MAGELLAN BEHAVIORAL HEALTH/ BLUE CROSS BLUE SHIELD OF NORTH CAROLINA

Guideline for the Diagnosis and Management of Generalized Anxiety Disorder for Primary Care Physicians

This guideline includes recommendations for the most appropriate method of diagnosing and managing Generalized Anxiety Disorder based on the medical literature and peer review. It does not address the treatment of depression, or of other anxiety-related disorders such as panic disorder, obsessive-compulsive disorder, or the treatment of personality disorders. This guideline is not a substitute for clinical judgment and may not apply to all patients. Following this guideline does not guarantee a good outcome for a specific patient, although following the guideline should result in the best outcome for most patients.

Establishing the Diagnosis of Generalized Anxiety Disorder

Anxiety disorders are the most frequently diagnosed family of mental illnesses. Among them, Generalized Anxiety Disorder (GAD) is the most common. (1) The disorder occurs most often in women, with a one-year population prevalence of about 3 percent. (2)

Table I

Diagnosis of GAD
1. This disorder is defined by an extended period of excessive anxiety and worry, which extends at least six months.
2. The patient cannot control the worry.
3. The worry is associated with 3 of the following symptoms:
a. restlessness or feeling keyed up or on edge
b. being easily fatigued
c. difficulty concentrating/mind going blank
d. irritability
e. muscle tension
f. sleep disturbance
4. The worry is not associated with another psychiatric illness.
5. The anxiety, worry, or physical symptoms cause significant distress and/or impairment in social, occupational, or other functioning.
6. The worry is not due to the effects of a substance, medication, or medical condition, and does not occur as a result of another psychiatric disorder. (3)

Source: American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, 1994.

Many more patients may suffer from severe anxiety, but may not meet all the DSM IV criteria for GAD. This group may be diagnosed as having anxiety, not otherwise specified, as acute distress disorder, or as adjustment disorder with anxious mood. Two thirds of patients diagnosed with GAD may have an associated psychiatric disorder such as major depression (48%). Another study found that at least 10% of patient with GAD also had panic disorder, phobias, and/or substance abuse problems. (2)

Risk factors for anxiety disorders include a family history of anxiety disorders and/or alcoholism, a history of depression, age less than 40 at onset of symptoms, and a history of alcohol abuse. (5)

Patients with GAD are at some risk for suicide. A suicide risk evaluation should be conducted on all patients with an anxiety-related diagnosis. The physician is directed to the Practice Guideline for Assessing and Managing the Suicidal Patient and accompanying tip sheet for an in depth instruction on evaluating suicide risk.

Patients with GAD often present to the primary care physician with a variety of complaints. Their dysphoria may be expressed as “feeling crazy” or “bad nerves.” Patients with this disorder often will express their anxiety in somatic terms. Patients with anxiety disorders often present with the following:

Table II **Presentation of GAD**

1. Multiple medical visits
2. Multiple unexplained symptoms
3. Work/relationship dysfunction
4. Unexplained fatigue
5. Weight gain or loss
6. Sleep disturbance
7. Multiple worries or distress
8. Medically unexplained symptoms of autonomic excitation:
    a. cardiac (chest pain, palpitations, dyspnea)
    b. gastrointestinal (especially epigastric distress, irritable bowel syndrome)
    c. neurologic (headache, dizziness, paresthesias)
    d. panic
    e. respiratory (hyperventilation)
9. Emergency room visits for unexplained somatic symptoms
10. Unexplained pain (2,5)

The primary care physician often is challenged in the elicitation of information from patients with GAD. People with anxiety disorders sometimes prefer to express their anxiety symptoms in physiologic terms and may be reluctant to label themselves as anxious. To gather diagnostic information the physician should take a non-critical, sympathetic approach. The following questions may be useful in the diagnostic interview:

Table III **Useful Questions in Diagnostic Interview**

1. Are you a worrier?
2. Are you a high-strung or nervous person?
3. Do you ever "out of the blue" experience an attack of intense fear or losing control, dying, fainting, "going crazy," or severe embarrassment?
4. Are there places (such as church, malls, crowds) that you avoid or endure?
5. Are there situations (parties, meetings, classes) that you avoid or endure?
6. How do your symptoms affect your daily life?

To assist physicians in screening for GAD, Bohn developed a mnemonic device: "Does Mr. Fisc worry excessively about minor matters?" In a diagnostic interview, the examiner merely substitutes "you" for "Mr. Fisc," saying "Do you worry excessively about minor matters?" If the patient answers in the affirmative, then the practitioner can determine if three or more of the motor symptoms associated with GAD by using the mnemonic "Mr. Fisc." Each letter of the mnemonic stands for:

Table IV

Mnemonic for GAD	
M =	Muscle tension
R =	Restlessness
F =	Fatigue
I =	Irritability
S =	Sleep
C =	Concentration (difficulty concentrating)(4)

Patients presenting with symptoms of severe anxiety may actually have an underlying medical illness that causes or contributes to their emotional symptoms. A careful past medical history is crucial to rule out medical disorders related to anxiety. The following are a number of medical illnesses that may display symptoms suggestive of anxiety disorders:

Table V	Medical causes of anxiety
	1. thyroid illnesses
	2. stroke
	3. pheochromocytoma
	4. parathyroid illness
	5. cardiac illness
	6. vestibular nerve disease
	7. mitral valve prolapse

Certain medications and substances of abuse have been demonstrated to contribute to anxiety disorders. Withdrawal from benzodiazepines, alcohol, cocaine, hypnotics, and amphetamines can be associated with increased anxiety. A careful history will ascertain the use of these medications/substances:

Table VI	Medications that can cause anxiety
	1. steroids
	2. thyroxine
	3. theophylline
	4. neuroleptics
	5. SSRIs
	6. tricyclic antidepressants
	7. antihistamines
	8. idiosyncratic reactions to other medications

Treatment of Generalized Anxiety Disorder

Both pharmacotherapy and psychotherapy have been demonstrated to be effective in treating GAD. In formulating a treatment plan, the practitioner should consider the severity of symptoms, presence of co-morbidity, presence of psychosocial stressors, and patient preferences. The PCP can provide education, support, and reassurance to the patient with GAD. This includes asking patients for their ideas of the causes of their anxiety. Ascertaining the patient's expectations of recovery is also critical. The practitioner must reassure the patient that anxiety symptoms are not dangerous and can be treated with adequate therapy, education, and medication. Referral to a mental health professional may be indicated if support and reassurance, along with pharmacological interventions, are not successful.

Cognitive-Behavioral Therapy

Cognitive-behavioral therapy (CBT) has been demonstrated to be efficacious in relieving the symptoms of GAD in randomized controlled trials. Recovery rates may be as high as 50% after six months of CBT. The combination of CBT and medication may prove to be more efficacious than either medication or psychotherapy alone.

Cognitive-behavioral therapy consists of the patient working with a therapist trained in cognitive-behavioral methods on a once per week basis over a six to twelve week period. The therapist assists the patient in identifying untrue thoughts associated with anxiety, and facilitates changing these thoughts to be more realistic. The therapist assumes an active role in treatment rather than to listen passively. The therapist is trained to correct bias, misinterpretation and unjustified generalizations of thoughts and perceptions. Homework is an essential part of this treatment. Patients are asked to keep a diary recording their thoughts and feelings, which cause and which relieve anxiety.

Medications

In establishing a supportive and collaborative relationship with each patient, the risk, benefits and side effects of each medication should be explained. It should also be emphasized that medications are not a panacea that solve all problems. After the first 4 to 8 weeks of treatment the physician and patient should be able to determine the efficacy and side effects of the medications chosen. Lack of efficacy after this

time may indicate a need to increase the dosage of medication or to change medications. One also should consider the accuracy of the diagnosis if early interventions fail to produce a positive result. (2)

Benzodiazepines

Benzodiazepines have the greatest degree of efficacy and safety in the treatment of GAD of any medication class. (2) Benzodiazepines with short half-lives (alprazolam and lorazepam) as well as those with long half-lives (clorazepate and diazepam) have been found to be efficacious in randomized double blind controlled trials. The use of these drugs should be limited to acute treatment (2-4 weeks) to prevent tolerance to therapeutic doses. These medications can be given on a prn basis. If multiple episodes of anxiety are to be treated with benzodiazepines, they should be interrupted by 2- to 4-week trials of benzodiazepine-free periods. A large number (40%-80%) of patients treated with these medications for 4 months or more develop tolerance and can have a discontinuation or withdrawal syndrome. Patients may experience rebound or withdrawal symptoms, which include tremor, anxiety, agitation, and dysphoria. Patients on this class of medications should be tapered according to the guide presented below:

Table VII **Tapering Benzodiazepines**

Length of treatment	Length of taper
2 weeks	0-2 days
4 weeks	0-2 weeks
8 weeks	2-3 weeks
6 months	4-8 weeks
$\geq$ 12 months	2-4 months

Some authors suggest adding other psychotropic medications to help ease withdrawal symptoms. These medications include tricyclic antidepressants, SSRIs, or buspirone before, during, and after the taper. (2)

5-HT(1a) Partial Agonists

Buspirone has been used to treat GAD for 25 years. Several studies indicate that buspirone has comparable efficacy to benzodiazepines in treating GAD. Patients on this medication may maintain their improvement longer than on treatment with benzodiazepines, although the onset of action is slower. Efficacy of buspirone may be decreased by recent benzodiazepine treatment. Side effects of this medication include gastrointestinal problems, excitement, dizziness, headaches, nervousness, and light-headedness. (5)

Tricyclics

Imipramine is the only tricyclic that has been demonstrated to be efficacious in the treatment of GAD. One study demonstrated that imipramine was more effective in the treatment of GAD, after 8 weeks of the medication, than diazepam. The most common drawbacks of tricyclics are their side effects. These include drowsiness, dry mouth, urinary hesitancy, constipation, weight gain, and tremor. Tricyclics can be lethal in overdose. (2,5)

Selective Serotonin Reuptake Inhibitors

To date, only paroxetine of this category of medications has been FDA approved for GAD. This medication at a dosage of 20-50mg per day was found to be more effective than benzodiazepines and placebo in reducing the symptoms of GAD in randomized controlled trials. Fluvoxamine and sertraline have also been shown to be effective in reducing GAD symptoms. Side effects of the SSRIs include mild nausea, sedation, dry mouth, headache, sexual dysfunction, and constipation. Central serotonin syndrome can occur if the SSRI is combined with other serotonergic agents.

Serotonin-Norepinephrine Reuptake Inhibitors

Venlafaxine XR has been approved by the FDA in the treatment of GAD. Studies demonstrated that dosages from 75-225 mg per day demonstrate efficacy. Several studies indicate superiority over buspirone

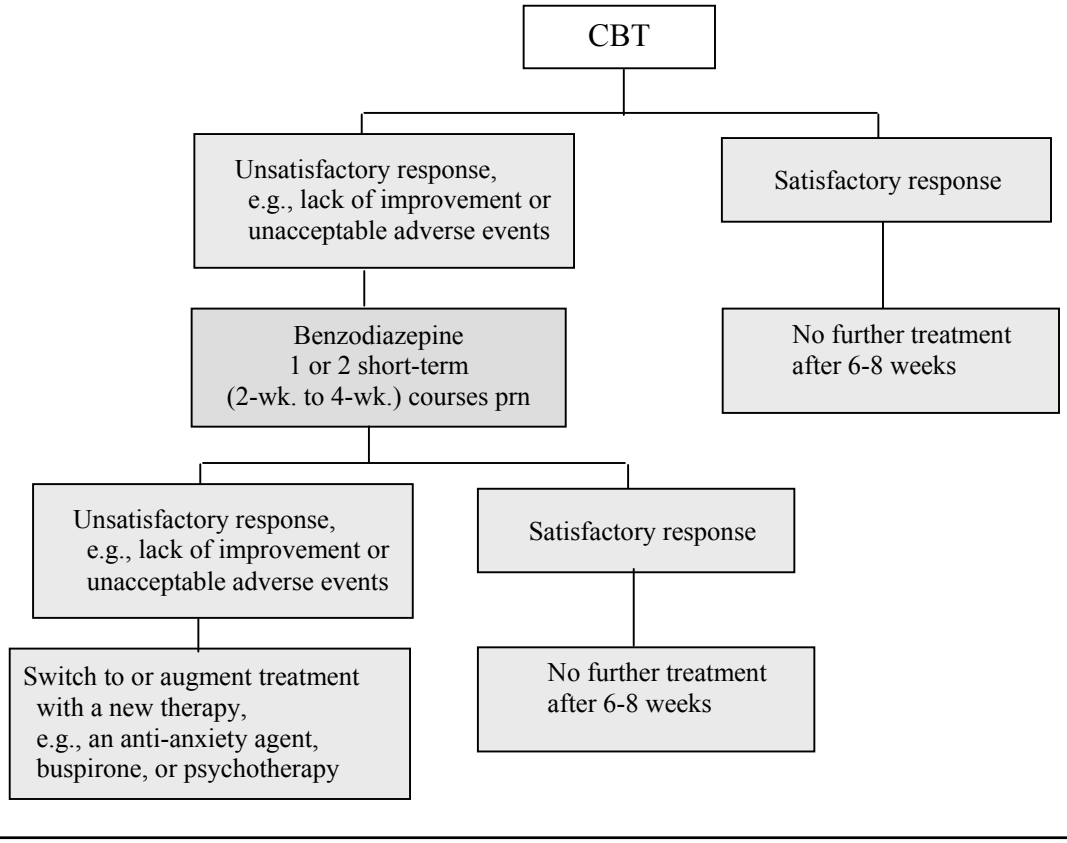
and placebo in randomized controlled trials. The most common side effects with this medication include somnolence, nausea, dry mouth, dizziness, sweating, sexual dysfunction, constipation, and anorexia.

Combination therapy

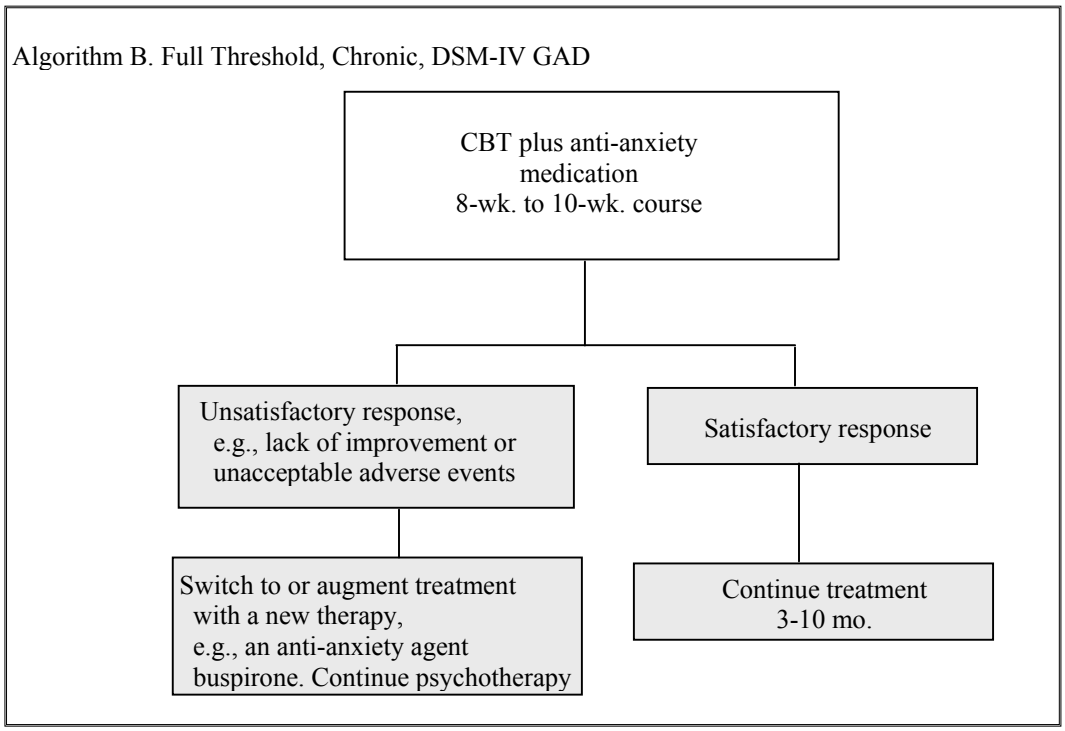
For some patients who do not respond to monotherapy with an SSRI or venlafaxine XR, addition of a benzodiazepine can be useful. Some practitioners recommend adding a benzodiazepine initially to an antidepressant, withdrawing it after 3-4 weeks when the antidepressant becomes effective. Benzodiazepines can provide early relief of the symptoms of GAD and can counteract early, mild side effects found with antidepressants.

Patients with symptoms of mild anxiety that wax and wane may be treated effectively with benzodiazepines alone according to the algorithm below adapted from Rickels, et al. (2)

Algorithm A. Sub-Threshold GAD Symptoms With a Short Duration (<6 months)



Patient with a more severe, resistant form of GAD may require combination therapy as illustrated in algorithm 2. (2)



The following table is a guide for anti-anxiety agent medication doses. Selection of an appropriate dose cannot be made from this table alone, and the practitioner is encouraged to consult with additional authoritative sources such as the Physicians Desk Reference or Merck Manual.

Before prescribing a dose, the practitioner should consider whether the patient's current behavioral and medical conditions, the patient's past and current responses to an agent, potential synergies with other medications, and any other factors that could alter an agent's pharmacodynamics or pharmacokinetics.

Be sure to review the side effects of the medication selected with the patient for common side effects. If the patient finds a side effect intolerable, do not hesitate to change medications. Have the patient consider whether or not the side effects are worse than the actual illness. Side effects may be reduced by trying to lower the dose or using 2- to 3-day drug holidays once or twice a month.

Table VIII- Medication Doses for Generalized Anxiety Disorder

Generic (trade) name	Starting dose (mg/day)	Usual adult dose (mg/day)	Dose reduction in older adults?
Selective Serotonin Reuptake Inhibitors			
paroxetine (Paxil)	10-20mg	20-50mg	yes
sertraline (Zoloft)	25-50mg	50-200mg	no
fluvoxamine (Luvox)	50mg	100-300mg	yes
Serotonin/Norepinephrine Reuptake Inhibitors			
venlafaxine XR (Effexor XR)	37.5-75mg	75-225mg	no
Non-benzodiazepine anxiolytic			
buspirone (BuSpar)	7.5-15mg	20-60mg	no
Benzodiazepine anxiolytics (short half-life)			
alprazolam (Xanax)	0.25-0.5mg	0.5-2mg	yes
lorazepam (Ativan)	0.5-1mg	1-4mg	yes
Benzodiazepine anxiolytics (long half-life)			
diazepam (Valium)	2mg	2-10mg	yes
clorazepate (Tranxene)	3.75-7mg	7-15mg	yes
chlordiazepoxide (Librium)	10-30mg	15-100mg	yes

References:

(1) Mental Health: *A Report of the Surgeon General*. Department of Health and Human Services, National Institute of Mental Health, 1999. 235-237.
(2) Rickels Karl, and Rynn Moira. *Pharmacotherapy of Generalized Anxiety Disorder*. Journal of Clinical Psychiatry 2002; 63:9-16.
(3) Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. American Psychiatric Association, 1994.
(4) Bohn Paul.Mnemotic Screening Device for Generalized Anxiety Disorder. American Journal of Psychiatry 2000; 157:837.
(5) Health Care Guideline: Major Depression, Panic Disorder and Generalized Anxiety Disorder in Adults in Primary Care. Institute for Clinical Systems Improvement. May, 2002: 3-55.
(6) *Clinical Practice Guidelines for Assessing and Managing the Suicidal Patient*. Magellan Behavioral Health 2000; Tip sheet 2002.