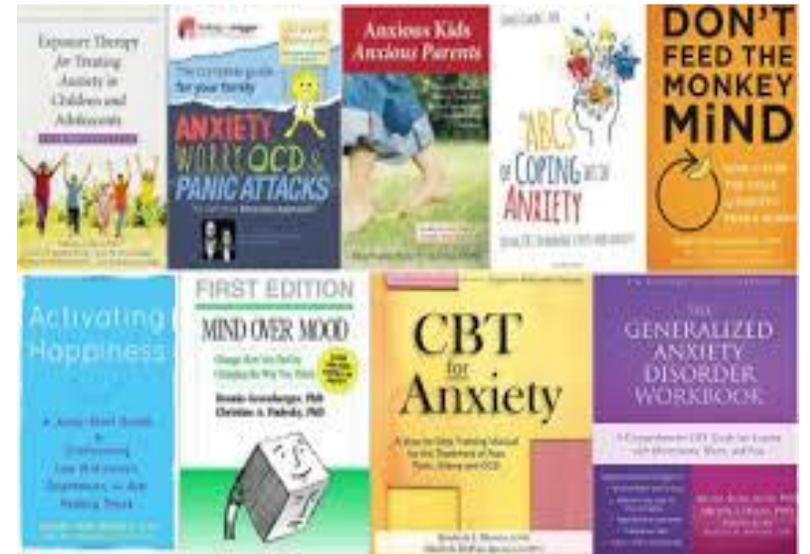
# Treatment Resistance in GAD

- Around half of the patients treated for GAD will fail to respond to initial treatment.
- Treatment-resistant (or refractory) GAD is defined as:
  - 1) failure to respond to at least 1 trial of SSRI or SNRI at adequate dose and duration.
- While benzodiazepines have shown benefit in the short-term use of TR-GAD, long-term use is not recommended secondary to the potential for dependence, misuse, and correlation to cognitive decline.



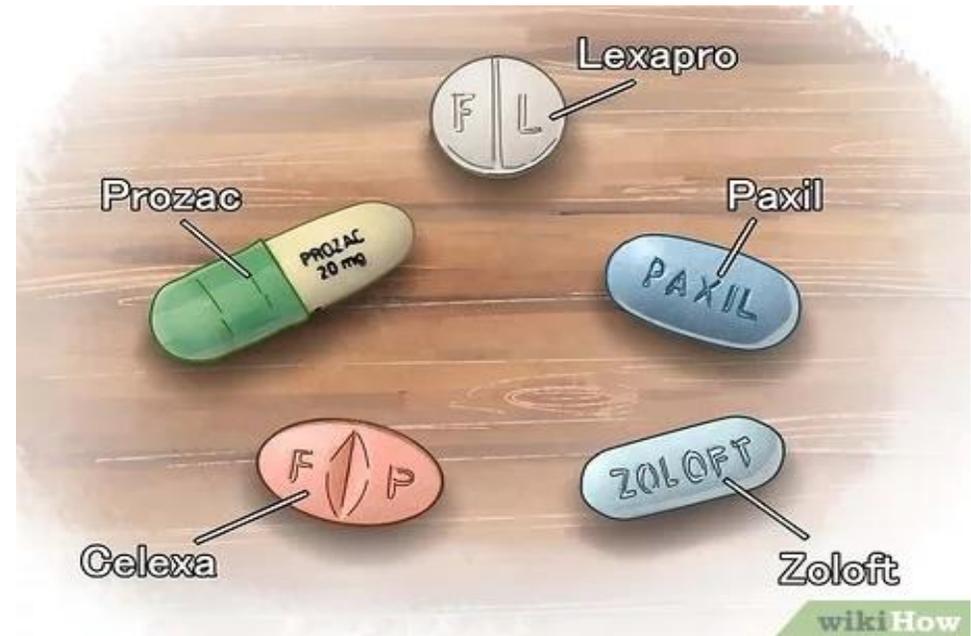
# Expectation management

- While a host of pharmacologic agents are available to treat GAD, it is estimated that as many as half of the patients treated will not respond adequately to selected therapy.
- Anxiety disorders **often take longer** for a treatment response compared to the treatment of depression, so an adequate duration of at least 8 weeks of treatment is warranted before considering the treatment a failure.
- If a first-line agent is not effective, another first-line agent can be tried.
- However, because there is a high partial or nonresponse rate in GAD treatment, augmentation strategies have been studied to guide pharmacologic therapy to help achieve the goal of remission.



# What to do with treatment-resistance in GAD?

- Review of the literature indicates several potential medication classes and individual agents that can be used as augmentation strategies to treat residual symptoms when recommended therapy per clinical practice guidelines fails:
  - Buspar
  - Mirtazapine
  - Anti-psychotics (off-label)
  - Anti-histamines (Hydroxyzine)

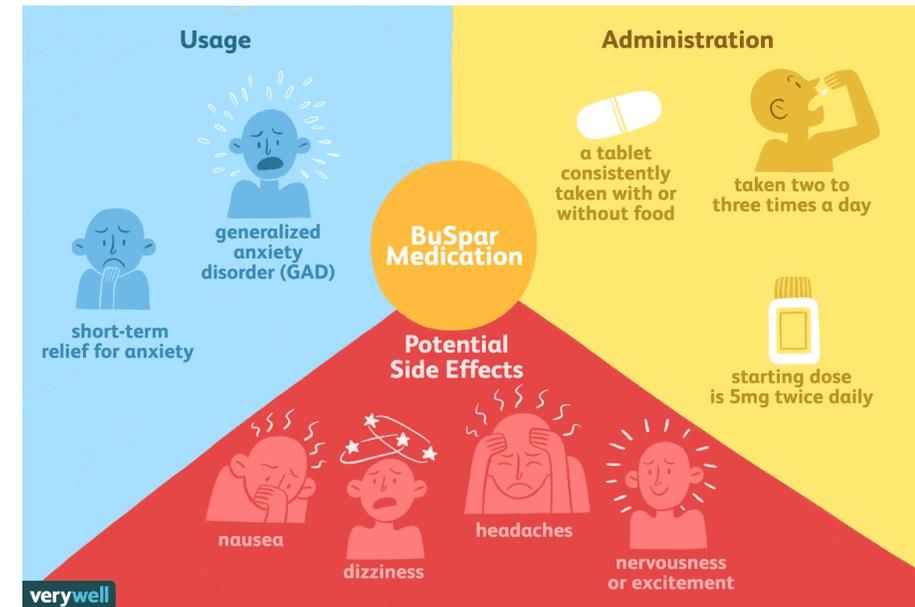


# Buspirone

- FDA-approved for use in anxiety, and is commonly used as an **adjunctive** treatment with SSRIs or SNRIs primarily for GAD.
- Buspirone is generally dosed two to three times a day and has a **gradual onset of action** of around 10 days to 4 weeks.
- A Cochrane review of buspirone for GAD found that it was superior to placebo but had a **smaller effect size** in GAD compared to benzodiazepines and antidepressants.
- It was not as well-tolerated (nausea and dizziness) and less effective in those with past benzodiazepine use.

Ref: Chessick CA, Allen MH, Thase M, Batista Miralha da Cunha AB, Kapczinski FF, de Lima MS, et al. Azapirones for generalized anxiety disorder. *Cochrane Database Syst Rev.* (2006) 2006:Cd006115. doi: 10.1002/14651858.CD006115

Ref: Chessick CA, Allen MH, Thase M, Batista Miralha da Cunha AB, Kapczinski FF, de Lima MS, et al. Azapirones for generalized anxiety disorder. *Cochrane Database Syst Rev.* (2006) 2006:Cd006115. doi: 10.1002/14651858.CD006115



# Mirtazapine

- Mirtazapine is FDA-approved for the treatment of MDD in adults.
- Benefits include:
  - positive effects on **sleep and appetite**
  - its general safety for elderly patients
  - less likelihood of sexual side effects compared to SSRIs and SNRIs
- Adverse effects include weight gain and other antihistamine effects like sedation and dry mouth.
- There are very few clinical trials assessing mirtazapine for anxiety disorders.
- In PD, one small randomized controlled trial (RCT) reported that mirtazapine was comparable in efficacy to escitalopram.
- In SAD, one RCT of women showed a significant improvement in anxiety symptoms compared to placebo.
- There are no controlled studies of mirtazapine in GAD to date.
- Overall, in the absence of further trials, the evidence has suggested that mirtazapine may have efficacy in improving anxiety but **primarily as an adjunctive agent**.

# Atypical antipsychotics

- Atypical antipsychotics, such as quetiapine, risperidone, and aripiprazole have demonstrated efficacy in the management of TR-GAD as adjunctive agents.
- Promising agents with positive results from smaller trials
- Improve residual symptoms but with higher side effect burden.

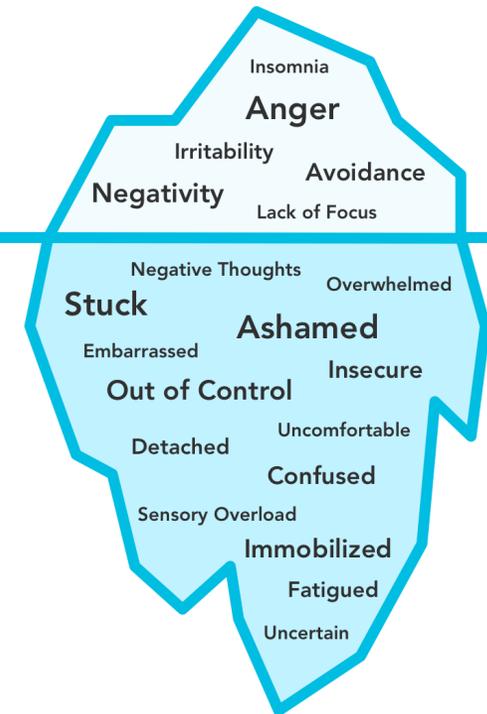
Ref: Wright BM, Eiland EH, Lorenz R. Augmentation with atypical antipsychotics for depression: a review of evidence-based support from the medical literature. *Pharmacotherapy*. 2013;33(3):344–59.

Ref: Lorenz RA, Jackson CW, Saitz M. Adjunctive use of atypical antipsychotics for treatment-resistant generalized anxiety disorder. *Pharmacotherapy*. 2010;30(9):942–51. DOI: 10.1592/phco.30.9.942

## Anxiety Iceberg

WHAT YOU SEE

WHAT YOU DON'T SEE



mindmypeelings

# Dosing atypical antipsychotics for GAD augmentation

In general, doses of atypical antipsychotics seem to be:

- 1) **less** than those typically used in schizophrenia and bipolar disorder can lead to symptom improvement.
- 2) more in line with **doses used for augmentation in the treatment of depression.**
- 3) with initiation at a **low starting dose** with titration based on clinical response.



# Aripiprazole (Abilify) augmentation

- Several open-label studies examined the use of aripiprazole as an augmenting agent to SSRIs with a partial response.
- Aripiprazole was initiated at 2.5 mg/day.
- Doses ranged from 7.5 to 30 mg/day. Mean dose was 13.9 mg/day. Goal dose similar to depression augmentation: 10-15 mg / day.
- Addition of aripiprazole to current regimen showed improvement in the HAM-A with the baseline mean of 26.2 to 14.2 ( $P < .0001$ )
  - (Ref:  $< 17$  = mild; 18-24 = moderate; 25-30 = severe).
- Side effects reported as mild to moderate included headache, nausea, dizziness, tiredness, weight gain, and increased anxiety. Akathisia at higher doses.
- Mean weight gain was  $1.1 \pm 1.9$  kg in an 8-week study.



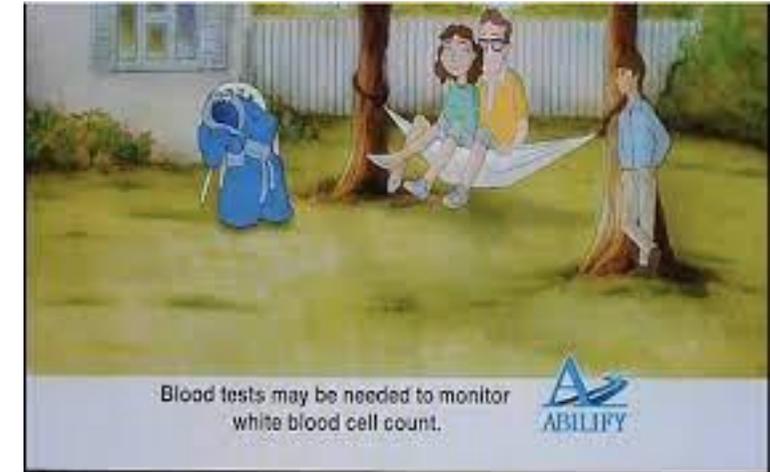
Ref: Worthington JJ, Kinrys G, Wygant LE, Pollack MH. Aripiprazole as an augmentor of selective serotonin reuptake inhibitors in depression and anxiety disorder patients. *Int Clin Psychopharmacol.* 2005;20(1):9–11. DOI: 10.1097/00004850-200501000-00002

# Risperidone (Risperdal) augmentation

- Several open-label trials of risperidone augmentation.
- Doses started at 0.5 mg/day and were titrated to 1.5 mg/day based on tolerability and response.
- Doses of risperidone ranged from 0.25 to 3 mg/day and resulted in an average decrease in HAM-A of 6.75 points ( $P = .0005$ ).
- Mostly commonly reported events were dizziness, somnolence, and blurred vision. Prolactin elevation (gynecomastia): 4X increased risk.
- Mean changes in weight between the groups was not statistically significant.

# Caveats to atypical antipsychotic augmentation

- One limitation in the use of atypical antipsychotics for the use in the treatment of TR-GAD is the incomplete evaluation of these medications on metabolic adverse effects:
  - Many trials **did not evaluate** lipid panels or fasting glucose measurements.
  - Many of these **studies are short in duration** (6-8 weeks) and therefore the long-term effect of these agents when used as adjunctive therapy in TR-AD has still not been elucidated.
- It is unknown if therapy for these agents should be continued indefinitely if symptom remission is achieved.
- Given the known adverse effects of these agents such as metabolic syndrome and their potential for extrapyramidal symptoms, usefulness should continually be evaluated and assessed for discontinuation or dose reduction.



# Hydroxyzine

- Hydroxyzine is the most studied antihistamine for anxiety and the only antihistamine which is **FDA-approved** for use in anxiety.
- Commonly used as **alternatives to benzodiazepines** for anxiety, panic attacks, and insomnia, in both inpatient and outpatient settings.
- Hydroxyzine and other antihistamines like diphenhydramine may also be safer to use in children and adolescents and in pregnant women.
- The primary drawback to this medication class is that patients tend to **develop tolerance** to antihistamines over time.
- A Cochrane review of 39 studies of GAD reported that hydroxyzine was superior to placebo and **comparable to benzodiazepines and buspirone** but the authors cited a **high risk of sedation** with hydroxyzine and study bias.
- To date, there have not been RCTs of hydroxyzine done in SAD and PD.

Ref: Ref: 3. Abejuela HR, Osser DN. The psychopharmacology algorithm project at the Harvard South Shore Program: an algorithm for generalized anxiety disorder. *Harv Rev Psychiatry*. 2016;24(4):243–56. DOI: 10.1097/HRP.0000000000000098



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# The “Klonopin” Bridge

- A 2014 review of clinical practice guidelines investigated the recommendation for short-term or long-term use of BZDs in GAD.
- In this review BZDs were recommended for short-term treatment of GAD, either **until the effects of the concomitantly started antidepressant were apparent**, or for use during an unexpected crisis where increased anxiety was identified.
- Maximal duration of BZD use in clinical practice guidelines **ranges from 2 to 8 weeks**, followed by a slow taper.

Ref: Tanguay Bernard M-M, Luc M, Carrier J-D, Fournier L, Duhoux A, Côté E, et al. Patterns of benzodiazepines use in primary care adults with anxiety disorders. *Heliyon*. 2018;4(7):e00688.DOI: 10.1016/j.heliyon.2018.e00688

Ref: Canadian Agency for Drugs and Technologies in Health. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2014. Jul 28, Short- and long-term use of benzodiazepines in patients with generalized anxiety disorder: a review of guidelines. [Internet] c2014 [updated. cited 2020 May 17] Available from: <https://www.ncbi.nlm.nih.gov/books/NBK254091/>

I've had obsessive-compulsive disorder my whole life, but until now I've resisted medication. I see a psychiatrist.



# Benzodiazepines (BZDs)

- Estimated past year prescription: 13% of U.S. adults (15% of those prescribed were prescribed >1 yr).
- Chronic use:
  - More likely to report tolerance over time
  - More likely to increase dose
  - Continued use over time may not treat anxiety but instead keep withdrawal symptoms at bay
  - Symptoms of withdrawal: anxiety, agitation, insomnia are difficult to differentiate from primary symptoms

Rossow & Bramness 2015. Barker et al 2004

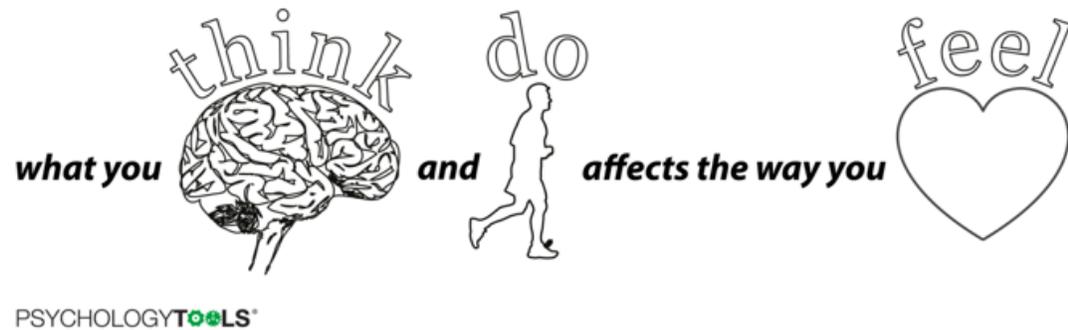


# BZDs: Summary of Treatment Guidelines

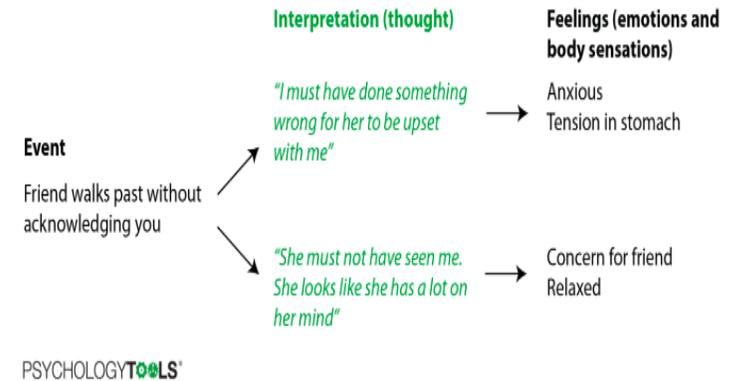
- NICE (for GAD & Panic): Long term use of BZD should never be implemented. Use limited 2-4 wks. Benzos have less favorable outcome for panic.
- APA 2009 (Panic): SSRIs/SNRIs best initial choice for many patients with panic disorder. Regular dosing preferred over PRN for prevention
- RACGP (Australian Guidelines): Long-term use of BZDs not recommended in clinical practice. Physical dependence arises even when taken as prescribed
- Mental Health Network 2009 (Panic): BZDs not recommended as 1<sup>st</sup> line treatments
- Magellan health services 2008 (GAD): BZD should be use for short-term (<4 wks) to avoid physical dependence and withdrawal
- Hunter/New England Area Health: Recommend that no person maintained on BZDs long-term



# Why is a partial response the norm? Anxiety – avoidance cycle



**Figure 3.1:** The basic message of CBT: what you think and do affects the way you feel.



**Figure 3.4:** How we interpret events determines how we feel about them.

The first interpretation personalises the events (“What have I done wrong?”) and results in feelings of anxiety. The second interpretation understands the friend’s behaviour in more neutral terms and leads to a different outcome.

RECORDING OF SESSION TO END

**\*\*SESSIONS ARE ON WEDNESDAYS FROM 12:00PM TO 1:30PM\*\***

<b>Dates</b>	<b>Session</b>	<b>Didactic Topics (in addition to case review)</b>
<b>Jan 19</b>	TeleECHO Session 1	<b>Attention Deficit Disorder – Diagnosis</b> (Sara Pawlowski, MD)
<b>Feb 2</b>	TeleECHO Session 2	<b>Attention Deficit Disorder – Management</b> (Sara Pawlowski, MD)
<b>Feb 16</b>	TeleECHO Session 3	<b>Resistant Depression</b> (Evan Eyler, MD)
<b>Mar 2</b>	TeleECHO Session 4	<b>Management of Sleep Disruption (including menopause) and Impact on Mental Health</b> (Jess Oehlke, MD)
<b>Mar 16</b>	TeleECHO Session 5	<b>Role of Electroconvulsive Therapy</b> (Evan Eyler, MD)
<b>Mar 30</b>	TeleECHO Session 6	<b>Mental Health in Patients with Substance Use Disorders</b> (Speaker TBD)
<b>Apr 13</b>	TeleECHO Session 7	<b>Eating Disorders</b> (Kathy Mariani, MD)
<b>Apr 27</b>	TeleECHO Session 8	<b>Chronic Pain and Mood Disorders</b> (Mark Pasanen, MD)
<b>May 11</b>	TeleECHO Session 9	<b>Mental Health in the Elderly</b> (Jennifer Hall, DO)
<b>May 25</b>	TeleECHO Session 10	<b>Bipolar Disease – Diagnosis</b> (Suzanne Kennedy, MD)
<b>June 8</b>	TeleECHO Session 11	<b>Bipolar Disease – Management</b> (Suzanne Kennedy, MD)
<b>June 22</b>	TeleECHO Session 12	<b>Resistant Anxiety</b> (Sara Pawlowski, MD)

# CONCLUSIONS

- Slides are posted at [www.vtahec.org](http://www.vtahec.org)
- Please complete evaluation survey
- Once evaluation is submitted, CE information will be emailed
- Please contact us with any questions, concerns, or suggestions:
  - [Mark.Pasanen@uvm.edu](mailto:Mark.Pasanen@uvm.edu)
  - [Elizabeth.Cote@uvm.edu](mailto:Elizabeth.Cote@uvm.edu)
- THANKS TO EVERYONE !!!!