BEST PRACTICES IN GENERALIZED ANXIETY DISORDER

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Learning Objectives

- Determine the most appropriate pharmacologic strategy to manage anxiety given a patient-specific case
- Identify the appropriate evidence-based pharmacologic treatment for generalized anxiety disorder
- Compare and contrast the adverse effects associated with medications used in the treatment of anxiety disorders
- Describe how to successfully taper benzodiazepines

Anxiety

- Anxiety is a normal response to stress
- Must distinguish between short-term symptoms of anxiety and anxiety disorders

"All of us worry about things like health, money, or family problems…"

https://www.nimh.nih.gov/health/publications/generalized-anxiety-disorder-gad/gad-trifold_124169.pdf

What is an anxiety disorder?

- Excessive anxiety leading to an uncomfortable and potentially debilitating condition causing both:
  - Psychological
    - Worry or feeling of a threat, difficulty concentrating
  - Physiological arousal
    - Tachycardia, shortness of breath, trembling, stomach upset, hyperventilation, chest pain, pacing
- May impair daily functioning and may occur without a stimulus

GAD: Course and Comorbidities

"Many individuals with generalized anxiety disorder report they have felt anxious or nervous all of their lives."

- Females are more likely to have comorbid unipolar depression
- Males are more likely to have comorbid substance use disorders
- Fewer than 1/3 of patients are adequately treated
- Up to 94% of these patients present to primary care with pain
  - 72% of these patients note pain as the main reason for their visit

From: DSM-5. Katzman MA, et al. BMC Psychiatry. 2014;14(Suppl 1):S1.

Anxiety Disorders in Primary Care

- **20%** of patients have >1 anxiety disorder
- **<60%** receive treatment
- Utilize primary care resources **1.5–4** times more
- Cost of anxiety disorders accounts for almost **1/3 of total mental health bill** and almost half of those costs are due to repeat use of health care services

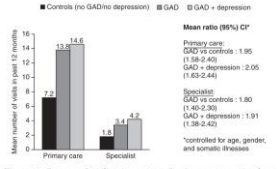
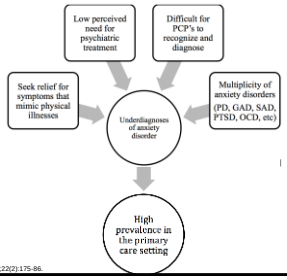


Figure 1. Increased utilization rates of primary care attenders with GAD (n=14,532) [Wittchen et al., 2001].

Kroenke et al. Ann Intern Med. 2007;146(5):317-25; Wittchen. Depress Anxiety 2002;16(4):162-71.

Contributing Factors to High Prevalence



Roy-Byrne P, et al. J Am Board Fam Med. 2009;22(2):175-86.

DSM-5 Diagnostic Criteria for GAD

Presence of at least 3 symptoms

- On edge
- Easily fatigued
- Difficulty concen-trating
- Irritable
- Tense
- Insomnia

Excessive anxiety or worry at least 6 mo

DSM-V. Available at: http://dsm.psychiatryonline.org/doi/book/10.1176/appi.books.9780890425596

Case

Tamara is a 45 year old woman and a new patient to your clinic. She presents with symptoms of generalized anxiety disorder, but you identify no recent triggers (e.g. psychosocial stressors) and note an abrupt onset. What factors might be contributing to her current presentation?

Medical Illnesses Associated with Anxiety Symptoms

Cardiovascular	Angina, arrhythmias, congestive heart failure, hypertension ischemic heart disease, myocardial infarction
Endocrine and Metabolic	Cushing's disease, hyperparathyroidism, hyperthyroidism, hypothyroidism, hypoglycemia, hyponatremia, hyperkalemia, pheochromocytoma, vitamin B12 or folate Deficiencies
Neurologic	Migraine, seizures, stroke, neoplasms, poor pain control
Respiratory system	Asthma, chronic obstructive pulmonary disease, pulmonary embolism, pneumonia
Others	Anemias, systemic lupus erythematosus, vestibular dysfunction, cancer

Melton ST, Kirkwood CK. Chapter 53. Anxiety Disorders I: Generalized Anxiety, Panic, and Social Anxiety Disorders. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. Eds. *Pharmacotherapy: A Pathophysiologic Approach, 9e*. New York, NY: McGraw-Hill; 2014. http://accesspharmacy.mhmedical.com/content.aspx?bookid=689&Sectionid=45310504. Accessed October 05, 2016.

Drugs Associated with Anxiety Symptoms

Anticonvulsants	Carbamazepine, phenytoin
Antidepressants	SSRIs, SNRIs, bupropion
Antihypertensives	Felodipine, clonidine
Antibiotics	Quinolones, isoniazid
Bronchodilators	Albuterol, theophylline
Corticosteroids	Prednisone
Dopamine agonists	Levodopa, amantadine
Herbal supplements	Ma huang, ginseng, ephedra
NSAIDs	Ibuprofen, indomethacin
Stimulants	Amphetamines, methylphenidate, caffeine, cocaine
Sympathomimetics	Pseudoephedrine, phenylephrine
Thyroid hormones	Levothyroxine
Medication toxicity	Anticholinergics, antihistamines, digoxin

Adapted from: Melton ST, Kirkwood CK. Chapter 53. Anxiety Disorders I: Generalized Anxiety, Panic, and Social Anxiety Disorders. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. Eds. *Pharmacotherapy: A Pathophysiologic Approach, 9e*. New York, NY: McGraw-Hill; 2014. http://accesspharmacy.mhmedical.com/content.aspx?bookid=689&Sectionid=45310504. Accessed October 05, 2016.

CLINICAL PRESENTATION

Generalized anxiety disorder (GAD)

GAD: Clinical Presentation

- Psychologic and cognitive symptoms
  - Excessive anxiety about a number of events/activities (≥6 months)
  - Worries difficult to control
  - Feeling keyed up or on edge
  - Poor concentration or mind going blank
- Physical symptoms
  - Restlessness
  - Fatigue
  - Muscle tension
  - Sleep disturbances
  - Irritability
- Impairment
  - Social, occupational, or other important functional areas
  - Poor coping abilities
  - Chronic course

GAD Baseline Assessment

- Review of systems
- Prescribed medications
- Over-the-counter agents
- Alcohol use
- Caffeine use
- Illicit drug use
- Level of functioning
- Target anxiety symptoms
- Laboratories
  - Complete blood count, electrolytes, lipids, glucose, thyroid stimulating hormone, liver enzymes, urine drug screen, if indicated

Katzman MA et al. BMC Psychiatry 2014;14(Suppl 1):S1.

TREATMENT

Generalized anxiety Disorder

GAD: Treatment Goals

- Acute episode
  - Decrease severity and duration of anxiety symptoms
  - Improve overall function
- Long-term goals
  - Remission
    - With minimal or no anxiety symptoms
    - No functional impairment
    - Improve patient quality of life (QOL)

GAD: Non-Pharmacologic Interventions & Patient Education

- Psychoeducation
- Cognitive behavioral therapy
- Signs of relapse
- Additional resources available
  - Anxiety and Depression Association of America
  - NIMH Generalized Anxiety Disorder: When Worry Gets Out of Control
- Exercise
- Meditation
- Discussion of treatment options, including potential adverse events
- Onset of action/efficacy of pharmacotherapy

Katzman MA et al. BMC Psychiatry 2014;14(Suppl 1):S1.

Best practices

What are your best practices when initiating pharmacotherapy in patients with GAD?

GAD: Pharmacologic Treatment

- If symptoms are severe enough to cause functional disability, pharmacologic treatment is indicated (think serotonergic antidepressants)
- May be combined with non-pharmacologic treatment, if available
- Treatment usually maintained for 12-24 months
- Onset is typically about 2-4 weeks but may be up to 12 weeks
- Start with low doses (1/2 of typical starting dose) and titrate slowly
- If benzodiazepines are used, short-term (i.e. 2-4 weeks) is recommended upon initiation of antidepressant treatment

Treatment Guidelines for GAD: Focus on Pharmacotherapy

Treatment	Recommendations	Comments
First-line	SSRIs: escitalopram, paroxetine, sertraline SNRIs: duloxetine or venlafaxine Pregabalin May also consider buspirone, hydroxyzine, benzodiazepines (BZDs)	The Psychopharmacology Algorithm Project at the Harvard South Shore Program (PAPHSS)[3] published in 2016 adds bupropion as a potential first-line option after the agents on the left (excluding venlafaxine, BZDs).
Second-line	Switch to another first-line option	Katzman et al[1] also recommend short-term use of BZDs, bupropion XL, imipramine, quetiapine XR, or vortioxetine. PAPHSS[3] also recommend venlafaxine, BZDs, or kava
Third-line	Other SSRIs (e.g., citalopram, fluoxetine) Divalproex Mirtazapine Imipramine Second-generation antipsychotics	PAPHSS[3] recommends divalproex only in males with treatment resistance SGAs with the best evidence include quetiapine and risperidone

[1]Katzman MA et al. BMC Psychiatry 2014;14(Suppl 1):S1.; [2]Baldwin DS et al. J Psychopharmacol. 2014;25(8):403-39.; [3]Abejuela HR, Osser DN. Harv Rev Psychiatry. 2016;24(4):243-56.

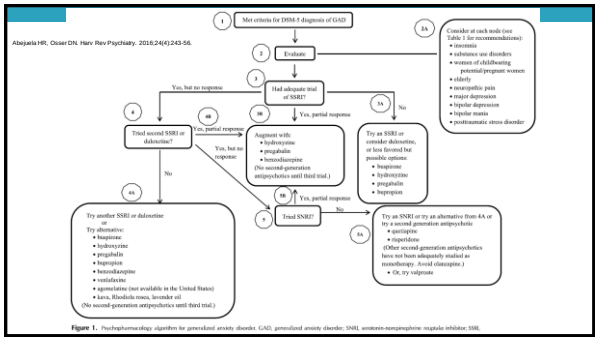
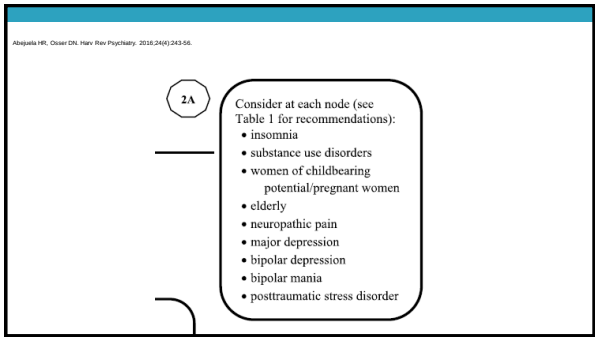
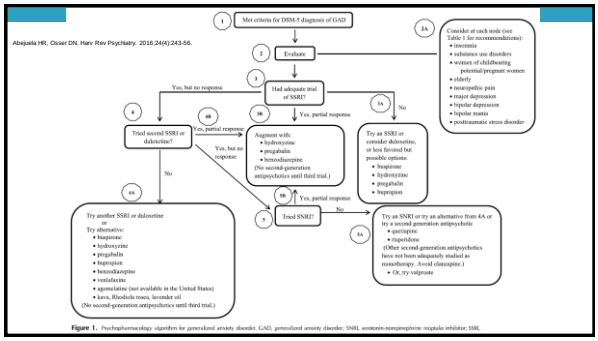


Figure 1. Psychopharmacology algorithm for generalized anxiety disorder. GAD, generalized anxiety disorder; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI,



Comorbidity/ Patient-specific factor(s)	Provider may consider…
Insomnia	Agents that are more sedating or those less likely to cause insomnia such as hydroxyzine and pregabalin; adjunctive trazodone
Elderly	Risks associated with: • SSRIs, including GI bleeding, bone loss, and hyponatremia • SNRIs, including elevated blood pressure • Pregabalin, including dizziness, somnolence, falls, fractures • BZDs, including falls, cognitive changes, dependence, additive sedation • Antipsychotics, including metabolic complications
Neuropathic Pain	Consider pregabalin
Pregnancy	Risks associated with BZDs, paroxetine, divalproex
Substance use	Consider risks associated with BZDs or pregabalin (schedule IV)
Depression	SSRIs or SNRIs
Bipolar depression	For GAD, consider pregabalin, hydroxyzine, or BZDs
Bipolar mania	Avoid antidepressants. Consider quetiapine or a mood stabilizer like lithium or divalproex.
PTSD	Add on prazosin for nightmares or insomnia.

Adapted from : Abejuela HR, Osser DN. Harv Rev Psychiatry. 2016;24(4):243-56.



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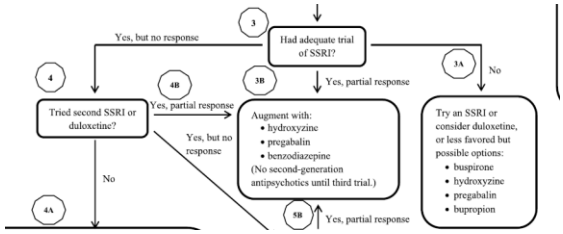

SSRIs & SNRIs

Medication	Key Considerations
Citalopram	Lower risk for insomnia, agitation, drug interactions Potential risk for dose-dependent QT prolongation
Duloxetine	May be useful for comorbid pain, may be associated with withdrawal symptoms if not tapered, greater risk for insomnia or agitation. Avoid in liver disease or heavy alcohol use
Escitalopram	As above; risk of QT prolongation is controversial
Fluoxetine	More activating, self-tapering due to long half-life. Concern for drug interactions.
Fluvoxamine	Withdrawal symptoms if not tapered, risk for drug interactions via inhibition of CYP1A2 and 2C19
Paroxetine	More sedating, less agitation, more anticholinergic effects, withdrawal symptoms if not tapered. May be associated with greater weight gain. Concern for drug interactions, use in pregnancy should be avoided due to cardiac septal defects.
Sertraline	Greater risk for insomnia, agitation, diarrhea
Venlafaxine	Greater risk for insomnia or agitation as well as increased blood pressure. May be useful for comorbid pain, few drug interactions, withdrawal symptoms if not tapered.

Adapted from : Craske M, Bystritsky A. Stein MB, Hermann R, eds. Approach to treating generalized anxiety disorder in adults. In: UpToDate. Last updated 4/15/16; Abejuela HR, Osser DN. Harv Rev Psychiatry. 2016;24(4):243-56.

General Recommendations

- Start with low doses and titrate gradually
  - Consider staring with about half of the recommended starting dose for the first week
  - Especially in elderly (e.g., citalopram 5 or 10 mg daily or sertraline 12.5 or 25 mg daily)
- Delayed treatment response of up to 12 weeks

Abejuela HR, Osser DN. Harv Rev Psychiatry. 2016;24(4):243-56.

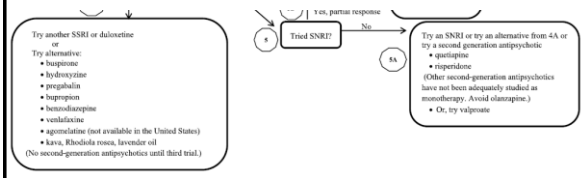

Figure 1. Psychopharmacology algorithm for generalized anxiety disorder. GAD, generalized anxiety disorder; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Other Agents

Medication	Key Considerations
Bupropion	Activating. Do not use if history of seizure disorder, head trauma, bulimia, anorexia, or electrolyte disturbance.
Buspirone	Slow onset, modest efficacy. May be helpful to augment therapy in those with a partial response to antidepressants. Not for patients with comorbid depression.
Hydroxyzine	Helpful with comorbid insomnia. Dose-related anticholinergic side effects.
Imipramine	Anticholinergic, cardiotoxic in overdose. Overall not well tolerated.
Mirtazapine	Helpful with comorbid insomnia. Lower doses are more sedating. May increase appetite; concern for weight gain.
Pregabalin	Sedation and dizziness are most common side effects. Schedule V controlled substance. Minimum effective dose for most patients is > 150 mg/day. Weight gain, especially with long-term treatment.
Quetiapine	Concern for metabolic side effects, sedation, EPS/TD (rare)

Adapted from : UMHS Depression Guideline. Available at: http://www.med.umich.edu/1info/FHP/practiceguidesdepress/depreccs.pdf and Craske M, Bystritsky A. Stein MB, Hermann R, eds. Approach to treating generalized anxiety disorder in adults. In: UpToDate. Last updated 4/15/16; Baldwin DS, et al. J Psychopharmacol. 2014;25(8):403-39.

Case

Stella is a 25 year old female on multiple medications, including escitalopram 20 mg daily to manage her anxiety. Escitalopram has been somewhat helpful, however, she is concerned about her lack of interest in sexual activity. What other pharmacologic treatment options may be helpful to target GAD and less likely to contribute to her concerns?

BZDs

- NOT recommended first-line
- Most effective and commonly prescribed drugs for acute anxiety symptoms
- Best utilized for 2-3 weeks after initiation of an antidepressant
- May be used intermittently or as adjunctive therapy for acute exacerbations of GAD
- Controlled substance – Schedule IV; risk for abuse and dependence
- More effective in relieving somatic and autonomic symptoms of GAD than antidepressants
  - Worry and apprehension better treated with antidepressants

Bandelow B, et al. World J Biol Psychiatry 2008;9(4):248–312.

Benzodiazepines

Anxiety	Sleep
Chlordiazepoxide (Librium®)	Estazolam (ProSom®)
Diazepam (Valium®)	Flurazepam (Dalmane®)
Clorazepate (Tranxene®)	Temazepam (Restoril®)
Alprazolam (Xanax®)	Quazepam (Doral®)
Oxazepam (Serax®)	Triazolam (Halcion®)
Lorazepam (Ativan®)	
Clonazepam (Klonopin®)	

All BZDs are equally effective.

Pharmacokinetic (PK) parameters and patient characteristics determine agent selection.

Case

Louis is a 66 year old male with GAD who you are starting on sertraline for management of his anxiety and comorbid depression. Given the need for acute relief of his symptoms, which benzodiazepine do you feel is most appropriate to also start at this time?

a) Alprazolam
b) Clonazepam
c) Diazepam
d) Lorazepam

Benzodiazepines

Medication	Total Daily Dose (mg)	Comparative potency (mg)	Onset (hours)	Metabolism	Clinically significant active metabolite	Half-life (hours)*
Alprazolam	0.5-6	0.5	1	CYP3A4	No	11-15
Clonazepam	0.5-4	0.25-0.5	0.5-1	CYP3A4	No	18-50
Diazepam	4-40	5	0.25-0.5	CYP2C19, CYP3A4	Yes	50-100
Lorazepam	0.5-6	1	0.5-1	Glucuronidation	No	10-14
Oxazepam	30-120	15-30	1-2	Glucuronidation	No	5-15

*In generally healthy adults

Adapted from : Craske M, Bystritsky A. Stein MB, Hermann R, eds. Approach to treating generalized anxiety disorder in adults. In: UpToDate. Last updated 4/15/16. Available at: https://www.uptodate.com/contents/approach-to-treating-generalized-anxiety-disorder-in-adults?source=search_result&search=generalized%20anxiety%20disorder&selectedTitle=1~125

BZDs: Dosing

- Dosage must be individualized
- Initiate with low doses
  - Alprazolam 0.25mg three times daily
- Titrate dose to relieve anxiety and avoid adverse effects
- Effective after first dose; can use PRN
- Duration for acute anxiety should not exceed 2 to 4 weeks
  - Utilize antidepressant if anxiety persists

Melton ST, Kirkwood CK, 2014.

BZDs: Metabolism

Steps:

1. Hepatic oxidation (via CYP3A4)
2. Glucuronide conjugation
3. Renal excretion

- Exceptions:
  - Lorazepam and oxazepam undergo conjugation only then are excreted
  - Clonazepam undergoes nitroreduction
  - Diazepam also through CYP2C19

Guthrie SK, Bostwick JR. Finley PR, Lee KC, eds. Anxiety Disorders. In: Applied Therapeutics, 10th edition. Alldredge BK, Corelli RL, Ernst ME, Guglielmo BJ, Jacobson PA, Kradjan WA, Williams BR. Lippincott Williams & Wilkins. Philadelphia, PA; 2013.

BZDs: Metabolism

- Oxidation impaired
  - Elderly
  - Liver disease
  - Use of drugs that inhibit oxidation
- Results in higher levels of parent drug and/or active metabolite
- Therefore lorazepam and oxazepam are preferred in elderly patients and those with liver disease

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BZDs: Metabolism

- Most BZDs converted to desmethyldiazepam (DMDZ)
  - Active metabolite with LONG half-life (about 100 hours)
  - Further oxidized to oxazepam
  - Multiple doses → accumulation

Guthrie SK, Bostwick JR. Finley PR, Lee KC, eds. Anxiety Disorders. In: Applied Therapeutics, 10th edition. Alldredge BK, Corelli RL, Ernst ME, Guglielmo BJ, Jacobson PA, Kradjan WA, Williams BR. Lippincott Williams & Wilkins. Philadelphia, PA; 2013.

BZDs: Metabolism

- Short half-life BZDs
  - Alprazolam
  - Oxazepam
  - Lorazepam

> **NOT metabolized to DMDZ**

- Oxazepam and lorazepam have NO active metabolites; preferred in elderly or those with liver disease

Guthrie SK, Bostwick JR. Finley PR, Lee KC, eds. Anxiety Disorders. In: Applied Therapeutics, 10th edition. Alldredge BK, Corelli RL, Ernst ME, Guglielmo BJ, Jacobson PA, Kradjan WA, Williams BR. Lippincott Williams & Wilkins. Philadelphia, PA; 2013.

BZDs: Physiologic Factors Impacting PK

Variable	Effects/Comments
Aging	Increased half-life; decreased clearance of drugs undergoing oxidation; decrease plasma protein, increasing free fraction of drug, decreased GI acidity leading to more rapid absorption Management includes using lower doses, extending dosing intervals, using agents that undergo glucuronidation
Gender	Age-related decrease in hepatic metabolism observed in men; increased CYP3A4 and CYP2C19 activity in premenopausal women, increasing clearance; reduced clearance via glucuronidation and lower plasma protein binding in women; increased volume of distribution in women due to lower lean body mass and more adipose tissue Management includes using lower doses in elderly men, evaluating the need for higher doses in premenopausal women, less frequent dosing in women due to long half-life
Obesity	Longer half-lives due to increased volume of distribution Management includes monitoring for drug accumulation; potential dose reductions

Adapted from: Guthrie SK, Bostwick JR. Finley PR, Lee KC, eds. Anxiety Disorders. In: Applied Therapeutics, 10th edition. Alldredge BK, Corelli RL, Ernst ME, Guglielmo BJ, Jacobson PA, Kradjan WA, Williams BR. Lippincott Williams & Wilkins. Philadelphia, PA; 2013.

BZDs: Physiologic Factors Impacting PK

Variable	Effects/Comments
Liver Disease	Decreased clearance and increased half-life of long-acting benzodiazepines and alprazolam in patients with cirrhosis and hepatitis; increased half-life of lorazepam in cirrhosis Management includes avoiding long-acting agents or use lower doses to avoid accumulation; decrease lorazepam dose or dosing interval in cirrhosis
Kidney disease	Decreased plasma protein binding resulting in increased drug availability Management includes dose reduction
Ethnicity	Decreased oxidative metabolism via CYP2C19 (diazepam and alprazolam) in Asians Management includes considering lower doses of these medications in this population

Adapted from: Guthrie SK, Bostwick JR. Finley PR, Lee KC, eds. Anxiety Disorders. In: Applied Therapeutics, 10th edition. Alldredge BK, Corelli RL, Ernst ME, Guglielmo BJ, Jacobson PA, Kradjan WA, Williams BR. Lippincott Williams & Wilkins. Philadelphia, PA; 2013.

Case

What are the key counseling points, including adverse effects, that you would want to discuss with Louis?

BZDs: Patient Education

- Anticipated length of therapy
- Potential side effects
- Consequences of ingesting alcohol and other CNS depressants
- BZDs treat symptoms but do not solve underlying psychological problems
- Do not increase or decrease dose without discussing with provider

BZDs: Adverse Effects

- CNS depression is the most common
  - Drowsiness, sedation, psychomotor impairment, and ataxia
    - Tolerance to sedation usually develops after first week
    - Respiratory depression may develop, especially IV
- Others
  - Disorientation, depression, confusion, irritability, aggression, excitement
  - Impairment of memory (anterograde amnesia)

BZDs: Adverse Effects

- May cause paradoxical reaction in children, cognitively impaired and elderly patients, mentally retarded patients, and post-head injury patients
  - Increased rage and hostility
- 25-30% of patients may not respond
- Potential increased risk for dementia
  - Risk increased with cumulative dose and treatment duration of long-acting agents
  - Additional data needed

Zhong G, et al. PLoS One. 2015;10(5):e0127836; Billioti de Gage S, et al. Expert Opin Drug Saf. 2015;14(5):733-47.

BZDs: Tolerance

- Tolerance is a decreased response due to continued use which may result in an increased dose to maintain effects
- Tolerance to anxiolytic effects not reported

BZDs: Abuse and Dependence

- Abuse is rare in general population of users
- Chronic illness therefore high risk of dependence
  - Withdrawal symptoms on abrupt discontinuation
    - Onset depends on half-life of BZD:
      24 to 48 hours for short half-life
      3 to 8 days for longer half-life
    - Higher risk with higher doses and long-term use

*BZDs should NOT be discontinued abruptly – may precipitate status epilepticus

BZDs: Dependence

- Withdrawal symptoms due to physiologic dependence
  - Rebound anxiety
  - Insomnia
  - Restlessness
  - Muscle tension
  - Irritability
  - Delirium
  - Hallucinations
  - Seizures (usually within 3 days of abrupt discontinuation)

Higher risk of seizures with higher doses, long-term use, and concurrent use of other drugs that lower seizure threshold

Melton ST, Kirkwood CK, 2014.

BZDs: Taper

- Taper BZD if administered for 10 days or longer
  - Decrease dose by 25% per week until 50% of dose is reached
  - Then reduce dose by 12.5% (1/8) every 4 to 7 days
- Duration exceeds 8 weeks – taper over 2 to 3 weeks
- Duration of 6 months – taper over 4 to 8 weeks
- Long-term use (1 year or longer) – taper over 2 to 4 months

Melton ST, Kirkwood CK, 2014.

BZDs: Taper

- Limited data support switching from a shorter-acting BZD to a longer-acting BZD prior to a gradual taper
  - This strategy may be useful if patient is:
    - On a high dose
    - Using short-acting BZDs
    - Maintained on BZDs long-term
    - Withdrawal symptoms are problematic with lowest tablet strength of short-acting agent

BZDs: Drug Interactions

- Potentiates action of other CNS depressants
  - Alcohol, narcotics, antipsychotics, antihistamines
  - Rarely life-threatening ALONE in an overdose
    - Combinations can be life-threatening
- Mostly CYP3A4 and CYP1A2 inhibitors and inducers (except lorazepam and oxazepam)

Melton ST, Kirkwood CK, 2014.

GAD: Treatment Summary

- Utilize non-pharmacologic therapy
- Antidepressants are treatment of choice for long-term management
  - SSRIs or SNRIs
  - Take time to elicit response, may co-prescribe short-term BZDs
- Benzodiazepines may be appropriate when:
  - Acute relief is necessary
  - Need to avoid antidepressants due to sexual dysfunction or comorbid bipolar disorder due to risk of inducing mania
  - Poor responder to antidepressants
- Buspirone or pregabalin are other reasonable options
- Consider comorbidities (e.g. depression, pain)

Tips for the Safe and Appropriate Medication Management of Anxiety

- Appropriate prescribing
  - SSRIs/SNRIs are considered preferred, first line agents for anxiety
    - Not useful for immediate relief
    - Start low and go slow to minimize risk of worsening anxiety; higher doses often required
  - Benzodiazepines are indicated for the short term relief (2 to 4 weeks) of anxiety that is severe, disabling or subjecting the individual to unacceptable distress.
  - Use of benzodiazepines to treat short term 'mild' anxiety is inappropriate
  - Long-term use may be associated with increase in mortality

Lader M. Br J Clin Pharmacol. 2014 Feb;77(2):295-301

Tips for the Safe and Appropriate Medication Management of Anxiety

- Selecting an agent
  - Fast acting BZDs are more likely to result in rebound anxiety, have an increased risk of withdrawal/dependence, and are more likely to be abused
    - Slower acting agents, such as clonazepam, are preferred over faster acting agents, like alprazolam
- Limit supply
  - BZDs for the treatment of severe anxiety and panic should be limited to 2-4 weeks of use
  - Avoid refills if possible
  - Recommend as needed use over scheduled dosing, if appropriate
  - Management of chronic anxiety should be with an SSRI/SNRI or related agent

References

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QUESTIONS

BEST PRACTICES IN GENERALIZED ANXIETY DISORDER

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