Current Diagnosis and Treatment of Anxiety Disorders

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ABSTRACT

Anxiety disorders are the most prevalent mental health conditions. Although they are less visible than schizophrenia, depression, and bipolar disorder, they can be just as disabling. The diagnoses of anxiety disorders are being continuously revised. Both dimensional and structural diagnoses have been used in clinical treatment and research, and both methods have been proposed for the new classification in the *Diagnostic and Statistical Manual of Mental Disorders IV (DSM-5)*. However, each of these approaches has limitations. More recently, the emphasis in diagnosis has focused on neuroimaging and genetic research. This approach is based partly on the need for a more comprehensive understanding of how biology, stress, and genetics interact to shape the symptoms of anxiety.

Anxiety disorders can be effectively treated with psychopharmacological and cognitive–behavioral interventions. These interventions have different symptom targets; thus, logical combinations of these strategies need to be further studied in order to improve future outcomes. New developments are forthcoming in the field of alternative strategies for managing anxiety and for treatment-resistant cases. Additional treatment enhancements should include the development of algorithms that can be easily used in primary care and with greater focus on managing functional impairment in patients with anxiety.

INTRODUCTION

Anxiety disorders are present in up to 13.3% of individuals in the U.S. and constitute the most prevalent subgroup of mental disorders.[1] The extent of their prevalence was first revealed in the Epidemiological Catchments Area study about 26 years ago.[2] Despite their widespread prevalence, these disorders have not received the same recognition as other major syndromes such as mood and psychotic disorders; in addition, the primary care physician is usually the principal assessor and treatment provider.[3,4] As a result of this management environment, anxiety disorders can be said to account for decreased productivity, increased morbidity and mortality rates, and the growth of alcohol and drug abuse in a large segment of the population.[5–7]

Anxiety disorders currently included in the *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed., text revision *(DSM IV-TR)* are listed in Table 1.[8]

Advances in anxiety research over the previous decade are likely to be reflected in modifications of diagnostic criteria in the upcoming *DSM-5*,[9] planned for publication in May 2013. For instance, post-traumatic stress disorder (PTSD) and obsessive–compulsive disorder (OCD) have been reclassified in the separate domains of Trauma and Stressor Related Disorders and Obsessive–Compulsive and Related Disorders, respectively.[10,11]

In this article, we review the challenges to the diagnosis of anxiety disorders, provide a model that explains how anxiety symptoms occur and change over time, highlight the neurotransmitter systems affected by these disorders, and discuss the roles and relative efficacy of pharmacological and non-pharmacological interventions.

DIAGNOSTIC DILEMMAS

Within the past 10 years or so, epidemiological data have been used in the attempt to refine the boundaries of diagnostic categories of anxiety disorders. The results of this approach have been progressively reflected from *DSM III* to *IIIR* to *DSM IV-TR* (see Table 1) and, finally, to *DSM-5*. However, this effort has been hampered by the extensive presence of comorbidities in patients with anxiety, as revealed by the National Comorbidity Survey (NCS).[11] For instance, in patients with some disorders such as generalized anxiety disorder (GAD) and social anxiety disorder (SAD), the presence of comorbidities is a rule rather than the exception.[12] In clinical practice and in research, it is not unusual to find the coexistence of two or more diagnosable conditions in the same patient or at least symptomatic overlap with several subsyndromal states. This is particularly true for symptom overlap between different anxiety disorders, depression, and alcohol and drug abuse.[13]

A related phenomenon is the emergence of different disorders in the same patient over a lifetime. For example, during an initial evaluation, the original diagnosis could be panic disorder that resolves after treatment, and then presents after a few years with symptoms more suitable to a diagnosis of OCD or GAD. Whether this process reflects a primary diathesis or two distinct entities is uncertain.

Another significant problem with the present classification of anxiety disorders is the absence of known etiological factors and of specific treatments for different diagnostic categories. Studying the genetic underpinnings of anxiety disorders using molecular biological techniques has failed to produce a single gene or a cluster of genes implicated as an etiologic factor for

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Table 1 Anxiety Disorders

Panic disorder (PD)
Specifier: with or without agoraphobia
Panic disorder with agoraphobia (AG, PDA)
Social phobia (SP)
Specifier: generalized
Specific phobias (SPP)
Specifier: animal, environmental, blood-injection injury, situational type
Post-traumatic stress disorder (PTSD)
Specifier: acute versus chronic, with delayed onset
Acute stress disorder
Obsessive–compulsive disorder (OCD)
Specifier: with poor insight
Anxiety disorders due to:
Specifier: with generalized anxiety, with panic attacks, with obsessive–compulsive symptoms

any single anxiety disorder, even though some genetic findings exist for OCD and panic disorder.[14,15] Despite a lack of specificity, family and twin studies point to the importance of genetic factors that are possibly shared among various anxiety disorders, depression, and alcohol and drug abuse.[16]

Despite these diagnostic ambiguities, the emergence of efficacious serotonergic medications that cut across a variety of categorical disorders (e.g., mood and anxiety) has led many to suggest that a dimensional model might be more applicable in the study and treatment of these conditions.[17] In this view, the disorder is seen as a complex set of coexisting symptom dimensions (e.g., panic, social awkwardness, and obsessiveness). Each of these dimensions can vary, depending on hypothetical, biological, or genetic factors, which may dictate separate biological or psychological treatment approaches.[9] The usefulness of the dimensional versus the categorical approach remains a highly debatable topic in research and in clinical practice and is one of the bases for the introduction of *DSM-5*.[18,19]

Within psychiatry, similarities between distinct disorders has led to the emergence of the term "spectrum" disorders, a concept initially developed for OCD.[20] This conceptualization was helpful in evaluating similar responses to pharmacological and psychological treatments and has been expanded to consider many other spectra such as social anxiety, panic–agoraphobia, and post-traumatic disorders.[21–23] This approach, although useful, can be overly inclusive and misleading because it sometimes lumps together disorders that have little in common, such as placing pathological gambling and body dysmorphic disorder (BDD) in the same OCD spectrum. So far, few genetic or neurocircuitry investigations have validated this concept.

Dimensional and categorical diagnosis in the *DSM-IV-TR* is usually produced by cross-sectional comparisons of distinct subject samples. However, diagnostic presentations in clinical practice occur in individuals treated sequentially and may therefore be better understood as part of a psychopathological process that unfolds over time. For example, although a patient might meet criteria for OCD purely on the basis of obsessions or compulsions, the latter usually arise later in the disorder as if to counteract the threat and anxiety associated with obsessive thoughts.[24]

Analogous viewpoints can be found in medical disease, with symptoms usually representing a combination of a noxious agent and the body's reaction to its presence. For instance, when the lungs are infected with the harmful organism *Mycobacterium tuberculosis*, they compensate by forming scars around the tissue. In the short run, this may be effective in walling off the infection (and may even elude clinical detection), but the strategy fails when pushed to the extreme, leading to respiratory compromise in some cases.

In recent years, scientists and clinicians have begun to realize that the processes underlying anxiety and fear might be similar among the various disorders. This has resulted in the implementation of uniform treatment regimens in primary care[25] and in the development of the unified theory of anxiety.[26]

THE 'ABC' MODEL OF ANXIETY

Understanding how emotional reactivity, core beliefs, and coping strategies interact in time should lead to more precise diagnoses and better management of anxiety disorders. We recently applied a mathematical model using nonlinear dynamics to describe these processes[27] and further developed this model to cover diagnostic presentations and their underlying processes.[28] The model that we, for simplicity, call the "ABC model of anxiety" could be viewed as an interaction in space and time of *a*larms, *b*eliefs and *c*oping strategies (Figure 1).

Alarms (A) are emotional sensations or physiological reactions to a trigger situation, sensation, or thought. A well-defined set of brain circuits rapidly processes information about the alarm.

The ensuing decision to act is made on the basis of beliefs (B) that rely heavily on previous experiences, personal and cultural background, and the information that is perceived by the sensory organs. Patients with anxiety disorders appear to process information about a supposedly dangerous situation with more focused attention compared with individuals without the disorder.[29] Accurate decision-making regarding beliefs is obscured by a flood of details, which leads to catastrophic thinking and indecision.

This, in turn, leads to coping strategies (C), for example, specific behaviors or mental activity aimed at reducing anxiety and avoiding the perceived "danger." Coping strategies can be considered adaptive or maladaptive, based on their efficacy in reducing the target anxiety. These processes evolve over time, forming a complex picture of a particular anxiety disorder.

As a clinical example, panic disorder may start as an initial devastating panic attack driven by activation of the brain's alarm networks. This event activates circuits that process information about danger and, when coupled with personal beliefs about the event, leads to increased concern about personal health and safety. This in turn leads to a specific attempt to decrease the danger of the situation (e.g., a medical workup that initially calms the fear).

These processes often occur in healthy people who might experience an unpleasant or dangerous situation; in patients with panic disorder, however, a regular medical workup is insufficient to calm them because they require a 100% assurance of "no danger." Because this is impossible to provide, worry and anticipation of another impending attack persist. The patient subsequently increases "safety" coping behaviors such as having repeated medical examinations (seeking reassurance) and having a "safe" person around at all times.

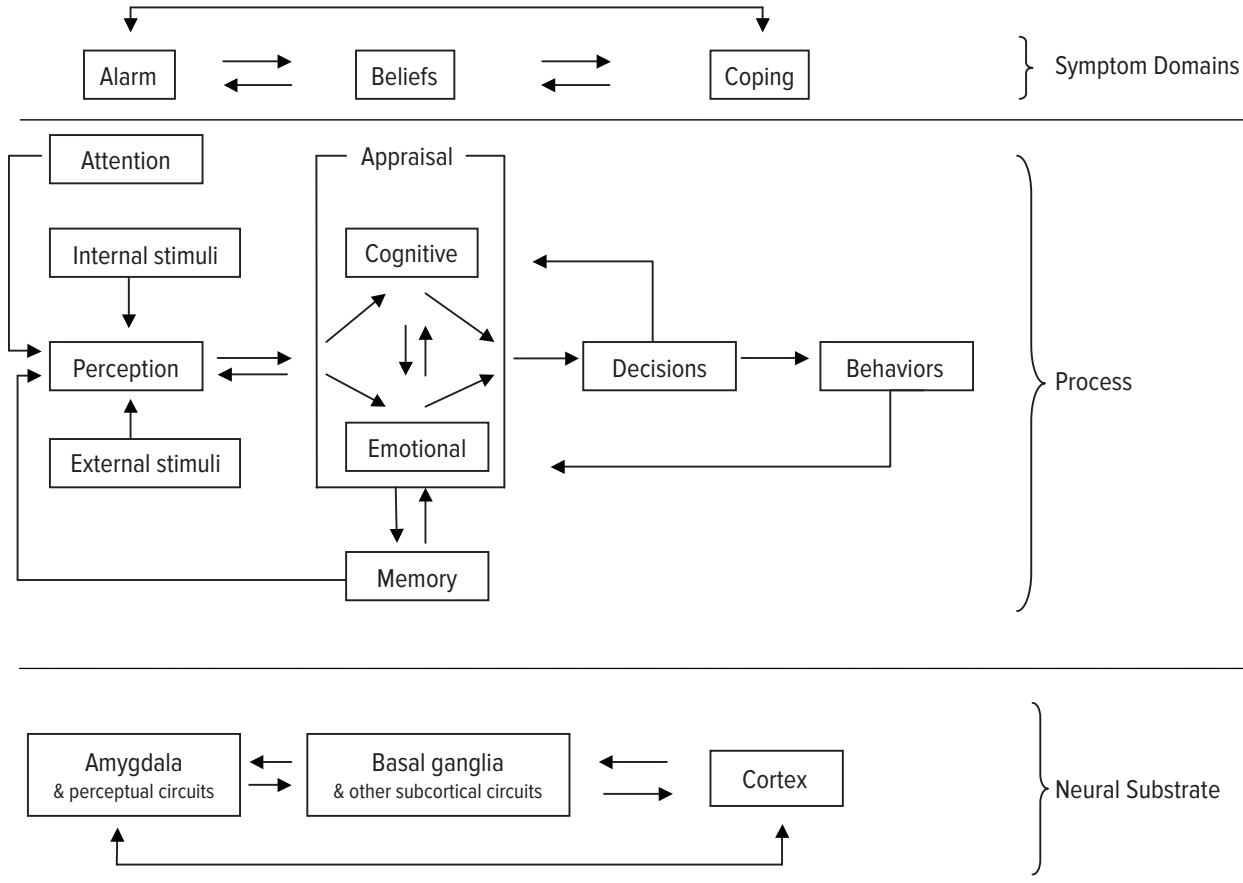


Figure 1 Schematic detailing the "ABC" model of anxiety. In this model, a variety of triggering events can elicit responses at the levels of *A*larm sensations, *B*eliefs, and associated *C*oping (ABC) strategies, including behaviors. Each of these processes originates in discrete brain circuits that are functionally connected. Over time, this perpetuates a vicious circle, shaping the presentation of a variety of anxiety disorders.

Unfortunately, because no absolute safety is to be found, these behaviors become more extensive and chronic in the attempt to alleviate anxiety. The fact that anxiety persists induces more worry and eventually distress, thus perpetuating the vicious circle of the disorder (recurrent panic attacks). If the pattern is uninterrupted, it eventually leads to even more inappropriate coping behavior, such as avoidance of any potential triggers of panic (agoraphobia), and can result in comorbid despair and depression. Most of the anxiety disorders follow this process even though different stages may predominate in different disorders; that is, ritualistic behavior is more characteristic of OCD, and avoidance predominates in social anxiety disorder.

We have found that patients quickly recognize and interpret their symptom patterns within the ABC model. We effectively incorporate this pattern with medication and behavioral techniques, as described in the previous studies.[30] We have also found that conceptualization of clinical cases using the ABC model is particularly helpful in teaching psychiatric residents. Using this model, residents are able to understand and to begin administering cognitive–behavioral therapy (CBT) within relatively few sessions.

Interplay Between Biological and Psychological Factors

In order to treat an anxiety disorder effectively, clinicians should understand how these conditions emerge and which factors are involved in maintaining them. In recent years, we have gained a better understanding of the interplay between genetic, biological, and stress factors that shape the presentation of the disorder, although it is not clear which factors are inherited.

One possibility is that abnormal cognition could be the inherited factor. Cognitive theory assigns a primary importance to abnormal or "catastrophic" cognition as an underlying mechanism of all anxiety disorders. Most cognitive strategies for treatment and research were developed in earlier years.

The ABC model focuses on the interaction of information processing and emotional and cognitive processes that are controlled by overlapping circuits and compete for the same brain resources.[27]

In most anxiety disorders, patients usually process fear-inducing information in excessive detail that overwhelms their ability to appraise it properly. They cope by separating the information into "good" and "bad" with no gray area in between. As a result, they consider the worst-case scenario (i.e., by catastrophizing about the situation) and then act to protect themselves against the perceived danger.

Stress

Stress also plays a major role in the pathology of anxiety

disorders. For example, PTSD is a condition in which stress is considered the main etiological factor, although there is a high degree of co-occurring stress reported by these patients. In other anxiety disorders such as GAD and OCD, the role of stress is less apparent. Nevertheless, patients with any anxiety disorder often pinpoint the onset of their disorder in relation to a striking stressful event or to a continuous persistent stressor. Whether a cause or a consequence, increased stress reactivity sometimes accounts for relapses in chronic anxiety conditions like GAD. According to some studies, a stressful event or a persistent and chronic disorder can even cause secondary biological changes in specific brain structures.[31,32]

The current *DSM-IV-TR* system does not adequately address the role of stressors. Although stressors are separately identified along Axis IV of the multiaxial system, the context for the patient is unclear. Perhaps a better way to address the patient's anxiety would be to indicate the source and rate the persistence (i.e., immediate, intermittent, or constant) and the degree of the stress (i.e., mild, moderate, severe, or catastrophic). With this approach, we might be better able to capture the landscape and dynamic of the stress. For example, panic disorder resulting from exposure to catastrophic combat may differ clinically from panic disorder that results from a persistent work-related stress or separation from family. Exploration of how stress affects biology and the course of anxiety disorders is clearly needed.

Biological Factors

Biological factors are of primary importance in anxiety disorders. Anxiety disorders can occur in the context of medical illness,[33] and the clinician should consider an intricate relationship between medical illnesses and anxiety disorders. This relationship could be manifold.

First, metabolic or autonomic abnormalities caused by the illness can produce the syndrome of anxiety (i.e., hyperthyroidism sometimes results in panic attacks). The symptom of medical illness can be a trigger for anxiety (i.e., sensations of arrhythmia can serve as a trigger for a panic attack). Sometimes medical illness can mimic the anxiety disorder (i.e., when perseverations in mental retardation are mistaken for OCD).

Finally, medical illness and an anxiety disorder can simply coexist in the same patient. One of the most interesting interactions between medical illness and anxiety disorders is pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS), which has been reported in a subset of OCD patients.[34]

Over the previous two decades, the main thrust of biological research in anxiety disorders has shifted from peripheral measures of autonomic and neurochemical parameters to identifying reactivity and neurochemistry of the living brain directly through advances in neuroimaging technology. Anxiety disorders are an appropriate target for neuroimaging research because it is easy to provoke specific symptoms in many cases. Much of the research on neural circuits has focused on models of anxiety and fear proposed earlier by basic scientists,[35,36] and a synthesis of current data has been attempted for panic disorder[37] and OCD.[38]

There have been some excellent reviews of neuroimaging experiments in anxiety,[39,40] but the picture remains incomplete, in part because of a lack of clinical trials addressing the long-term integration of threat responses. As in the dynamical model, every anxiety disorder may be viewed as an interplay of anxious feelings, abnormal processing of information, and inadequate coping strategies. In accordance with this model of anxiety, overlapping neuronal circuits are responsible for alarm reactions, processing of perceived threats, and behavioral coping (see Figure 1). This model attempts to simplify complex brain circuitry that needs to be studied over the next several decades before we can truly understand how the brain processes threats over time.

For simplicity we identify Alarm circuits (A), in which the amygdala is the structure of primary importance. These circuits also include periaqueductal gray matter and multiple nuclei in the brainstem.[41] The disturbance of anxiety circuits results in a lower threshold for alarm reactions that leads to spontaneous panic attacks. These circuits are possibly responsible for the quick response to a threat.

Circuits associated with Beliefs (B), responsible for processing information related to "threats," are probably closely associated with the basal ganglia, cingulum, and corticostriatal connections, which are typically affected in OCD.

Abnormalities in Coping (C) should be governed by distributed cortical networks and are difficult to tease apart. Thus, a convenient mnemonic explaining these circuits could be A (Alarm, amygdala), B (Beliefs, basal ganglia), and C (Coping, cortex).

How Anxiety Affects Neurotransmitters

Neuronal circuits are governed by multiple neurotransmitter systems; the most extensive of these are gamma-aminobutyric acid (GABA) and glutamate. The neural systems of the three major neurotransmitter systems—serotonin, dopamine, and norepinephrine—have been extensively studied in normal and pathological anxiety states.[40,42] The significance of these systems in anxiety is apparent from the fact that most effective therapies for these disorders affect one or several of them. However, anxiety disorders are not simply a deficiency of one neurotransmitter or another. The networks governed by these transmitters have extensive interrelationships, multiple feedback mechanisms, and complex receptor structures.[43] This complexity helps to explain the unpredictable and sometimes paradoxical responses to medication.

Research involving other neurotransmitter systems has been fruitful in elucidating their function in anxiety but thus far has failed to produce new treatments. The primary neurotransmitter and receptor systems implicated in the pathogenesis of anxiety disorders are discussed next.

Serotonin

The primary serotonergic pathways originate in the raphe nuclei and project widely to numerous targets throughout the forebrain.[44] These circuits play a fundamental role in regulating brain states, including anxiety, and modulate the dopaminergic and noradrenergic pathways as well.[45] Increased serotonergic tone appears to be correlated with a reduction in anxiety; however, the mechanism underlying this correlation is not known.

There are also numerous serotonin receptor subtypes whose roles may vary, depending on location. For example, the serotonin-1a receptor serves as both a mediator and an

inhibitor of serotonergic neurotransmission, depending on whether it is located on the presynaptic or the postsynaptic neuron.[46] Furthermore, not all serotonin receptor subtypes mediate anxiolytic effects; this is demonstrated by the fact that serotonin-2a receptor agonism underlies the psychedelic properties of drugs such as lysergic acid (LSD) and mescaline.[47]

Despite this complexity, it is recognized that medications that inhibit the reuptake of serotonin, presumably increasing serotonergic neurotransmission, result in a reduction in symptoms of anxiety for many patients.[48]

Gamma-aminobutyric Acid

GABA is the main inhibitory neurotransmitter in the central nervous system (CNS). Increases in GABA neurotransmission mediate the anxiolytic effect of barbiturates and benzodiazepines.[49] Medications in these classes do not bind directly to the GABA receptor; instead, they promote the open configuration of an associated chloride channel. Barbiturates do this by increasing the duration of the channels' open state, whereas benzodiazepines increase the frequency of opening.

Although modulation of GABA-ergic pathways can reduce anxiety almost immediately, compensatory mechanisms associated with these circuits and the use of barbiturates and benzodiazepines can result in tolerance and potentially fatal withdrawal.[50] Further, these drugs impair memory encoding and thus may undermine the efficacy of concomitantly administered psychotherapy.

Anticonvulsant agents also alter GABA transmission and are used to treat anxiety.[51] This class of medications affects GABA transmission indirectly by blocking calcium channels, resulting in a lower potential for withdrawal and addiction.[52]

Dopamine

The principal dopaminergic pathways originate from the midbrain in the ventral tegmental area and substantia nigra, with projections to the cortex, striatum, limbic nuclei, and infundibulum. Dopamine's role in normal and pathological anxiety states is complex, and dopaminergic pathways may affect anxiety states in several ways.[53] It is well known that dopamine D_2 blockade, the characteristic mechanism of antipsychotic medications, is also anxiolytic.[54]

This class of medications has been widely used in the treatment of anxiety. However, as a catecholamine, dopamine is up-regulated with norepinephrine in anxiety states, whereas increases in dopaminergic signaling also appear to mediate feelings of self-efficacy and confidence—which can act to reduce anxiety.[55, 56] The result of this complexity is a variation in responses to medications that increase dopamine. Some patients with anxiety disorder respond well to pro-dopaminergic drugs such as bupropion (Wellbutrin, GlaxoSmithKline); other patients find that such agents exacerbate their symptoms.

Norepinephrine

Noradrenergic neurons originate primarily in the locus coeruleus in the pons and project widely throughout the CNS.[57] Like dopamine, norepinephrine is a catecholamine that is up-regulated in anxiety states, but it has a complex and potentially bidirectional role in mediating normal and pathological anxiety. Many of the physiological symptoms of anxiety are mediated by norepinephrine, and antagonists of various norepinephrine receptor subtypes are used to combat particular aspects of anxiety.

For example, propranolol, an antagonist of the $beta_2$-norepinephrine receptor, is used to reduce the rapid heart rate, hand tremor, and quivering voice that might accompany public speaking or other activities associated with performance anxiety.[58] Although propranolol has been useful in targeting these physiological symptoms of normal anxiety, it has not been particularly effective in reducing the emotional or cognitive aspects of anxiety and is not generally used as a therapy for anxiety disorders.

Similarly, prazosin (Minipress, Pfizer), an antagonist of the $alpha_1$-norepinephrine receptor, is used to reduce the intensity and frequency of nightmares associated with PTSD but has not been effective in relieving other symptoms of anxiety disorders.[59,60] Serotonin–norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine (Effexor, Wyeth/Pfizer) and duloxetine (Cymbalta, Eli Lilly), have been effective in the treatment of anxiety disorders.[61] These medications also help to reduce neuropathic pain and may target the agonal component of anxiety.

Glutamate

Glutamate is the primary excitatory neurotransmitter in the CNS and is involved in virtually every neuronal pathway, including those underlying normal and pathological anxiety states.[62,63] The *N*-methyl-D-aspartate (NMDA) receptor subtype may be particularly important in anxiety disorders, as it is believed to mediate learning and memory. Activation of the NMDA receptor triggers protein synthesis, which appears to strengthen the connection between neurons when they fire concurrently. Therefore, glutamatergic pathways are probably involved in both conditioning and extinction, the processes associated with the development and treatment of anxiety disorders, respectively.[64]

Preliminary evidence suggests that both augmentation and antagonism of NMDA-mediated pathways are effective in the treatment of anxiety disorders, although no glutamatergic medications have received an FDA indication for this use. D-cycloserine enhances glutamatergic neurotransmission and has been effective in augmenting the effects of exposure therapy for anxiety disorders.[65] However, the NMDA receptor antagonists memantine (Namenda, Forest) and riluzole (Rilutek, Sanofi) have evidence supporting their efficacy in the treatment of OCD.[66] Interestingly, memantine appears to be much less effective in the treatment of GAD, suggesting that different pathways may underlie different anxiety disorders.[67]

Other Neurotransmitters

Many other neurotransmitter systems participate in the biological mechanisms of fear and anxiety. Neuropeptides, including substances P, N, and Y; corticotropin-releasing factor (CRF); cannabinoids; and others, modulate fear in animal models.[68–70] However, none of the experimental agents that utilize these systems have been translated into FDA-approved treatments.[71] Stringent criteria for approval, along with high placebo responses typical in anxiety trials, could be responsible.[72]

PHARMACOLOGICAL THERAPY

Numerous neurotransmitters play a role in normal states and in pathological anxiety states. Each of these systems is a

potential target for pharmacological intervention, but relatively few classes of medications are used in clinical practice for the treatment of anxiety. These drug classes are briefly discussed next.

Selective Serotonin Reuptake Inhibitors

SSRIs, usually indicated in depression, are considered to be the first line of therapy for anxiety disorders. This drug class includes fluoxetine (Prozac, Eli Lilly), sertraline (Zoloft, Pfizer), citalopram (Celexa, Forest), escitalopram (Lexapro, Forest), fluvoxamine (Luvox, Solvay), paroxetine (Paxil, GlaxoSmithKline), and vilazodone (Viibryd, Forest).[72] The essential characteristic of the medications in this class is that they inhibit the serotonin transporter and appear to cause desensitization of postsynaptic serotonin receptors, thus normalizing the activity of serotonergic pathways.

The mechanism by which this leads to amelioration of anxiety symptoms is not fully understood. Vilazodone, the most recently approved medication in this class (although indicated for major depressive disorder), also acts as a partial agonist at the serotonin-1a receptor, which may contribute to anxiolysis.[73] Buspirone (BuSpar, Bristol-Myers Squibb), which is not a serotonin reuptake inhibitor (SRI), is also a 5-HT_{1a} agonist and is frequently used as a single agent or as augmentation to SSRI therapy.[74]

Serotonin–Norepinephrine Reuptake Inhibitors

SNRIs, which inhibit the serotonin and norepinephrine transporters, include venlafaxine, desvenlafaxine (Pristiq, Pfizer), and duloxetine.[75] Milnacipran (Savella, Cypress/Forest) is rarely, if ever, used to treat anxiety because its only FDA-approved indication is for fibromyalgia.[76] SNRIs are typically used after failure or inadequate response to an SSRI. They are used in place of augmentation to SSRIs because the combination of these two drug classes may result in serotonin syndrome.

Patient responses to SNRIs can vary widely; some patients may experience an exacerbation of the physiological symptoms of anxiety as a result of the increased norepinephrine-mediated signaling caused by inhibition of the norepinephrine transporter. For patients who do not experience this effect, the increased noradrenergic tonus may contribute to the anxiolytic efficacy of these medications.

Benzodiazepines

Although benzodiazepines were widely used in the past to treat anxiety conditions, they are no longer considered to be first-line therapies because of the risks associated with their chronic use.[75] They are very effective in reducing acute anxiety but are associated with problematic adverse effects when used for a long time in high doses, including:

- physiological and psychological dependence.
- potential fatalities upon withdrawal.
- impaired cognition and coordination.
- a potentially lethal overdose when they are mixed with alcohol or opioids.
- inhibition of memory encoding, which can interfere with the efficacy of concomitant psychotherapy.

For these reasons, the use of benzodiazepines is often restricted to the short-term treatment of acute anxiety or as therapy for refractory anxiety after failed trials of several other drugs. Of note, some subgroups of patients do well with low doses of benzodiazepines and are able to safely taper from high doses, especially when cognitive–behavioral therapy (CBT) is added.[77]

Antiseizure Medications

Because of the side effects of benzodiazepines, antiepileptic agents have been used more extensively for the treatment of anxiety. Antiseizure drugs were initially used for mood stabilization in mood disorders; however, their anxiolytic properties were quickly noted. Many agents in this drug class are being used in an off-label fashion to treat anxiety, especially gabapentin (Neurontin, Pfizer) and pregabalin (Lyrica, Pfizer).[51,78] Less information is available for topiramate (Topamax, Janssen), lamotrigine (Lamictal, GlaxoSmithKline), and valproate (Depacon, Abbott).[79] In higher doses, the antiseizure class can produce adverse effects similar to those of the benzodiazepines.[80]

Tricyclic Antidepressants

All tricyclic antidepressants (TCAs) function as norepinephrine reuptake inhibitors, and several mediate serotonin reuptake inhibition as well. Although several medications in this drug class are comparable in efficacy to the SSRIs or SNRIs for anxiety disorders, TCAs carry a greater number of adverse effects and are potentially lethal in an overdose. For this reason, TCAs are rarely used in the treatment of anxiety disorders. A notable exception is clomipramine (Anafranil, Malinckrodt), which may be more efficacious than SSRIs or SNRIs in patients with OCD.[81]

Additional Medications

Hydroxyzine (Atarax, Pfizer), mirtazapine (Remeron, Organon), nefazodone (Bristol-Myers Squibb), and atypical neuroleptic agents are commonly used to treat anxiety.[82] Although all of these medications are efficacious for anxiety disorders, especially OCD, they are not considered first-line treatments and are typically used as an adjunct to an SSRI or an SNRI. Hydroxyzine is indicated for anxiety and probably achieves anxiolysis by inhibiting the histamine H_1 receptor and the serotonin-2a receptor.[83]

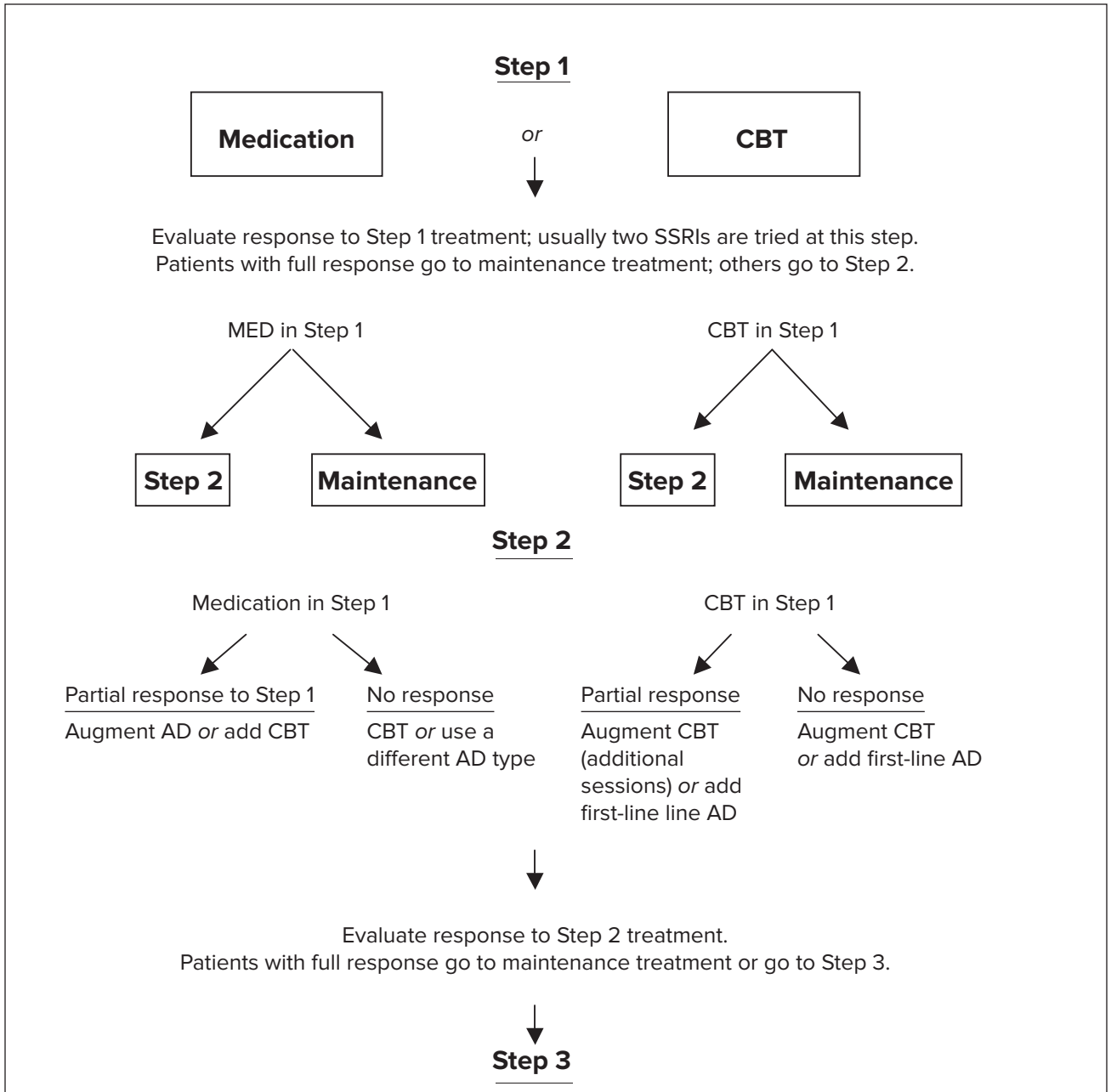
TREATMENT STRATEGIES

Initial Treatment Algorithms

During the 1990s, mainstream psychological and pharmacological treatments of anxiety disorders were developed and tested, leading to an initial algorithm that is similar for all major anxiety disorders.[84,85] The typical algorithm, adapted from Roy-Byrne et al.,[25] is presented in Figure 2.

In general, clinicians must choose between CBT and an SSRI and then try another SSRI if the first one did not work or was not tolerated. None of the SSRIs has shown superiority to another. The choice of an SSRI is usually based on the side-effect profile, pharmacokinetic and pharmacodynamic properties, and potential interactions with coadministered medications.

Several excellent reviews of SSRI therapies for anxiety disorders have been published.[86] A general principle with SSRIs is to "start low and go slow," starting with approximately half the dose of that used for depression and slowly titrating the dose upward, with no more than a once-weekly change in the dosage.



1. Consider a trial of a second or third type of antidepressant.
2. Schedule intensive CBT (several times a week).
3. Augment antidepressant therapy (if patient has had a partial response to an antidepressant in step 2).
4. Referral to specialty mental health care for ongoing treatment if more complex problems are present (e.g., childhood abuse, post-traumatic stress syndrome).
5. Repetitive TMS (rTMS), electroconvulsive therapy, deep-brain stimulation, vagal nerve stimulation, and other techniques used for refractory anxiety.

Figure 2 Stepped-care treatment algorithm. AD = antidepressant therapy; CBT = cognitive–behavioral therapy; MED = medication; rTMS = repetitive transcranial magnetic stimulation; SSRI = selective serotonin reuptake inhibitor. (Adapted from Roy-Byrne, et al. *Arch Gen Psychiatry* 2005;62[3]:290–298;[3] and Roy-Byrne et al. *JAMA* 2010;303[19]:1921–1928.[25])

Antidepressants with broader mechanisms of action (i.e., venlafaxine and clomipramine) have been tried in nonresponders. The rationale for this practice is that these medications affect more than one neurotransmitter system and have some, albeit weak, meta-analytic data supporting their superiority in depression and OCD.[87] Benzodiazepines are generally avoided except in acute states or treatment-resistant chronic conditions.

Few data have been published about what to do after the few initial steps of treatment, such as how long maintenance therapy should last. Based on clinical experience, we generally recommend continuing treatment until the patient has achieved marked symptom reduction for at least 6 months. More research on this topic is needed.

Further testing of combined treatments at the initial and later steps of the typical algorithm was subsequently performed.[88,89] In the later stages of anxiety treatment, GABA-ergic antiepileptic drugs and atypical antipsychotic agents may be tried. Atypical neuroleptic medications have shown even better evidence of efficacy in anxiety disorders, according to some placebo-controlled trials.[90]

Side-Effect Profiles

Patients and physicians need to be aware of adverse drug reactions. An extensive review of the side effects of SSRIs has been published by Valuck.[91] In other studies, SSRIs and SNRIs were found to increase the risk of suicidality[92] and atypical neuroleptic agents caused tardive dyskinesia and arrhythmias.[93] All of these drugs can cause weight gain and sexual dysfunction. Because polypharmacy is becoming the rule rather than the exception, especially in complex and treatment-resistant anxiety, practitioners should be cognizant of potential drug–drug interactions.[94]

Serotonin syndrome and neuroleptic malignant syndromes, although rare, should be kept in mind. Discontinuation of SSRIs has not been well studied, but a withdrawal syndrome upon abrupt discontinuation of SSRIs (and SNRIs) is common. Symptoms may include paresthesias, nonvertiginous dizziness, nausea, diaphoresis, and rebound anxiety.[95] For this reason, stopping SSRIs and SNRIs should involve a gradual tapering and should take place, if possible, in parallel with CBT.

Cognitive–Behavioral Therapy and Medications

CBT has received the greatest amount of empirical support for the psychological treatment of anxiety disorders.[96] In our treatment algorithm, CBT stands with the SSRIs as a first-line treatment choice (see Figure 2). Combining drug therapy and CBT has shown mixed results in favoring one approach over the other, depending on the type of anxiety disorder.

A review and meta-analysis approached the question of combination treatment over monotherapy or CBT in anxiety by hypothesizing that CBT would be more successful compared with medications; however, the medication held an advantage over CBT in depression.[97] Within the anxiety disorders, there was great heterogeneity in their responsiveness to either CBT or medication, with CBT holding an advantage over medication in patients with panic disorder. By contrast, patients with social anxiety disorder were more responsive to medication.

The choice of medication or CBT, alone or in combination, is based on several variables, including the availability of a therapist; the affordability of CBT, which costs more than medication, especially if drugs are prescribed in primary care settings; and patient preference.

Cognitive–Behavior Therapy Alone

It is generally acknowledged that the treatment of anxiety disorders is suboptimal because of a lack of CBT therapists or the availability of affordable sessions. There is a great need to distill the essence of good therapy and to bring it into the primary care setting, with an emphasis on education and staff training.[25] Oxford University Press has published many excellent manuals that include both therapist and patient guides.[98] The proliferation of the Internet-based, self-administered therapies calls for further research into the efficacy of this method of dissemination.[99] Complex anxiety disorders might not be able to be self-treated adequately, whereas a specific phobia might be self-treated alone or with the support of a friend of family member.

Koszycki et al.[100] discussed whether self-administered CBT could stand alone or could be optimized with therapist-directed CBT, self-administered CBT, or medication augmented with self-administered CBT. Their work suggested that even self-administered treatment might be an effective addition to the CBT armamentarium.

Although many treatments are effective for anxiety, not all of them can help everyone and not all of them are effective for all anxiety disorders. A simple phobia is easier to treat than a complicated case of PTSD. The most empirically supported treatments are SSRIs and CBT. Relapse rates for CBT, compared with medication, are an understudied area, although our clinical experience suggests that CBT has a longer treatment effect if the patient continues to use the skills and tools learned in therapy.

Technique

CBT shares much in common with other more dynamically based forms of psychotherapy. A patient seeks help from an expert caregiver who treats the patient in a warm and nonjudgmental relationship in an attempt to help the patient function and feel better in a reality-oriented setting. However, CBT is directive and collaborative; the therapist establishes clear and specific goals with the patient and uses evidence-based techniques to elicit the patient's feelings and bodily sensations (Arousal, or Alarm), dysfunctional and irrational thinking (Beliefs), and subsequent behavior (Coping).

The helping relationship is less emphasized in CBT as a curative factor, but it is considered important in building trust and support, serving as a springboard for patients to consider their erroneous beliefs and behaviors that cause them anxiety and fear. The therapist is explicit about conceptualizing the patient's disorder, with regard to the genesis, evolution, and maintenance of the disorder over time. The therapist often incorporates manuals or other psychoeducational materials and may propose daily homework to help the patient learn more adaptive ways to manage and reduce the alarm (A), change irrational and dysfunctional beliefs (B), and develop adaptive coping (C) mechanisms, often through exposure exercises. To the most appropriate extent possible, patients are taught the ABC model to help them understand the dynamic and reciprocal

relationship among feelings, thoughts, and behaviors.

Patient compliance with therapy is directly proportional to the treatment's effectiveness. Motivational interviewing, which is used to help patients examine the cost–benefit ratio of their maladaptive thoughts and behavior, often increases compliance and, subsequently, effectiveness.[101] Patients are taught self-monitoring and symptom-reduction techniques to increase their motivation to confront their anxiety. Breathing and relaxation techniques can be explained as mental hygiene to raise one's threshold for the onset of alarm reactivity and for increasing the patient's ability to notice whether an alarm reaction is mounting over the course of the day.

The linchpin in the CBT model of anxiety is considered to be the patient's thoughts.[102] Misguided beliefs must change for both the alarm to down-regulate and for subsequent adaptive coping to replace avoidant and escape-based coping. Although beliefs are the linchpin, exposure to the anxiety-producing thought, image, or situation is often the essential CBT component for jogging the linchpin loose. This too is a dynamic process. Cognitive restructuring techniques aimed at reducing catastrophic thinking help to diminish irrational or exaggerated thoughts, thereby allowing patients to become more willing to test those beliefs through exercises involving exposure.

Exposure

Exposure is the gradual and systematic presentation of the anxiety-inducing thought, image, or situation for a long enough time for patients to see that their anxious feelings can be decreased without engaging in avoidance or escape. For example, a patient who is afraid of dogs might first be shown a picture of a dog, then stand across the street from a pet shop, and finally hold a dog in his or her arms. The patient would engage in each of these steps repeatedly and in a concentrated but not overwhelming way.

Ideally, the patient would experience a gradual lessening of anxiety at each step before moving on to the next. The patient would experience the alarm being reduced, and the exaggerated belief that all dogs are dangerous could be modified to a more accurate belief that most pet dogs are not threatening. The hoped-for outcome would be that the patient would no longer have a phobic avoidance of all dogs.

Mindfulness (The Third Wave)

A final emerging area in the evolution of CBT is the approach based on mindfulness (acceptance). This is the "third wave" in CBT, the first wave being the strict behavioral approach and the second wave emphasizing the cognitive approach.[103]

Mindfulness is a type of meditation that has been adapted from Buddhist psychology. One definition is "awareness of present experience with acceptance."[103] These therapies owe a debt of gratitude to Jon Kabat-Zinn's Mindfulness-Based Stress Reduction (MBSR) program, which began at the University of Massachusetts in 1979.[104]

Mindfulness-based cognitive therapy (MBCT) is one component of the integration of mindfulness into CBT.[105] MBCT has been applied to the treatment of panic disorder and other anxiety disorders, but more carefully controlled research is needed in this area.[106] MBCT emphasizes the prevention of relapse through a meta-cognitive or mindful awareness that leads patients to realize that their current symptoms do not necessarily mean that they are relapsing.

Acceptance and commitment therapy involves a mindful focus; many exercises are aimed at the meta-cognitive level to help patients perceive their thinking and subsequent anxiety to be separate from, and less identified with, their sense of self. Anxiety-causing thoughts are to be observed and accepted, not to be struggled with and changed, as in more traditional CBT and Western psychological approaches.[107]

Shifting Treatment to Primary Care

In today's managed care environment, the treatment of anxiety usually takes place in the primary care setting. Given the increasing limits on primary care physicians' time, it is not surprising that anxiety disorders are underrecognized and undertreated. At the same time, SSRIs (antidepressants) are increasingly used in primary care, and physicians in fact are the largest group of prescribers. This is a mixed blessing for several reasons:

- SSRIs are often prescribed quickly in response to emotional distress that might not meet criteria for an anxiety disorder.
- The dose and duration of therapy might be inadequate.
- Adverse effects might not be managed by any means other than by discontinuation of the treatment.

This state of affairs may partly explain why psychiatrists are seeing more patients who are disenchanted with numerous failed attempts at pharmacotherapy.

Another problem in primary care is a lack of understanding of behavioral strategies that result in low referral rates to mental health professionals. There has been a trend toward developing comprehensive treatments for panic disorder to be delivered by primary care physicians.

In one study, an algorithm was tested for the treatment of panic disorder.[108] This study reflected the trend of how psychiatrists became more like consultants to primary care physicians, assisting them with correct initial management plans and taking over the management of more severe and treatment-resistant anxiety.

Management of Treatment-Resistant Anxiety

In managing refractory anxiety, it is important to start with a re-evaluation of the patient, including the diagnosis; comorbidities; and the interplay of cognitive, stress-related, and biological factors. Inadequate coping strategies on the part of patients and their family members should be reviewed. Doses and duration of the initial treatments should be assessed.

Initially, more intensive CBT, combined with an adequate trial of SSRIs, SNRIs, or both, may be needed in refractory anxiety. After that, the treatment may progress to a combination of SSRIs with antiepileptic or atypical neuroleptic agents, especially if bipolar disorder or a psychotic disorder is suspected.[109,110] Later, partial hospitalization in specialized centers with more extensive CBT and medication management might be recommended.[111]

Although other forms of therapy have not demonstrated efficacy in anxiety disorders, they may be helpful for addressing personality issues in chronically anxious patients.

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Experimental and Off-Label Nonpharmacological Treatments

Therapies for anxiety disorders, beyond combining conventional treatments, using off-label antiepileptic and antipsychotic agents, and introducing more intensive CBT programs, are mostly experimental. Promising medications have included intravenous clomipramine, citalopram, and morphine.[109] Many other treatments targeting more specific neurotransmitter systems have failed.[72]

A handful of invasive therapies have emerged. These options may be considered after several off-label pharmacotherapy and psychotherapeutic approaches have failed or when significant functional impairment remains. They are typically reserved for the most treatment-resistant cases, typically those involving severe OCD. Invasive treatments often target brain circuits implicated in the processing of fear and anxiety.

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) involves the application of brief electrical impulses to the scalp to induce large-scale cortical neuronal discharges, eventually producing generalized seizure activity. Although ECT is effective in treatment-resistant mood disorders, data regarding its efficacy in anxiety disorders are limited.[112] The mechanism and focal targets of ECT have not yet been determined.

Vagal Nerve Stimulation

Initially developed as an antiepileptic treatment, vagal nerve stimulation (VNS) was used in psychiatric patients after sustained mood improvements were noted with this therapy.[113] VNS is thought to stimulate brain networks relevant to anxiety and fear processing (taking place in the amygdala, hippocampus, insula, and orbitofrontal cortex) via the afferent vagal nerve. This modality is not routinely used to treat anxiety, and evidence of its effectiveness in resistant anxiety disorders is limited.[114] To date, no randomized controlled trials have investigated this intervention further.

Repetitive Transcranial Magnetic Stimulation

Focal magnetic stimulation of the scalp is used with the goal of invoking excitation or inhibition of cortical neurons. Repetitive transcranial magnetic stimulation (rTMS) is less invasive than ECT; anesthesia induction is not required, and rTMS does not elicit generalized seizure activity in the brain. It also has the advantage of being able to target brain regions thought to be involved in anxiety disorders.

The main limitations of rTMS include the inability to penetrate deeper brain structures implicated in OCD (the caudate nucleus, thalamus, and anterior capsule fiber tracts) or in panic disorder (the amygdala, hippocampus, and anterior cingulate); there is also a lack of specificity at the site of stimulation.

rTMS has not been approved as a treatment for any anxiety disorder, probably because of the paucity of large-scale studies. There is limited evidence for efficacy in treating OCD, although larger treatment effects have been reported by altering the stimulation site.[115,116] rTMS has been reported to improve anxiety symptoms in PTSD and panic disorder, although the approach has not been incorporated into clinical practice.[117]

A small study reported significant anxiety reductions in patients with generalized anxiety disorder (GAD) using a symptom-provocation task during functional magnetic resonance imaging (fMRI) to guide individual selection of the rTMS site.[118] No studies have investigated the role of rTMS in social anxiety disorder.

Surgery

Although psychosurgery has been used for various treatment-resistant anxiety disorders such as GAD, panic disorder, and social phobia, long-term follow-up studies in these patients have revealed adverse cognitive outcomes, including apathy and frontal lobe dysfunction.[119] Consequently, surgical approaches are usually reserved for OCD, given the disproportionate functional deficits that are a hallmark in treatment-refractory cases.

Several surgical approaches have been used, including anterior capsulotomy (which targets the anterior limb of the internal capsule), anterior cingulotomy (which targets the anterior cingulate and cingulum bundle), subcaudate tractotomy (which targets the substantia innominata, just inferior to the caudate nucleus), and limbic leucotomy (which combines anterior cingulotomy with subcaudate tractotomy).[120,121]

Cingulotomy remains the most commonly used psychosurgical procedure in North America, probably because of its clinical efficacy as well as low morbidity and mortality rates. Postsurgical effects have included transient headache, nausea, or difficulty urinating. Postoperative seizures, the most serious common side effect, have been reported from 1% to 9% of the time.

Patient outcomes cannot be fully assessed until at least 6 months to 2 years after the definitive procedure, suggesting that postoperative neural reorganization plays an important role in recovery. Direct comparisons of each lesion approach within studies are rare.

Overall, the long-term outcomes of these approaches have demonstrated significant therapeutic effects of each procedure. In general, reported response rates vary from 30% to 70% in terms of remission, response, and functional improvements in quality of life.

Deep-Brain Stimulation

Deep-brain stimulation (DBS) involves the insertion of small electrodes under precise stereotactic MRI guidance. The major advantage of DBS over ablative surgery is the ability to adjust and customize neurostimulation.[122] Following implantation, parameters of electrode stimulation (electrode polarity, intensity, frequency, and laterality) can be modified. Parameters can be optimized by a specially trained clinician during long-term follow-up.

Several studies with blinded stimulation have been conducted with moderate-to-fair results.[123] More recently, structures adjacent to the internal capsule have also been targeted.[124,125] In all trials, response rates have been consistently reported in the 50% range.[125]

Postoperative complications (e.g., infections, lead malfunctions) occur more commonly with DBS because of the prosthetic nature of the procedure. Batteries must also be periodically explanted and replaced. Stimulation-related side effects have been reported, including mood changes (transient sadness, anxiety, euphoria, and hypomania), sensory disturbances

(olfactory, gustatory, and motor sensations), and cognitive changes (confusion and forgetfulness). These side effects are typically stimulation-dependent and disappear after the stimulation parameters are altered.

Complementary and Alternative Medicine

During the 1990s, many alternative treatment strategies for anxiety disorders emerged.[126] These included herbal medications (with St. John's wort the most frequently used), vitamins, nutritional supplements, magnetic and electroencephalographic synchronizing devices, "energy" treatments, and meditation-based therapies (see Mindfulness on page 38).

These treatments may be provided by alternative medicine practitioners within the scope of a health care model, such as acupuncture, homeopathy, Ayurvedic medicine, Reiki, and healing touch. Because of minimal FDA regulation and widespread over-the-counter availability, many of these same treatments are self-selected and used by patients. Herbs are the most commonly used complementary and alternative medicine (CAM) products and are particularly popular with those with psychiatric disorders. Anxiety is one of the strongest predictors of herbal remedy utilization,[127] and patients often use these treatments without the knowledge of their physician. Consequently, clinicians and pharmacists are advised to regularly monitor the full range of treatments used by their patients, including a thorough medication reconciliation of prescription and nonprescription products, herbs, and supplements at each visit.

Results of herbal trials for anxiety disorders have been mixed. The widespread use of *Piper methysticum* (Kava) for anxiolysis was curtailed by reports of hepatotoxicity, prompting government warnings and withdrawal of the product from the market in many Western countries.[128,129] However, a randomized placebo crossover trial using a supposedly benign aqueous formulation reported moderate reductions in anxiety symptoms in a small sample of patients with mixed anxiety disorders.[128,130] Both *Hypericum perforatum* (St. John's wort) and *Silybum marianum* (milk thistle) have been used for the treatment of OCD symptoms, although no placebo-controlled trials revealed any significant differences in symptoms or adverse effects between treatment groups.[131,132] Lower-quality studies of CAM have reported modest treatment effects for interventions such as mindfulness meditation, yoga, and acupuncture.[133]

Despite a lack of data on efficacy, many patients continue to use CAM therapies, prompting a need to monitor use for potential interactions with prescription medications.[134] For instance, St. John's wort is known to interact with many medications because of the induction of cytochrome P450 (CYP) isoenzymes 3A4 and 2C9. Of relevance in anxiety disorders, CYP3A4 may cause a decrease in serum levels of alprazolam (Xanax, Pfizer) and clonazepam (Klonopin, Roche). Combining St. John's wort with SSRIs also increases the risk of serotonin syndrome. Milk thistle inhibits CYP3A4 and has the potential to increase levels of other medications metabolized by this pathway. Kava has been linked with inhibition of several CYP isoenzymes, including 1A2, 2D6, 2C9, and 3A4.[135] Further exploration of the efficacy of these alternative strategies for anxiety disorders is needed.

Functional Status

Although many patients with anxiety disorders experience symptom relief with treatment, residual symptoms still have an impact on everyday functions. Even subclinical anxiety can produce disability sometimes exceeding that seen in other severe mental illnesses.[111,136] In addition, chronic, persistent anxiety disorders have a significant impact on patients' lives, often leading to deficits in social and work skills. Yet there are few clear interventions or programs with a focus on rehabilitation and restoration of function in these patients.

Stress is an important factor in the emergence and maintenance of anxiety syndromes. Patients who need to return to the workforce can experience increased stress that in turn may cause re-emergence of the symptoms, again resulting in decreased productivity and even loss of employment. More research is needed to address this problem.

CONCLUSION

Anxiety disorders are treatable. Effective treatments have been developed, and algorithms have been refined. However, more work needs to be directed toward merging of our knowledge of the biological mechanisms of anxiety with treatment in order to more accurately predict and improve treatment response. Dynamic models of anxiety—such as the ABC model—can be helpful in understanding the interplay between processes responsible for development and maintenance of the symptoms over time and between biological and psychological factors affecting them.

We need to learn how to better administer existing efficacious treatments in real-world health care environments, such as in primary care, and to inform the public via media outlets. We should continue to test alternative therapies for treating and preventing anxiety disorders and to help patients whose anxiety is resistant to conventional treatments.

Finally, we need to consider the patient's feelings about mental illness and address their responses early in treatment. All of these measures will enhance the care of patients with anxiety.

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