Solving Clinical Challenges in Generalized Anxiety Disorder

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Faculty Disclosure

- **Dr. Stein**: Consultant—Aptinyx, Bionomics, Greenwich Pharmaceuticals, Janssen, Jazz Pharmaceuticals, Otsuka Pharmaceuticals, Oxeia Biopharmaceuticals; Grant/Research Support—National Institutes of Health, US Department of Defense, US Department of Veterans Affairs; Editorial—*UpToDate*, *Biological Psychiatry*, *Depression and Anxiety*.

Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
  - Dr. Stein will be discussing off-label use of prescription medications in the presentation and will identify those issues.

- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

- This activity has been independently reviewed for balance.

Learning Objectives

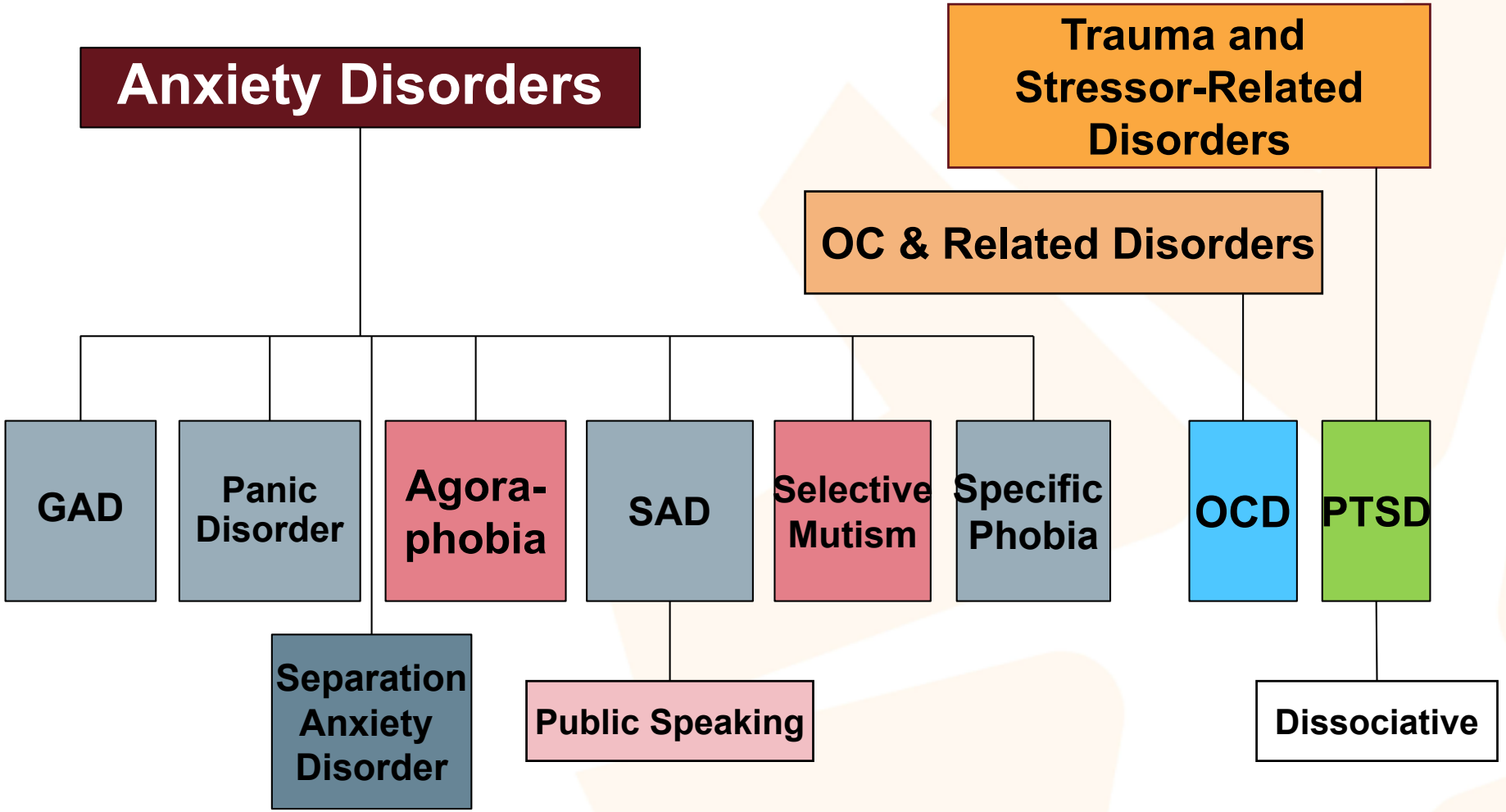
- Discuss diagnosis of generalized anxiety disorder (GAD) and its relationship to other mental disorders
- Review evidence-based treatment approaches to patients with GAD and consider individualized aspects of treatment
- Identify special considerations in use of benzodiazepines

Solving Clinical Challenges

All questions/cases in this presentation were submitted by clinicians within the Psych Congress database which includes conference attendees, newsletters subscribers, and more.

Part I:
Diagnostic Nosology, Accuracy, and Screening

Anxiety Disorders: *DSM-5* Classification



GAD = generalized anxiety disorder; OCD = obsessive-compulsive disorder; SAD = social anxiety disorder.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.* Arlington, VA: American Psychiatric Association Publishing; 2013.

Diagnostic Criteria

Table 1. Criteria for the Diagnosis of Generalized Anxiety Disorder.*

Excessive anxiety and worry about various events have occurred more days than not for at least 6 months.
The person finds it difficult to control the worry.
The anxiety and worry are associated with at least three of the following six symptoms (only one symptom is required in children): restlessness or a feeling of being keyed up or "on edge," being easily fatigued, having difficulty concentrating, irritability, muscle tension, and sleep disturbance.
The anxiety, worry, or associated physical symptoms cause clinically significant distress or impairment in important areas of functioning.
The disturbance is not due to the physiological effects of a substance or medical condition.
The disturbance is not better accounted for by another mental disorder.

* All the features listed must be present in order to make a diagnosis of generalized anxiety disorder. Adapted from the American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition.[1]

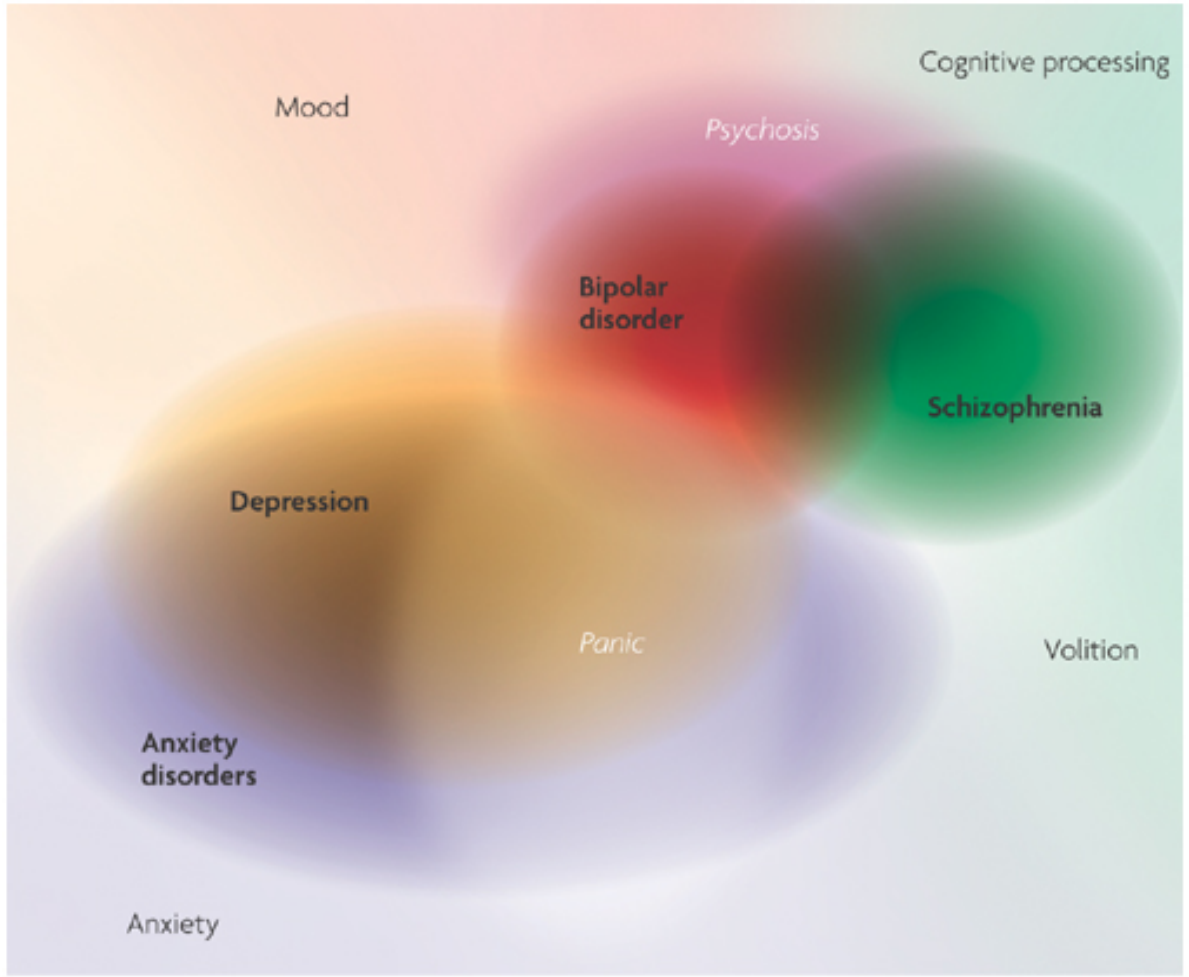
Stein MB, et al. *N Engl J Med*. 2015;373(21):2059-2068. Adapted from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.* Arlington, VA: American Psychiatric Association Publishing; 2013.

Question

GAD is so often comorbid with other anxiety disorders (panic disorder, SAD, subthreshold OCD).

How important is a precise diagnosis in working with "overlapping" diagnoses?

Genetic Vulnerabilities for Mental Disorders



Burmeister M, et al. *Nat Rev Genet*. 2008;9(7):527-540.

Comorbidity Cues and Complications

- Major depression co-occurs in 40% to 75% of patients with GAD
- May be considered as “major depression with anxious distress”
  - Anxious distress specifier met in 78% of patients with a principal diagnosis of major depression in 1 study
  - Anxious distress associated with increased disability and reduced quality of life

- Anxiety symptoms may be especially common in bipolar disorder
  - Panic attacks
  - And/or chronic anxiety symptoms
    - Should prompt wariness about treatment with antidepressants alone

Zimmerman M, et al. *Depress Anxiety*. 2019;36(1):31-38. Simon NM, et al. *Am J Psychiatry*. 2004;161(12):2222-2229.

Questions

Which scales and screeners do you recommend using for anxiety disorders?

Which tools other than the GAD-7 do you routinely use to screen for GAD?

Over the past 2 weeks, how often have you been bothered by the following problems? (*Use "✓" to indicate your answer*)	Not at All	Several Days	More Than Half the Days	Nearly Every Day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Having trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid, as if something awful might happen	0	1	2	3

Figure 1. Generalized Anxiety Disorder 7-Item Questionnaire.

The total score (0 to 21) is the sum of the individual items. Total scores of 5 to 9 indicate mild, probably subclinical anxiety, and monitoring is recommended. Total scores of 10 to 14 indicate moderate, possibly clinically significant anxiety, and further evaluation and treatment (if needed) are recommended. Total scores of 15 to 21 indicate severe, probably clinically significant anxiety, and treatment is probably warranted. Data are from Spitzer et al.[22]

Stein MB, et al. *N Engl J Med*. 2015;373(21):2059-2068. Data from Spitzer RL, et al. *Arch Intern Med*. 2006;166(10):1092-1097.

If you're really short on time (or paper) …

GAD-2

Over the last 2 weeks, how often have you been bothered by the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3

Part II:
Pharmacologic Treatments

Pharmacotherapy of Generalized Anxiety Disorder 2019

FDA-Approved

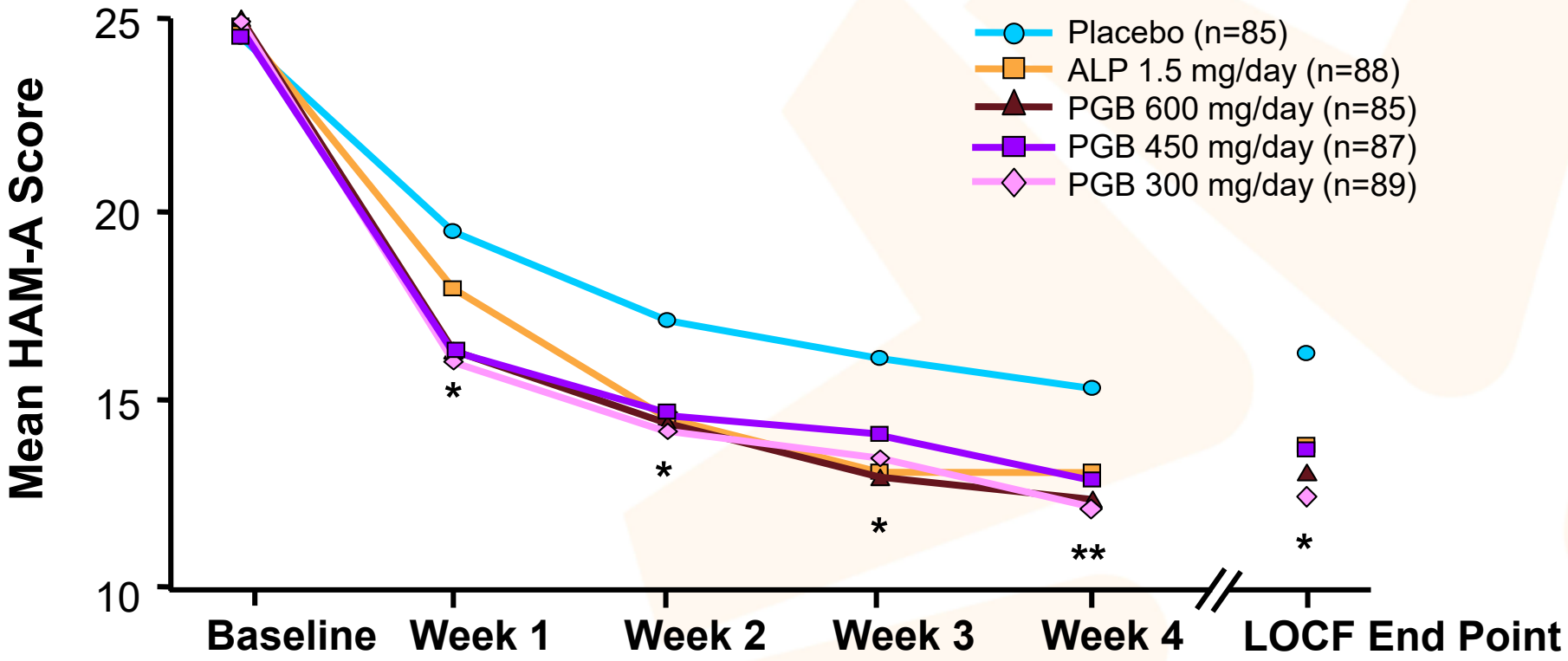
- Several SSRIs and SNRIs
  - Paroxetine
  - Escitalopram
  - Venlafaxine ER
  - Duloxetine
- Buspirone

Not FDA-Approved

- Benzodiazepines (approved for short-term treatment of anxiety)
- Pregabalin
- TCAs and MAOIs
- Quetiapine and other atypical antipsychotics
- Newer antidepressants
  - Vortioxetine

MAOI = monoamine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin–norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.

Efficacy of 3 Doses of Pregabalin vs Alprazolam in Reducing the HAM-A Total Score



All medications dosed TID.

***P*≤.05 vs placebo (ANCOVA) for all medications. ****P*≤.05 vs placebo (ANCOVA) for PGB 300 mg/day and PGB 600 mg/day only.**

ALP = alprazolam; PGB = pregabalin; HAM-A = Hamilton Anxiety Rating Scale.

Rickels K, et al. *Arch Gen Psychiatry*. 2005;62(9):1022-1030.

Case
48-year-old woman with chronic anxiety

Chronic Anxiety

- 48-year-old woman with 20+ years of (mostly pharmacologic) treatment of depression (MDD) and anxiety (GAD)
    - No history of childhood maltreatment
    - No history of alcohol or other substance abuse
- Rx: venlafaxine 225 mg/day and clonazepam 2 mg bid
    - Recent evidence of dose escalation of clonazepam
        - "Lost" scripts and "dropped" pills
        - Very reluctant to reduce clonazepam dose
            - » Eventually required inpatient detoxification
    - 3 months after detoxification; anxiety "out of control"
    - After a long line of trying other adjunctive Rxs (pregabalin, risperidone, quetiapine)
        - Benefited from adjunctive buspirone (increased over 2 months to) 30 mg bid

MDD = major depressive disorder.

Buspirone

- Much maligned as a treatment for GAD (or anything)
- Only indication is GAD
    - Multiple negative trials in other anxiety disorders
  - Not indicated if substantial comorbid depressive symptoms are present
  - May not work in many (most?) patients with GAD
  - Worth trying in patients with non-comorbid (moderate-to-severe) MDD
  - Worth trying in patients where Rx of benzodiazepines is (relatively) contraindicated
  - When dosing, start low and go slow, but be persistent in dose escalation as needed

Stein MB, et al. *N Engl J Med*. 2015;373(21):2059-2068.

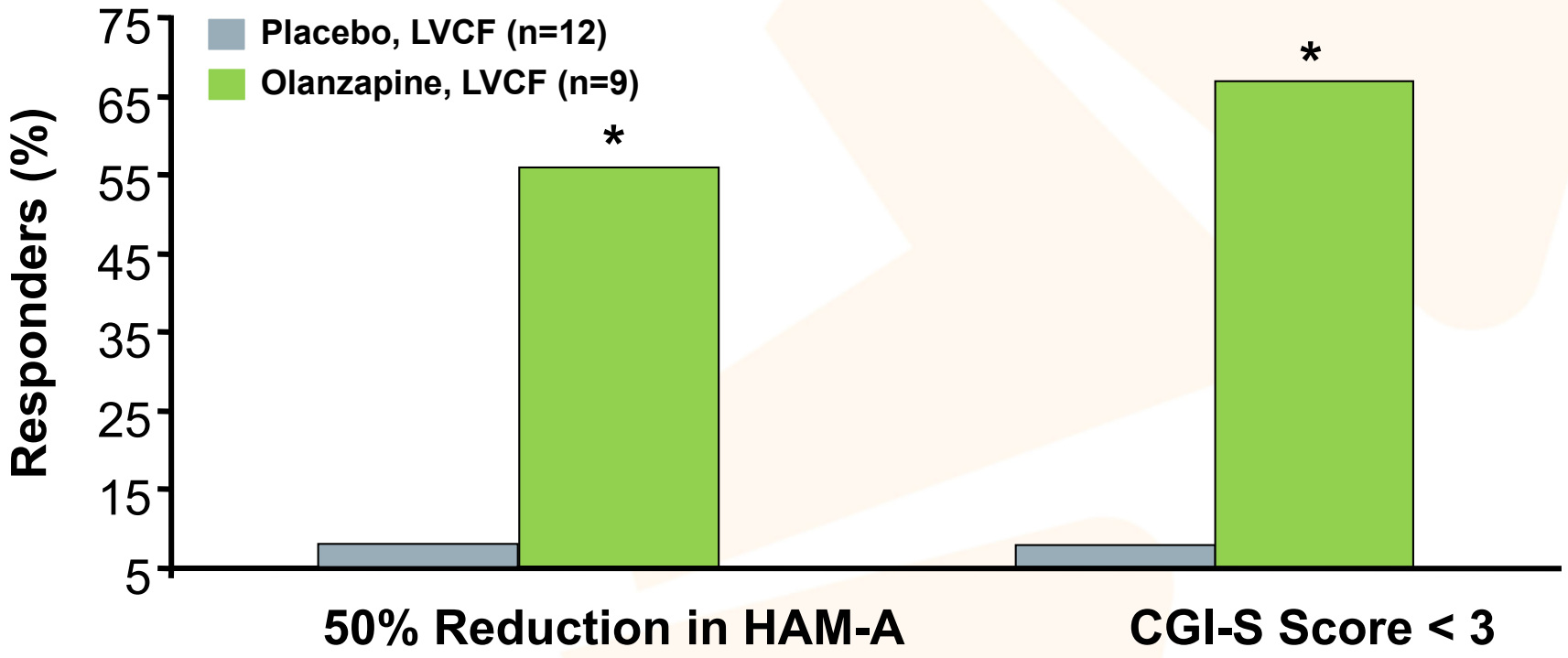
Pharmacologic Augmentation for SSRI-Resistant Generalized Anxiety Disorder

Pregabalin Augmentation for Partial SRI Response in Generalized Anxiety Disorder

- Patients with GAD not responding to SRI Rx
- Double-blind randomized addition of
    - Pregabalin (N=180) [150–600 mg/day]
    - Placebo (N=176)
        - 8 weeks of augmentation
  - Well tolerated
    - Adverse event-related discontinuations infrequent
        - Pregabalin (4%) vs Placebo (2%)
  - HAM-A responder rates (< 50% reduction)
    - Pregabalin (47.5%) vs Placebo (35.2%)
        - » *P*=.0145

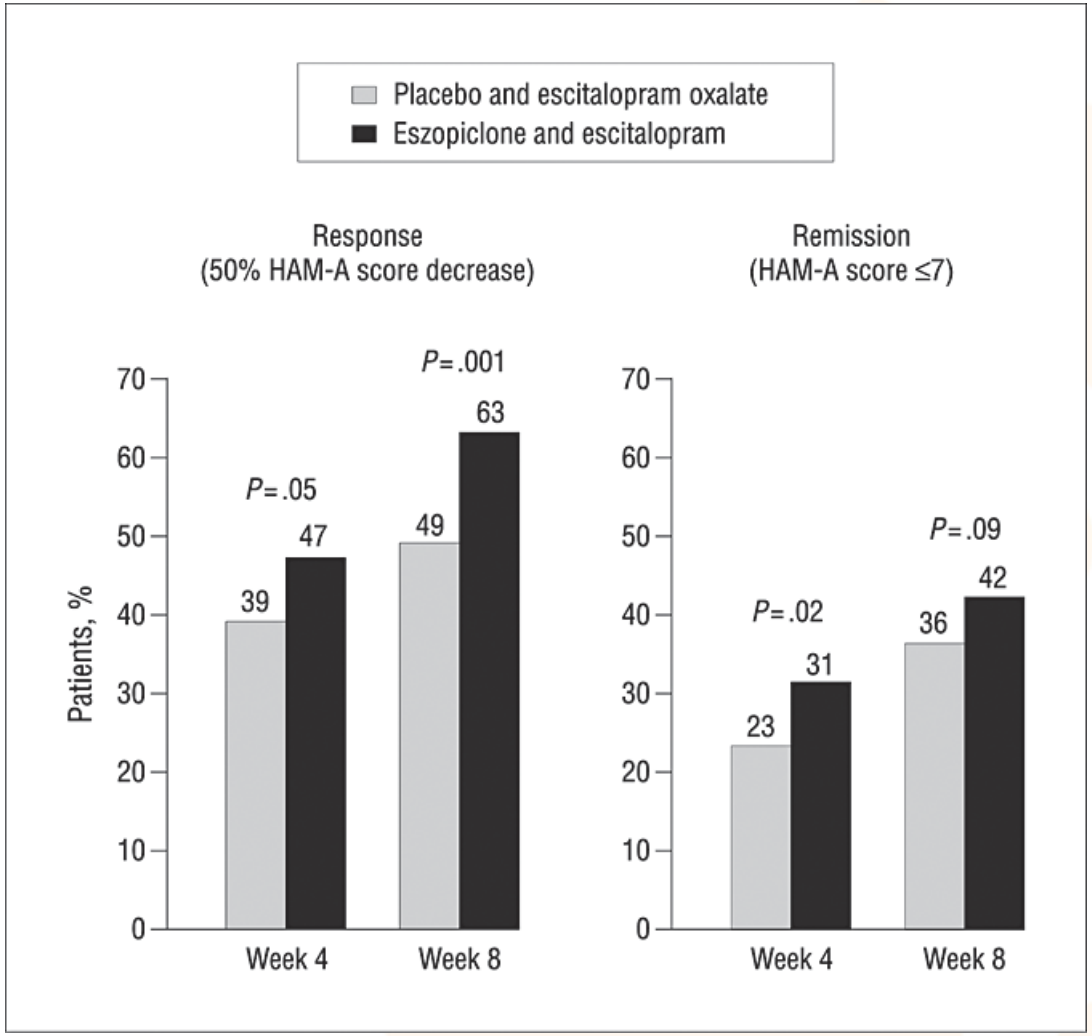
Rickels K, et al. *Int Clin Psychopharmacol*. 2012;27(3):142-150.

Olanzapine Augmentation of SSRI-Resistance: Generalized Anxiety Disorder RCT



*P<.05. N=45. Patients with one postrandomization visit (N=21).
CGI = Clinical Global Impression; LVCF = last visit carried forward; RCT = randomized controlled trial.
Pollack MH, et al. *Biol Psychiatry*. 2006;59(3):211-215.

Response and Remission in Patients with Insomnia and Comorbid GAD Treated with Placebo and Escitalopram or Eszopiclone and Escitalopram



Pollack M, et al. *Arch Gen Psychiatry*. 2008;65(5):551-562.

Questions:
Benzodiazepines

- Increasingly, our profession is becoming wary of benzodiazepines. However, our patients are often wary of giving them up. *How do you recommend bridging these different agendas*?

- *What is your opinion about the use of benzodiazepines for the treatment of anxiety disorders*?

- *What are your thoughts about the long-term use of benzodiazepines in GAD*?

- *How often do you use benzodiazepines in GAD and panic disorder*?
- *Do you absolutely NOT use benzodiazepines in patients who have a history of alcohol use disorder, sedative/hypnotic use disorder, or other substance use disorders*?
- If you do use them in these cases, *how much time since last abuse do you normally require before prescribing a benzodiazepine or do you not require a period of abstinence before prescribing them*?

“As Needed” or PRN Dosing with Benzodiazepines

- Rarely indicated
- Difficult for patients to know when “needed”
- Rationale is to prevent anxiety
- Exceptions
    - SAD
        - » Public speaking
    - Infrequently recurring specific phobias
        - » Flying
        - » Bar mitzvah or wedding speeches

Ravindran LN, et al. *J Clin Psychiatry*. 2010;71(7):839-854.

Information Needed to Assess and Manage Current Benzodiazepine Use

- Regular or “prn” use (daily “prn” is regular)
- Duration of use
- Dose history (Escalation? Over what time period?)
- History of substance abuse
    - Including alcohol
  - Confirmation of diagnosis
    - “GAD” diagnosis could indicate occult substance abuse, personality disorder, anxious depression, or unrecognized bipolar illness or ADHD

ADHD = attention-deficit/hyperactivity disorder.

Opinion (mine)-Based Medicine about Use of Benzodiazepines for Generalized Anxiety Disorder

- Try (almost) everything else first
  - SSRIs
  - SNRIs
  - +/- pregabalin
  - Buspirone
  - Maybe not atypical antipsychotics (risk–benefit ratio may be better for benzodiazepines)
- In patients without major concern of abuse
  - Consider Rx of regular (not “prn”) clonazepam qhs or bid
    - 0.25 mg bid, increasing incrementally to up to 1 mg bid
      - » Higher doses make me anxious
    - Aim for a 6-month trial with attempt at taper
      - » GAD, like MDD, does fluctuate in intensity
    - Start of intensity psychotherapeutic approaches

Part III:
Side Effect Management

Question

Do you feel it is routinely appropriate to use benzodiazepines to help a patient deal with early side effects of SSRIs in GAD?

Routine Use of Benzodiazepines When Starting SRIs

- The short answer is NO
- I rarely (never) simultaneously start a benzodiazepine to prevent anxiety when starting an SRI
- Benzodiazepines are difficult to stop once started

(*You paid big bucks to have me tell you that, right*?)

- Educate patients about anticipated side effects
- Express your availability should concerns arise

Questions

Often, patients become very anxious about the side effects of medications. It's as if anxiety itself makes one hyperaware of internal somatic state. This leads to many people stopping medications before they've had a chance to work.

How do you suggest navigating this?

How do you educate patients about possible medication side effects?
Do you provide educational handouts on side effect management?

Side Effect Management in Anxiety

- Anxious patients are very focused on changes in their body or psyche
- They are prone to experiencing medication (and many other) effects as aversive and frightening

- Educate patients about anticipated side effects
  - Explain that some are common and mostly very manageable
  - And that some are rarer, but also mostly very manageable
  - Provide (*I usually do it verbally, but sometimes write notes for patients*) the most common examples

- Express your availability should concerns arise
  - Be clear that you will work with them to mitigate discomfort
  - Be equally clear that you want them to stay on the medicine in order to benefit!

Part IV:
Nonpharmacologic Treatments

Questions

Avoidance, it seems, is the quintessential behavior in anxiety. This often leads to patients not wanting to do psychotherapy for anxiety, especially exposure work. *How do you navigate this avoidance*?

Which nonpharmacologic treatments do you routinely recommend?

What do you consider the most effective nonpharmacologic treatment in GAD?

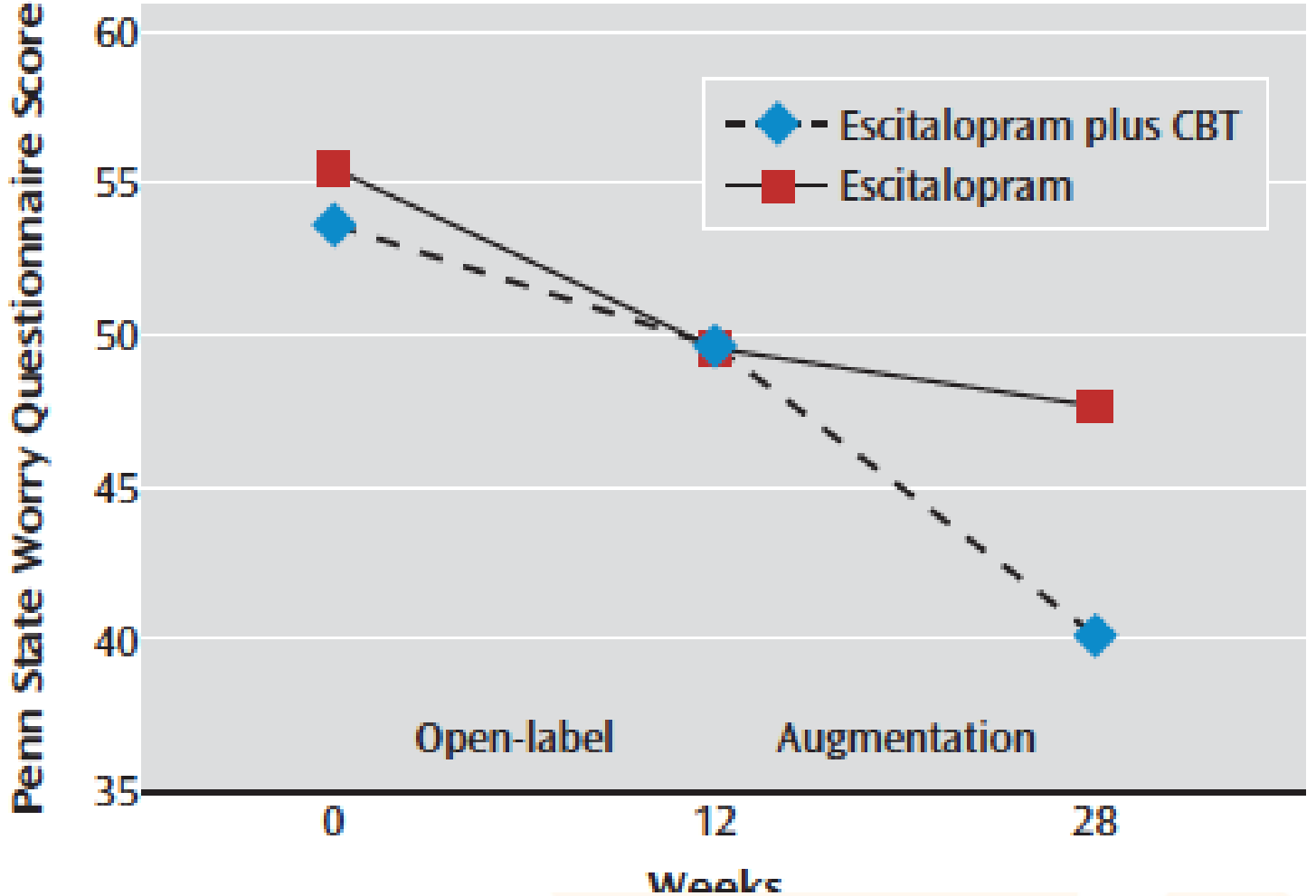
Nonpharmacologic Approaches to Generalized Anxiety Disorder

- Cognitive-behavioral therapy
  - Focused on awareness of and management of somatic symptoms
  - Often includes approach to managing insomnia
  - Worry control may be incorporated
  - GAD is often more difficult to manage with CBT than panic or phobic disorders
- Mindfulness-based approaches, including “alternative” medicine approaches such as yoga
  - Evidence growing as to usefulness
- Dietary
  - Assess and recommend limitations (dose and timing) on caffeine, “energy drinks,” “energy supplements”
- Exercise
  - Prescribe and monitor!!!

CBT = cognitive-behavioral therapy.

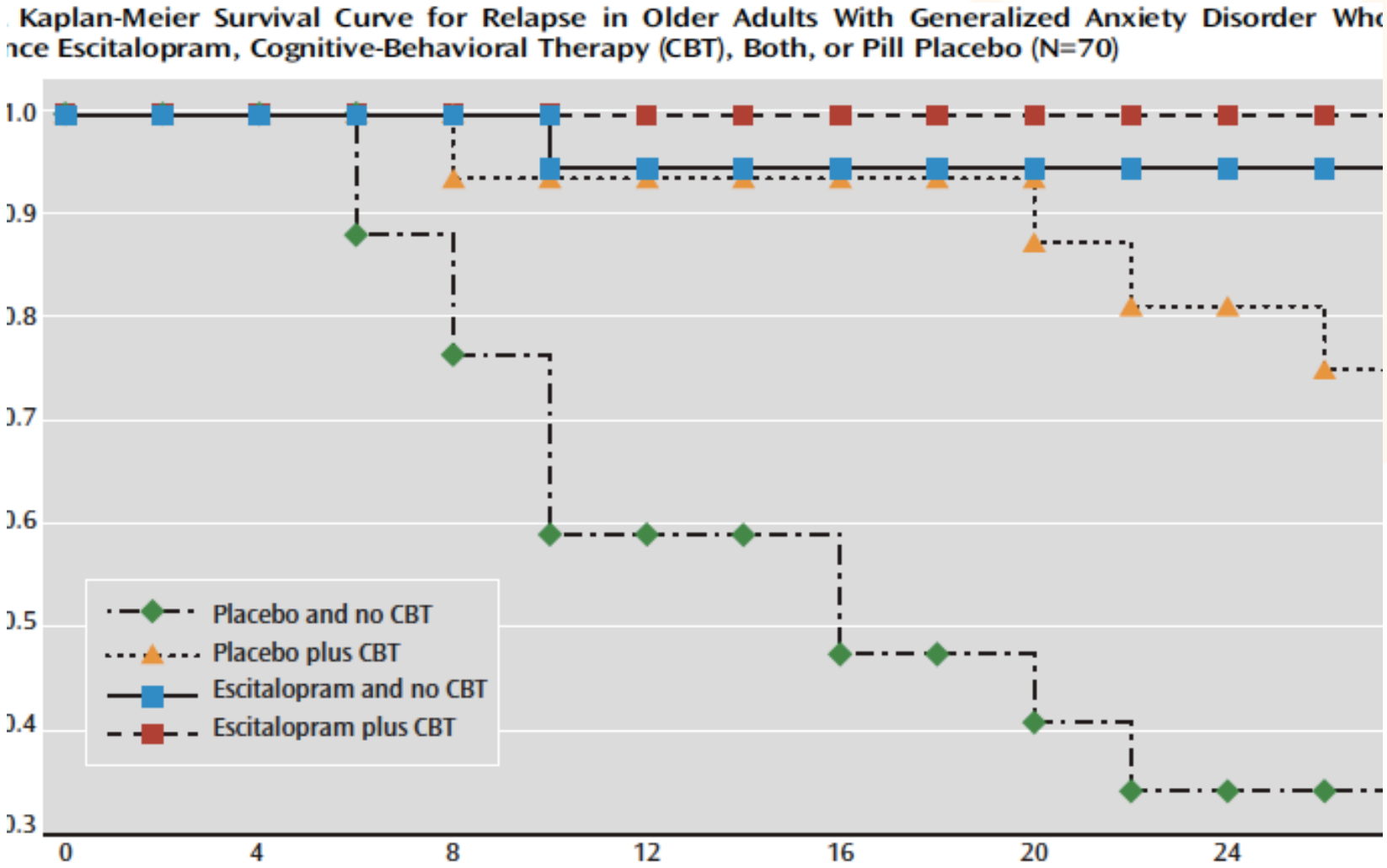
Stein MB, et al. *N Engl J Med*. 2015;373(21):2059-2068.

CBT Augments Worry Effect of SSRI in Geriatric Generalized Anxiety Disorder



Wetherell JL, et al. *Am J Psychiatry*. 2013;170(7):782-789.

Generalized Anxiety Disorder Relapse Prevention: SSRI Most Important, CBT Next



Wetherell JL, et al. *Am J Psychiatry*. 2013;170(7):782-789.

Table 2. Stepped-Care Approach for Management of Generalized Anxiety Disorder.*

Assessment Phase
Gather a detailed history of symptoms of generalized anxiety disorder and effect on functioning.
Ensure that generalized anxiety disorder is the principal or one of the principal diagnoses.
Evaluate patient for common co-occurring mental health conditions (e.g., depression, other anxiety problems, and substance-use disorders).
Evaluate patient for suicidal ideation, plans, or attempts.
Rule out treatable physical conditions such as thyroid and cardiac problems.
Use the Generalized Anxiety Disorder 7-Item Questionnaire or another suitable measure to gauge severity and track progress.
Step 1. All known or suspected cases of generalized anxiety disorder
Educate patient and family members about generalized anxiety disorder with use of self-help sites (e.g., that of the Anxiety and Depression Association of America [www.adaa.org]).
Educate patient about lifestyle changes that can reduce symptoms of generalized anxiety disorder. Discuss strategies for improving quality and quantity of sleep and encourage regular exercise (such as aerobic exercise and yoga). Encourage patient to minimize caffeine and alcohol use and to avoid nicotine and illicit drugs.
Monitor patient's progress with lifestyle changes.
Step 2. Diagnosed generalized anxiety disorder that has not improved after education and active monitoring in primary care
Suggest low-intensity psychological interventions such as individual nonfacilitated self-help (e.g., books and high-quality websites), individual guided self-help, educational groups, computer-assisted cognitive behavioral therapy.
Step 3. Generalized anxiety disorder with an inadequate response to step 2 interventions
Provide choice of a high-intensity psychological intervention or a drug treatment according to patient's preference and then refer patient for individual or group-based cognitive behavioral therapy (8–16 sessions) or for prescription of first-line pharmacologic treatments (SSRIs or SNRIs).
Step 4. Complex or treatment-refractory generalized anxiety disorder
Refer patient for specialized care by a mental health professional who will prescribe other first-line pharmacologic treatments or adjunctive treatment with a long-acting benzodiazepine (to be avoided among patients who are receiving opioids and among the elderly), buspirone, pregabalin, or quetiapine, and who will consider more intensive cognitive behavioral therapy, other forms of psychotherapy (such as psychodynamic therapy and acceptance and commitment therapy), or both.

* Adapted from United Kingdom's National Institute for Health and Care Excellence guidelines: (www.nice.org.uk/guidance/cg113/chapter/1-recommendations). SNRI denotes serotonin–norepinephrine reuptake inhibitor, and SSRI selective serotonin-reuptake inhibitor.

Stein MB, et al. *N Engl J Med*. 2015;373(21):2059-2068.

Practical Take-Aways

- Although there is controversy around the long-term use of benzodiazepines due to the potential for misuse and concerns about long-term adverse cognitive effects, with careful monitoring they can be used long-term in select patients with treatment-resistant GAD

- There is an emerging body of literature on the positive impact of physical exercise and complementary and alternative treatments (therapeutic massage, yoga, meditation, and others) in the treatment of GAD

- Although, there is uncertainty in the management of treatment-resistant GAD, clinicians should reassess the diagnosis, re-consider management of co-occurring mental and physical conditions, and consider more intense cognitive-behavioral approaches and/or other pharmacotherapies

Sources of Quality Information for Consumers

ANXIETY AND DEPRESSION ASSOCIATION OF AMERICA

www.adaa.org

National Institute of Mental Health
Transforming the understanding and treatment of mental illness through research

www.nimh.nih.gov

Anxiety Disorders Association of Canada
Association Canadienne des Troubles Anxieux

www.anxietycanada.ca