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Treating Anxiety Disorders in Primary Care

"The suspense: the fearful, acute suspense … the racking thoughts that crowd upon the mind, and make the heart beat violently, and the breath come thick, by the force of the images they conjure up before it; the desperate anxiety to be doing something to relieve the pain, or lessen the danger, which we have no power to alleviate; the sinking of soul and spirit, which the sad remembrance of our helplessness produces; what tortures can equal these; what reflections of endeavours can, in the full tide and fever of the time, allay them!"

Charles Dickens, Oliver Twist, *1838*

Anxiety disorders are the most prevalent mental health problem worldwide. Collectively, these disorders are at the core of 20% of primary care visits in the United States, but the heterogeneity of presenting symptoms, comorbidities, and fluctuating diagnostic criteria over time contribute to difficulties with recognition and to misdiagnosis. Untreated anxiety is associated with psychosocial and occupational impairment, and also is a risk factor for developing other mental health disorders and is a risk factor for suicide. Early and appropriate intervention is key to modulating these outcomes.[1,2]

The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) delineates specific diagnostic criteria for each disorder contained under the general umbrella of anxiety disorders. These include generalized anxiety disorder (GAD), social anxiety disorder (SAnD), panic disorder (PD), specific phobias, agoraphobia, separation anxiety disorder, anxiety disorder unspecified, selective mutism, substance/medication-induced anxiety disorder, and anxiety disorder due to another medical condition.[3]

Close to 30% of the U.S. adult population will experience at least one of these conditions at some point in a lifetime.[4] Understanding the current conceptualization of these disorders offers the primary care provider (PCP) a foundation to build a systematic approach for patients presenting with symptoms of each of these disorders.

However, before viewing anxiety as a disorder, it is useful to reflect that anxiety is a universally experienced human emotion. References to this state appear throughout human history, with pictographs, mythology, and primitive writings depicting anxiety and associated states. The term, derived from the Germanic "angh" (to narrow or constrict) with echoes in the archaic Greek term anchein (to strangle or suffocate), illustrates an early understanding of the association of anxiety with tightness and/or constriction in the chest or throat — a phenomenon still recognized today as part of an anxiety response.[5]

Interestingly, anxiety often is adaptive, assisting in sending signals of approaching danger and helping mobilize focus and necessary energy. Anxiety

EXECUTIVE SUMMARY

Anxiety disorders are the most prevalent mental health problem worldwide and collectively result in 20% of primary care visits in the United States.

- The diagnosis may be complicated, since patients often delay seeking treatment until the development of somatic symptoms. More than one-third of patients turn to self-medication and more than 80% have a comorbid diagnosis, such as major depressive disorder.
- The typical course is chronic and persistent, with complete remission in only about 20% of patients at five years.
- The Generalized Anxiety Disorder-7, a seven-item questionnaire, is the most commonly used screen, with a score of 8 or greater calling for further evaluation.
- Treatment includes self-help groups, cognitive behavioral psychotherapy, and psychopharmaceuticals.
- Medications typically include selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, buspirone, tricyclic antidepressants, gamma aminobutyric acid agonists, and benzodiazepines. The use of cannabidiol is controversial.
- Panic disorder and social anxiety disorder have specific diagnostic criteria requiring more targeted therapeutic approaches.

can be appropriately associated with avoidant behavior or other compensatory strategies, all of which may help an individual function at optimal levels.

But if an anxiety response begins to interfere, rather than assist, with a desired level of functioning, the concept of a disorder becomes relevant. The majority of patients with disorders of anxiety seek care and advice from a PCP, frequently presenting with somatic symptoms, such as insomnia or gastrointestinal complaints. In many cases, the perception of anxiety is "masked" by such symptoms; a comprehensive history, physical examination, and appropriate medical workup is critical to accurate diagnosis and appropriate treatment.[1,2,4] Treatment for anxiety disorders involves psychotherapy and/or psychopharmaceuticals, with medical investigations demonstrating similar overall efficacy for each approach.[1,2,4]

This article reviews in-depth several common disorders of anxiety — GAD, PD, and SAnD — with a focus on diagnosis and treatment relevant to the PCP. Patient examples are included for illustrative purposes.

Generalized Anxiety Disorder

M.P., a 45-year-old retail worker and separated mother of a young teen, with no chronic medical conditions, presents with insomnia and daytime fatigue worsening over the last year, and frequent headaches and forgetfulness starting about two months ago. She notes that her work productivity is slipping, and that she has less patience at home, stating, "Now that I have a teenager, there's more to worry about." She explains that she also is worried "something is wrong with me … maybe I have a brain tumor?" Additionally, she notes the glass of wine at night she has been drinking to help with sleep no longer is effective, and she wonders about medication for sleep.

GAD is a chronic disorder of anxiety with progression of symptoms over time. Hallmarks of this disorder are:

- excessive worry about a variety of events or topics; the worry is experienced as being difficult or unable to be controlled, for at least six months;
- three or more of the following symptoms (only one symptom in children is needed to diagnose): restlessness/feeling on edge, easy fatigue, concentration difficulty, irritability, muscle tension, sleep disturbance;
- an impairment in functioning related to the worry and/or somatic symptoms;
- the symptoms are not better explained by another medical problem, mental illness, or substance use.[6]

The diagnosis of GAD may be complicated, since patients often delay seeking treatment or medical advice until somatic symptoms emerge. Additionally, more than one-third of these patients will turn to self-medication (drugs and/or alcohol) for symptom management, and more than 80% will have a comorbid diagnosis, such as major depressive disorder or another anxiety disorder. A careful history with an accurate timeline often is critical in diagnosis and appropriate treatment focus.[7]

Epidemiology

GAD has a worldwide lifetime prevalence of 3.7%, with higher prevalence in higher income countries (4.1% lifetime prevalence in the United States), and occurring with greater frequency in middle-aged, widowed, or divorced women. Estimates are that up to 14.8% of patients presenting to a PCP will meet criteria for this diagnosis.[7,8] The typical course is chronic and persistent. Symptom management and functional improvement are the main goals of treatment. Studies show complete remission occurs in only about 20% of patients at the five-year mark.[7-9]

Genetics play a role in the expression of most mental illnesses; GAD is not an exception. Twin studies indicate heritability influences about 31% of emergence, with psychosocial and other environmental factors affecting the remaining portion. There is an overlap of heritability with separation anxiety disorder, PD, and the phobias. Research in pharmacogenetics points to a promising role in identifying genetic factors predictive of a response to selective serotonin reuptake inhibitors (SSRIs).[10]

Differential Diagnosis and Screening Tools

A comprehensive history and physical examination, employing

nonjudgmental interview techniques with open-ended questions, is key to accurate diagnosis and treatment. Screens are useful in pointing an interview toward a specific direction but are not to be used as a stand-alone diagnostic tool.[7-9]

As with most anxiety disorders, checking for medical disorders that may exacerbate or mimic anxiety symptoms is an important component of the initial workup. Thyroid disease, vascular disease, disorders causing dysregulation of blood glucose, withdrawal from pharmaceuticals (including antidepressants and antianxiety agents) and withdrawal from substances of abuse (including caffeine) are among the differential. Check for subtle signs suggestive of neurological dysfunction, especially in the elderly presenting with cognitive impairment.[11]

Common medications that may cause or worsen anxiety include analgesics, antihypertensives, anticholinergics, antihistamines, levodopa, SSRIs, opioids, and muscle relaxants. A careful history examining the temporal relationship between the onset or worsening of anxiety symptoms and starting/stopping medication is helpful in elucidating such a relationship.[7-9,11]

Given the high comorbidity of GAD and other disorders of mental health, careful evaluation for underlying disorders of depression or other anxiety disorders is necessary. Check also for comorbid substance use or abuse, since this will have implications for the direction of treatment.[7-9,11]

The Generalized Anxiety Disorder-7 (GAD-7), a seven-item questionnaire, is among the most commonly used screens for GAD. This screen is completed by the patient, often in the waiting area of the clinic. The maximum score on the GAD-7 is 21, with a response gradient from 0 to 3, according to symptom frequency for each of the seven questions.

In general, a score of 8 or higher should lead to further evaluation for anxiety. The final item on the GAD-7 asks for a subjective evaluation of level of functioning. Although this item is not used for scoring, it is useful for following a response to treatment over time.[12,13]

Another general method to screen patients for GAD is simply to ask, "How often do you worry too much about minor matters?"

M.P. has no specific findings on a physical exam, scores a 12 on the GAD-7, and says, "I guess I have always been a worrier. It runs in my family." When asked more about substance use, she notes that she had been using marijuana for sleep for several years but stopped six months ago when her child started to notice this habit. She then tried a glass of wine at night, but still has sleep problems, stating, "I think if I could sleep, I would probably feel better during the day." She does not endorse symptoms of depression, has not experienced specific panic episodes, and enjoys socializing with a small group of coworkers. She had not connected the sleep problem with her tendency to worry but is open to considering a relationship.

Treatment

Guidelines for the prevention and treatment of anxiety disorders, and GAD in particular, are converging on a "stepped care" model, currently recommended by the United Kingdom's National Institute for Health and Clinical Excellence.

The principle of this model is to conserve mental health resources by starting with the least intensive intervention for mild symptoms and only progressing to further treatment if clinically indicated.

Most stepped care models for GAD start with "watchful waiting," including frequent re-evaluation and self-monitoring while improving lifestyle factors (exercise and diet, for example) that are affecting symptoms.

If there is no clinical improvement, the next step typically is a referral to a self-help group or internet-based cognitive behavioral psychotherapy (CBT). If there still is an inadequate response, psychopharmaceuticals and/or more intensive psychotherapy — in part, depending on patient preference — are recommended.

The final step in the sequence, if there remains a poor response, is referral to a specialist.[14]

Medication and/or Psychotherapy

The literature is mixed regarding the relative efficacy of psychopharmacological vs. psychotherapeutic treatments in GAD; level of functional impairment, factors such as age and comorbidities, and methodological variations of relevant studies complicate drawing firm conclusions from meta-analysis.[7-9,11]

Multiple studies show that psychotherapy, specifically CBT (compared with patients on a wait list as a control group), is effective for treatment of GAD and that medication, specifically SSRIs or serotonin-norepinephrine reuptake inhibitors (SNRIs), is more effective than placebo in the treatment of GAD. Recent investigations suggest a combination of these modalities is more efficacious than either intervention alone, with a larger effect size and better overall outcomes.[7-9,11]

In practice, patient preference and treatment affordability and availability often determine treatment modality. Many patients report an initial sense of relief after hearing from a provider that there is effective treatment for the symptoms of GAD. Involving the patient in decision-making assists in strengthening a sense of control and often is critical to patient engagement and treatment compliance.[8,9,11,15]

Psychotherapy

CBT is a type of talk therapy that generally involves specific mental exercises (introduced during sessions and practiced at home) designed to recognize and change dysfunctional thinking patterns and unhelpful behaviors. CBT is based on moving forward and emphasizes developing effective coping skills. Multiple large-scale trials have confirmed the efficacy for treatment of GAD using this technique.[15]

Access to high-quality CBT is a major stumbling block to use of this treatment. However, a recent study demonstrated significant positive results with decreased worry and overall symptom reduction for both clinician-guided and self-guided remote therapy at 24-month follow-up in patients with GAD. Although further studies are needed to confirm

these findings, this early study may have significant implications for the future treatment direction for GAD.[15,16]

Medication

First-line medications used in the treatment of GAD are SSRIs, followed by SNRIs. Large clinical trials point to the effectiveness of the SSRIs paroxetine, escitalopram, and sertraline, and the SNRIs venlafaxine and duloxetine. Table 1 displays typical dose ranges.[11,15]

When using these agents for the treatment of anxiety, it is recommended to start at a low dose to avoid jitteriness. Proceed with frequent monitoring and slow upward adjustment, while reminding the patient that full clinical response may take four to six weeks.[11,15]

Typically, SSRIs and SNRIs are well tolerated. However, serious side effects include emergence of suicidal thinking (especially in teens and young adults); inform patients to monitor thoughts and report any unusual thought patterns.

Use these medications with caution in elderly patients because of the possibility of gastrointestinal bleeds, syndrome of inappropriate antidiuretic hormone secretion, and falls. Additionally, let patients know there is a potential for decreased libido and sexual side effects associated with these agents.[11,15]

When response is incomplete, or a first-line agent is unable to be tolerated, there are several alternative treatment strategies. Buspirone is an anti-anxiety agent that may take up to six weeks to show a response. Typically, this agent is taken on a twice-daily schedule but it can be started at 5 mg three times a day. This medication usually is combined with an SSRI or SNRI and has no potential for abuse or dependence.[17]

A 2010 Cochrane review of the antihistamine hydroxyzine found this agent (dosed from 50 mg to 200 mg daily) is more effective in reducing anxiety than placebo, but a lack of robust studies and bias in studies are barriers to recommending first-line use of hydroxyzine for GAD.[18]

Quetiapine is a sedating atypical antipsychotic that may be used alone or in combination with a first-line medication for GAD. Side effects include sedation, significant weight gain, and the potential for metabolic syndrome.[15,19]

Tricyclic antidepressants (TCA) may be used as an alternative treatment when other options fail or there are specific medical contraindications to first-line agents. TCAs are antidepressants burdened with anticholinergic and antihistaminic side effects. Use very cautiously in elderly patients and be aware of the potential for lethality in overdose.[19]

Gamma aminobutyric acid agonists (GABA-A) include benzodiazepines and some anticonvulsants with GABAergic properties, including pregabalin and gabapentin.[15,19]

Pregabalin is approved in Europe (but not in the United States) for treatment of GAD, is administered in divided doses from up to 600 mg per day, and seems to have a one- to two-week lag period before evidence of clinical response. Although there are limited studies validating the use of pregabalin in GAD, some appear promising. Pregabalin is a Schedule V (controlled substance with low potential for abuse) drug in the United States.[20]

Gabapentin also is used off-label for anxiety, but research evidence supporting this is extremely limited.[20]

Benzodiazepines are commonly prescribed sedative-hypnotic agents and are acutely effective in reducing the somatic symptoms associated with GAD.

However, the potential of abuse, dependence, and withdrawal, and the lack of long-term efficacy, make benzodiazepines a poor choice for most patients with GAD. It is recommended to use this class of medication only for patients presenting with severe, disabling anxiety and/or insomnia, to monitor use carefully, and to overlap with a first-line treatment (such as an SSRI) and/or buspirone. Plan to gradually taper the benzodiazepine over a few weeks, while giving the other agent time to show clinical efficacy.

The use of psychotherapy over this period may be particularly helpful in addressing lifestyle issues and supporting a transition off the benzodiazepine.[15,19,20]

M.P. is open to the idea that anxiety may play a role in her presenting symptoms. She is agreeable to obtaining screening labs to rule out other etiologies and is more interested in a CBT program than starting medication, especially since she is aware this is covered by her Employee Assistance Program (EAP) and there are online options. She agrees to stop substance use and focus on sleep in her CBT program. She is interested in coming back in a few weeks for follow-up, will track her symptoms, and may consider medication when she returns if clinical need remains. She states, "Just having a diagnosis makes me feel better already and gives me some hope!"

Clinical Pearls for Generalized Anxiety Disorder

- GAD is the most common of the anxiety disorders presenting to PCPs.
- It has chronic and persistent symptoms.
- It often presents with somatic symptoms.
- The highest prevalence in middle-aged females (widowed or divorced).
- Treatment is aimed toward areas of functional impairment.
- CBT has established evidence of efficacy.
- SSRIs or SNRIs are used for first-line medication: start low.
- There is limited use for benzodiazepines.

Panic Disorder

L.G., a 22-year-old, unmarried graduate student, is a referral after he presented to the emergency room last month with acute onset severe chest pain, palpitations, dizziness, and a choking sensation. "I thought I was dying," he says. An electrocardiogram in the emergency room was without abnormalities, his blood work (including a toxicology screen) was unremarkable, and his symptoms responded to 1 mg intravenous lorazepam within minutes. He tells you this was his most severe episode, but that he has had similar weekly experiences since moving to begin graduate school about one year ago. "I like it here," he

Table 1. SSRI/SNRI Recommended Doses for GAD, PD, and SAnD[2,11,24]

Medication	Drug Class	Dose Range	First-Line?	FDA-Approved for GAD?	FDA-Approved for PD?	FDA-Approved for SAnD?
Paroxetine (Paxil, Pexeva)	SSRI	10 mg to 50 mg (start low; advise against sudden discontinuation)	Yes	Yes	Yes	Yes
Sertraline (Zoloft)	SSRI	50 mg to 200 mg (start as low as 25 mg)	Yes	No*	Yes	Yes
Escitalopram (Lexapro)	SSRI	5 mg to 20 mg (start low)	Yes	Yes	No	No
Citalopram (Celexa)	SSRI	10 mg to 40 mg (start at 10 mg)	Yes	No	No	No
Fluoxetine (Prozac)	SSRI	10 mg to 60 mg (start low; long half-life: low potential for withdrawal)	Yes	No	Yes	No
Fluvoxamine CR (Luvox CR)	SSRI	100 mg to 300 mg per day, divided doses	Yes	No	No	Yes
Duloxetine (Cymbalta, Drizalma)	SNRI	60 mg to 120 mg (start at 30 mg)	Yes	Yes	No	No
Venlafaxine XR (Effexor XR)	SNRI	75 mg to 225 mg (start at 37.5 mg)	Yes	Yes	Yes	Yes

SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor; GAD: generalized anxiety disorder; PD: panic disorder; SAnD: social anxiety disorder; FDA: Food and Drug Administration

*Supported by large clinical trials

notes, "but I do not like being so far from my family." He is considering dropping out of his program, stating "I can't keep going on like this, wondering if it will happen again."

PD is characterized by unexpected panic attacks, associated with at least four of the following symptoms:

- palpitations, pounding heart, or rapid heart rate;
- sweating;
- trembling/shaking;
- feeling of choking;
- chest pain or discomfort;
- nausea or abdominal distress;
- feeling dizzy/unsteady/lightheaded;
- sensations of chills or heat flashes;
- numbness or tingling;
- feelings of unreality (derealization) or feeling detached (depersonalization);
- fear of losing control or "going crazy."

In addition, at least one of the panic attacks has been followed by one month or more of persistent fear of a recurrent panic episode and/or a maladaptive change in behavior related to the panic episodes.

Finally, the panic episode is not better explained by another mental disorder, a physical condition, or substance use.[21]

Often, a first panic episode will occur in response to an acute stressor, but subsequent events are spontaneous and without clear precipitants. Older diagnostic criteria linked PD to agoraphobia (irrational fear of public spaces where one might feel trapped). However, although about 25% of patients with PD develop agoraphobia as a result of avoiding situations that may induce panic, these are thought to be two separate diagnoses with distinct patterns of onset and course.[21,22]

The natural course of PD is episodic and relapsing, with recent studies indicating about one-third of patients will experience a recurrence within one year of remission.[22]

Epidemiology

The lifetime prevalence of PD is 5%, with occurrence in females about twice as often as in males. The prevalence in primary care is slightly higher at 6% (but lower than the up to 14.8% prevalence of GAD in this setting). The mean age of onset is younger than for GAD and typically occurs in early adulthood. Notably, PD tends to be comorbid with other disorders of mental health, including the other anxiety disorders, depressive disorders, and substance abuse.[22]

Genetic studies suggest that 30% to 40% of disease emergence is attributable to hereditary factors, while environment accounts for the remainder. Research suggests that early

experiences with abuse, medical illness, or other factors that affect attachment may cause a psychologic vulnerability that can be triggered by events later in life. The theory is that full expression of PD occurs in those individuals with both psychologic and biologic or genetic vulnerability.[22,23]

Differential Diagnosis and Screening Tools

A careful history and physical examination with attention paid to distinguishing features of PD is helpful in determining if symptoms can best be explained by a different mental illness, such as post-traumatic stress disorder (PTSD) or an adjustment disorder with anxiety. The key feature of PD is unexpected, recurrent panic episodes. Although panic attacks may occur in the setting of other disorders of mental health, if the episodes are predictable and/or in response to an identified stressor, the diagnosis is unlikely to be PD.[22,24]

Note that 80% to 90% of patients with PD have comorbidities, and that the majority of these involve another mental illness. In other words, a patient may have symptoms of both GAD and PD or PD and major depression. Understanding how to differentiate these allows more precise targeting of treatment.[22,24]

Medical problems, such as thyroid dysfunction (hypo or hyper), pheochromocytoma, mitral valve prolapse, vestibular nerve disease, and substance-induced panic, all should be considered and ruled out before diagnosis. Any patients with cardiac symptoms will need an appropriate cardiac workup.[22,24]

Screens specific for PD are not used as commonly in the PCP office as are general screens for anxiety, such as the GAD-7. Unfortunately, the GAD-7 does not measure PD, since there are no questions pertaining specifically to panic on this screen. A screen such as the Panic Disorder Severity Scale (PDSS) is a seven-item validated tool to measure and track the degree of impairment in individuals with PD. Questions on this survey are related directly to intensity and frequency of panic episodes and associated behaviors. The PDSS is designed to be self-administered; patients can complete the questionnaire in a waiting area or may choose to download a free app that calculates the score and allows an individual to quantitate progress during treatment. The maximum score is 28, with higher scores indicating more self-assessed impairment from symptoms related to PD.[25]

L.G. scores 9 on the GAD-7 (mild to moderate anxiety) but a 13 on the PDSS, indicating significant impairment from panic. He is interested in a prescription for lorazepam, since it was helpful for him acutely in the emergency room. He denies any use of drugs and rarely drinks. He notes that sleep is becoming a problem — he finds himself worrying that he may have a panic episode when he is alone at night. His weight has been dropping ("I don't want to eat because I may have a panic attack and choke"), and when asked about suicidal thoughts, he notes, "I would not kill myself, but I just find myself wishing life was over already. Every day feels too hard."

Treatment

The initial treatment strategy for PD is aimed at interrupting the cycle of acute panic episodes. In this regard, and because of the highly episodic nature of panic attacks, treatment is very different than for the other disorders of anxiety, most of which are characterized by chronic and persistent symptoms.[22,24]

As with the other disorders of anxiety, a combination of CBT and psychopharmacological interventions appears to have the largest effect on symptom reduction as compared to either intervention in isolation. Treatment choice is determined by patient preference, availability of interventions, and affordability. The PCP is instrumental in providing information allowing each patient to make informed decisions.[22,24]

Acute Panic

A benzodiazepine is the agent of choice for acute panic and for stopping progression. These agents need to be used with caution and with proper patient education regarding dependence, tolerance, cognitive dulling, the potential for rebound anxiety, and withdrawal. In general, the use of benzodiazepines in PD is best reserved for the acute phase, with plans to phase out after allowing an SSRI or SNRI to gain full clinical strength. Ideally, a two- to four-week course of these agents while the SSRI or SNRI is initiated, followed by a gradual taper, is recommended.[26,27]

There are several choices of benzodiazepines. Often, clonazepam is chosen for PD because of a relatively long half-life and the low potential for rebound anxiety. In the elderly, alprazolam may be preferred because of a short half-life and the lack of active metabolites. In all patients, advise of the potential for sedation and cognitive impairment associated with this class of drugs. Warn that operating machinery and driving are not recommended after use.[26-28]

In addition, it is not recommended to use this class of medication in patients with a history of drug or alcohol abuse.

Although there is no evidence from clinical trials, hydroxyzine (typically 25 mg to 50 mg taken as needed for acute panic) is Food and Drug Administration-approved for anxiety in general and often is used in this population as an alternative to benzodiazepines. Other options are buspirone and risperidone.[26-28]

There is controversy in the literature regarding the long-term use of benzodiazepines for PD, with some evidence that chronic use may be required to prevent attacks. On the other hand, there also is evidence that benzodiazepine use is associated with poorer outcomes from CBT.[26-28]

Long-Term Treatment

As noted earlier, starting an SSRI or SNRI in conjunction with a benzodiazepine often is an effective treatment strategy in PD. Large-scale efficacy studies confirming usefulness in PD are available for sertraline, paroxetine, and venlafaxine; there are suggestive positive results from studies of the other SSRIs as well. As with all anxiety disorders, starting any of these drugs at a low dose is essential to prevent the agitation and increased anxiety associated with starting at higher doses. A clinical response may be seen in a few weeks but may not be fully expressed

until two to three months. Tracking symptoms and the frequency of panic episodes is useful to gauge clinical improvement or response over an extended time.[22,24]

See Table 1 for recommended dosages of SSRIs/SNRIs. Typically, these medications can be discontinued gradually after one to two years of treatment. However, building in strategies to recognize and control panic is central to maintaining remission.[22,24]

If a patient is unable to tolerate or does not respond to an SSRI or SNRI, the first step typically is to switch to another agent within this category. Second-line agents include TCAs (start low and go slow with these also), with reasonable evidence of efficacy for imipramine in particular. Nortriptyline in very low doses (10 mg to 30 mg) may be a better fit for elderly patients because of a lower risk of cardiac side effects and less of a potential for orthostatic hypotension when compared with other medications in this class. The limiting factor for TCAs in general is significant adverse side effects at therapeutic doses, including dizziness, weight gain, insomnia, and headache. These should be avoided in patients with narrow angle glaucoma and significant benign prostatic hypertrophy.[22,24,28]

There is very limited data on the use of atypical antipsychotics, such as quetiapine or risperidone, in PD. High-quality studies are needed to draw conclusions regarding use of these agents. Other medications sometimes used off-label for refractory PD are clonidine, valproic acid, and pindolol, with anecdotal evidence to support the use of each agent.[29]

Psychotherapy

About 30% of patients with PD prefer nonpharmaceutical interventions to address symptoms. CBT shows efficacy in treatment of this disorder.

Studies are mixed in head-to-head comparisons of treatments (CBT vs. pharmaceutical agents). A large meta-analysis in 2015 found a greater effect on symptom reduction from medication alone than from CBT. However, there are limitations to this work and conclusions, making generalization difficult.

The jury still is out regarding any one best intervention for PD; it may be that individualized treatment with options to combine modalities to precisely target impairing symptoms is key.[30,31]

The goal of CBT in PD is to teach alternative ways of reacting to the feelings that accompany or presage a panic attack. Given that there are physical sensations linked to anxiety during a panic episode, individuals can learn to use these sensations as cues and react in a new way.[30-32] Traditional CBT involves six to 12 weekly sessions. Recent studies evaluating intensive short-term therapy and exploring remote delivery of CBT show promise. However, it is notable that about 50% of patients are unable to obtain full remission with CBT alone.[31-33]

Current studies investigating several variants of CBT (panic-focused CBT and acceptance and commitment CBT) aim toward identifying patient populations most likely to respond to each distinct psychotherapeutic treatment modality.[32,33]

*L.G. remains interested in pharmaceutical options for his symptoms, saying, "I don't think therapy will help — I think talking about panic will make it worse!" He is agreeable to starting sertraline 25 mg daily for the first week and clonazepam 0.50 mg twice daily and is given a limited prescription for both. He understands that he will need frequent reassessment over the next several weeks to manage dose changes and that the goal is to increase the sertraline and slowly cut back on clonazepam. He is interested in tracking the frequency and intensity of panic attacks with a free app and documenting the results via secure email in the electronic medical record. Although he is resistant to CBT, he likes the idea of obtaining control over his symptoms and is willing to purchase a workbook such as "*Mastery of Your Anxiety and Panic*" to identify behavioral strategies that could assist with self-regulation.*

Clinical Pearls for Panic Disorder

- It is the second most common anxiety disorder presenting to PCP (after GAD).
- It typically presents during adolescence or early adulthood.
- Episodic and recurrent panic episodes are associated with somatic symptoms and often a sensation of being unable to breathe.
- Treatment is biphasic and initially aimed at acute relief.
- Benzodiazepines may be used with caution during acute treatment while waiting for clinical effect of first-line agents (SSRIs or SNRIs).
- Start low and go slow for SSRIs, SNRIs, or TCAs to avoid jitteriness and agitation seen with starting at higher doses.
- The efficacy of CBT is established; be familiar with options for CBT and variations of this therapeutic technique to provide patients with referral information.

Social Anxiety Disorder

J.L., a 35-year-old single professional who is being treated for GAD (escitalopram 10 mg daily; taken inconsistently), comes in for follow-up. She states, "I know 2020 was a hard year for most people, but I have never felt better!" She explains that the reduced in-person expectations for work and social situations lessened her anxiety enough that she stopped her medication. "I am more productive than ever. I exercise and read in my spare time, I stopped all alcohol and caffeine, and I finally am sleeping well," she notes. "However," she adds, "now I may have to return to in-person work and that is why I am here today. Can you give me a letter certifying that I should continue remote work because of my anxiety?"

Social anxiety disorder (SAnD) is characterized by the manifestation of severe symptoms of anxiety when faced with a need for interaction or socialization. The DSM-5 criteria for SAnD include:

- "marked fear or anxiety" when an individual is exposed to possible scrutiny by others;
- fears that the individual will "act in a way or show anxiety symptoms" that others will evaluate negatively;
- most any situation where there is social anxiety provokes anxiety response — often socialization is avoided;

• anxiety that is out of proportion to any stimulus and has been occurring for more than six months;
• an anxiety response that causes dysfunction or significant distress;
• symptoms that are not better explained by the use of a substance, another disorder of mental health, or a medical condition.[34]

SAnD naturally runs a chronic and unremitting course. SAnD can be viewed on a continuum from shyness to seasonal affective disorder, with functional impairment as a critical distinguishing factor.[35]

Epidemiology

This common disorder has a lifetime prevalence of 8% to 12% in the United States. In 2017, the World Health Organization (WHO) conducted an international epidemiologic survey regarding this condition. Data from more than 140,000 respondents confirmed that SAnD is a fairly common condition worldwide, with an overall lifetime prevalence of 4.0% and with higher prevalence in higher-income countries.[36]

These numbers may be misleading, since social anxiety per se typically is not the impetus for a visit to a provider. Often, the diagnosis is made after many years of progressive isolation, or when the status quo is unable to be maintained.[36,37]

Typically, signs and symptoms emerge in early adolescence (mean age of onset of 14.1 years). Girls are affected more commonly than boys. There is a high chance of comorbid mood and depressive disorders. In addition, substance abuse is high in those with untreated SAnD, with up to 48% of patients with SAnD developing alcohol abuse during a lifetime.[35-37]

Although there is no known inheritance pattern, parental depression or anxiety is a risk factor for the development of SAnD in offspring. Other risk factors include parental overprotection and child abuse.

Causation has not been established and research is continuing; it may be that SAnD is similar to the other disorders of anxiety and that emergence is contingent on both biologic predisposition and environmental/social factors.[35-37]

Differential Diagnosis and Screening Tools

The differential involves mainly other disorders of mental health, including depressive disorder (with social withdrawal), avoidant personality disorder, schizoid personality disorder, and prodromal or early signs of schizophrenia with social avoidance or paranoia.[35,37]

A careful history, including the age of onset and association with any other symptoms, can help distinguish these diagnoses. It is useful to keep in mind the likelihood of comorbidity, especially if symptoms have been persistent over years.[35,37]

There are screening tools to assess the degree of impairment from symptoms of SAnD. Perhaps the most widely used and well-validated screening tool is the Liebowitz Social Anxiety Scale (LSAS). This 24-item, clinician-administered questionnaire was developed by Michael Liebowitz in 1987. Since then, a self-administered version of the LSAS has been introduced. The intensity of thoughts and actions (ranging from fear to avoidance) during recent social situations is rated on a scale from 0 to 4.[38] Although this scale is not diagnostic, results can guide the clinician toward appropriate interview questions to make an accurate diagnosis.[38]

The Social Anxiety Session Change Index is a different type of tool used in the treatment of SAnD. This four-item self-report is used to measure the change in symptoms during treatment and record progress.[39]

J.L. scores a 64 on the LSAS, indicating the likelihood of a moderate–marked degree of social anxiety affecting her daily life. However, her GAD-7 score is fairly benign at 6. She explains, "The first test (LSAS) asks me if I feel uncomfortable and avoid specific situations. The second test (GAD-7) asks if I worry a lot and if I can relax. Since I am able to avoid most of the places where I feel anxious, I feel pretty good most of the time. That is why I stopped my medicine!" When asked if she would consider a treatment protocol for SAnD rather than a letter certifying a need to continue remote work, she says, "Could we consider doing both?"

Treatment

As with the other disorders of anxiety discussed earlier, there are evidence-based psychopharmacologic and psychotherapeutic interventions available for SAnD. The evidence is stronger toward CBT, with psychopharmacology reserved for those who refuse therapy.

CBT generally is conducted in 12 to 16 weekly hour-long sessions, with response often seen by week 6. The specific psychotherapeutic focus for SAnD includes a combination of social skills training, exposure therapy, and recognizing and correcting cognitive distortions.[40]

The 2020 (United Kingdom) National Institute for Health and Care Excellence (NICE) guidelines strongly support CBT as the first-line treatment intervention for SAnD, citing concerns regarding short- and long-term side effects from pharmaceutical agents, and a paucity of evidence regarding long-term efficacy.

These guidelines take into account the difficulty of assessing the effect of any treatment in SAnD — psychopharmaceutic or therapeutic. That is, any repetitive social interaction (including a provider appointment) may be effective in helping an individual with SAnD function based on repeated exposure to social interaction alone.[41]

Even keeping this caveat in mind, there is strong evidence supporting CBT in the treatment of SAnD, in prevention of functional deterioration and in supporting remission. However, even with CBT, response rates hover around 70%.

There is little evidence that a combination of medication and CBT is any more effective than either intervention alone. Research looking at the likelihood of response to a specific intervention has the potential to clarify appropriate treatment.[40,41]

The FDA-approved medications for SAnD are paroxetine, sertraline, extended-release venlafaxine, and extended-release fluvoxamine. Table 1 provides dosages. A 2017 Cochrane

review points to low to moderate evidence suggesting that 50% to 75% of patients with SAnD will respond to medication alone, that initial response may be delayed until week 12, and that the risk of relapse is high if medication is discontinued within the first five months of treatment. Clinicians are advised to recommend medication use for at least one year from symptom remission and then to taper the dose gradually, with frequent reassessment.[42-44]

Second-line agents include a limited role for benzodiazepines and the potential for propranolol. This beta-blocker may be useful for specific forms of SAnD, especially related to performance and especially if tremor is part of a target symptom. Typically, 10 mg taken one hour before an anticipated anxiety-provoking event aids with symptom control.[44]

There is limited evidence for a role for the atypical antipsychotics in SAnD, but some promising emerging studies are looking at gabapentin and pregabalin for use in this disorder when other options have failed.[44]

J.L. is intrigued with a social anxiety diagnosis, saying, "I never thought about my anxiety in that way." She says she was inconsistent with medication in the past because "it never seemed to help." She is willing to try an SNRI rather than an SSRI (venlafaxine XR starting at 37.5 mg), and have frequent rechecks to adjust the dose up. She may be willing to consider CBT. J.L. and her PCP agree that the PCP will write a note recommending continuation of remote work, but will document a limited time frame as her treatment for SAnD proceeds and, they hope, her symptoms begin to remit.

Clinical Pearls for Social Anxiety Disorder

- SAnD is a common disorder, but it is not often the focus of a visit to PCP.
- It emerges in early adolescence and more often affects girls vs. boys.
- It is highly comorbid with depression, mood disorders, and/or substance abuse.
- The response rate is 70% with SSRIs/SNRIs and with CBT focused on social skills and exposure training.

Cannabinoids in the Treatment of Anxiety Disorders

Cannabinoids include at least 66 compounds found in the cannabis plant. Perhaps the two most well-known of these compounds are tetrahydrocannabinol (THC) — the main psychoactive compound — and cannabidiol (CBD). Although popular sentiment may lean toward using these substances for relief of anxiety, high-quality medical studies regarding the treatment of anxiety with cannabinoids are lacking. There is some limited evidence for efficacy of CBD in the treatment of GAD, PD, and SAnD and no indication that CBD increases anxiety. However, there is evidence that THC may worsen anxiety, especially as the dose is increased.[44,45]

Kava

The data indicate that controlled trials lag behind interest in the use of herbal preparations for anxiety. Kava, an extract derived from the roots of a South Pacific plant, is perhaps the most studied herbal preparation for anxiety and currently is used for anxiety relief in many parts of the world. This compound appears to modulate GABA-A receptors in a manner similar to benzodiazepines. A 2003 Cochrane meta-analysis noted beneficial effects of kava on anxiety, while more recent investigations are less positive and note insufficient evidence to recommend kava in the treatment of anxiety. Kava is linked to a potential for liver toxicity; this serious side effect is noted in all of the studies.[44]

Physical Activity

A recent meta-analysis found that high-intensity exercise may have a beneficial role in alleviating symptoms of anxiety, particularly in patients with symptoms below the threshold of a DSM-5 diagnosis. In addition, there appears to be an inverse association between the level of physical activity and anxiety disorder symptoms, but a causative relationship is not established. The effect of regular exercise on symptoms of anxiety in patients with GAD, PD, or SAnD warrant further investigation. However, there is no evidence of a negative effect on anxiety from this health-promoting intervention.[46,47]

A Note About Suicide

Patients with anxiety and comorbid substance abuse and/or major depression are at higher risk for suicide attempts. A 2017 study revealed close to one-half of adults completing suicide had contact with a PCP within a month before death; 80% had contact in the year preceding suicide.

Patients may not express thoughts about suicide directly, but often will respond to open-ended queries. Asking patients with anxiety, especially patients with comorbid substance abuse or affective illness, about suicidal thoughts, plans, or intentions can open a discussion.[48]

Refer patients with high risk factors and suicidal intention to a specialist. There is growing evidence that collaborative care models, with a team led by the PCP and containing mental health professionals, leads to more effective care for complex, high-risk patients with anxiety. Telemedicine consultation also has shown evidence of efficacy and can assist in bringing specialty care to previously underserved communities. Regardless of the manner of delivery, it is useful for the PCP to have a strong working relationship with professionals in the mental health community.[49]

Take-Home Points

1. Anxiety disorders are highly comorbid; when patients present with a disorder of anxiety, assess carefully for substance abuse, mood/affective illness, and/or another disorder of anxiety.
2. Consider anxiety when patients present with insomnia, headache, nonspecific gastrointestinal complaints, or cognitive concerns.
3. Conduct a careful history and physical examination; consider and rule out medical etiologies.
4. Determine if anxiety disorder is chronic or episodic.
5. Assess for suicide risk (especially if comorbid with depression or substance abuse).

6. Assess for key symptoms of panic and for avoidant behaviors.

7. Offer patients targeted psychotherapeutic interventions and psychopharmaceuticals; encourage patients to be active participants in treatment decisions.

8. Consider SSRIs or SNRIs for long-term management of anxiety; for acute management of PD, consider benzodiazepines, hydroxyzine, and/or buspirone.

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CME Questions

1. Which of the following is true of patients with generalized anxiety disorder (GAD)?
   a. They often present with panic and socially avoidant behavior.
   b. They often present with vague somatic symptoms and functional deterioration.
   c. They often present with numbness, tingling, and falls in older adults.
   d. They often present as high achievers with fear of failure.
2. Which of the following is true of patients with panic disorder (PD)?
   a. They often present with episodic panic attacks and fear of dying.
   b. They often present with hallucinations and agitation.
   c. They often present with episodic panic attacks associated with electrocardiogram abnormalities.
   d. They often present without comorbidities.
3. Which of the following is true of patients with social anxiety disorder (SAnD)?
   a. They often present as older adults with new onset socially avoidant behavior.
   b. They often present with episodic panic, insomnia, and poor appetite.
   c. They often present with multiple, vague somatic complaints.
   d. They often present with socially avoidant behavior for years.
4. Which of the following is correct regarding initial treatment for GAD?
   a. It includes benzodiazepines, cognitive behavioral therapy (CBT), and atypical antipsychotics.
   b. It includes selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) starting at a low dose to prevent initial jitteriness.
   c. It includes SSRIs or SNRIs starting at a high dose to obtain rapid relief.
   d. It includes a moderate-dose SSRI, counseling, and exercise.
5. Which of the following is correct regarding the initial treatment for PD?
   a. It often includes benzodiazepines, counseling, and buspirone.
   b. It often includes exposure therapy, reassurance, and propranolol.
   c. It often includes CBT, benzodiazepines, and SSRIs/SNRIs.
   d. It often includes hospitalization and intravenous benzodiazepines, then starting an SSRI/SNRI after the acute phase.
6. Which of the following is correct regarding the initial treatment for SAnD?
   a. It includes benzodiazepines, CBT, and a high-dose SSRI/SNRI.
   b. It includes CBT with social skills training and/or a low-dose SSRI/SNRI.
   c. It includes pregabalin, CBT, and a high-dose SSRI/SNRI.
   d. It includes benzodiazepines and the avoidance of situations causing anxiety.
7. Which of the following are common comorbidities with anxiety disorders?
   a. Mood and affective illness, substance use disorders, and other anxiety disorders
   b. Cardiovascular disease, diabetes, and mood disorder
   c. Schizophrenia, affective illness, and substance use disorder
   d. Cardiovascular disease, diabetes, and substance use disorder
8. Which of the following is true regarding the use of tricyclic antidepressants for the treatment of anxiety?
   a. They often are overlooked despite being well tolerated by most patients.
   b. They are a cheaper and safer alternative to SSRIs/SNRIs.
   c. They have limited efficacy in most anxiety disorders.
   d. They should be avoided in patients with narrow angle glaucoma, benign prostatic hyperplasia, and acute suicidal thoughts.

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