Chapter 5
Anxiolytics

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Anxiety will frequently be encountered in the clinical setting as the prevalence in the general population is approximately 2% [1], while in the elderly, the prevalence range is between 10% and 20% [2]. This makes anxiety disorders more common in the elderly than either dementia or major depressive disorder [2]. In the healthcare setting, there is an even greater presence of anxiety disorders. Anxiety disorders are associated with an increased risk of depression, the perception of worse physical or mental health compared to peers, an increased use of healthcare resources as well as a greater number of comorbidities. These contribute to a lower quality of life [3]. Other studies of the general population found decreased role functioning at work and in family, in addition to decreased quality of life for people with generalized anxiety disorder (GAD) [4]. Finally, there may be physiological effects as late-life GAD is associated with increased risk of stroke and other cardiovascular diseases [5, 6].

The relationship between anxiety and dementia is complex. For some patients, it should be noted anxiety may be a harbinger of dementia, partially because of patients being aware of their difficulties [7]. Anxiety increases the risk of progression of mild cognitive impairment (MCI) to Alzheimer's disease [8]. There are other anxiety disorders; however, the focus here will be on GAD and panic disorder. As can be seen from Table 5.1, rates of anxiety are high in many neurological conditions. Thus, there is a paramount need to understand the available treatment options. As the following case history demonstrates, anxiety is often seen in the setting of another illness, making management even more difficult.

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Table 5.1 Rates of anxiety in neurological conditions

Neurological condition	Rates of anxiety	References
Seizure disorders	Panic disorder: 5.7–70%	[9]
	GAD: 9.1–39%	
Multiple sclerosis	Pooled mean prevalence of anxiety: 22.1%	[10]
Migraine headaches	GAD: 21.9%	[11]
Strokes	10-year prevalence of anxiety: 32–38%	[12]
Parkinson's disease	Anxiety in early, drug naïve Parkinson's patients: 15.8%	[13]
Major neurocognitive disorder, Alzheimer's type	Pooled prevalence of anxiety: 39%	[14]
Major neurocognitive disorder, vascular type	Anxiety: 28%	[15]

Case Study

The patient is a 67-year-old married, Caucasian, man, retired physician. He had severe Parkinson's disease requiring placement of a deep brain stimulator. He had an anxiety attack at the time of placement of the deep brain stimulator, which he described as psychological torture. At his first clinic visit, he described feeling antsy, on edge, and tense which worsened as the day went on. He also had a persistent low-level anxiety. Distraction would help. He reported feeling anxious about a quarter of the time. He was worried about falling and had fallen two times in the week prior to the appointment. Crowds bothered him as he worried about a need to stop quickly. He had sleep apnea but was compliant with CPAP and described his sleep as fine. He reported to having power naps in the afternoon though stated it did not help his energy. Appetite was not changed, but he was much less active and therefore had gained a lot of weight. He reported no symptoms of depression. He did report violent dreams which he acted on. He denied feeling restless. His muscles would become tense with activity. Alcohol use was one to two drinks per week, and there was no history of substance misuse.

Significant medications were carbidopa-levodopa 25–250 1½ tablets at 6 am and 1 tablet QID and pramipexole 1.5 mg TID. Clonazepam 0.5 mg BID as needed was added at the first clinic visit.

He was involved in an intensive occupational therapy program to prevent falls so felt he did not have time to participate in psychotherapy. Instead, he was encouraged to engage in exercise, yoga, and massage.

At a 1 month follow-up, he had taken only one dose of clonazepam and felt better within 20–30 min. He was pleased with his status, and no changes were made. Two months later, he had used only 4.5 tablets of the clonazepam, all used in the afternoon or evening. He also admitted to taking ½ tablet with alcohol and becoming very confused. He reported feeling restless several times per day. However, he requested no medication changes.

Case Points

Anxiety symptoms occur in 5–60% of Parkinson's patients [16]. Most frequently seen are GAD, panic disorder, and social phobia [17, 18]. Interestingly, an anxiety disorder may occur long before the motor symptoms of Parkinson's are evident [19]. Additionally, anxiety disorders can easily lead to social withdrawal.

Patients frequently present with features of both GAD and panic disorder and rarely fulfill the complete *Diagnostic and Statistical Manual of Mental Disorders 5th Edition* (DSM-5) [20] criteria for either diagnosis.

Although clonazepam is often not a first-line agent, it did produce an adequate response for the patient. With such intermittent and mild symptoms, it did not make sense to place the patient on a scheduled medication that could lead to increased falls and other side effects.

Evaluation

While there are evidence psychotherapies, especially cognitive behavioral therapy (CBT) or medications can be used to treat anxiety disorders, this chapter focuses only on medication management. Some patients with GAD do not respond well to medications for reasons which will be discussed later. In a 2011 review, 25–40% of patients did not respond to existing medications in clinical trials [21].

The first step begins with evaluation. The evaluation starts with the patient interview. It is necessary to determine if the patient has panic disorder symptoms or GAD symptoms. The key feature of panic disorder is the abrupt onset of fear with at least four co-occurring symptoms. The essence of GAD is persistent worry with at least three symptoms over a period of 6 months. Risk of suicide can be increased in anxiety patients, so suicidality should be assessed.

For GAD, the symptoms must cause significant distress or impairment in role functioning. For both GAD and panic disorder, the symptoms should not be due to any medications, illegal drugs, or underlying medical illnesses. Additionally, neither of these should be better explained by the presence of another mental disorder.

It is important to question the patient or family about a multitude of other physical conditions which can lead to anxiety. Neurological patients, especially those with communication difficulties, may appear anxious due to restlessness from elimination difficulties such as constipation or incontinence. Those with aphasia may be angry or anxious due to frustration of inability to make themselves be understood. Pain can make patients hypermobile and thus appear anxious.

A careful review of medications is imperative. Several classes of medications can provoke an anxiety condition or unmask an underlying anxiety disorder (Table 5.2). If possible, gradually taper and discontinue any medications which may be contributing to the anxiety symptoms.

Table 5.2 Medications associated with anxiety symptoms

Medication class	Examples	Anxiety prevalence	Comments	Major metabolic pathways
Neurologic				
	Carbidopa-levodopa	Anxiety 2–8%		
	Ropinirole	Anxiety 2–6% in advanced Parkinson's when used with levodopa		CYP1A2
	Pramipexole	Not listed as significant	May worsen restless leg syndrome in 10–12%; akathisia 2–3%	
	Phenobarbital		Agitation and anxiety present but frequency not defined	CYP2C9
	Phenytoin	Not defined		CYP2C19 CYP2C9
	Levetiracetam		>10% behavioral problems which includes anxiety, restlessness, and irritability	
	Rivastigmine	Transdermal: agitation 1–4%	Oral: restlessness 1–3%; nonlinear pharmacokinetics at doses >3 mg BID	
		Oral: anxiety 1–5%		
	Memantine	XR formulation: anxiety 4%		
Psychiatric				
	Bupropion	Anxiety 3–8%	Agitation 2–32%	CYP2B6
	Haloperidol		Frequency not defined	CYP3A4
	Aripiprazole	Anxiety 17%	Akathisia 2–25%; agitation 19%	CYP2D6 CYP3A4
Stimulants				
	Methylphenidate	Anxiety 8%	Irritability 6–11%; restlessness 3%	
	Modafinil	Anxiety 5%; dose related	Nervousness 7%; agitation 1%; hyperkinesia 1%	CYP3A4
	Caffeine		Agitation and restlessness, appears serum concentration related	CYP1A2
Sedative				
	Alprazolam		Irritability 33%; akathisia 2%	CYP3A4

(continued)

Table 5.2 (continued)

Medication class	Examples	Anxiety prevalence	Comments	Major metabolic pathways
Cardiovascular				
	Digitalis	Frequency not defined		CYP3A4
	Amiodarone		Tremor up to 40%	CYP3A4 CYP2C8
	Clonidine		Irritability 5–9%; nervousness 1–3%	
Endocrine				
	Levothyroxine	Frequency not defined	Nervousness, irritability frequency not defined	
	Testosterone	Frequency not defined	Irritability 2%; aggression 1%	
	Conjugated estrogen	Anxiety 6%		CYP1A2 CYP3A4
	Tamoxifen	Anxiety 6%	Insomnia 9%	CYP2D6
				CYP2C9 CYP3A4
Respiratory				
	Albuterol	Anxiety <3%	Nervousness 4–15%	
	Theophylline	Frequency not defined		CYP1A2
	Diphenhydramine		Frequency of excitement, nervousness, restlessness not defined	CYP2D6
	Pseudoephedrine		Frequency of CNS stimulation, excitability, nervousness not defined	
Analgesics				
	Celecoxib	Anxiety <2%		CYP2C9
	Tramadol	Anxiety up to 5%	CNS stimulation 7–14%; agitation and restless up to 5%	CYP2D6 CYP3A4
	Oxycodone	Anxiety 1–5%	Irritability 1–5%	CYP3A4
Antispasmodics				
	Baclofen	Anxiety <1%	Agitation and tremor up to 1%	
	Cyclobenzaprine	Anxiety <1%	Irritability 1–3%	CYP1A2 CYP2D6 CYP3A4
	Oxybutynin		Restlessness and irritability not defined	
Gastrointestinal				
	Metoclopramide	Not significant	Restless in approximately 10% and rare akathisia	

Data from online.lexi.com accessed 12/20/16 and 2/14/17

As can be seen from the above table, many medications produce anxiety or symptoms that can easily be mistaken for anxiety. Akathisia is easily mistaken for anxiety with its sense of inner restlessness; however, it does not have the psychological features of anxiety, such as fear and worry. Irritability is also a symptom that is easy to mistake for anxiety. With it though, you will see an angry affect versus a fearful affect. Major metabolic pathways were included to emphasize the importance of being aware that anxiety may arise when a medication is added to an already complex medication regimen. An unexpected medication may produce anxiety by inhibiting the metabolism of one of the above agents and raising their blood level. Particular attention should be paid to medications for Parkinson's disease; due to their dopaminergic effects, they can be quite activating and cause patients to be anxious. Levetiracetam can produce anxiety symptoms as well.

Obtain lab work to ensure an undetected medical condition is not evoking the anxiety. Labs such as CBC, electrolyte levels, thyroid-stimulating hormone level, and blood glucose levels are all needed for a complete evaluation. Anemia can lead to anxiety symptoms, especially if hemoglobin is less than 10. Thyrotoxicosis is a classical condition leading to anxiety. In addition, anyone with hypoxia may be anxious, and the hypoxia may be the result of respiratory insufficiency from the underlying neurological condition. Adjust treatment plans to treat any newly discovered underlying illness.

The use of an anxiety scale to document baseline severity and treatment response is also recommended. It is best to find a scale that is not cumbersome to work with and applies to the patient's condition.

Anxiety Assessment Instruments

There are numerous anxiety scales with the clinical setting determining which scale is used. Each scale has its own unique focus and advantages/disadvantages. The challenge of most scales is its use in patients with physical illnesses, like the Parkinson's patient of the case study. In fact, anxiety scales have been criticized as not being particularly useful in Parkinson's disease [22]. The GAD committee for DSM-5 recommended using the generalized anxiety disorder 7 (GAD-7) as a screening tool [23]. Finally, although these scales are trying to measure anxiety, it is difficult to differentiate between anxiety and depression. This is only a brief overview of commonly used scales.

GAD-7

The GAD-7 is a valid tool to test for anxiety in both clinical and research settings [24]. In the GAD-7 individuals rate how often they experienced a symptom during the previous 2 weeks. The response ranges from "not at all" (0), "several days" (1),

"more than half the days" (2), and "nearly every day" (3). A score of 10 gives acceptable sensitivity and specificity for GAD. GAD-7 was developed for ease of testing [24].

The Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) is also composed of seven items. The focus of the HADS is for outpatients age 16–65 years old. Questions are directed at how individuals feel at the current moment, based on a four-point scale for each answer. Total scores range from 0 to 21. Less than 7 is normal, 8–10 is mild anxiety, 11–14 is moderate anxiety, and 12–21 is severe anxiety. A score of greater than 9 is considered positive for significant anxiety. This can either be a self-administered test or given by an interviewer. The HADS has been shown to have high reliability, validity, and sensitivity. The advantage is the brevity and ease of testing. The major disadvantage is the decrease in validity in the elderly population [25].

Zung Self-Rating Anxiety Scale

The Zung Self-Rating Anxiety Scale was originally developed by WK Zung. This is a self-administered test composed of 20 questions. Each question is on a four-point scale. Individuals answer each question with an answer ranging from a little of the time to most of the time with corresponding numerical scores from 1 to 4. Scores below 45 indicate norm, 45–59 is minimal to moderate anxiety, 60–74 is moderate to severe anxiety, and greater than 75 is extreme anxiety. The advantage of the Zung is the fact it is a self-administrated test, therefore, decreasing the bias of administration [26].

State-Trait Anxiety Inventory (STAI)

The State-Trait Anxiety Inventory (STAI) is another self-reported test. There are versions for both children and adults. There are two subscales; one scale evaluates the individual in their current state (S-anxiety), while the trait anxiety (T-anxiety) takes into account the general state one feels. Unlike the previous tests, the STAI is a much longer test made up of 40 items, 20 items of S-anxiety and 20 items of T-anxiety. S-anxiety items are scored for feelings at the current moment from "not at all" (1) to "very much" (4). The T-anxiety scores for the frequency of feelings scored from "almost never" (1) to "almost always" (4). A higher score suggests a greater degree of anxiety. A score of 39–40 indicates significant anxiety in the S-anxiety scale. The STAI has poor validity at differentiating between anxiety and depression; this is one of the greatest disadvantages to this test. The STAI has been well researched and has been used extensively in generalized anxiety disorder [25].

Beck Anxiety Inventory (BAI)

The Beck Anxiety Inventory (BAI) is also a self-reported scale. Similar to previous scales, individuals rate symptoms on a four-point scale from "not at all" (0) to "severely" (3). The individual answers a total of 21 items as they have experienced in the previous week. Scores are from 0 to 63. Less than 9 is clinically not significant, 10–18 indicates mild to moderate anxiety, 19–29 indicates moderate to severe anxiety, and 30 and above are indicative of severe anxiety. Due to the focus on somatic symptoms, the BAI is effective with older adults. A possible drawback of using this scale is the fact it is copyright protected [25].

Geriatric Anxiety Inventory

The Geriatric Anxiety Inventory is a 20-item self-report scale, and responses are simply yes or no. One point is scored for each positive response. A cutoff point of 10/11 produces acceptable specificity and sensitivity for GAD. The advantage of this scale is less response options make it more user friendly [27]. The Geriatric Anxiety Inventory has been validated in Parkinson's patients [28].

Medication Management

General Guidelines

Anxiety patients require much education and support to provide for a successful medication trial. Patients with anxiety disorders are sensitive to medications and are vigilant of bodily sensations, which they tend to label as side effects. The patient should be warned that one side effect at the beginning of treatment, especially SSRIs, is a short-term increase of anxiety. Due to this, the provider might want to consider adding a benzodiazepine for a short period. One additional benefit of using BZDs is improvement in sleep. Extensive education on side effects is one key to success of medication management. Patients need to be forewarned by the provider of the common side effects as there is a tendency of these patients to develop any side effect listed on the pharmacy information sheets. Assuring the patient of your availability and willingness to work with them through the side effects may improve medication adherence.

For patients who do not respond to medication therapy, the clinician should first consider nonadherence to treatment. Again, it cannot be overemphasized that anxiety patients are very sensitive to the side effects of medications and they are very sensitive to bodily sensations which they frequently attribute to medication side effects. Commonly, they will have adjusted their medication dosage downward in between appointments. Additional considerations for nonresponse include substance abuse, underlying undiagnosed medical condition, personality disorder, inadequate dose, or simply having chosen the wrong medication.

Medication options for the treatment of anxiety include selective serotonin reuptake inhibitors (SSRIs), serotonin/norepinephrine reuptake inhibitors (SNRIs), buspirone, and benzodiazepines. Agents are chosen based primarily on patient factors. Considerations include success of past treatments for the patient, response of family members, and history of substance abuse. Because of addictive potential, benzodiazepines should be avoided in those with any history of substance abuse, especially alcohol. The most recent treatment guidelines for GAD indicate SSRIs and SNRIs may have similar efficacy [29].

An additional factor to heavily weigh is the patient's age. With medication management in the elderly, there are two key points. The first is to gradually decrease medications with anxiety-causing properties. The second is the adage of "start low and go slow." In the geriatric population, the beginning dose should be ¼ to ½ the dose of an adult. Additionally, as the dose is being increased, the increments should remain ¼ to ½ of a dose increase for a healthy, younger adult.

It is best to see patients every 1–2 weeks when starting medications such as the SSRIs or SNRIs. Doses should be increased at each visit if the patient is tolerating adequately. The goal would be to reach the target dose in about 4 weeks. Of note, patients will frequently need higher doses of medication to treat anxiety than what would be used for depression. If a patient has no response after about 2 weeks at a good therapeutic dose, the practitioner should consider changing to an alternate agent. If there is only a partial response at about 2 weeks, then consider adding a medication to augment the original agent. Although the focus here is on medication interventions, psychotherapy can be a very useful augmentation strategy or primary treatment, especially if the patient is exquisitely sensitive to medications. If the patient does not respond to the above in about 6 weeks, then consider a referral to a psychiatrist (APA guidelines). A major problem is that up to half of the patients do not have an adequate response to medications [30]. Therefore, these techniques may need to be frequently invoked. Figure 5.1 presents the approach to GAD. Figure 5.2 presents the approach to panic disorder.

It is recommended that medications be continued for at least a year to provide an opportunity to achieve remission [23]. Medications for anxiety should always be tapered to prevent withdrawal symptoms or recurrence, unless there is a compelling medical reason to not taper. When considering a taper of medications, take into account the severity of the patient's presenting symptoms, how long they have been stable, current stressors, and their wishes regarding a taper. When a decision is made to taper therapy, it should be done slowly over 3–4 months (APA guidelines).

Selective Serotonin Reuptake Inhibitors

Some of the most common medicines used to manage anxiety disorders are the serotonin reuptake inhibitors (SSRIs). In general, the SSRIs are well tolerated; however, there is moderate risk of gastrointestinal side effects, which are primarily decreased appetite and nausea at the start of treatment. It needs to be noted that SSRIs may cause GI/other bleeding [31]. Insomnia can be a major symptom of

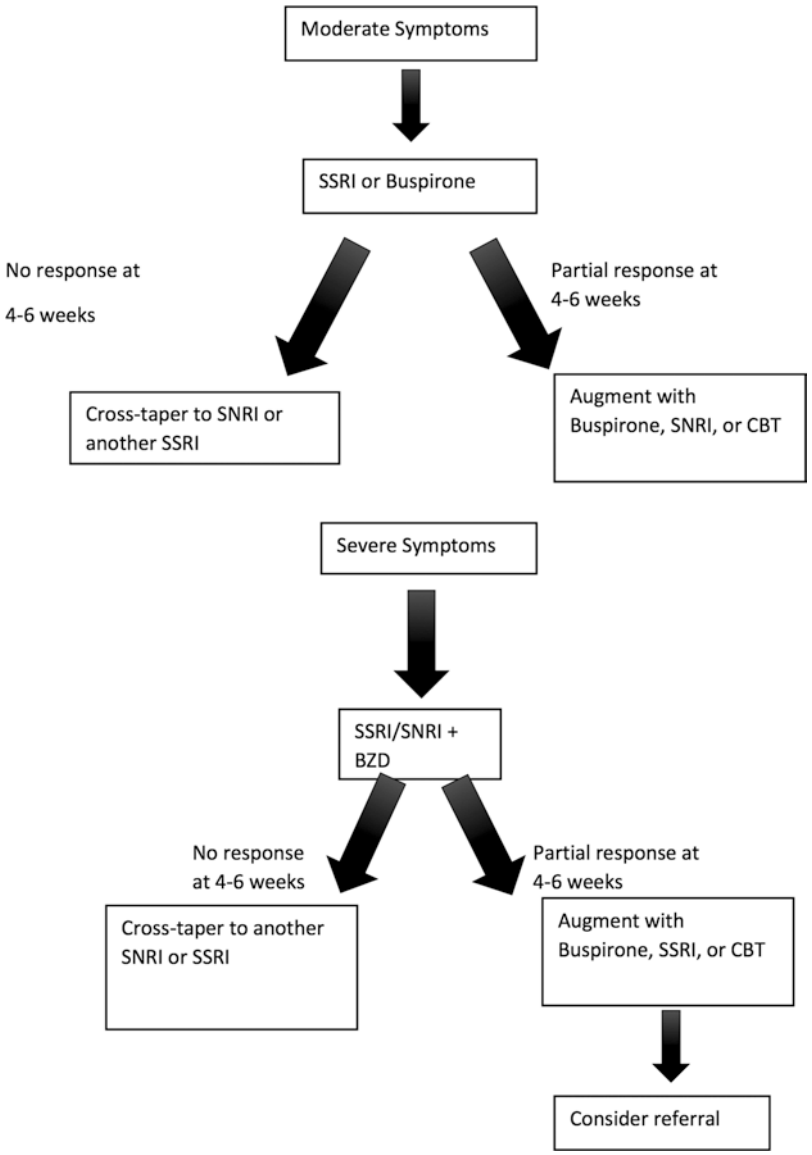

Fig. 5.1 The approach to GAD

GAD. In fact, one study showed that treating the insomnia specifically with hypnosis improved the response [32].

A meta-analysis looking at panic disorder found citalopram, sertraline, paroxetine, fluoxetine, and venlafaxine effective for panic symptoms: citalopram the least effective, venlafaxine the most effective, and the other three being of intermediate effectiveness. For anxiety symptoms in general, the rank order of effectiveness was

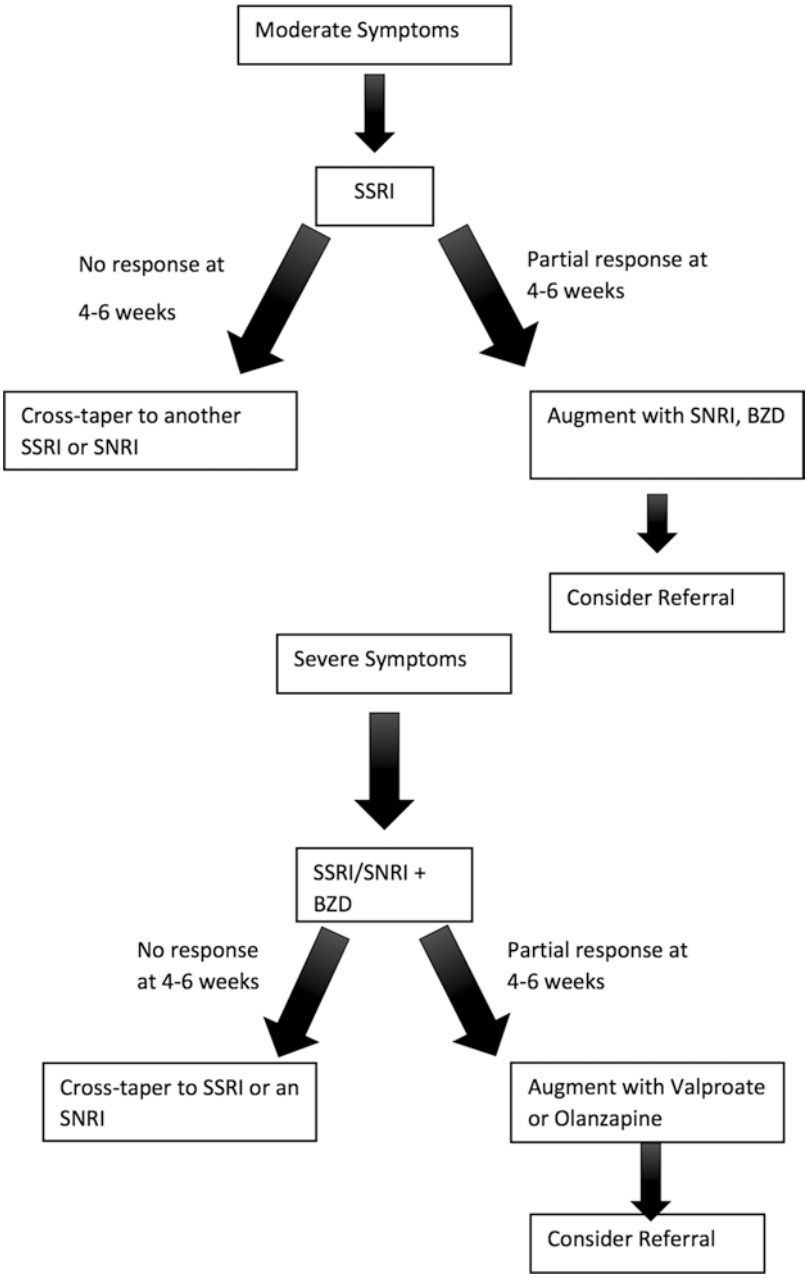

Fig. 5.2 The approach to panic disorder

paroxetine, fluoxetine, fluvoxamine, citalopram, venlafaxine, and mirtazapine. Based on having newer options, monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) should not be used as first-line therapy, and their use should be limited, so they will not be discussed further here. Fluoxetine may be more effective than other SSRIs in patients with a shorter duration of illness. The effectiveness of paroxetine and venlafaxine may increase over time [33]. The specifics of individual agents will now be discussed and are summarized in Table 5.3.

Fluoxetine

Fluoxetine dose range is from 10 to 80 mg daily. It tends to be relatively well tolerated and has a half-life in a range of 7 days, which may be an advantage in patients who are marginally adherent. It has significant CYP2D6 inhibition such that drug-drug interactions may be problematic. A feature relatively unique to fluoxetine is long term; it can be associated with an apathy syndrome. This syndrome may be particularly difficult to assess in neurological patients, some of whom tend to suffer from lack of motivation from the underlying neurological condition. There is a preparation of fluoxetine for weekly dosage, so this may be even more helpful if medication adherence is an issue.

Paroxetine

Paroxetine can be particularly helpful for selected patients. Like fluoxetine, it has significant CYP2D6 inhibition, so it may have multiple drug-drug interactions. It is associated with more sedation and weight gain than other SSRIs. There are no data to indicate that doses over 20 mg are more helpful for GAD. Although the recommended starting dose is 10 mg, clinically it can be useful to start at 5 mg or even 2.5 mg to ease side effect burden. Since it has sedative properties, it is best to be given after the evening meal. Although paroxetine's half-life is in the range of 24 h, it has more withdrawal symptoms than other SSRIs, so it should be carefully tapered before discontinuation.

Sertraline

Sertraline has been studied in multiple anxiety disorders and has a wide range of FDA indications for anxiety disorders. It is administered in the morning. Drug-drug interactions seem to be less than with some of the other SSRIs. A notable side effect of sertraline is diarrhea upon initiation of treatment. This information needs to be conveyed by the prescriber. Although guidelines are to start at 25 mg daily, frequently, older patients tolerate sertraline better if started at 12.5 mg daily.

Table 5.3 Medications for anxiety disorders

Class	Medication	FDA indication	Dose range	Positives	Negatives
SSRIs					
	Fluoxetine	Yes panic disorder; no GAD	10–60 mg daily; may increase by 10 mg/week	Long half-life so better for minimally compliant patients	Multiple drug-drug interactions
	Paroxetine	GAD and panic disorder	10–60 mg daily; increase dosage weekly	May be more effective than other meds	Drug-drug interactions
	Fluvoxamine	Obsessive Compulsive Disorder, Social Phobia	25–200 mg daily; increase by 25 mg weekly		Drug-drug interactions; wide dose range
	Sertraline	Yes panic disorder; no GAD	25–200 mg daily; may increase by 25 mg weekly	Fewer drug-drug interactions than other SSRIs	Wide dose range
	Citalopram	Not labeled for any anxiety disorders but used off-label	10–40 mg daily; increase by 10 mg weekly	Few drug- drug interactions; relatively less GI upset	Questionable QT prolongation at doses >20 mg
	Escitalopram	Yes GAD; no panic disorder	10–20 mg daily; start at 10 mg and increase to 20 mg in 1 week	Narrow dose range; few drug-drug interactions; minimal GI upset	Possible QT prolongation
SNRIs					
	Venlafaxine	GAD and panic disorder but only ER formulation	ER 37.5–225 mg daily; may increase by 37.5 mg or 75 mg weekly	Can use in Parkinson's disease; few drug-drug interactions	May increase diastolic blood pressure
	Duloxetine	GAD only	60–120 mg daily; increase by 30 mg weekly	Multiple indications	Drug-drug interactions
Other antidepressants					
	Mirtazapine	None	15–45 mg at bedtime; increase by 15 mg every 1–2 weeks	No abuse potential; helps sleep; may quickly alleviate insomnia	Not indicated; sedation; weight gain
	Vilazodone	None	10–40 mg daily; increase by 10 mg weekly	Narrow dose range	Cost
	Vortioxetine	None	10–20 mg daily	No dose adjustment needed for geriatric or renal patients	Cost

(continued)

Table 5.3 (continued)

Class	Medication	FDA indication	Dose range	Positives	Negatives
Benzodiazepines					
	Clonazepam	Panic disorder	0.25–4 mg BID maximum dosage; increase by 0.25 mg q 3 days	Multiple uses	Long half-life; may accumulate
	Lorazepam	Anxiety disorders	1 mg BID to TID maximum dosage 10 mg/day	Multiple uses	Wide dose range
	Alprazolam	GAD and panic disorder	0.25–0.5 mg TID to maximum of 4 mg/day; may increase 0.25–0.5 mg every 4 days	Quickly effective	Short half-life, so patients may withdraw before next dose
			Panic: 5–6 mg/day-10 mg/day		
Antihistamine					
	Hydroxyzine	Anxiety	50–100 mg QID	May be used as needed; nonaddictive; older drug so inexpensive	Increase confusion; paradoxical reactions
Non-benzodiazepine anxiolytic					
	Buspirone	GAD	7.5–30 mg BID; increase every 3 days by 2.5 mg	Low side effect profile; No abuse potential	Effects may be delayed; wide dose range
Anticonvulsants					
	Gabapentin	None	300 mg daily to maximum 3600 mg daily; increase as tolerated	No hepatic metabolism	Needs adjustment for renal impairment
	Pregabalin	None (GAD in Europe)	75 mg BID to maximum 300 mg BID; increase weekly	No hepatic metabolism	Abuse potential
Antipsychotics					
	Quetiapine XR	None	50–300 mg at bedtime; increase by 50 mg every 3 days	Wide range of use	Weight gain; black box warning; QT prolongation

Data from online.lexi.com accessed 12/20/16 and 2/14/17

Citalopram

Citalopram tends to be very well tolerated with few drug-drug interactions. It, however, should be avoided in those with certain cardiac disorders and has been associated with QT prolongation and sudden death. Dosages of citalopram and escitalopram have been capped for those 60 and older. These recommendations have been somewhat controversial [34]. Although the recommended starting dose is 10 mg daily, there tends to be better tolerance when starting at 5 mg daily.

Escitalopram

Escitalopram is chemically closely related to citalopram. Although it does not have FDA approval for panic disorder, the American Psychiatric Association (APA) guidelines include the use of citalopram and escitalopram for panic disorder (APA guidelines).

Fluvoxamine

Fluvoxamine is included in the APA guidelines for treatment of panic disorder. This medication can be sedating, so it is best to give it after the evening meal. Clinically it is less familiar to most practitioners as it is not indicated for depression.

Serotonin/Norepinephrine Reuptake Inhibitors

In the Parkinson's patient, a serotonin/norepinephrine reuptake inhibitor (SNRI) may be a preferred agent as the SSRIs have the potential to decrease dopamine transmission in the brain. The most commonly used SNRI is venlafaxine. Duloxetine will also be discussed.

Venlafaxine

Venlafaxine was the first SNRI to be FDA approved. It has a reputation of more quickly alleviating anxiety than the SSRIs. It is relatively well tolerated. It like the SSRIs can produce significant GI side effects. It does have the potential to raise diastolic blood pressure, especially at higher doses. There is some evidence that venlafaxine may help with diabetic neuropathic pain [35], so it may be a good

choice in those with anxiety and neuropathic pain. It has two formulations, immediate release (IR) and extended release (ER). Extended release tends to be better tolerated with less GI upset. A major problem with venlafaxine IR is the short half-life such that patients may go into withdrawal with increased anxiety and flu-like symptoms prior to the next dose. Even though the ER is generic, some insurances will require a prior authorization. Only the ER formulation has been studied and approved for use in anxiety disorders.

Duloxetine

Duloxetine is an additional SNRI and has an indication for GAD. It has a wide range of indications including depression, neuropathic pain, musculoskeletal pain, and fibromyalgia. It may be a particularly attractive medication for patients with any of those disorders. Unlike venlafaxine, it has no or minimal effect on blood pressure. About one-third of the patients given duloxetine experience sedation. It may be best to start by giving a dose after the evening meal. GI upset can occur so it should be given after meals; however, it may produce less GI side effects than venlafaxine. The major problem with duloxetine is profound inhibition of CYP2D6. This inhibition can lead to drug-drug interactions, thus should not be given with SSRIs. Like venlafaxine, duloxetine has efficacy in diabetic neuropathy [35]. This is a medication that might best be started at 30 mg in the evening. Additionally, it should be used with caution in patients with renal insufficiency. Two newer SNRIs are desvenlafaxine and levomilnacipran although neither has an indication for use in anxiety disorders.

Other Antidepressants

Mirtazapine

Mirtazapine is not formally indicated for any anxiety disorders. However, a relatively recent review found evidence for its effectiveness in panic disorder [36]. Clinically the authors have seen improvements in GAD as well. It may be particularly useful for anxiety-associated insomnia. Anxiety patients will commonly complain of GI upset. Mirtazapine could be a good choice for those patients, as it is associated with less GI upset than SSRIs or SNRIs. Some patients may respond to doses as low as 7.5 mg at bedtime. Theoretically, patients should have less sedation as the dose is increased; however, that is not always seen. Unfortunately, it tends to produce weight gain making it not a good choice for those with diabetes or other metabolic disorders.

Vilazodone

Vilazodone is an SSRI in addition to a 5-HT1A receptor agonist, approved for major depression. Doses of 20–40 mg daily have been shown to be effective for the anxiety symptoms of GAD but not the associated disability. The most frequent side effects were GI related, nausea, and diarrhea [37]. It has extensive liver metabolism and a long half-life. It does not have an indication for anxiety disorders. With its relatively tight dose range and ability to be titrated weekly, it can quickly reach a maximum therapeutic dose. Vilazodone should be taken after eating to both decrease its GI side effects and improve its absorption. It also has less sexual dysfunction compared to either the SSRIs or SNRIs.

Vortioxetine

A meta-analysis of vortioxetine in the treatment of GAD concluded its effects were inconsistent. Only four studies were included. It did separate from placebo in those with more severe anxiety. So, this would be an alternative medication; however, the evidence for it is weak [38]. In a head-to-head trial with duloxetine and placebo, duloxetine separated from placebo, and there was only a weak signal for efficacy of vortioxetine 10 mg daily. Vortioxetine, however, was well tolerated [3]. It has a long half-life and is metabolized by the liver. This medication also has a very narrow dose range and can quickly be titrated so can reach maximum dosage within 2 weeks. In CYP2D6 poor metabolizers, its maximum dose is 10 mg per day. In clinical practice, the dosage can be started at 5 mg per day. It should not be used in those with severe hepatic impairment.

Benzodiazepines (BZDs)

Benzodiazepines are a class which can quickly alleviate anxiety symptoms, whether it is GAD, non-specific anxiety, or panic disorder. Caution must be observed in the use of these medications because of the increased potential for abuse. They are remarkably similar, with main difference being onset of action and half-life. Additionally, BZDs have fewer GI side effects than SSRIs or SNRIs; in fact, at times they are used to treat nausea. One major concern with BZDs is their side effects of dizziness, unsteadiness which can increase falls, as well as cognitive impairment in older adults.

Diazepam

Historically, one of the most frequently prescribed BZDs is diazepam. This drug has a long half-life and active metabolites which may lead to accumulation, which may be especially pronounced in the elderly and can lead to confusion. It is subject

to extensive liver metabolism. With the presence of active metabolites and extensive liver metabolism, diazepam is used much more frequently than should be the case. It does have a quick onset of action and is associated with significant abuse potential. It has many other uses such as in seizure disorders, as a muscle relaxant, and for some sleep disorders. Thus, it may be a good choice in those settings. It is listed in the APA guidelines as useful in panic disorder. Patients may respond to doses lower than listed in Table 5.3. Patients may in fact do well with just one or two doses per day.

Oxazepam

An often-overlooked benzodiazepine is oxazepam as it is an older medication. It does seem to have less abuse potential, which may be due to slower absorption. Although GI upset is not common with BZDs, oxazepam seems to have even less than others. It does have a short half-life with minimal if any liver metabolism, hence ideal for those with hepatic impairment. With its slow onset of action, it may be useful in patients who are overly concerned about dizziness or unsteadiness. Due to its short half-life, it is best given three to four times per day with dosing based on the severity of the anxiety.

Clonazepam

Clinically clonazepam is used for both anxiety and some seizure disorders. Additionally, it is used for restless leg syndrome, rapid eye movement (REM) sleep behavior disorder and other sleep disorders, muscle spasms, mood stabilization, and tremor as off-label uses. It has a long half-life and may accumulate in older patients. It seems to have moderate abuse potential. It is extensively metabolized by the liver. In clinical settings, it can be dosed daily to BID with the last dose given at bedtime.

Lorazepam

This medication is also commonly used for anxiety disorders and is among one of the best known antianxiety agents. Its advantage is an intermediate half-life and minimal hepatic metabolism. Due to its intermediate half-life, some patients may benefit from once-daily dosing given at bedtime. Most often it is prescribed every 8 h. It can be used in seizure disorders and in chemotherapy-induced nausea and vomiting.

Alprazolam

Alprazolam is a short-acting BZD with a moderate to high abuse potential. It is widely used with indications for both GAD and panic disorder; with the advantage, it quickly quells symptoms. Disadvantages would be the need for multiple doses through the day, usually every 6–8 h. Occasional patients may metabolize this medication very quickly and need four to six doses per day. Those patients may have increased anxiety before the next scheduled dose due to withdrawal effects. Another disadvantage of alprazolam is a relatively wide dose range so it may take a long time to titrate to clinical effectiveness. Finally, it can be difficult to taper and stop this medication. To avoid withdrawal, it may need to be tapered very slowly.

Antihistamines

Hydroxyzine

Hydroxyzine is one of the oldest antianxiety medications. Its effectiveness is comparable to benzodiazepines and buspirone [29]. It has a syrup formulation, so it can be given in doses as low as 10 mg or even less. These ultra-low doses would be useful in a debilitated patient. Additionally, hydroxyzine may help with nausea. One of the disadvantages is it can lower the seizure threshold so it would need to be used with caution in those with a seizure disorder. As it is antihistaminic/anticholinergic, it should be used with caution in the elderly as it may produce or increase confusion.

Non-benzodiazepine Anxiolytic

Buspirone

Buspirone is in a class by itself. It is indicated for GAD. It has a very benign side effect profile and does not create the GI side effects which are prevalent with the SSRIs and SNRIs. It also has minimal, if any, drug-drug interactions. It can be useful as an augmenting agent for depression. With the significant overlap between anxiety and depression, this may be a useful feature. However, it is not indicated and should not be used in panic disorder or on an as needed basis. Another drawback is it may need dosage adjustment in patients with renal or hepatic disorders. There are two significant problems with buspirone. The first is a wide dose range; on occasions, patients may respond to doses as low as 5 mg daily and then not do as well at higher doses. The lower doses may be tried in those who are debilitated or in the elderly. However, most patients require high doses, and in fact, many require the maximum dose of 30 mg BID. Therefore, dose titration can be a major issue. The

second problem with buspirone is the time to response is delayed with onset of action taking 2 weeks or more. The time to response is typically longer than SSRIs or SNRIs.

Anticonvulsants

Gabapentin

Gabapentin is not formally indicated for any anxiety disorders but is included in the APA guidelines. It does have an indication as an adjunctive agent for partial onset seizures, so is a medication neurologists are familiar with. It also has an indication for postherpetic neuralgia. For those who are frail, the dose can be started as low as 100 mg at bedtime. It is relatively well tolerated, and there are no common drug-drug interactions, so it may be an option for those who are very ill. Dosages do need to be adjusted for renal impairment but not hepatic impairment. Of note, its bio-availability may decrease at higher daily doses.

Pregabalin

Pregabalin is structurally similar to gabapentin. In Europe, it has received approval for GAD in addition to neuropathic pain. However, in the US, the FDA has only approved it for fibromyalgia, and it does not have a formal indication for anxiety. The British guidelines indicate pregabalin has efficacy in both acute and chronic GAD [39]. Pregabalin is also generally well tolerated [40]. It has a short half-life and no hepatic metabolism with few drug-drug interactions. It is usually given two to three times per day. It does need to be dose adjusted for renal insufficiency. This would be another medication which may be considered as a third or fourth line agent.

Antipsychotics

Quetiapine

For those who do not respond to other treatments, quetiapine may be considered, as it has some short-term efficacy [41]. There are studies showing quetiapine XR used off-label is effective for GAD [42]. Required dosage is lower for anxiety disorders than in other psychiatric disorders. It is used in an array of psychiatric disorders. There are several difficulties for this medication including sedation and weight gain. One must be aware of its potential to produce orthostatic hypotension, especially early in treatment. It also has a reputation of worsening Parkinson's symptoms in patients though probably less so than other antipsychotics. It is also associated with

QT prolongation. At this point, there is little evidence for the effectiveness of other second-generation antipsychotics in the treatment of GAD [43].

Miscellaneous

In terms of refractory panic disorder, there is good evidence for the augmentation effect of cognitive behavioral therapy (CBT). There is some support for the use of olanzapine as a single agent. Pindolol, divalproex sodium, aripiprazole, and olanzapine may be effective as augmenting agents [44]. However, based on the metabolic side effect burden associated with the second-generation antipsychotics, they should be considered only in refractory cases of anxiety or panic disorder [29]. An additional caveat is the black box warning concerning increased mortality relative to the use of all antipsychotics, even in low doses, in dementia patients. Consequently, antipsychotic use for anxiety should be avoided for this population.

Clinical Pearls

1. Rule out substance abuse, medication side effects, and medical illnesses which could be contributing to anxiety symptoms.
2. For mild to moderate anxiety, use an SSRI with few side effects such as escitalopram, citalopram, or sertraline.
3. For severe anxiety, use an SSRI or venlafaxine with a benzodiazepine.
4. For extreme anxiety, use a BZD to provide the patient with quick relief of symptoms.
5. For those with substance abuse issues, avoid the use of BZDs, and try to manage with an SSRI or SNRI.
6. BZDs are the most effective for the acute management of anxiety. Most other medications have delayed effect due to dose titration and time to onset of action.
7. For patients who do not respond to any of the above agents, consider one of the atypical agents.
8. Beware of drug-drug interactions.
9. Buspirone has no role in the management of acute anxiety or panic disorder.

Conclusion

Anxiety will frequently be seen by clinicians. The presentation of an anxiety disorder will rarely be clear cut. Additionally, there can be multiple co-occurring physical illnesses, medications, or substance use, all of which can worsen the anxiety disorder. The clinician does have multiple medications in addition to

psychotherapy to help the patient. These patients require education, support, and patience to manage their illness. However, successful treatment can markedly increase their quality of life.

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