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Case 1: The salutatorian who couldn't speak: selective serotonin reuptake inhibitor (SSRI)-refractory anxiety in an adolescent

The Question: What do you do when anxiety fails to respond to multiple SSRIs and cognitive–behavioral therapy (CBT)?

The Psychopharmacological Dilemma: Whether and when to add adjunctive benzodiazepines remains unclear for many clinicians

Pretest self-assessment question

Which of the following represents an evidence-based intervention for a patient with treatment-resistant anxiety?

A. Duloxetine (Cymbalta)
B. High-dose escitalopram (Lexapro)
C. Adjunctive clonazepam (Klonopin)
D. Guanfacine (Tenex, Intuniv)
E. All of the above

Answer: C (Adjunctive clonazepam, Klonopin)

Patient evaluation on intake

- A 17-year-old African American high-school senior with severe social anxiety
- Severe social anxiety disorder and possible generalized anxiety disorder
- Her social anxiety symptoms have led to significant avoidance, and this avoidance and anticipation of catastrophic social criticism has perpetuated her anxiety, thus creating a vicious cycle
- There are concerns that family factors may galvanize her anxiety; these concerns include accommodation
- She readily acknowledges the excessive nature of these fears, yet still has some degree of belief in them and certainly experiences subjective fear about them
- She recognizes that her chronic anxiety interferes with her life, is preventing her from enjoying her senior year and her time with friends, and could threaten her success at college

Psychiatric history

- Social anxiety symptoms began when the patient was in the fifth grade
- In middle school, she struggled to do group work, was anxious about going out with friends, and could not spend the night at friends' houses

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- In high school, her social anxiety intensified. She dreaded being called on in class, or having to give presentations, and she felt so uncomfortable in the cafeteria that she ate her lunch in the school guidance counselor's office. She avoided going with her family to restaurants, and could not order her own food because she feared that she might say something incorrectly or that she would embarrass herself
- Despite her anxiety, she excelled academically and was the class salutatorian. However, she would often think about the salutatorian's public address at graduation, and this caused her significant distress
- Initial insomnia with a sleep latency of 1–2 hours, which is worse on school nights. She feels fatigued and has difficulty concentrating, but denies depressed mood
- When the family goes to restaurants, her parents frequently order her food. At larger family events, such as Christmas at her aunt's home, her parents arrange for her to sit in the car or to go to a quiet room, away from the family, if her anxiety becomes overwhelming
- Her parents are very concerned about her anxiety and about her being able to attend college. Of note, she has been accepted at three colleges, including her "dream school," which is located 5 hours away from her parents' home

Social and personal history

- Lives with her mother and father
- She is in the 12th grade at an all-girls high school and excels academically, although her anxiety makes some engagement with teachers difficult
- She is not currently in a relationship
- There is no history of abuse or trauma

Medical history

- Delivered at 40 weeks to a 37-year-old mother and 40-year-old father
- Normal developmental milestones, although separation anxiety persisted until age 8–9
- Seasonal allergies for which she takes cetirizine 10 mg daily
- Chronic recurrent abdominal pain, which is worse on school days

Family history

- Father with panic disorder and generalized anxiety disorder
- Mother with social anxiety and major depressive disorder
- Maternal grandmother with anxiety, posttraumatic stress disorder (PTSD), and depression

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Medication history

- Currently treated with escitalopram (Lexapro) 20 mg daily (3 months)
- No response to sertraline, which was titrated to 200 mg daily (4 months)
- Bupropion extended-release formulation (Wellbutrin SR) 100 mg twice daily worsened her anxiety and initial insomnia as a tremor was associated with it; it was discontinued within 2 weeks of initiation
- Fluoxetine 10 mg daily was discontinued after 2 weeks secondary to feeling "jittery," worsening anxiety, and two symptom-limited panic attacks
- Divalproex extended-release formulation (Depakote ER) 500 mg twice daily was discontinued because of nausea
- Quetiapine (Seroquel) 50 mg every night at bedtime, which was associated with sedation

Current medications

- Cetirizine (Zyrtec) 10 mg every morning
- Escitalopram (Lexapro) 20 mg every morning

Psychotherapy history

- She worked with an "art therapist" weekly for 2–3 months when she was a junior in high school. She enjoyed this therapy, but her anxiety failed to improve
- Thereafter, she transitioned to a cognitive–behavioral therapist and worked primarily on her thoughts and "anticipation of what might happen"
- Her anxiety persisted despite both therapies

Further investigation

Is there anything else that you would like to know about the patient? What about details related to her prior medication trials? What are the side effects that she experienced with fluoxetine (Prozac) and bupropion SR (Wellbutrin SR)?

- She experienced both symptoms of activation (e.g. restlessness, worsening anxiety, "jitteriness") with fluoxetine, and a tremor as well as worsening insomnia with low-dose bupropion extended-release formulation (100 mg twice daily)
- Side effects of both medications emerged relatively early during treatment

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What about additional physical symptoms and vital signs?

- No reports of depressed mood, guilt, anhedonia, or suicidal ideation
- Vital signs are within normal limits; her body mass index (BMI) is in the 75th percentile for age and sex
- There is no heat or cold intolerance, recent weight loss, or dysmenorrhea
- She denies cardiac symptoms, including palpitations

Attending physician's mental notes: initial psychiatric evaluation

- This patient has severe social anxiety disorder and some features of generalized anxiety disorder
- Her symptoms are in the severe range, and there is a suggestion of medication resistance
- There are also concerns related to *accommodation*
  - Her parents find it difficult not to attend to their daughter's anxiety and inadvertently reinforce her anxiety and catastrophic reactions. Over time, this has actively reduced her distress by facilitating avoidance. This is intuitively understandable, as accommodation (i.e. attention to anxious behavior and facilitating avoidance) perpetuates anxiety
  - From a family standpoint, effective interventions will require not only treating the patient's anxiety but also helping her parents to re-engage their daughter in life activities, rather than reinforcing avoidance, as well as reinforcing coping and tolerance of anxiety distress rather than dysregulated and anxious behavior
- Regarding side effects of prior medication trials, it is noteworthy that this patient had poor tolerability – within a very short time – with two medications that are metabolized primarily by CYP2D6. The side effects (activation with fluoxetine, and anxiety/tremor with bupropion) may be related to blood levels (i.e. exposure). This raises the possibility that the patient is a poor CYP2D6 metabolizer. Also, consistent with this notion, side effects from both medications emerged early during treatment

Question

This patient has had two psychotherapy trials and trials of several SSRIs, although her social anxiety symptoms have persisted and are severe. Which of the following would be your next step?

- Discontinue escitalopram (Lexapro) and begin duloxetine (Cymbalta)
- Titrate escitalopram (Lexapro) from 20 mg daily to 30 mg daily

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- Begin adjunctive clonazepam (Klonopin)
- Reattempt a trial of an adjunctive mixed dopamine serotonin receptor antagonist
- Initiate a trial of high-frequency left dorsolateral prefrontal cortex transcranial magnetic stimulation (TMS) for 6 weeks

Case outcome: first interim follow-up (week 4)

- At the patient's last visit, escitalopram was increased from 20 mg to 30 mg daily
- She reports excellent adherence and no side effects
- There has been a slight decrease in her anxiety, but overall this is only about a 20% improvement

Attending physician's mental notes: first interim follow-up (week 4)

- Given the patient's minimal response to two SSRIs that are metabolized by CYP2C19 (sertraline and escitalopram), and the fact that she is African American, there is a reasonable chance that she is an ultra-rapid metabolizer (i.e. she has one or two *17 alleles for the *CYP2C19* gene)
- Therefore, the decision was made to increase escitalopram from 20 mg to 30 mg. If she is an ultra-rapid metabolizer, this would produce blood levels comparable to those in a normal metabolizer treated with 20 mg daily (Strawn et al. 2018b)
- However, this failed to produce significant improvement in her anxiety symptoms

Question

This patient has had two psychotherapy trials and also trials of several SSRIs. Titration of escitalopram to 30 mg produced a mild improvement, but her social anxiety symptoms have persisted and are severe. Which of the following would be your next step?

- Discontinue escitalopram (Lexapro) and begin duloxetine (Cymbalta)
- Begin adjunctive clonazepam (Klonopin)
- Re-attempt a trial of an adjunctive mixed dopamine serotonin receptor antagonist
- Initiate a trial of high-frequency left dorsolateral prefrontal cortex TMS for 6 weeks

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Case outcome: second interim follow-up (week 8)

- After beginning clonazepam 0.5 mg twice daily, the patient's anxiety rapidly improved
- She re-engaged in psychotherapy with a new therapist
- Following a brief scheduled phone check-in, clonazepam (Klonopin) was titrated to 0.5 mg every morning and every afternoon, with 1 mg every night at bedtime

Attending physician's mental notes: second interim follow-up (week 8)

- After beginning clonazepam, the patient's anxiety rapidly improved and there were no tolerability concerns
- Increasing the evening dose to address her persistent initial insomnia is a reasonable option, although the prudent psychopharmacologist will monitor for early-morning sedation, especially if the patient drives herself to school, and also depending on whether she has an attentionally demanding first-period class
- The fact that the patient re-engaged in psychotherapy is important, although the psychopharmacologist will need to collaborate closely with the psychotherapist. There is concern that the earlier psychotherapeutic strategies were too cognitively focused and did not include sufficient exposure work. Exposure work is the key ingredient for child and adolescent anxiety (Peris et al. 2015, 2017)
- The psychotherapist will also need to work with the patient's family to address accommodation within the family, which can perpetuate adolescent anxiety (Peris et al. 2012)

Case outcome: third interim follow-up (week 12)

- The patient's sleep has normalized, and her anxiety symptoms are in remission
- Psychotherapy is going well, although she notes that the exposures, such as ordering her own food at a drive-thru, have been difficult from time to time
- Her psychotherapist further reports that she is doing well with session homework, following session structure, and has developed an exposure hierarchy. The psychotherapist shared with the treating psychiatrist that during the patient's last session they completed two in-session exposure tasks which involved calling several restaurants for directions. They discussed the patient's expectation that she is "inconveniencing others" and the fact that these exposures have been associated with a clear violation of expectations, which were discussed

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- She feels increasingly motivated and committed to taking better care of herself, and denies side effects
- She is exercising regularly and has begun a "metabolism-boosting diet" that was featured on a national talk show
  - Her diet consists of unlimited vegetables at lunch and dinner, a serving of protein at two meals per day, and half a grapefruit at every meal
- However, over the past 3–4 weeks she has been feeling tired, and she fell asleep twice while at school, after lunch

Attending physician's mental notes: third interim follow-up (week 12)

- The psychopharmacologist was initially concerned about non-adherence, given the abrupt onset of symptoms; however, a careful history revealed the cause of these new side effects to be grapefruit
- Grapefruit significantly affects the pharmacokinetics of most benzodiazepines (and other medications that are metabolized by CYP3A4). In fact, grapefruit increases peak benzodiazepine blood levels (C_{MAX}) by almost 60%, increases the time to maximum concentration (t_{MAX}) by 80%, and boosts absorption by up to 50%
- The psychopharmacologist also considered the possibility that the patient's tiredness was related to antihistaminergic effects, which can occur at high doses with escitalopram. However, this was less likely given that these were not present previously
- The psychopharmacologist enquired too about the possible addition of a proton pump inhibitor for the patient's indigestion, which could have affected escitalopram levels, resulting in a "new" escitalopram-related side effect

Case outcome: fourth interim follow-up (week 16)

- The patient is encouraged by her weight loss and feels better; she wishes to continue the "Grapefruit Diet." Therefore her clonazepam dose is reduced by 50%, with a contemporaneous improvement in tiredness
- She agrees to speak with her psychopharmacologist when she changes her diet, so that her benzodiazepine regimen can be re-evaluated

Take-home points

- Anxiety disorders often begin in childhood and, if untreated, can result in accumulated impairment that puts adolescents and young adults at risk for poor adaptation and maladaptive behaviors

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- In children and adolescents, anxiety behavior may be reinforced and may thus recur when it leads to successful avoidance of anxiety triggers. This cycle worsens when parents inadvertently reinforce this behavior by accommodating avoidance behavior
- Benzodiazepines, although not first-line treatments for anxiety, have an important adjunctive role, particularly in patients with a partial response to "first-line" interventions
- When selecting benzodiazepines, consider risk factors for substance use disorders and the pharmacology of the benzodiazepine (e.g. lipophilicity, half-life, etc.)
- Interactions, especially CYP3A4 interactions, are particularly important for benzodiazepines

Performance in practice: confessions of a psychopharmacologist

- A benzodiazepine might have been tried earlier, particularly given that the patient is an adolescent, there is a lack of risk factors for abuse, and she has previously had a trial of another CYP2C19-metabolized SSRI (sertraline) at a high dose
- Since drinking grapefruit juice in significant quantities is uncommon in this age group, the patient's clinician did not discuss it with her. If such a discussion had taken place earlier on it could have prevented this interaction

Tips and pearls

- SSRIs and psychotherapy remain the mainstay of treatment of pediatric anxiety disorders (Locher et al. 2017; Strawn et al. 2018b, 2021)
- Meta-analyses reveal that SSRIs produce greater and faster improvement compared with serotonin–norepinephrine reuptake inhibitors (SNRIs) in children and adolescents with generalized, separation, and social anxiety disorders (Figure 1.1). Additionally, in these meta-analyses, SSRI-related improvement occurs early in the course of antidepressant treatment (week 2 for both SSRIs and SNRIs). In fact, approximately 50% of the treatment-related improvement, at week 12, occurred by week 4 of treatment (Strawn et al. 2018b)
- For adolescents with social anxiety disorder, some suggest treatment with an SSRI prior to initiating psychotherapy, based on

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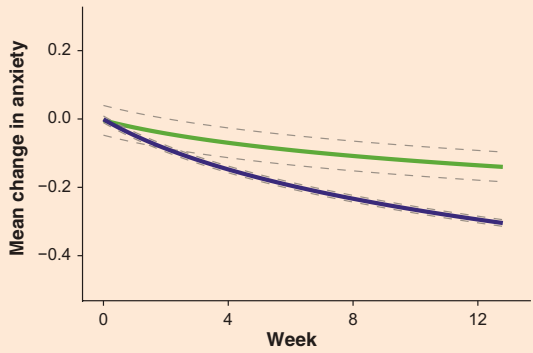

Figure 1.1 Response trajectory in antidepressant-treated pediatric patients with generalized, separation, and social anxiety disorders. Green and blue lines represent SNRIs and SSRIs. *Reproduced from* Strawn et al. (2018b).

data from the Child/Adolescent Anxiety Multimodal Study (Compton et al. 2014; Walkup et al. 2008)

- Benzodiazepines are often forgotten, but they represent a powerful tool for adjunctively managing anxiety, particularly in the "right" patient

Mechanism of action moment

- All benzodiazepines share a common mechanism of action but vary in their pharmacological characteristics (Strawn and Stimpfl 2023)
- Benzodiazepines are positive allosteric modulators of γ-aminobutyric acid A ($GABA_A$) receptors. The combination of benzodiazepines and GABA increases the frequency of opening of the inhibitory chloride channels (although it does not increase either the conductance of chloride across the individual channels or the length of time for which the channel is open) (Figure 1.2)
- It has been hypothesized that benzodiazepines modulate excessive amygdala output during fear responses in patients with anxiety disorders. This amygdala activity is theoretically reduced by enhancing the phasic inhibitory actions of benzodiazepine positive allosteric modulators at postsynaptic $GABA_A$ receptors within the amygdala to blunt fear outputs (Stahl et al. 2021)
- Benzodiazepines can be categorized based on their lipophilicity, and these differences affect their clinical profile (Figure 1.3)

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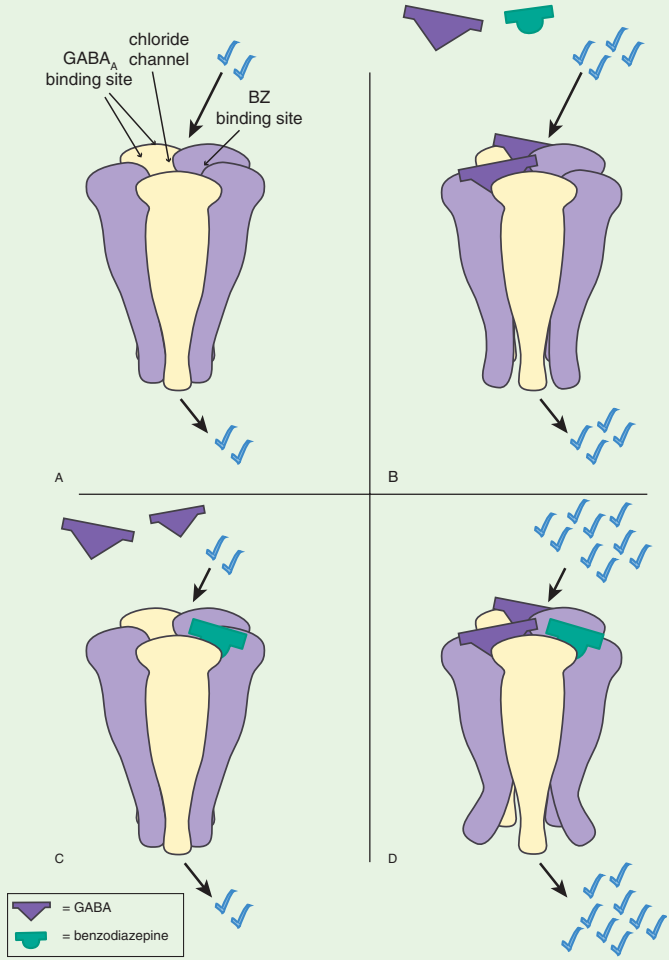

Figure 1.2 Positive allosteric modulation of GABA$_A$ receptors. (A) Benzodiazepine (BZD)-sensitive GABA$_A$ receptors, like the one shown here, consist of five subunits with a central chloride channel, and have binding sites not only for GABA but also for positive allosteric modulators (e.g. benzodiazepines). (B) When GABA binds to its sites on the GABA$_A$ receptor, it increases the frequency of opening of the chloride channel, and thus allows more chloride ions to pass through. (C) When a positive allosteric modulator such as benzodiazepine binds to the GABA$_A$ receptor in the absence of GABA, it has no effect on the chloride channel. (D) When a positive allosteric modulator such as benzodiazepine binds to the GABA$_A$ receptor in the presence of GABA, it causes the channel to open even more frequently than when GABA alone is present. Reproduced from *Stahl's Essential Psychopharmacology*, 2021.

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Highly Lipophilic	Less Lipophilic
• Enter the brain more quickly • "Turn on" the effect promptly • "Turn off" the effect more quickly and disappear quickly into fat • More intense effect	• Less lipophilic BZDs (e.g. lorazepam) produce slower effect • Provide more sustained relief, despite a shorter half-life • Less intense effect

Figure 1.3

Two-minute tutorial: benzodiazepines

- Despite the fact that trials of benzodiazepines in adults with anxiety disorders consistently demonstrate benefit (Strawn et al. 2018a; Williams et al. 2017), benzodiazepine trials in pediatric patients have produced mixed results, and double-blind placebo-controlled trials and meta-analyses do not reveal differences between benzodiazepines and placebo (Dobson et al. 2019). However, these studies were small and included very young children and high doses of short-acting benzodiazepines (e.g. alprazolam)
- In these pediatric benzodiazepine trials, the poor tolerability – particularly in younger patients, unlike the patient described in this case – may be related to age-related pharmacodynamic factors
- Importantly, the pharmacodynamics of the GABA receptor in children and adolescents differ from those in adults, with adult expression/function not being achieved until age 14–17½ years for subcortical regions and 18–22 years for cortical regions (Figure 1.4), although adult expression of GABA receptors occurs slightly earlier in girls than in boys (Chugani et al. 2001)
- Interactions are particularly important with benzodiazepines, and these interactions are often overlooked
- Clinically significant interactions for benzodiazepines include grapefruit juice (CYP3A4 inhibition), food, and antacids (Figure 1.5)
- Grapefruit juice boosts the peak benzodiazepine blood level (C_{MAX}) by almost 60%, increases the time to maximum concentration (t_{MAX}) by 80%, and significantly increases absorption by up to 50% (Figure 1.5)
- Food slows down benzodiazepine absorption, although it does not alter the total absorption (Figure 1.6)
- Antacids decrease the peak benzodiazepine blood concentrations (C_{MAX}) and the rate of absorption; medication requires longer to reach maximum concentration (t_{MAX}) (Greenblatt et al. 1980) (Figure 1.6)

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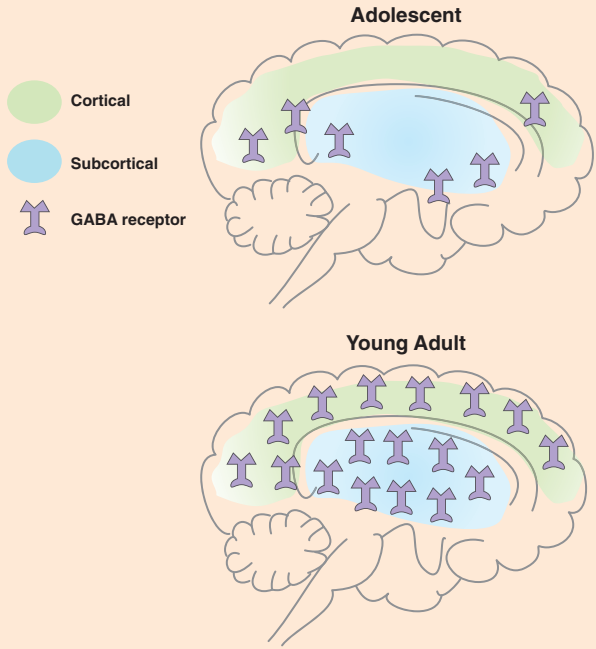

Figure 1.4 Benzodiazepine receptor expression changes significantly during development. This difference may affect the tolerability of these medications in children compared with adolescents and adults.

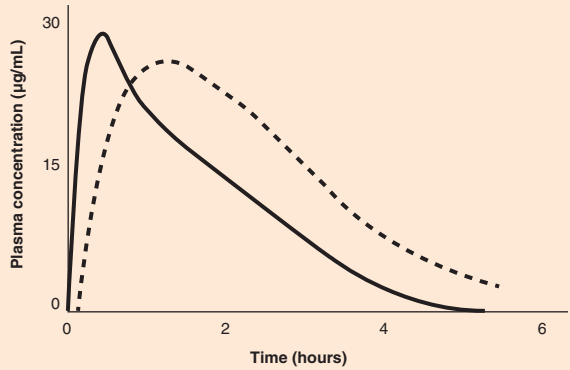

Figure 1.5 Grapefruit juice significantly alters the pharmacokinetics of several benzodiazepines. Dashed and solid lines represent diazepam with and without grapefruit juice, respectively. In this study, administration of the benzodiazepine with grapefruit juice increased absorption by 50% and altered the time to maximum concentration (t_{MAX}) by 80%. Adapted from Kupferschmidt et al. (1995).

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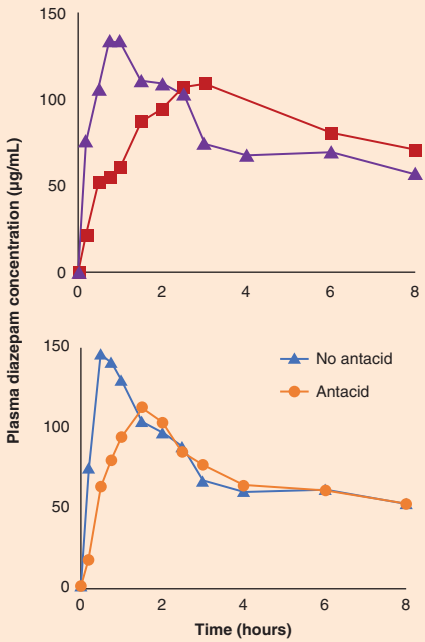

Figure 1.6 Food and antacids can significantly affect the pharmacokinetics of benzodiazepines. Red squares and purple triangles represent diazepam administration with and without food, respectively.

Post test question

Which of the following represents an evidence-based intervention for a patient with treatment-resistant anxiety?

A. Duloxetine (Cymbalta)
B. High-dose escitalopram (Lexapro)
C. Adjunctive clonazepam (Klonopin)
D. Guanfacine (Tenex, Intuniv)
E. All of the above

Answer: C (Adjunctive clonazepam, Klonopin)

Duloxetine is approved by the U.S. Food and Drug Administration (FDA) to treat generalized anxiety disorder in adolescents (Strawn et al. 2015); however, SNRIs are less efficacious compared with SSRIs in pediatric anxiety disorders (Strawn et al. 2018b). High-dose escitalopram, in and of itself, is unlikely to help with refractory anxiety disorders, and it places pediatric patients at risk of side effects, particularly those who are CYP2C19 poor metabolizers

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(Aldrich et al. 2019; Strawn et al. 2019). Guanfacine extended-release formulation has been examined in one small trial of children and adolescents with generalized, separation, and social anxiety disorders, and produced a greater response compared with placebo (Strawn et al. 2017), but it has not been studied in pediatric patients with SSRI-refractory anxiety disorders.

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