



**Magellan Clinical Practice Guideline
for the Assessment and Treatment of
Generalized Anxiety Disorder in Adults**

Magellan Clinical Practice Guideline Task Force

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Purpose of This Document

Magellan Health Services (Magellan) has developed the *Clinical Practice Guideline Assessment and Treatment of Generalized Anxiety Disorders (GAD) in Adults* for use by providers working with Magellan members who may have these disorders. This guideline is a research-based document that covers the psychiatric management of adult patients with GAD, reviews clinical features, epidemiology, assessment and treatment planning including psychotherapy and pharmacotherapy. For detailed information on the management of children and adolescents with GAD, see the American Academy of Child and Adolescent Psychiatry (AACAP) *Practice Parameter for the Assessment and Treatment of Children and Adolescents with Anxiety Disorders (2007)*.

The purpose of this document is to summarize recommendations from a literature review conducted for GAD through March 2010. The rationale for this summary, presented in table format, is to avail clinicians of evidence- and consensus-based guidance on assessment and treatment of GAD in one location for ease of use and reference. However, clinicians also should become familiar with the references cited in the document.

As with all guidelines, this document is intended to augment, not replace, sound clinical judgment. As a matter of good practice, clinically sound exceptions to this practice guideline should be noted in the member's treatment record, with documentation of the clinical reasoning for making the exception. Magellan periodically requests treatment records from providers in order to monitor compliance with clinical practice guidelines. Additionally, this guideline does not supersede Food and Drug Administration (FDA) determinations or other actions regarding withdrawal or approval of specific medications or devices, and their uses. It is the responsibility of the treating clinician to remain current on medication/device alerts and warnings that are issued by the FDA and other regulatory and professional bodies, and to incorporate such information in his or her treatment decisions.

Provider Feedback

Magellan welcomes feedback on our clinical practice guidelines. We take all suggestions and recommendations into consideration in our ongoing review of the guidelines. Questions or comments may be submitted via mail or e-mail to:

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Generalized Anxiety Disorder in Adults: Table of Recommendations Based on Recent Literature Review

Magellan conducted a review of the clinical literature on assessment and treatment of GAD in adults. Key relevant recommendations from this literature are summarized below. Magellan encourages providers to be familiar with this information and consult the referenced research articles.

GENERALIZED ANXIETY DISORDER (GAD) IN ADULTS	
Procedure	Recommendations
Assessment	<p>Generalized anxiety disorder (GAD) is a common condition with a lifetime prevalence of 5.7% and a 1-year prevalence of 3.1%. (Bandelow et al., 2008; Kessler, Chiu, et al. 2005) The age of onset of GAD differs from that with other anxiety disorders, the majority of cases presenting were between 35 to 45 years of age. It may be the most common anxiety disorder among the older population (55 to 85 years). Typically, symptoms fluctuate in intensity over time, but GAD is usually a chronic condition where patients report reduced quality of life related to general physical, mental and social health and being unable to function as usual an average of 1.5-5.4 days per month. (Collins et al., 2009; Baldwin, 2004) GAD appears to be more common in primary care than in the general population, suggesting that these patients are high users of primary care resources. GAD is diagnosed more frequently in women than in men (about 2 to 1). (Canadian Psychiatric Association Anxiety Disorder Guidelines, 2006) Although GAD does “stand on its own as a disorder with distinct onset, course, impairment and prognosis...” it is one of the most highly comorbid psychiatric conditions. (Hales et al., 2010, para. 2)</p> <p>According to the <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)</i>, published by the American Psychiatric Association in 2000, GAD is an anxiety disorder characterized by persistent, excessive and difficult-to-control worry, which may be accompanied by several psychic and somatic symptoms, including suicidality. Clinical presentations often include somatic illness, pain, fatigue, depression and problems sleeping. Diagnosis of GAD must meet the following DSM-IV-TR criteria:</p> <ul style="list-style-type: none"> • Determine if symptoms are characterized by persistent and excessive anxiety and worry about common events or activities, occurring on more days than not, for 6 months or more. Worry may focus on finances, marriage, children, personal or family health, job performance, or security; the extent of anxiety is in excess of what might be considered reasonable given the reality of the situation. • Assess if difficulty controlling worry is associated with at least three additional symptoms, including restlessness or feeling keyed up or on edge, easy fatigability, difficulty concentrating or mind going blank, irritability, muscle tension and sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep). • Determine if the focus of the anxiety is confined to features of an Axis I disorder. The diagnosis of GAD should be made only when the focus of anxiety or worry is unrelated to the other disorder, such as worry about entering a social situation (social anxiety disorder) or as a response to an identified stressor (adjustment disorder), having a panic attack (as in panic disorder), gaining weight (as in anorexia nervosa), being contaminated (as in obsessive-compulsive disorder), having multiple physical complaints (as in somatization disorder), having a serious illness (as in hypochondriasis). Also, in GAD, the worry does not occur exclusively during post-traumatic stress disorder. • Ascertain whether the anxiety, worry or physical symptoms cause clinically significant distress or impairment in social, occupational or other important area of function.

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	<ul style="list-style-type: none"> Verify that 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, and does not occur exclusively during a mood disorder, a psychotic disorder or a pervasive developmental disorder. (DSM-IV-TR, 2000) <p><u>Assessment Scales</u> – There is evidence from a criterion-standard study that the seven-item anxiety scale (GAD-7) has reliability, criterion, construct, factorial and procedural validity, and may be an efficient tool for screening for GAD and assessing its severity in clinical practice and research. (Spitzer, 2006) Two other symptom severity measurement instruments have been developed and tested for GAD. The Generalized Anxiety Disorder Severity Scale (DGSS) is comprised of eight DSM-IV GAD symptoms for assessment of frequency and intensity. The DGSS demonstrated good internal reliability with the Hamilton Anxiety Scale (HAM-A) and Clinical Global Impression Severity Scale (CGI-S) (Stein, Fincham et al., 2009). The newly developed Daily Assessment of Symptoms-Anxiety (DAS-A) scale was also shown to have validity as a new instrument to assess onset of symptomatic improvement in GAD. (Feltner et al., 2009)</p> <p><u>Epidemiological Data</u> – Data from the U.S. National Co-morbidity Survey Replication (NCS-R) showed that GAD prevalence rates changed when using a broader definition of episode from the required 6 months. Community epidemiological data for the range of 1-12 months showed that <i>lifetime prevalence</i> changed from 6.1% to 4.2-12.7%; <i>12 month prevalence</i> changed from 2.9% to 2.2-5.5% and <i>30 day prevalence</i> changed from 1.8% to 1.6 to 2.6%. Cases with episodes of 1-5 months did not differ greatly from those with episodes greater than or equal to 6 months in onset, persistence, impairment, co-morbidity, parental GAD or socio-demographic correlates. These findings suggest that a large number of people suffer from a GAD-like syndrome with episodes of less than 6 months duration and question the basis for excluding these people from a diagnosis of GAD. (Kessler, Brandenburg, et al. 2005)</p> <p><u>Risk Factors</u> – A recent study found that GAD (co-morbid or pure) was associated with several risk factors across multiple domains of risk during childhood: maternal internalizing symptoms (i.e., the mother’s symptoms of anxiety and depression manifesting as insomnia, hopelessness, tension, somatic complaints), low socioeconomic status, maltreatment, internalizing, conduct problems and negative emotionality. (Moffitt, Caspi, et al. 2007)</p> <p><u>Co-morbid psychiatric conditions</u> – In the majority of cases, GAD presents with other psychiatric conditions, including major depression, dysthymia, bipolar disorder, panic or other anxiety disorders, alcohol and other substance abuse, and personality disorders. The co-morbidity rate with major depression is about 59% and 56% with other anxiety disorders. (Hales et al., 2010; Canadian Psychiatric Association Guideline, 2006) One study showed that the generalized anxiety disorder – major depression disorder (GAD-MDD) co-morbidity may affect more of the adult population and constitute a greater health burden than previously thought. Another study of the association between GAD and MDD demonstrated that generalized anxiety usually began before or concurrently in 37% of depression cases, but depression began before or concurrently in 32% of anxiety cases. Also, cumulatively, 72% of lifetime anxiety cases had a history of depression, but 48% of lifetime depression had anxiety. This study challenged the prevailing notion of a predominant pattern in which generalized anxiety usually develops into depression by showing that depression develops into generalized anxiety almost as often. (Moffitt, Harrington, et al. 2007) In addition, the co-occurrence of GAD and bipolar disorder was reported from baseline data of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) Study. The investigation revealed that 18% of subjects with bipolar disorder had a lifetime occurrence of GAD (somewhat higher for bipolar I than for</p>

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	<p>bipolar II disorder) and 51% of bipolar patients had at least one type of lifetime anxiety disorder. (Simon, 2009)</p> <p><u>Co-morbid Physical Conditions</u> – Anxiety disorders have been shown to be independently associated with several physical conditions. Results from a large study, The German Health Survey, revealed that after adjusting for socio-demographic factors and other common mental disorder, the presence of an anxiety disorder was significantly associated with thyroid disease, respiratory disease, gastrointestinal disease, arthritis, migraine headaches, and allergic conditions. This co-morbidity was also shown to be significantly associated with poor quality of life and disability. (Sareen, Jacobi, et al. 2006)</p> <p><u>Suicide Ideation and Suicide Attempt</u> – Two studies demonstrated that as a group of disorders, anxiety disorders were highly prevalent among those with suicidal behavior in large community samples. One study showed that anxiety disorders were independent risk factors for suicidal behavior, even after adjusting for co-morbidity with common mental disorders. Also, the presence of an anxiety disorder in combination with a mood disorder was associated with increased likelihood of suicidal behavior, compared with those with mood disorder alone. (Hawgood et al., 2008; Sareen, Cox, et al. 2005) Another study of adolescents and young adults aged 16-18, 19-21 and 21-25 years showed that anxiety disorders were associated with moderate increases in suicidal behavior and may account for approximately 7-10% of this population’s rate of suicidal behaviors. There was evidence to suggest that GAD was more strongly associated with suicidal ideation, and that panic disorder was more strongly associated with suicide attempts, than other anxiety disorders. Also, the rates of suicidal behavior increased in proportion to the number of anxiety disorders present. (Boden, 2006)</p>
Patient and Family Education	<p>All patients should receive education from their physician that includes information about their anxiety disorder, treatment choices, and general prognosis. Physicians should identify alleviating and aggravating factors, and signs of relapse for each patient. In addition, information on local self-help groups, self-help reading material describing evidence-based treatment strategies, and other resources such as websites, may be helpful. To support informed decision-making, patients should be informed about effectiveness, common side effects of medications, probable duration of treatment, any costs they might incur, and what to expect when treatment is discontinued. (Canadian Psychiatric Association Guideline, 2006)</p> <ul style="list-style-type: none"> • One study examined whether telephone-based collaborative care for patients with panic disorder and/or GAD improves clinical and functional outcomes more than the usual care provided by primary care providers. Care managers called patients at regular intervals and provided them with psycho-education; assessed preferences for guideline-based care, monitored treatment responses, and informed physicians of their patients’ care preferences and progress via an electronic medical record. Compared with the outcomes achieved by primary care physicians’ usual care for panic and GAD, the telephone-based collaborative intervention significantly reduced anxiety and depressive symptoms, improved mental-health related quality of life, and improved employment patterns during the 12-month course of follow-up. (Rollman, 2005)
Psychotherapy Treatments	<p>The efficacy of Cognitive Behavioral Treatments (CBT) for anxiety in adults has been supported as a consistent and empirically validated form of psychotherapy for GAD in the <i>Consensus Statement on Generalized Anxiety Disorder from the International Consensus Group on Depression and Anxiety</i>. (Ballenger, 2001) Additionally, the <i>Canadian Psychiatric Association Clinical Practice Guidelines on the Management of Anxiety Disorders</i> (2006) notes that CBT research demonstrates that it is more effective than no treatment and non-specific psychological methods for GAD, and that the magnitude of benefits is comparable to those</p>

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	<p>reported in studies of antidepressant drugs. In addition, these guidelines note that CBT appears to be beneficial in both individual and group settings where the benefits tend to be maintained during 6 months to 2 years of follow-up. Several common problems have been identified among individuals with GAD, including intolerance of uncertainty, poor problem-solving approaches, and beliefs that worry is a helpful way to deal with problems. The aforementioned guidelines note that CBT interventions targeting these aspects were effective in clinical trials. (Canadian Psychiatric Association Guideline, 2006)</p> <p>Important research findings on psychotherapy for the treatment of GAD include studies on CBT, Worry Exposure, Applied Relaxation, Muscle Relaxation and Short-term Psychodynamic Psychotherapy summarized as follows:</p> <ul style="list-style-type: none"> • One meta-analysis looking at the efficacy of CBT compared to pharmacological therapy showed no significant differences in their efficacy in the treatment of GAD. The attrition rates were lower for CBT, which indicated that it was better tolerated by patients. Also, because most comparisons of CBT treatments were with the benzodiazepine drug class, more research is needed to compare CBT to other psychotropic agents, i.e., Selective Serotonin Reuptake Inhibitors (SSRIs), Selective Serotonin and Norepinephrine Re-uptake Inhibitors (SNRIs) and buspirone. (Mitte, 2005) • Another meta-analytic review of CBT in adults across all anxiety disorders showed that cognitive therapy and exposure therapy alone, in combination, or combined with relaxation training were efficacious across the anxiety disorders, with no differential efficacy for any treatment components for any specific diagnoses. When comparing across diagnoses, outcomes for GAD and post-traumatic stress disorder (PTSD) were superior to those for social anxiety disorder. (Norton, 2007) • A large meta-analysis reviewed some 27 studies that examined the efficacy of CBT versus placebo in the treatment of all adult anxiety disorders. In comparing the average effect size estimates of CBT, treatment efficacy for both anxiety symptoms (Hedges' $g = 0.51$) and depressive symptoms (Hedges' $g = 0.38$), GAD ranked among the lowest effect sizes with the exception of panic disorder. The strongest effect size estimates for CBT were for obsessive-compulsive disorder and acute stress disorder. (Hofman et al., 2008) • One study combined meta-analysis to determine overall effect size of CBT in the treatment of both GAD and panic disorder and meta-regression to determine the factors that had an impact on this effect size. The study findings showed that CBT is significantly less effective for patients with a severe form of both disorders. Also, trials that compared CBT to a wait-list control group found significantly larger effect sizes than those comparing CBT to an attention placebo, but not to a pill placebo. Also, these findings noted that most studies used psychologists as providers and recommended that more studies are needed with other professional groups as well as other modes of administration (e.g., telephone, computer). (Haby, 2005) • There are emerging new approaches in the cognitive behavioral treatment of GAD as it is a chronic condition that remains the least-successfully treated of the anxiety disorders – e.g., client returning to normative levels on key outcome measures. These concerns have led to the development of new treatments that expand CBT approaches in order to better target the function of worry and the nature of GAD. (Roemer, 2007) One meta-analysis that focused specifically on the efficacy of CBT for pathological worry among clients with GAD showed that CBT is effective, with the largest treatment gains evidenced for younger adults and for those who underwent individual

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	<p>CBT treatment. (Covin, 2007)</p> <ul style="list-style-type: none"> • Stand-alone worry exposure therapy (WE) without further CBT interventions was evaluated in a randomized controlled study of 73 patients with GAD. Subjects were allocated to either WE or applied relaxation (AR) for 15 sessions. Results showed that patients in both groups exhibited distinct improvements on all primary and secondary measures where symptoms of anxiety, depression, excessive worrying, negative metacognitive appraisal of worrying and thought suppression were reduced. These treatment effects were stable at 6 month and 1 year follow-up. (Hoyer et al., 2009) • A randomized clinical trial of elderly patients (n=134) examined the effect of CBT relative to enhanced usual care (EUC) conducted in a primary care setting. Patients who received EUC were telephoned biweekly during the first 3 months of the study by the same therapist to provide support, ensure patient safety and remind them to call staff if symptoms worsened. Findings showed that patients receiving CBT had greater improvement in worry severity, depressive symptoms, and general mental health than those receiving EUC. Mean change in GAD severity following CBT was meaningful but not significantly than following EUC. (Stanley et al., 2008) • A clinical review of muscle tension in GAD evaluated 13 controlled studies and found that muscle relaxation therapy and CBT are the most effective treatments for GAD. The investigators indicated that the efficacy of muscle relaxation therapy for GAD lies primarily in its function of stress-reduction and in helping to distract from excessive worry by focusing on the muscles. Authors suggested that other therapies using cognitive distraction should be developed and studied for the treatment of GAD and muscle tension. (Pluess et al., 2009) • Short-term psychodynamic psychotherapy and CBT were compared with regard to treatment outcome. Patients with GAD were randomly assigned to receive either CBT (n=29) or short-term psychodynamic psychotherapy (n=28) according to treatment manuals on a weekly basis for 30 weeks. Results showed both CBT and short-term psychodynamic psychotherapy yielded significant, large and stable improvements using the primary outcome measures symptoms of anxiety and depression. CBT was superior in secondary measures of trait anxiety, worry and depression. Researchers noted that outcomes in psychodynamic psychotherapy may be optimized by employing a stronger focus on the process of worrying as is the case in CBT. (Salzer et al., 2010) Investigators also proposed the conceptualization of worry in psychodynamic psychotherapy as “a mechanism of defense that protects the subject from fantasies or feelings that are even more threatening than the contents of his or her worries.” (Salzer et al., 2010, p.5)
Pharmacology Treatments	<p>In 2008, the <i>World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders-- Revised</i> were published to include treatment recommendations for GAD. (Bandelow et al., 2008) The WFSBP Task Force rank-ordered clinical trials based on the quality of evidence for efficacy and risk/benefit assessment. Strongest evidence of clinical efficacy in the treatment of GAD was found for SSRIs – escitalopram, paroxetine, sertraline; SNRIs – venlafaxine, duloxetine; the calcium channel modulator – pregabalin; and second generation antipsychotic (SGA) – quetiapine. (Allgulander 2010; Bandelow et al., 2008)</p> <p>The WFSBP Guidelines ranked the tricyclic antidepressant (TCA) imipramine as a secondary drug of choice, despite its efficacy, due to the higher toxicity and adverse event burden. In addition, these guidelines cited strong evidence and recommended the benzodiazepines, alprazolam and diazepam, for treatment-resistant cases with no history of</p>

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	<p>addiction and as adjuncts for immediate relief of anxiety during the initiation of other agents and for use in episodes of acute exacerbation. The WFSBP Guidelines also indicated that the antihistamine, hydroxyzine, is effective but has sedating properties. Lastly, these guidelines specified that in treatment-refractory GAD patients, augmentation of SSRI treatment with risperidone and olanzapine (SGAs) may be used. (Allgullander 2010; Bandelow et al., 2008)</p> <p>An effect-size analysis of 21 double-blind placebo controlled trials of pharmacologic treatments for GAD showed that mean effect sizes (ES) by drug (or drug classes) were as follows: pregabalin (0.50); antihistamines (0.45); SNRIs (0.42); benzodiazepines (0.38); SSRIs (0.36) and azapirones (0.17). (Hidalgo et al., 2007) Moreover, all of these drugs precipitate response (50% improvement in symptom severity) in approximately two-thirds of patients and remission (a reduction in symptom severity clinical measurement scores to the normal range) in approximately one-half of the responders or one-third of total patients. (Collins et al., 2009; Hidalgo et al., 2007)</p> <p>An earlier published summary of all peer-reviewed meta-analyses and randomized placebo-controlled trials on the pharmacological treatment of GAD concluded that trials with escitalopram, paroxetine, sertraline and venlafaxine indicate that treatment with Selective Serotonin Reuptake Inhibitors (SSRIs) and Selective Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs) can be efficacious in the acute management of GAD. There was also some evidence for the efficacy of certain benzodiazepines, buspirone, imipramine, hydroxyzine and trifluoperazine. (Baldwin, 2005) Similarly, The International Consensus Group on Anxiety and Depression recommends an SSRI, SNRI or non-sedating tricyclic antidepressant (TCA) as the first-line pharmacotherapy for the treatment of GAD. (Rickels, 2006; Ballenger, 2001)</p> <p>The Federal Drug Administration (FDA) has approved the following drugs in their respective classes for the treatment of GAD: (1) azapirone anxiolytic – buspirone (2) SNRIs – venlafaxine and duloxetine (3) SSRIs – paroxetine and escitalopram (4) benzodiazepines – diazepam, lorazepam and alprazolam (5) first generation antipsychotic (FGA) – trifluoperazine (6) antihistamine – hydroxyzine. Findings support pharmacological treatment for patients with GAD for at least 6 months and up to a year. (Collins et al., 2009; Davidson 2009; Baldwin, 2005) In spite of some convincing efficacy data, the Psychopharmacologic Drugs Advisory Committee of the FDA voted against first-line treatment of GAD with quetiapine due to the potential metabolic consequences of maintenance treatment, the potential for extrapyramidal adverse events and the risk of sudden death due to ventricular arrhythmia. (Allgullander, 2009)</p> <p>In 2010, <i>The International Psychopharmacology Algorithm Project (IPAP)</i> published a psychopharmacological treatment algorithm to be used for all patients in the treatment of GAD. It addresses the needs of patients who may achieve a good response, partial response, non-response or loss of previous response. (Davidson et al., 2010) The IPAP consultants developing the algorithm indicated that once the diagnosis of GAD has been established, an evaluation for co-morbidities should be done at this point, and at every subsequent point of assessment throughout the course of treatment. This includes a careful evaluation for suicidality, insomnia, substance abuse, non-compliance, childbearing potential, elderly patient problems and cultural issues. They also recommended that stabilization of co-morbid disorders should be attempted prior to treatment of GAD. (Davidson et al., 2010)</p> <p>Proposed Treatment Steps: The following summarizes important clinical information from the decision points and action steps conveyed in the IPAP review and treatment</p>

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	<p>algorithm for GAD: (Davidson et al., 2010; IPAP GAD Algorithm Flowchart, 2009)</p> <ul style="list-style-type: none"> ● Expert consensus indicates that an SSRI or SNRI monotherapy may be the initial choice of medication of a treatment-naïve patient presenting with GAD. Other antidepressants (i.e., imipramine and trazodone) have shown efficacy, but are not recommended as first-line treatments due to poor tolerability and high risk of potential serious side effects. ● If rapid response is warranted, or insomnia is predominant symptom, a concomitant benzodiazepine may be used for a short period of time in patients with no history of substance abuse. ● Response time to antidepressant drug treatment in GAD is usually 4-12 weeks. A partial response should occur by the initial evaluation point after 4-6 weeks with adequate dosing. ● In cases where there is a good response after an adequate trial, medications should be continued for at least one year. ● Current state of knowledge permits the prescriber to increase dose, augment, switch or wait longer when there has been a partial response. A switching strategy should be considered where adequate drug trial has not elicited at least a 25% symptom improvement from baseline using a valid clinical measurement scale. <ul style="list-style-type: none"> ➤ Augmenting agents: atypical antipsychotics (risperidone and olanzapine), benzodiazepines, antihistamine (hydroxyzine), buspirone or anticonvulsant agent, tiagabine (use with caution for patients with a history of seizure disorder or predisposition). ➤ Switching to another antidepressant within the same class or to a different class e.g., SSRI to SNRI or SNRI to SSRI. ➤ Psychotherapy may be added to the regimen. ● Insomnia must also be addressed when evaluating a partial response with the suggested use of hypnotic agents: non-benzodiazepine GABAergic hypnotic drugs, benzodiazepines, trazodone or mirtazapine. A sedating antihistamine may be added. Patient should be counseled on possible lifestyle changes. ● If the patient has improved or achieves remission with these new drugs, continue treatment for one year. ● At this stage, if there is still a partial or non-response, the clinician must evaluate for the presence of a significant co-morbid disorder. Recommended drugs are as follows: <ul style="list-style-type: none"> ➤ Co-morbid depression – adequate dose of an antidepressant or augmentation with bupropion, buspirone, atypical antipsychotic, or the nutritional supplement, chromium picolinate. Severe depression may need ECT. ➤ Co-morbid stable bipolar disorder – add mood stabilizer, anticonvulsant or atypical antipsychotic drug. May need laboratory monitoring. ➤ Co-morbid panic disorder – add TCA or SSRI/SNRI or benzodiazepine. ➤ Co-morbid social anxiety disorder – add benzodiazepine, SRI, atypical antipsychotic, pregabalin or anticonvulsant agent, levetiracetam. ➤ Co-morbid obsessive-compulsive disorder – add SSRI or clomipramine.

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	<ul style="list-style-type: none"> ➤ Co-morbid posttraumatic stress disorder – add SSRI, SNRI, atypical antipsychotic or sympatholytic drug, prazosin. • If there is no co-morbid disorder, switch to another combination that includes SSRI, SNRI, noradrenergic and specific serotonergic antidepressant (NaSSa), or TCA or add a third drug of different class from the other two. Psychotherapy may be added to the regimen at this phase of treatment. <p>Other important research findings on recommended drugs to treat GAD are summarized below:</p> <p><u>Benzodiazepines</u> – Evidence-based reviews have demonstrated that benzodiazepines are an effective and rapid treatment for many patients with GAD. (Baldwin, 2005; Mitte, 2005; Chessick, 2007) However, the benzodiazepines have limited efficacy in the treatment of GAD and co-morbid depression. (Baldwin, 2005) Baldwin et al. concluded that treatment with benzodiazepines should be for a short-term duration (up to 4 weeks) in order to avoid the risk of physical dependence and withdrawal resulting from long-term usage. Other unwanted effects of benzodiazepines may include sedation, memory disruption and psychomotor impairment, with an associated increased risk of traffic accidents. Other safety concerns with the use of benzodiazepines in the elderly population have been noted due to the high incidence of falls, hip fracture, withdrawal difficulties and increased risk of cognitive impairment. (Davidson et al., 2010; Collins et al., 2009; Pollack et al., 2009; Baldwin, 2005; Mitte, 2005)</p> <p><u>Azapirones</u> – Two meta-analyses have shown that buspirone (an azapirone anxiolytic with partial agonist properties at 5-HT_{1A} receptors) has comparable efficacy to benzodiazepines in the treatment of GAD and seems to be a suitable alternative for long-term treatment of the condition with side effects that are mild and non-serious. (Baldwin, 2005; Mitte, 2005) Another meta-analytic review showed that buspirone appears to be useful in the treatment of GAD, particularly for those patients who had not been on a benzodiazepine, because it may be less effective than benzodiazepines. Also, these findings were inconclusive about buspirone’s long-term efficacy and its superiority to antidepressants, psychotherapy or kava kava. (Chessick, 2007) Currently, buspirone is rarely used as monotherapy in GAD but is more frequently used as augmentation to first-line agents due to its slow onset of action, variable tolerability and overall lack of benefit against other co-morbid disorders. (Davidson et al., 2010; Pollack, 2009)</p> <p><u>Selective Serotonin Reuptake Inhibitors (SSRIs)</u> – Several SSRI antidepressant drugs are currently used in the treatment of GAD. Efficacy findings with the best levels of evidence support escitalopram, paroxetine-immediate release and sertraline. The IPAP consultants noted that of these three aforementioned agents, sertraline has the best safety data in pregnancy and lactation. (Davidson et al., 2010; Bandelow et al., 2008) Studies have been conducted to determine whether some of the SSRIs have more advantages than the others:</p> <ul style="list-style-type: none"> • A published review of research findings from paroxetine clinical trials (3 short-term and 1 long-term relapse study), showed that it is an effective short- and long-term treatment agent for GAD, demonstrating substantial patient improvement in family, social and work functionality, achieving remission, and in relapse prevention. Researchers note that paroxetine has demonstrated efficacy in depression and in several anxiety disorders (e.g., panic, OCD, social anxiety and PTSD) making it a favorable option to treat core symptoms of GAD along with disorders that are commonly co-morbid with it. (Rickels, 2006) • Study findings support the clinical efficacy of short-term treatment with sertraline,

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	<p>resulting in significant improvement in both psychic and somatic anxiety symptoms, including quality of life and work productivity. (Allgulander, 2004)</p> <ul style="list-style-type: none"> • A study comparing the efficacy of sertraline and paroxetine in the treatment of GAD showed no difference in therapeutic efficacy or tolerability. (Ball, 2005) Another study showed there were no differences in efficacy between escitalopram (10-20 mg/day) and paroxetine (20-50 mg/day) in the treatment of GAD. However, patients treated with paroxetine reported significantly more side effects (e.g., insomnia, constipation, sexual dysfunction, weight gain) than with escitalopram. (Bielski, 2005) • GAD patients who were treatment responders were prescribed escitalopram for 24-76 weeks. Findings showed that escitalopram (20 mg/day) significantly reduced the risk of relapse in these patients – risk of relapse was 4.04 times higher in the placebo group. (Allgulander, 2005) • A randomized controlled study of 177 adults, aged 60 years and older, evaluated the use of escitalopram 10 to 20 mg/day against placebo during 12 weeks in the treatment of GAD. Researchers found a statistically significant difference in the mean cumulative response rate (i.e., decrease in anxiety symptoms and improvement in role functioning) for escitalopram (69%) compared with placebo (51%). Response rates were not significantly different when using an intention-to-treat (ITT) analysis. Further study is necessary to assess safety and efficacy compared to longer term treatment. (Lenze et al., 2009) <p><u>Selective Serotonin and Norepinephrine Re-uptake Inhibitors (SNRIs)</u> – Venlafaxine extended release (XR) was the first SNRI antidepressant to receive U.S. Food and Drug Administration (FDA) approval for the treatment of GAD followed by duloxetine. (Collins et al., 2009; Davidson 2009; Baldwin, 2005)</p> <ul style="list-style-type: none"> • An open trial demonstrated equal efficacy and tolerability during 8 weeks in patients with GAD who received venlafaxine XR or paroxetine. Double-blind, placebo-controlled, comparison studies are needed to draw definitive conclusions. (Kim, 2006) • A trial of duloxetine showed its superiority to placebo in the short-term management of GAD with its demonstrated efficacy, safety and tolerability leading to improvement in symptom severity and functioning. The adverse effects most frequently associated with duloxetine were nausea, dizziness and somnolence. Another study, which pooled data from two multi-center trials, evaluated the efficacy of duloxetine (60-120 mg/day) in patients with GAD and significant pain symptoms. It showed that the drug is effective in reducing anxiety symptoms, pain severity and in improving patient functioning. (Rynn, 2007) • Retrospectively derived pooled data from five studies reported efficacy of venlafaxine XR in patients with GAD who are age 65 and older but there were findings of intolerance in frail elderly subjects. (Davidson et al., 2010) • Further post hoc analysis of previous duloxetine clinical trial data assessed painful physical symptoms in patients with GAD using two 9-10 week efficacy trials (n=840) and one relapse prevention trial (n=887) comprising both a 26 week open-label treatment phase and a 26-week double-blind, placebo-controlled treatment continuation phase. Findings showed that both short- and long-term duloxetine treatments were associated with improvement in painful physical

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	<p>symptoms in GAD. Additionally, patients who responded to duloxetine treatment and subsequently discontinued treatment experienced a worsening of painful symptoms. (Beesdo et al., 2009) Another large (n=668) clinical trial of adult patients treated with duloxetine compared to placebo (n=495) showed an almost 2:1 rate of substantial return to normative functioning and quality of life – i.e., global role functioning, subjective well-being and perceived health. (Pollack et al., 2007)</p> <ul style="list-style-type: none"> • A non-inferiority comparison of duloxetine 60-mg/day and venlafaxine extended-release (XR) 75-227 mg/day for the treatment of adults with GAD pooled data from nearly identical 10 week, multicenter, randomized, placebo-controlled, double-blind studies. Non-inferiority trials are designed to analyze the amount of drug/placebo difference between two treatments. An independent expert consensus panel determined the statistical and clinical criteria for non-inferiority and clinical response (i.e., $\geq 50\%$ reduction in HAMA Rating Scale total score). Findings showed that duloxetine 60-120 mg/day met all of the criteria for non-inferiority and exhibited a similar safety and tolerability profile compared with venlafaxine XR 75-225 mg/day. (Allgulander et al., 2008) <p><u>Tricyclics (TCAs)</u> – In a 2003 Cochrane review of antidepressants used to treat GAD, Kapczynski et al. noted that the tricyclic antidepressant, imipramine, has been studied as early as 1988 for its comparative effectiveness against alprazolam, and in a later study (1993) compared to trazodone, diazepam and placebo. Published results of these early studies demonstrated that imipramine was effective in alleviating such symptoms as dysphoria, anticipatory negative thinking, apprehension and worry. This Cochrane meta-analytic review concluded that available evidence suggests that imipramine, venlafaxine and paroxetine are superior to placebo in treating GAD in adults. Sertraline had been shown to be superior to placebo in treating GAD in children and adolescents. This study was not able to assess the differences in efficacy between imipramine and venlafaxine, or venlafaxine and paroxetine, as there were no direct comparisons of these agents in this review. This review also noted findings suggesting that paroxetine and imipramine are similar in terms of efficacy and tolerability. (Kapczynski, 2003) While imipramine is effective in the treatment of GAD, it is currently considered a second-line option due to its lower tolerability profile and potential lethality in overdose. (Davidson et al., 2010; Bandelow et al., 2008)</p> <p><u>Noradrenergic and specific serotonergic antidepressant (NaSSA)</u> – Findings from a trial of mirtazapine (fixed dose 30 mg for 12 weeks) supported its efficacy and tolerability for the treatment of GAD. Further randomized placebo-controlled studies are needed to explore the utility of this agent in the treatment of anxiety disorders. (Gambi, 2005) Mirtazapine may be considered to treat insomnia in patients with GAD who have had an otherwise good response to SRI drugs. (Davidson et al., 2010)</p> <p><u>Antipsychotics</u> – A published literature review on the efficacy of typical and atypical antipsychotics for primary and co-morbid anxiety symptoms or disorders noted that there is fair evidence that typical antipsychotics, especially trifluoperazine, were effective in the short-term treatment of GAD. (Gao, 2006) Data from a small (N=30) open-label, flexible-dose study of adjunctive risperidone suggest that augmentation of an adequate dose of an SSRI, SNRI or benzodiazepine, with low-dose risperidone initiated at least eight weeks prior to the study, may be a useful option for patients with GAD, panic disorder and social anxiety disorder refractory to adequate initial pharmacotherapy. Results showed significant reduction in anxiety symptoms, and while two patients reported mild akathisia (one was persistent), no patients developed dystonias. (Simon, 2006)</p>

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Procedure	Recommendations
	<ul style="list-style-type: none"> Olanzapine, risperidone and quetiapine immediate-release (IR) have all been studied as adjunctive agents to antidepressants and/or anxiolytics in the treatment of refractory GAD with inconsistent results. (Gao et al., 2009) However, quetiapine extended-release (XR) 150 mg/day monotherapy yielded consistent anxiolytic effects across three studies that were superior to placebo and as effective as paroxetine 20 mg/day and escitalopram 10 mg/day but with an earlier onset of action. Also, in a 52-week treatment of GAD, quetiapine-XR was superior to placebo in the prevention of anxiety relapses. (Gao et al., 2009; Bandelow et al., 2008) One study investigated the efficacy of atypical antipsychotic monotherapy in mood disorders co-morbid with GAD. Patients (n=111) with bipolar disorder co-morbid with GAD (88%) or panic disorder (59%) were randomly assigned to receive risperidone 0.5mg-4mg/day or placebo monotherapy for 8 weeks. Out of the 63 patients who completed the study, there were no statistically significant differences between risperidone or placebo on the primary outcome measure for anxiety or secondary outcome measures for panic depression, mania and disability. (Gao et al., 2009) <p>As noted in the Assessment section, GAD may be the most common anxiety disorder in the elderly population. Therefore, clinicians should be aware of a FDA Alert that was issued notifying healthcare professionals that both conventional and atypical (SGA) antipsychotics are associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis. (FDA Alert 6/16/08)</p> <p><u>Non-benzodiazepine hypnotics</u> – Zolpidem extended-release co-administered with escitalopram in patients insomnia and co-morbid GAD was studied in a multicenter, double-blind, parallel-group trial. Patients (n=383) received open-label escitalopram 10mg/day and were randomized to either adjunctive zolpidem extended-release 12.5 mg or placebo. Findings showed that combination zolpidem and escitalopram improved all measures of sleep to a significantly greater degree than escitalopram and placebo. Improvements were also seen in many measures of daytime functioning and quality of life. Zolpidem extended-release did not significantly augment the anxiolytic effects of the escitalopram and there was no associated rebound upon withdrawal of therapy. (Fava et al., 2009)</p> <p><u>Anticonvulsants</u> – As noted earlier, the <i>World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders-Revised</i> classify pregabalin as a first-line treatment for GAD. Conversely, the IPAP pharmacological algorithm consultants do not yet support the position of pregabalin due to a relative lack of clinical experience in use for treatment of GAD to date and a deficiency of data to establish efficacy for co-morbid conditions. (Davidson et al., 2009) While pregabalin is not indicated for treatment of GAD in the United States, it is indicated for this use in Europe. (Pollack, 2009)</p> <ul style="list-style-type: none"> A study compared pregabalin (300 mg/day, 450 mg/day and 600 mg/day) to alprazolam 1.5 mg/day and placebo. The pregabalin treatment was associated with significant end-point improvement on the Hamilton Anxiety Rating Scale (HAM-A), which was comparable to alprazolam at all three doses at the end of four weeks of treatment and two follow-up visits during drug discontinuation. (Rickels, 2005) A recent literature review of the evidence on the role of anticonvulsant drugs in the treatment of anxiety disorders showed that the strongest evidence (level 1 – meta-

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	<p>analysis and replicated randomized controlled trials) was for pregabalin in GAD with or without co-morbidity. (Mula, 2007)</p> <ul style="list-style-type: none"> • Pooled data were analyzed from six double-blind, placebo-controlled trials where response to treatment for GAD was evaluated for three fixed-dose pregabalin groups (150, 300-450, 600 mg/day) and for a benzodiazepine group. In the high-insomnia subgroup, the anxiolytic efficacy of pregabalin 300-600 mg was comparable with alprazolam/lorazepam. Whereas the 150 mg dose of pregabalin was associated with improvement in anxiety measurement scores, it did not have a significant effect on insomnia symptoms. (Montgomery et al., 2009) • Another pooled analysis of the same six trials (above) examined the efficacy of pregabalin in depressive symptoms associated with GAD through a post-hoc analysis of the existing clinical trial database. Findings showed that in patients with GAD, pregabalin reduced associated symptoms of depression in the 150, 300-450 and 600mg/day groups where pregabalin 300-450 mg/day dosage demonstrated the most beneficial response. (Stein, Baldwin et al., 2009) • Tiagabine is a selective gamma-aminobutyric acid (GABA) reuptake inhibitor that increases synaptic GABA availability. Study conclusions were mixed. While tiagabine demonstrated efficacy in one randomized controlled trial, it did not show benefit in subsequent combined analysis of three additional trials. (Davidson et al., 2010; Pollack, 2009) • <u>Novel Agents</u> - Antidepressants may have many shortcomings in the treatment of anxiety states in that they do not work quickly, may have significant side effects (e.g., nausea, agitation, sexual dysfunction) and may be associated with distressing symptoms upon discontinuation. Therefore, search for novel pharmacological agents for GAD continues. (Starcevic, 2007) Riluzole, a presynaptic glutamate release inhibitor used in the treatment of amyotrophic lateral sclerosis (ALS), has demonstrated very promising results in reducing symptoms of anxiety in GAD patients in a recent clinical trial. An 8-week, open-label, fixed-dose trial of riluzole in 18 outpatients with GAD resulted in a significant reduction in anxiety symptoms where 67% of patients responded and 44% entered remission by the end of the study. (Pollack, 2009; Gao et al., 2009) <p><u>Complementary and Alternative Medicine (CAM)</u> – At the present time, <i>Piper methysticum</i> (kava), has been the most widely used and studied herbal medicine for the treatment of GAD and other anxiety disorders. Reported meta-analytic findings of 11 randomized controlled trials of kava monopreparations (60-280 mg) demonstrated significant anxiolytic activity compared to placebo in all but one trial. (Sarris et al., 2009). Kava is currently restricted from use in the United Kingdom, Canada and the European Union due to concerns about hepatotoxicity reported in some 93 cases resulting in the call for removing kava from over-the-counter public use to prescription only. (Sarris et al., 2009)</p> <ul style="list-style-type: none"> • The first randomized, double-blind, placebo-controlled efficacy and tolerability trial of <i>Matricaria recutita</i> (Chamomile extract) was conducted using 57 outpatients with mild to moderate GAD where 28 patients received chamomile and 29 patients received placebo. Chamomile (220 mg) or placebo therapy was initiated daily at week 1 and increased to 2 tablets daily during the second week. Patients with a 50% reduction or less in HAM-A scores from baseline were increased 1 tablet each week up to week 5 if they still continued to have a 50% reduction or less in symptom improvement (up to 5 capsules daily during week 5-8 of therapy). Results showed that patients had a significantly greater reduction in mean total HAM-A

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Procedure	Recommendations
	scores with chamomile versus placebo treatment. (Amsterdam et al., 2009)
Combined Treatments	<p>Both the <i>Canadian Psychiatric Association Clinical Practice Guidelines on the Management of Anxiety Disorders</i> (2006) and <i>The International Psychopharmacology Algorithm Project (IPAP)</i> report and psychopharmacological treatment algorithm indicated that there is no current evidence to support the routine combination of CBT and pharmacology in the treatment of GAD. Pharmacological or psychological treatments have broadly similar efficacy in the acute treatment of GAD, but the comparative efficacy of combined drug and psychological approaches for a long-term period is not established. Both the IPAP report/algorithm and the Canadian Guideline recommend that as in other anxiety disorders, when patients with GAD do not benefit from CBT or have a limited response, a trial of pharmacotherapy is advisable. Similarly, patients who show limited benefit from pharmacotherapy may benefit from CBT. The Canadian Guideline also emphasizes that studies are required to evaluate whether CBT reduces the rate of relapse when pharmacologic treatment is discontinued. (Davidson et al., 2009; IPAP GAD Algorithm Flowchart, 2009; Canadian Psychiatric Association, 2006)</p> <p>An area of emerging interest and research is the sequential treatment of pharmacotherapy and CBT as a two-staged intensive approach to the treatment of anxiety disorders and mood disorders. (Pull, 2007) In reviewing published studies of sequential use of pharmacotherapy and psychotherapy in mood and anxiety disorders, Fava et al. noted that available studies on anxiety disorders (panic disorder and obsessive-compulsive disorder) do not substantiate long-term benefits from the sequential combination of pharmacotherapy and psychotherapy as was demonstrated for recurrent unipolar depression. (Fava, 2005) Since the sequential approach has not yet been applied to GAD, social phobia and post-traumatic stress disorder, Fava suggests the need for such research in the treatment of these conditions.</p> <ul style="list-style-type: none"> • A trial evaluated the specific effectiveness of CBT combined with medication tapering (i.e., benzodiazepine discontinuation) among GAD patients compared to GAD patients receiving non-specific psychological therapy with medication tapering. Those patients receiving CBT had a markedly better benzodiazepine cessation rate (75% to 37%) with this group's discontinuation rate being twice as high. The number of patients who no longer met GAD criteria was also greater in the CBT group. The addition of specific CBT components targeting manifestations of the disorder, apprehension related to ending medication, and behavioral and cognitive factors involved in the maintenance of excessive worry may facilitate benzodiazepine cessation among patients suffering from GAD. (Gosselin, 2006)

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Procedure	Recommendations
Monitor Progress and Address Sub-optimal Recovery	<ol style="list-style-type: none"> 1. Psychiatric Co-morbidity and Recovery/Recurrence – Findings from a 12-year prospective study that examined the long-term course of GAD showed that it is a chronic anxiety disorder with low probability (0.58) of achieving recovery. After 12 years, 42% of GAD patients remained in their intake episode. Of those who did recover, nearly one-half subsequently had a recurrence. Researchers noted that these results are clearly inconsistent with earlier assumptions, reflected in the DSM-III criteria, that GAD is a residual and innocuous condition that usually does not lead to significant impairment. Rather, the long-term course appears to be chronic in nature, with more recent studies showing significant impairment across multiple domains. For those patients suffering with major depressive disorder co-morbid with anxiety disorder, the likelihood of recovering from the depression is reduced. (Bruce, 2005) 2. Pharmacology and Relapse – One of the main problems with the pharmacotherapy of anxiety states is a high rate of relapse upon discontinuation of the medication. Strategies have been proposed to improve this situation – longer pharmacological treatment in order for remission to occur. (Starcevic, 2007) Also, there is evidence to suggest that early lack of improvement (at weeks 1 and 2) on a drug may be a strong negative predictor of improvement at the 8th week. These findings were demonstrated for all three agents in a comparative trial of placebo, diazepam and a serotonin receptor (5HT-1A) partial agonist. (Rynn, 2006) (N.B. Refer to previous discussion of the WFSBP Guidelines on page 7 and summarization of the IPAP psychopharmacological treatment algorithm on page 8, 9 for strategies to manage treatment resistance). 3. Standard Tools to Assess Response – The <i>Canadian Psychiatric Association’s Clinical Practice Guidelines on the Management of Anxiety Disorders</i> (2006) notes that the 14-item Hamilton Anxiety Rating Scale (HARS) can be used by clinicians to assess GAD illness severity and response to therapy. Self-rated tools may also be appropriate for GAD, such as the Penn State Worry Questionnaire and the Generalized Anxiety Disorder Questionnaire-IV. The Canadian guideline also notes that response to clinical trials of pharmacotherapy is often defined as a Clinical Global Improvement (CGI) score of ≤ 2 (very much or much improved) or a 50% reduction in the HARS score. Remission is usually defined as a HARS score ≤ 7 (no or minimal anxiety) and full recovery in GAD should be defined as no longer meeting the diagnostic criteria for the disorder (symptom resolution), as well as a return to pre-morbid functioning in all aspects of life. (Canadian Psychiatric Association Guideline, 2006)

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