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Generalized Anxiety Disorder

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Phenomenology

Symptoms

Although "anxiety neurosis" has long been described, generalized anxiety dis-

order (GAD) per se is a relatively new diagnosis. In DSM-III (American Psychiatric Association 1980), GAD was in some ways a "wastebasket" diagnosis that applied only to those who suffered from anxiety symptoms but did not meet diagnostic criteria for any of the other anxiety disorders. However, in DSM-III-R and DSM-IV, GAD was increasingly conceptualized as an important independent disorder.

In DSM-IV-TR (American Psychiatric Association 2000), the diagnosis of GAD (Table 7–1) includes two major aspects: 1) uncontrollable, unrealistic worry about more than one topic and 2) accompanying physiological symptoms including muscle tension, difficulty sleeping, fatigue, restlessness or feeling keyed up/on edge, irritability, and difficulty concentrating. These symptoms must be relatively persistent for a 6-month period and be distressing or interfere with functioning to meet criteria for GAD.

Table 7–1 is currently at the end of the chapter. It will be positioned about here at a later phase of production.

In addition, if anxiety symptoms are better accounted for by another disorder, the diagnosis of GAD is not made (see "Differential Diagnosis" section below). According to DSM-IV-TR, the diagnosis of GAD cannot be made when the disorder's symptoms occur solely during an episode of a mood disorder (i.e., major depression or dysthymia). The basic assumption behind this decision is that most individuals who are depressed are also anxious (Barlow 2002). Substance use disorders and general medical disorders should also be excluded.

AUTHOR: Barlow (2002) is cited above. Please add an entry for this author to the References section.

Associated Features

GAD may be associated with significant comorbidity and morbidity. Early authors did not see GAD as an independent entity, partly because comorbidity is so common. Nevertheless, rates of comorbidity in GAD are no higher than those seen in depression. Furthermore, community studies demonstrate that the disability associated with GAD is as great as that associated with de-

pression.

Whereas GAD typically starts in childhood or early adulthood, oftentimes a major stressor will exacerbate symptoms. Research (Wells 1994) and our clinical experience with GAD has led us to believe that people with GAD are often driven toward being perfectionistic, feel a greater need for control in their environment, have difficulty tolerating ambiguity, and feel increased personal responsibility for negative events that occur or are predicted to occur in their environment.

Epidemiology

GAD is a relatively common disorder. Judd et al. (1998), for example, reported a lifetime prevalence of DSM-III-R GAD, as diagnosed using the Structured Clinical Interview for DSM-IV and using hierarchical exclusion rules for current panic and depression, of 3.6%. More recent results, using DSM-III-R criteria, from the National Comorbidity Survey found a 12-month prevalence of 3.1% and a lifetime prevalence of 5.1% (Wittchen et al. 1994). Furthermore, GAD is the most common anxiety disorder in primary care settings. GAD is approximately twice as common in females as in males.

A range of data indicate that GAD is a relatively chronic disorder (Brown et al. 1994). In view of such data, some argue that in contrast to other anxiety disorders, a subtype of GAD (chronic, pervasive symptoms since childhood) may be better conceptualized as an underlying personality trait that increases one's vulnerability to developing anxiety disorders per se (Sanderson and Wetzler 1991). However, recent research suggests that some anxiety disorders such as social phobia may be likely to precede GAD (Brown et al. 2001).

Assessment

Differential Diagnosis

Anxiety secondary to an underlying general medical disorder must be distinguished from GAD. Table 7–2 provides a list of general medical disorders that may be associated with anxiety symptoms.

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Differentiating GAD from other anxiety disorders can be complicated. First, worry is a relatively generic feature of anxiety disorders (e.g., worry about panic attacks, worry about embarrassing oneself). In addition, there is a high level of comorbidity among the anxiety disorders and GAD in particular, which requires one to consider diagnosing multiple disorders as well as making differential diagnoses. The primary distinction between GAD and other anxiety disorders is the focus of the patient's concern. Patients with GAD experience uncontrollable worry about a number of different areas in their life. In fact, they often worry about their worrying (known as *metaworry;* Wells 1994). In contrast, the focus of concern for patients with other anxiety disorders is specific to their respective disorder.

Panic Disorder

Patients with panic disorder are worried about having a panic attack or the consequences of experiencing certain bodily sensations. Their focus is on internal states. What makes the differential diagnosis particularly confusing is that the worry experienced by patients with GAD can lead to a panic attack. However, unlike patients with panic disorder, patients with GAD are concerned primarily about some future event, not having a panic attack or the symptoms of anxiety per se. Another distinction is the course of onset of worry versus panic. Some patients with GAD are focused on the physical symptoms of their anxiety, and this can lead one to think that the preoccupation with bodily sensations is a sign of panic disorder. However, the onset of a panic attack is sudden and its peak typically lasts for several minutes, whereas the onset and course of GAD-related anxiety is usually longer and more stable.

Social Phobia

Because social concerns are a common area of worry for patients with GAD, they are often found to have comorbid social phobia (Sanderson et al. 1990). However, some guidelines for differentiating the two disorders can be made. The basic distinction is that GAD concerns are more global, focused on a number of different areas that may include social situations. In contrast, patients with social phobia are specifically concerned with being evaluated, em-

barrassed, or humiliated in front of others.

AUTHOR: The sentence above that begins "Because social concerns" cites Sanderson et al. (1990). Should the citation instead be Sanderson et al. (1991) or Sanderson et al. (1994)? If not, please add an entry for Sanderson et al. (1990) to the References section.

Obsessive-Compulsive Disorder

Although the differentiation between obsessive-compulsive disorder (OCD) and GAD seems obvious because of the behavioral rituals that are unique to OCD (Brown et al. 1994, 2001), there are still some cases that can be extremely difficult to differentiate. This is especially true of patients with OCD who do not have compulsions or have only mental rituals. The differentiation can be made, however, by assessing the focus of concern. Obsessions are focused on exaggerated or unrealistic expectations and are usually short-lived (e.g., "If I don't seal this envelop correctly, my kids will be injured on the way home from school"). In addition, obsessions often take an "if-then" form (e.g., "If I do/don't do/think something, then something bad will happen") or include vivid imagery (Wells 1994). Worry, on the other hand, is usually focused on future negative events that are not caused by the patient. According to nonanxious subjects, worry lasts longer, is more distracting, and usually consists of predominantly verbal thoughts as opposed to images (Wells and Morrison 1994). The thought content of a worry may be specified in a "what if" fashion, without a consequence being stated ("What if I get ill?"). Another difficult aspect of the differentiation of GAD and OCD is the fact that patients with GAD may engage in reassurance-seeking behaviors that can be somewhat ritualistic and superstitious. Patients with GAD may report feeling compelled to act to neutralize this worry (Wells and Morrison 1994) (e.g., to call one's wife at work to lessen a worry about something happening to her). However, these behaviors are not as consistent, methodical, or ritualized as compulsive behaviors in patients with OCD.

Mood Disorders

The final differentiation to be made is between GAD and mood disorders, especially major depression and dysthymia. More often than not, anxiety symptoms occur within the context of depression, and thus GAD is diagnosed as

a separate disorder only when the symptoms have occurred at least at some point independent of depression. However, regardless of DSM exclusionary criteria, the nature of cognitions associated with each disorder can be distinguished: Ruminations (common in depressive disorders) tend to be negative thought patterns about past events, whereas worries (associated with GAD) tend to be negative thought patterns about future events. This is consistent with theoretical conceptualizations of anxiety and depression that posit that depression is a reaction to uncontrollable, inescapable negative events, leading to feelings of hopelessness and helplessness and deactivation, whereas anxiety is a reaction to uncontrollable negative events that the person attempts or plans to escape from. (For a more detailed explanation, see Barlow et al. 1996.) Brown et al. (2001) presented data suggesting that without the rule-out criteria, 90% of patients with diagnosed dysthymia and 67% of patients with diagnosed major depression would be found to have concurrent GAD, but that with the rule-out criteria, only 5% had diagnosed GAD.

Assessment Measures

A number of self-report and interviewer rating scales can be used to assess and diagnose GAD. There has been considerable controversy about the reliability of the Hamilton Anxiety Rating Scale (Ham-A), but Shear et al. (2001) have recently developed a coding system that greatly improves the interrater reliability of this measure. In addition, for diagnostic purposes, the Anxiety Disorders Interview Schedule for DSM-IV-TR has been shown to reliably diagnose GAD in terms of severity. (See Brown et al. 2001 for more details.) A number of self-report measures can be used to determine the severity of GAD. In our review of the literature, the only measure that was common to all outcome studies was the Beck Depression Inventory (Beck et al. 1961). However, there are other scales exist more specifically related to GAD, including the Penn State Worry Questionnaire (Meyer et al. 1990), which measures uncontrollable worry; the Depression, Anxiety, and Stress Scales (Lovibond and Lovibond 1995), which measures stress-related symptoms; and the GAD questionnaire for DSM-IV-TR (GADQ-IV; Newman et al. 2002), which follows DSM criteria for GAD. These have all been shown to differentiate GAD from other anxiety disorders.

Pathogenesis

Worry

Worry is the major cognitive component of GAD. People who have GAD tend to worry most of the day, nearly every day. However, worry in itself is not pathological. It is an attempt to predict future danger and/or an attempt to gain control over events that appear uncontrollable (and usually negative or dangerous). However, it is clear that pathological worry is dysfunctional in that it is, by definition, excessive and/or unrealistic and feels uncontrollable. As a result, patients overpredict the likelihood of negative events and exaggerate consequences if the events were to occur. In a study by Abel and Borkovec (1995), 100% of patients with GAD described their worry as uncontrollable, whereas none of the nonanxious control subjects did. In addition, anxious subjects tend to selectively attend to threatening, personally relevant stimuli (Mathews 1990). Frequently, there is an implied belief that worry will make the world more controllable and predictable. Consistent with this, worriers report five major functions of worry: 1) superstitious avoidance of catastrophes, 2) actual avoidance of catastrophes, 3) avoidance of deeper emotional topics, 4) coping preparation, and 5) motivating devices (Borkovec 1994).

Research supports the idea that pathological worry has a functional role for people with GAD. Ironically, worry inhibits autonomic arousal in patients with GAD when they are shown aversive imagery. Worrying may cause the avoidance of aversive imagery, which is associated with an even greater emotional arousal (Borkovec et al. 1991). Thus, worry may be maintained by both the avoidance of certain affective states and the reduction of anxious states through the decrease in arousal that occurs along with worry or by the latter alone. Research has recently supported the role of worry in avoidance of emotions (Mennin et al., in press; Roemer and Orsillo 2002). Counterintuitively, relaxation has been shown to increase the amount of worry in some patients with GAD (Borkovec et al. 1991). It may be that for these patients relaxation signals a lack of control, triggering an increase in anxiety, or that patients sit quietly with their thoughts, causing greater exposure to their worries.

AUTHOR: 1) Borkovec et al. (1991) is cited twice above. Please add an entry for these authors to the References section.

2) Mennin et al. (in press) is cited above. Please update the citation if publication details are available.

Somatic Symptoms

In addition to worry, patients with GAD experience unpleasant somatic sensations. Although these usually increase during the course of a worry episode, both the worry and the somatic sensations can be described as relatively persistent and pervasive. The most common somatic symptom reported by patients with GAD is muscle tension. Often associated with worry and tension, patients may experience other symptoms, including irritability, restlessness, feeling keyed up or on edge, difficulty sleeping, fatigue, and difficulty concentrating.

Neurobiology

Multiple neurochemicals and neurotransmitter systems have been implicated as potential contributors to the development of GAD. These include the g-aminobutyric acid (GABA)–benzodiazepine (BZ) complex, serotonin (5-HT), norepinephrine, cholecystokinin, corticotropin-releasing factor, the hypothalamic-pituitary-adrenal axis, and neurosteriods (Connor and Davidson 1998). Work on the GABA–BZ complex and the serotonin system is perhaps particularly relevant to the clinical setting and to current pharmacological treatments of GAD.

Indeed, in view of the link between early antianxiety treatments and GABA, it was logical to focus on the role of the GABA–BZ complex in GAD. Studies have shown a lower number of peripheral BZ binding sites on platelets and lymphocytes in patients with GAD. This finding was reversed when patients were treated with a BZ (Rocca et al. 1991; Weizman et al. 1987). The development of BZ ligands has allowed work demonstrating decreased BZ binding in the left temporal lobe.

A range of preclinical studies demonstrate that the 5-HT system plays an important role in mediating anxiety. Patients with GAD have a decrease of 5-

HT in the cerebrospinal fluid (Brewerton et al. 1995) and reduced platelet paroxetine binding (Iny et al. 1994). Patients with GAD demonstrate exacerbation of anxiety symptoms after administration of the serotonin agonist m-chlorophenylpiperazine. In addition, several serotonergic agents are effective in the treatment of GAD.

AUTHOR: Brewerton et al. (1995) is cited above. Please add an entry for these authors to the References section.

Pharmacotherapy

The acute phase of anxiety in chronically anxious patients is managed best by anxiolytic medications such as BZs. However, remission of anxiety symptoms may not be sustained; less than 50% of chronically anxious patients will have sustained remission of symptoms after stopping acute medication treatment (Rickels and Schweizer 1990). Some chronically anxious patients may need to be treated for years. BZs have been used for a long time for the treatment of anxiety; however, they are sedating and with prolonged use do cause physical dependence (American Psychiatric Association 1990). Consequently, there has been a search for non-BZ anxiolytics; this initially produced buspirone and then the newer antidepressants (see Table 7–3).

Table 7–3 is currently at the end of the chapter. It will be positioned about here at a later phase of production.

Antidepressants

Given that comorbidity is common in GAD and that most antidepressants have shown treatment efficacy for GAD, antidepressants comprise a useful treatment choice for patients with GAD.

Tricyclic antidepressants such as imipramine have the advantages of single daily dosing and well studied and available generic preparations, which may result in cost savings for some patients. The disadvantages are the delayed onset of a number of weeks, anticholinergic side effects, potentially associated weight gain, orthostatic hypotension side effects, and high overdose lethality.

Imipramine is started at 25–50 mg/day and slowly increased each week. Therapeutic benefit is usually obtained at lower doses as compared to that of panic disorder, with the maximum dose of 300 mg. The main problem with this class of antidepressants is its side effect profile.

Venlafaxine, a serotonin norepinephrine reuptake inhibitor (Rickels et al. 2000), was the first antidepressant to receive U.S. Food and Drug Administration (FDA) approval for the treatment of GAD. Studies support both the short-term and long-term efficacy of this agent. Medication can be initiated at either 25 or 37.5mg/day, then titrated up to 75 mg/day of the sustained release form. The sustained release form helps to minimize potential side effects. The onset of action is 2–4 weeks or longer. Side effects are nausea, sweating, dry mouth, blurred vision, dizziness, and sexual dysfunction. Some of these side effects, such as the nausea, diastolic hypertension, and sexual dysfunction, appear to be dose related.

Selective serotonin reuptake inhibitors (SSRIs) are increasingly used in the treatment of anxiety disorders. Recently, paroxetine has been approved by the FDA for the treatment of GAD (Pollack et al. 2001). The advantage of this group of antidepressants lies in their relative tolerability and safer side effect profile. Patients with GAD require usual antidepressant doses of the SSRIs, although in some cases it is useful to begin with a relatively low starting dose (e.g., sertraline, 25mg; fluoxetine, 10mg; paroxetine, 10 mg) before titrating upward. Side effects may include transient gastrointestinal effects, weight changes, and sexual dysfunction.

It appears that antidepressants work more slowly than BZs but are slightly more efficacious than buspirone after 8 weeks of treatment. Given the fact that many patients treated for GAD may require chronic or intermittent pharmacotherapy, it is important to choose an antidepressant that can be well tolerated over the long term.

Benzodiazepines

Multiple randomized double-blind trials, many of them placebo-controlled, have definitively demonstrated the efficacy of BZs in the acute treatment of GAD (Greenblatt and Shader 1983a, 1983b; Rickels and Schweizer 1990). BZs have an early onset of efficacy (1 week) and continue to demonstrate efficacy after 4–8 weeks. Studies have employed primarily diazepam and

clorazepate or desmethyl diazepam but have also used alprazolam and lorazepam.

BZs are generally considered safe medications with a wide "therapeutic window" (Busto et al. 2000; Greenblatt and Shader 1983b; Rickels et al. 1990). Nevertheless, a variety of behavioral adverse effects have been attributed to BZs, particularly when administered in higher doses. These include sedative, attentional, and memory-impaired effects; rebound anxiety; and physical dependence and discontinuation symptoms after prolonged use (Greenblatt and Shader 1983a; American Psychiatric Association 1990).

Tolerance to the sedative effects may develop early, despite continued anxiolytic effects. However, on withdrawal of BZs, particularly those with a short half-life, 20% or more of patients were found to temporarily have HAM-A scores that were equal or higher than their pretreatment baseline score, indicating a rebound anxiety that, it has been speculated, might be an early precursor of BZ withdrawal syndrome (Rickels et al. 1988a). Other studies have reported similar rates of rebound anxiety when short-term BZ therapy was discontinued abruptly, ranging from 25% to 44% (Fontaine et al. 1984).

Alprazolam is often used for GAD, but its short half-life necessitates frequent dosing. The starting dose is 0.25–0.5mg every 4–6 hours. The dose should be increased every 4–6 days until relief is obtained. Clonazepam is an alternative that has a longer half-life, which allows for less frequent dosing. It is started at a dose of 0.5mg/day and increased to every 3–5 days until relief is obtained. Dependence may occur even after only a few weeks of use, and BZs must be discontinued carefully to avoid withdrawal symptoms.

Other than buspirone, BZs have until recently been the only class of drugs that was approved by the FDA for the treatment of GAD. Survey data (Balter and Uhlenhuth 1992) suggest that at least 10% of the adult population in the United States in 1990 had used a BZ at some time during the previous year. Recent community surveys found that almost 50% of patients meeting criteria for GAD have been treated with medication (Wittchen et al. 1994), with BZs being by far the most common class of drugs used (Woods et al. 1992). However, in view of their associated problems, BZs have been relegated by many physicians to treating only acute anxiety symptoms (Ashton 1994; Lader 1998).

AUTHOR: Woods et al. (1992) is cited above. Please add an entry for these authors to the References section.

Buspirone

Since the 1980s a number of double-blind studies, some of them placebo-controlled, have confirmed buspirone's efficacy in the alleviation of anxiety symptoms in patients with GAD. Most of these were placebo lead-in, randomized, double-blind studies designed to minimize any placebo effect. The primary measure of efficacy was the Ham-A. One of the most salient clinical features of buspirone, compared with the BZs, is its gradual, relatively slow onset of action, with many patients' symptoms taking several weeks to respond. This slow onset makes buspirone less useful for the treatment of transient, situational, or acute anxiety and may account for the perception by some clinicians that buspirone is a slightly less effective anxiolytic than BZs (Deakin 1993).

AUTHOR: Sentence above, "Since the 1980s" (ms: "In the past 20 years"): OK as edited to avoid dating the text?

A similar slow onset of action has been reported for the treatment of anxiety symptoms with antidepressants (Rickels et al. 1993). Psychic symptoms of anxiety such as worry, anger, irritability, and difficulty concentrating, which are diagnostically considered core features of GAD in DSM-IV-TR, respond better to buspirone when compared to BZs, whereas the reverse is true for somatic symptoms such as muscle tension and insomnia (Pecknold et al. 1989; Rickels et al. 1982). Similar observations have been made for antidepressant treatment of GAD (Rickels et al. 1993, 2000).

AUTHOR: Pecknold et al. (1989) and Rickels et al. (1982) are cited above. Please add entries for these authors to the References section.

5-HT_{1A} drugs such as buspirone appear to act as partial agonists at the postsynaptic 5-HT_{1A} population of serotonin receptors located at the hip-

pocampus, but as full agonists at the presynaptic 5-HT_{1A} serotonergic autoreceptors located in the dorsal raphe nucleus. Binding to these receptors enables these drugs to influence the activity of serotonergic neurons through receptor down-regulation. Chronic administration of azapirones, as with traditional antidepressants, causes a down-regulation of 5-HT_2 receptors, possibly explaining their limited antidepressant properties. Thus, patients with GAD and subsyndromal depressive symptoms may also demonstrate a decrease in depressive symptoms during treatment with buspirone (Feighner et al. 1982).

AUTHOR: Feighner et al. (1982) is cited above. Please add an entry for these authors to the References section.

Buspirone is 100% absorbed after oral administration (Jajoo et al. 1989). The oral bioavailability is approximately 5% after extensive first-pass metabolism, and a linear relationship between acute oral dose and area under the plasma concentration–time curve was demonstrated. The first-pass metabolism of buspirone is decreased by taking food with buspirone, but the clinical significance of these findings is not known. Buspirone is more than 95% bound to plasma proteins. It undergoes extensive metabolism so that less than 1% of an administered dose is excreted unchanged in the urine. There are seven major and five minor metabolites that have been identified; the major metabolic pathways are hydroxylation and dealkylation. The elimination half-life of buspirone in healthy subjects ranges from 2 to 11 hours.

AUTHOR: Jajoo et al. (1989) is cited above. Please add an entry for these authors to the References section.

Because buspirone does not exhibit cross-tolerance to BZs and thus does not block BZ withdrawal symptoms, patients should never be abruptly switched from a BZ to buspirone. When switching BZ-treated patients to buspirone, it is beneficial to initiate buspirone therapy concurrently for 2–4 weeks before tapering BZ gradually. Some studies in which BZ was abruptly replaced with buspirone have shown no benefit for buspirone facilitating BZ withdrawal, whereas other studies have shown some beneficial results when buspirone was started several weeks before the BZ taper process was initiated.

The recommended initial dosage of buspirone is 15 mg/day administered in 2–3 divided doses. The dosage should be increased to 30 mg daily to achieve an optimal therapeutic response. The recommended maximum daily dosage is 45 mg in the United Kingdom and 60 mg in the United States. There are no firm recommendations regarding dosage adjustments in patients with hepatic or renal insufficiency. Although there appears to be some reduction in the elimination of buspirone or the active *N*-dealkylated metabolite (1-PP) in such patients, interpatient variation in pharmacokinetic parameters is substantial. Nevertheless, dosage adjustments may be necessary in patients with severe renal or hepatic impairment. No age-related dosage adjustments are necessary in elderly patients.

AUTHOR: In the sentence above that begins "Although there appears to be": Please verify the term "1-PP" and spell out or define it if necessary.

The side effect profile of buspirone makes it a positive option for patients who do not require immediate relief of symptoms and who have not had previous treatment with a BZ. The most commonly reported adverse events are dizziness, nausea, headache, fatigue, lightheadedness, and dry mouth. There are very little published data on buspirone overdose, and the data that are available suggest that buspirone is not toxic in overdose. No deaths have been associated with an overdose of buspirone alone (Newton et al. 1986).

Hydroxyzine

Hydroxyzine is the only antihistamine studied in the early 1960s as an anxiolytic, and in the United States this agent has an indication for use in the symptomatic relief of "anxiety symptoms and tensions associated with psycho-neurotic condition or physical disease state." Hydroxyzine acts as an antagonist at H_1 receptors and to a lesser extent at muscarinic receptors and 5-HT_2 receptors. It has even less binding to $a_1$and dopamine 2 receptors (Kubo et al. 1987; Snyder and Snowman 1987). A large multisite family practice study, for example, compared a low dose of hydroxyzine (50 mg/day), given in divided doses, to placebo (Darcis et al. 1995). Statistically significant differences in favor of hydroxyzine were present at week 4, and this improvement was maintained for 1 additional week while patients received a placebo.

Thus, no evidence for discontinuation symptoms or withdrawal symptoms was observed after 4 weeks of hydroxyzine treatment. This provides an alternative for patients needing anxiolytic treatment and who may not want or be appropriate candidates for BZ treatment even for the short term.

AUTHOR: 1) Please cite the source of the quotation within the sentence above that begins "Hydroxyzine is the only antihistamine."

2) The sentence above that begins "Hydroxyzine acts as" cites Kubo et al. (1987) and Snyder and Snowman (1987). Please add entries for these authors to the References section.

Maintenance Pharmacotherapy

There are limited empirical data to direct the length of GAD treatment. Rickels et al. (1991) found that 25% of patients who had been treated for an average of 8 years and had been without BZ treatment for 3 years still had marked levels of anxiety. It appears that GAD is a chronic problem. For most patients, it is perhaps advisable to continue therapy for 6–12 months and then to discuss with the patient a trial period without the medication, monitoring closely for signs of relapse. Patients with more persistent GAD may require long-term treatment.

AUTHOR: The sentence above that begins "Rickels et al. (1991) found that" cites an author for which there is no entry in the References section. Please add one there.

Psychotherapy

In *Textbook of Anxiety Disorders*, we report on all outcome studies that have been published since 1990 and briefly describe a number of reviews (Huppert and Sanderson 2002). Here we summarize these findings. The Task Force of the Division of Clinical Psychology of the American Psychological Association, involved with identifying empirically supported treatments, has found that only techniques used in cognitive-behavioral therapy (CBT) meet crite-

ria to be included as empirically supported treatments for GAD (Chambless et al. 1998; Woody and Sanderson 1998). Although preliminary evidence (Durham et al. 1994) suggests that both long- and short-term psychodynamic treatments for anxiety disorders may be effective, adequate controlled studies have yet to be conducted.

AUTHOR: 1) Chambless et al. (1998) is cited above. Please add an entry for these authors to the References section.

2) Durham et al. (1994) is cited above. Please add an entry for these authors to the References section.

There have been eight studies conducted since the publication of DSM-III-R that have used these more conservative diagnostic criteria to examine the efficacy of CBT. Most studies have used CBT and at least one other treatment group, a minimum of a 6-month follow-up assessment, and a variety of outcome measures, usually a combination of clinician-rated and self-report measures. Possibly because of the fact that the eight studies used a variety of different methodologies and outcomes measures, there is a relatively wide range of improvement found across the studies. Consistently, improvement was rated greater by clinicians blinded to patients' treatment protocols than by patients' self-reports. Clinicians rated patients who participated in CBT to be improved between 34% and 68%; self-report measures yielded between 16% and 71% improvement. In addition, four of six studies showed further improvement at follow-up evaluation, whereas two showed no change. Behavior therapy or relaxation yielded slightly lower effects, with clinician ratings ranging between 17% and 61% and self-report measures showing between 11.3% and 42% change. Two studies showed continued improvement, two demonstrated maintained gains, and one reported deterioration at follow-up evaluation. The only other group reported in a number of studies was wait list, which demonstrated either no change or deterioration at both post-treatment and follow-up evaluations.

AUTHOR: In the sentence above that begins "Consistently, improvement was rated," does the edited phrase "clinicians blinded to patients' treatment protocols" express what was meant by "blind clinicians" in ms?

Most reviews have concluded that the effects of CBT, although significant and similar to most medications, are clinically modest and that improvements in treatment were still warranted. According to one review, studies that demonstrated the greatest effects were those that included patients who were not taking any medications. In addition, patients appeared to make greater treatment gains if they were recruited outside of psychiatric settings (e.g., by primary care physicians or through newspaper ads; Durham and Allan 1993). The data on the effect of comorbidity (both Axis I and Axis II) on outcome has been inconsistent (Durham and Allen 1993); however, presence of comorbid personality disorders likely increases dropout rates.

A number of techniques comprising the treatments in the above-mentioned studies appear to have positive additive influence on treatment outcomes (Huppert and Sanderson 2002): psychoeducation, self-monitoring, cognitive restructuring, relaxation, worry exposure, and worry behavior control. These techniques should be taught in the context of a good therapeutic alliance. Each is discussed briefly below.

Psychoeducation

Providing education about GAD is a way to introduce the treatment rationale and thus possibly facilitate treatment compliance. We recommend that psychoeducation be provided first in written form and then discussed in a session.

Self-Monitoring

Self-monitoring is one of the most basic yet essential parts of CBT. Monitoring is used both as an assessment procedure (to identify the context and content of worry) and a treatment strategy (becoming aware of patterns and focusing on worry and anxiety may lead to reduction in anxiety and worry). Each time the patient feels anxious, he or she should record when, where, and the intensity of the experience, including what symptoms are present. The ba-

sic aspects of worry monitoring are date, time begun, time ended, place, event (trigger), average anxiety (from 1to 8), peak anxiety (1–8), average depression (1–8), and topics of worry. Once cognitive restructuring is introduced, monitoring the specific thought process involving worries is added.

AUTHOR: Should the head below that begins "Cognitive Therapy" instead read "Cognitive-Behavioral Therapy: Restructuring the Worry"?

Cognitive Therapy: Restructuring the Worry

As stated above, worry is a predominantly cognitive process, thereby making cognition an important aspect of to be addressed. Cognitive therapy is an effective strategy for this purpose. Patients with anxiety disorders, and with GAD in particular, overestimate the likelihood of negative events and underestimate their ability to cope with difficult situations (Beck and Emery 1985). These cognitive distortions can play a major role in the vicious circle of anxiety, and they accentuate the patient's feelings of danger and threat. Thus, cognitive therapy targets the faulty appraisal system and attempts to guide the patient toward more realistic, logical thinking.

Relaxation

Relaxation exercises are an important component of most CBT-oriented treatments for GAD. Their function is to reduce the physiological correlates of worry and anxiety by lowering the patient's overall arousal level. Most recent methods of relaxation have adapted a flexible concept of teaching relaxation, rather than insisting on any particular method. Thus, although progressive muscle relaxation techniques are emphasized for most patients and have the most empirical support, if a patient prefers another method and is able to use it effectively, then we recommend continued use of that strategy.

Worry Exposure/Stimulus Control

Another technique that has recently been developed but has not gained empirical support to date is worry exposure. As noted above, perpetuation of worry in patients with GAD may be due to ineffective processing that is a result of avoiding concentration on the worry itself. Instead of focusing on a

worry, patients attempt to avoid fully processing the worry through various behaviors, as well as through constant shifting of worries. Thus, Brown et al. (1993) described a technique in which patients purposely expose themselves to both worry and images associated with the worry for an extended period of time. The purpose is to have the patient activate the worst possible outcome in order to process it and habituate to the anxiety associated with it. Borkovec (1983) developed a similar technique that he referred to as "stimulus control."

AUTHOR: Brown et al. (1993) is cited above. Please add an entry for these authors to the References section.

2) Borkovec (1983) is cited above. Please add an entry for these authors to the References section.

Worry Behavior Prevention

Many patients who worry may behave in certain ways to try to avoid it. As noted above, uncontrollable worry, although an aversive experience, may still serve the function of avoiding an even more intolerable experience (i.e., by focusing on the worry instead of the other experience). To prevent worry behaviors, the patient carefully monitors his or her actions when he or she notices the onset of worry. Both subtle and explicit variants of these avoidance behaviors are detected through careful monitoring, assessment, and questioning. Then, similar to what is done in the technique of response prevention used in the treatment of OCD, the patient is asked to refrain from these behaviors and instead to use the techniques described above to cope with the worry. If there are many behaviors or if the patient is too anxious to just give up the worry behaviors, hierarchies are created to assist the patient in systematically giving up the behaviors, starting with easier ones and moving on to more difficult behaviors, making the task considerably less overwhelming (e.g., checking the child's forehead once daily, then every other day, and so on).

Other Techniques

If some people with GAD are avoiding affect, then simply eliminating the worry through relaxation and cognitive techniques will not work unless they

are taught other strategies to deal with the triggers for the affect. A number of groups are attempting to address these issues through different techniques. Borkovec (1997) proposed that interpersonal strategies (Safran and Segal 1990) and emotion-focused strategies (Greenberg and Safran 1988) be tested in addition to cognitive techniques, to see whether processing of interpersonal difficulties facilitates activation and modification of affective structures (Foa and Kozak 1986). Similarly, Mennin et al. (in press) are working on new cognitive-behavioral strategies to accomplish the same goals. Roemer et al. (2002) have worked on integrating treatment strategies from a form of therapy that focuses on preventing experiential and behavioral avoidance called Acceptance and Commitment Therapy (Hayes et al. 1999). Sanderson et al. have used schema-focused therapy with those patients whose disorder had not responded to traditional CBT (McGinn et al. 1994). This approach focuses on addressing underlying "early maladaptive schemas" that theoretically influence current symptomatology. On the basis of these ideas, one of us (J.D.H.) has recently begun to use new strategies, including having the patient develop a list of all emotions, rank-ordering the difficulty they have in coping with them, and then going through a cognitive-behavioral analysis of each emotion. This is followed by a hierarchy of imaginal and in vivo situations that encourage the emotional experiences that have previously been avoided. Clinical experience suggests that these additional techniques may lead to further symptom improvement for patients with GAD.

AUTHOR: Borkovec (1997) and Greenberg and Safran (1988) are cited above. Please add entries for these authors to the References section.

2) If publication details are available, please update the above citation of Mennin et al. (in press).

3) The sentence above that begins "Sanderson et al. have used schema-focused" ends with a citation for McGinn et al. (1994). Should this be Sanderson et al. (1994)? Please correct as necessary.

Conclusion

GAD is a common, persistent, debilitating disorder that often goes untreated.

Both pharmacological and psychosocial treatments, especially CBT, help alleviate many of the symptoms of GAD. However, more research is needed on how to further improve patients' quality of life and on the optimal combination and sequencing of CBT and medication.

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Table 7–1. DSM-IV-TR diagnostic criteria for generalized anxiety disorder

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).

B. The person finds it difficult to control the worry.

C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not for the past 6 months). **Note:** Only one item is required in children.
   (1) restlessness or feeling keyed up or on edge
   (2) being easily fatigued
   (3) difficulty concentrating or mind going blank
   (4) irritability
   (5) muscle tension
   (6) sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)

D. The focus of the anxiety and worry is not confined to features of an Axis I disorder, e.g., the anxiety or worry is not about having a panic attack (as in panic disorder), being embarrassed in public (as in social phobia), being contaminated (as in obsessive-compulsive disorder), being away from home or close relatives (as in separation anxiety disorder), gaining weight (as in anorexia nervosa), having multiple physical complaints (as in somatization disorder), or having a serious illness (as in hypochondriasis), and the anxiety and worry do not occur exclusively during posttraumatic stress disorder.

E. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

F. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism) and does not occur exclusively during a mood disorder, a psychotic disorder, or a pervasive developmental disorder.

Table 7–2. General medical disorders associated with anxiety symptoms

Anemia
Arrhythmias
Angina
Asthma
Early dementia
Fibromyalgia
Gastroesophageal reflux disease
Hyperparathyroidism
Hyperthyroidism
Hypoglycemia
Irritable bowel syndrome
Mitral valve prolapse
Obstructive lung disease
Parkinson's disease
Paroxysmal atrial fibrillation
Pheochromocytoma
Pulmonary embolus
Substance abuse/withdrawal (including narcotics, benzodiazepines, or β-blockers)
Seizure disorders
Supraventricular tachycardia
Vestibular dysfunction

AUTHOR: please double-check all dosages in Table 7–3.

Table 7–3. Medications for generalized anxiety disorder

Class of medication	Dose range	Advantages	Disadvantages
Antidepressants			
Selective serotonin reuptake inhibitors	Fluoxetine, 20–60 mg Paroxetine, 20–60 mg Sertraline, 50–200 mg	Single daily dosing Effective at lower doses No concern with addiction Low lethality for overdose	Delay of onset of action Sexual dysfunction Weight gain Insomnia Discontinuation syndrome
Serotonin and noradrenaline reuptake inhibitor	Venlafaxine XR, 150–300 mg	Single daily dosing with an extended release preparation No concern for addiction Low lethality for overdose	At higher doses, some incidence of increased blood pressure Nausea Insomnia Sexual dysfunction Withdrawal syndrome
Tricyclic antidepressants	Imipramine, 150–250 mg	Single daily dose Low cost of medication	Delayed onset of action High overdose lethality Anticholinergic Weight gain

Table 7–3. Medications for generalized anxiety disorder *(continued)*

Class of medication	Dose range	Advantages	Disadvantages
Benzodiazepines			
Long-acting	Diazepam, 5–15 mg Clonazepam, 0.5–2 mg	Long half-life Acute onset of action Withdrawal better tolerated Low cost of medication	Twice-daily dosing Sedation Withdrawal/dependence Effects motor coordination and memory Alcohol interaction
Short-acting	Alprazolam, 1–6 mg	Acute onset of action Low cost of medication	Short half-life Dosing three to four times a day Withdrawal/dependence Effects motor coordination and memory Alcohol interaction

Table 7–3. Medications for generalized anxiety disorder *(continued)*

Class of medication	Dose range	Advantages	Disadvantages
Azaspirones			
Buspirone	15–60 mg	No concern with addiction Low lethality Treats comorbid major depressive disorder No motor or memory impairment No withdrawal or dependence	Twice-daily dosing May be less effective in patients also taking benzodiazepines Dizziness Nausea Headache