Magellan's 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 Healthcare (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. It 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 updated the recommendations from a literature review conducted on GAD through May 2016 by reviewing the research published between 2016 and May, 2018. The rationale for this updated summary, presented in table format, offers clinicians 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 content of the articles referenced in the document.

As with all guidelines, this document is intended to augment, not replace, sound clinical judgment. As a matter of good practice, providers should note clinically sound exceptions to this practice guideline 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. Comments may be submitted to:

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Executive Summary

(A discussion of additions/changes in this updated guideline.)

The Diagnostic Manual of Mental Disorders (DSM-5)

DSM-5 did not adopt the considered term "generalized worry disorder" although chronic and excessive worry that interferes significantly with psychosocial functioning is a core and defining feature of generalized anxiety disorder (GAD) (Stein and Sareen, 2015). According to the DSM-5, the worries occur for at least six months, often occurring without precipitants. Three or more of the following symptoms are associated with GAD: restlessness/being on edge, being easily fatigued, trouble concentrating, irritability, muscle tension and disturbed sleep (APA, 2013). Comorbidities often include major depression, panic disorder and obsessive-compulsive disorder.

Epidemiology

Epidemiologic surveys show the prevalence of GAD is 5.7 percent during a patient's lifetime and 3.1 percent in the previous year, with higher prevalence among women than men. Most cases of GAD begin in early adulthood, and often in the context of chronic physical health conditions (Stein and Sareen, 2015). GADS are the second most common anxiety disorders for older adults (after phobias), occurring in 1.2% to 4.6% of those in a community-based sample (Aggerwal et al, 2017). Half of such cases have onset after the age of 50. Its prevalence in the primary care setting is 7-8 percent of patients, but it is not always detected or recognized because anxiety symptoms are not often the presenting complaints. Most patients with GAD present with complaints of physical symptoms offering a significant challenge to practitioners (Baldwin et al., 2014).

Assessment/Diagnostic/Planning

The British Association of Psychopharmacology's revised guidelines for the evidence-based pharmacological treatment of anxiety disorders include recommendations in the detection and diagnosis of GAD including (Baldwin et al., 2014):

- Recognition of the symptoms/signs of GAD
- Assessment of coexisting depressive symptoms
- Inquiring about long-standing anxiety symptoms in patients with unexplained physical symptoms
- Assessment of comorbid physical illness.

Assessment Scales

A recent study focused on the development of the Computerized Adaptive test for Anxiety (CAT-ANX) (Gibbons et al., 2014). Authors reported on the analysis of data from psychiatric participants (n=798) and non-psychiatric community comparison subjects (n=816). The computerized adaptive testing allowed the selection of only a small set of items for each patient from a large bank of test items based on prior item responses. Results of this study showed CAT-ANX scores strongly related to generalized anxiety disorder diagnosis. Authors stated, "The resulting increase in measurement efficiency permits anxiety screening of large populations for epidemiologic studies and determining phenotypes for large-scale molecular genetic studies. The scientific contribution of this study lies in our demonstration that the use of computerized adaptive testing based on multidimensional item response theory generalizes to the measurement of other psychopathologic conditions beyond depression" (Gibbons et al.,

p. 192). They further noted how routine anxiety screening of patients in primary care is improved by CAT-ANX and is administered in minutes using the internet, without clinician assistance.

Investigation of Biomarkers through neuroimaging, genetics and neurochemical measurements

According to Maron and Nutt (2018), research on biomarkers may significantly improve the etiology and treatments for GAD. Their recent review of neuroimaging, genetic and neurochemical research concluded that while there is significant overlap with depression the biology underlying depression and GAD are very different and consequently they are two separate disorders. They further acknowledged that this might explain why depression often follows GAD, demonstrating an inability of the body to successfully launch compensatory strategies to manage the constant stress caused by the GAD. The authors concluded that other biological based studies are needed to better target the biomarkers that could contribute to better treatments for individuals with GAD.

Management of Patients with Generalized Anxiety Disorder

Management of care may include the following: (Baldwin et al., 2014)

- Education of patient and family (lifestyle changes, strategies including exercise and yoga, and minimization of alcohol use) while monitoring patient's progress
- Low intensity psychological interventions, e.g., individual self-help, educational groups, computer-assisted cognitive behavioral therapy
- Choice of high-intensity psychological intervention, i.e., individual or group-based cognitive behavioral therapy, or first-line pharmacological treatment, i.e., selective serotonin-reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs), based on patient's preference
- Specialized care by mental health professions including other first-line pharmacologic treatments or adjunctive treatments with other medications, e.g., benzodiazepine (avoid in elderly patients and in those receiving opioids), buspirone, pregabalin, or quetiapine, and more intensive cognitive behavioral therapy or other psychotherapy.

Psychological Interventions

A recent meta-analysis examining the effects of psychological treatment of GAD included 41 randomized studies and adults (n = 2132) with a diagnosis of GAD (Cuijpers et al., 2014). Trials compared psychotherapy, e.g., CBT, with untreated controls, with pharmacotherapy, and with other psychotherapies. Results suggested that CBT is more effective than applied relaxation as a first line treatment of GAD and it may have longer-lasting effects compared to usual care. Internet-based treatments and face-to-face therapies had comparable outcomes. Studies comparing psychological treatment to medication suggested psychological treatment to be at least as effective as medication. Authors concluded that these results, demonstrating large and clinically relevant effects of psychotherapy, suggests that psychological treatment, especially CBT, is as effective as medication in treating GAD in adults and may be the treatment of choice (Cuijpers et al., 2014).

A recent randomized trial examined the impact of integrating motivational interviewing (MI) and CBT for treatment of GAD (Westra et al., 2015). Adults with GAD (n = 85) who scored above the high severity cutoff on the Penn State Worry Questionnaire were randomized to 15 weekly sessions of CBT alone or to 4 weekly sessions of MI followed by 11 weekly CBT sessions integrated with MI (MI-CBT). The primary outcome measure was the Penn State Worry Questionnaire (PSWQ). Results found no effect of

treatment group on worry level or rate of change at session 15, but at 6-month and 12-month follow-up, patients receiving MI-CBT had a steeper rate both of worry decline and of distress reduction. Additionally, twice as many drop-outs occurred in the CBT group compared with the MI-CBT group. Researchers concluded, "These findings suggest that explicit training in empathy (i.e., MI-CBT therapists) greatly improves performance on this vital dimension compared to standard CBT training (CBT alone group)" (Westra et al., p. 11). They indicated that this is consistent with recommendations to "include guidance in systematic process observation and ongoing identification of motivational markers that indicate the need for responsive intervention using MI spirit and skills" (Westra et al., p. 11).

Worry outcome monitoring is considered one of many cognitive behavioral components of cognitive behavioral therapy (LaFreniere and Newman, 2016). In a recent randomized controlled trial evaluating the efficacy of worry outcome monitoring in the treatment of GAD, participants (n = 51) with GAD and over 18 years of age were randomized to a treatment, Worry Outcome Journal (WOJ) or to a control condition, Thought Log (TL), for a period of 10 days. In worry outcome monitoring the participants were asked to record on paper their worry content and predictions about the future, as well as to rate the degree of distress caused by the worry. Participants tracked outcomes in a "worry outcome diary." Paper contents were entered online each night. Twenty days after the 10-day period of worry recording, participants reviewed each of the entries in the journal and indicated whether the worries came true and whether they were as expected in terms of distress. Participants in the Thought Log condition recorded on paper thoughts, not worries, and rated any distress related to the thought and recorded online each night. Twenty days after the period of thought recording, they reviewed their entries without indicating whether outcomes came true. Outcome measures including the PSWQ showed a significant reduction in worry during the 10 day intervention period which was maintained for 20 days following the trial in the WOJ group compared to the TL group. Researchers suggested, "Repeated present moment awareness of the content, distress and interference created by even a few worries may be enough to reduce worrying"… and that "writing about thoughts and emotions can have positive effects on mental and physical health" (LaFreniere and Newman, p. 9). They concluded that the WOJ may be a first line treatment for patients with GAD before more intensive therapist-dependent treatment.

A recent randomized clinical trial compared two therapist-delivered treatments, telephone-delivered CBT (CBT-T) and telephone-delivered non-directive supportive therapy (NST-T), in the treatment of rural adults (n = 141) aged 60 years and older with GAD (Brenes et al., 2015). The comparison included the effects of CBT-T and NST-T on anxiety, worry, GAD symptoms and depressive symptoms at four-month randomization. Primary outcome measures were the Hamilton Anxiety Rating Scale (HAMA) and the Penn State Worry Questionnaire-Abbreviated (PWSQ-A). CBT-T included 9-11 weekly 50-minute telephone therapy sessions with CBT techniques, while NST-T included 10 weekly 50-minute therapy sessions with supportive and reflective communications (no advice, suggestions or coping methods). Results showed that both CBT-T and NST-T reduced symptoms of GAD, worry and depression, although the decline in symptoms was significantly greater among the participants in CBT-T.

A recent study performed secondary data analyses of a randomized controlled trial of CBT for late-life GAD compared with usual care (UC) in a combined sample of

community and Veteran participants. (Barrera et al., 2014) The results showed significant improvements in GAD severity and anxiety in participants treated with CBT relative to UC. The secondary analyses were performed in the Barrera et al. study to further evaluate the outcomes for CBT within the community vs. the Veteran group and to examine predictors of outcomes in the Veterans sample. Results suggested that treatment effects with a standard CBT package were larger in community participants than in Veterans. Analyses in Veterans found that poorer outcomes were associated with poorer perceived social support. Researchers emphasized the complexity of treating Veterans with anxiety, and suggested particular attention to social support to improve the efficacy of CBT for Veterans (Barrera et al., 2014).

A recent review of literature and clinical synthesis focused on structured internet-delivered cognitive behavioral therapy (iCBT) for anxiety disorders and depression (Titov et al., 2014). Authors noted the variation between iCBT interventions, e.g., number or lessons/modules, organization of modules, and duration of intervention (generally over 4-16 weeks). More than 150 clinical trials evaluating iCBT for GAD generally have reported the efficacy of iCBT while also finding that superior clinical outcomes result from therapist-guided iCBT compared with self-guided CBT. Authors emphasized the assumption in psychotherapy that "the therapist is essential for effective treatment, and that therapist training, expertise and skill are the most important predictors of clinical outcomes" (Titov et al., p. 303). They concluded that blended mental health services, e.g., internet-delivered psychological treatment along with face-to-face services, will increase access to evidence-based care for patients who might not otherwise either receive or seek treatment.

Hall et al (2017) recently completed a review and meta-analysis of the efficacy of CBT with older adults with GAD. The authors reviewed 14 RTC studies that used the Penn State Worry Questionnaire as the outcome measure. They concluded that, significant treatment effects favoring CBT were found in comparison to a waitlist or treatment-as-usual at conclusion of treatment and at six months follow-up. Treatment effect size of CBT for GAD was significantly associated with attrition rates and depression outcomes.

Pharmacological Interventions

A recent literature search was conducted to provide an update of pharmacological treatments for GAD in adults (Reinhold and Rickels, 2015). Authors noted the difficulty in recognizing and treating GAD in primary care as clinical presentation is variable among patients. They estimated that the rate of correct recognition and diagnosis is 34 percent in primary care with somatic concerns often obscuring the psychiatric symptoms. Additionally, they noted that 90 percent of patients with GAD also have a comorbid psychiatric illness, e.g., depressive disorder. Authors reviewed trials that established specific drugs as first- or second-line therapies and also reviewed some new pharmacologic treatment modalities. A recent resurgence of interest in the role of benzodiazepines in the treatment of GAD led the authors to evaluate published comparisons of benzodiazepines with antidepressants in the treatment of GAD (Reinhold and Rickels, 2015). Following is a summary of highlights of the review:

- SSRIs – Paroxetine has demonstrated significant improvement in HAM-A scores compared to placebo with response rates as high as 80 percent for those completing an eight-week study. Studies demonstrated that sertraline was

superior to placebo in improving the Hamilton Rating Scale for Anxiety (HAM-A) score, and escitalopram demonstrated superior efficacy compared to placebo in the long-term treatment of GAD and prevention of relapse. SSRIs were also associated with adverse events, e.g., weight gain, sexual dysfunction, agitation/jitteriness in acute phase of treatment, and discontinuation syndrome on abrupt cessation (authors suggested that this discontinuation syndrome parallels that of the benzodiazepines).

- SNRIs – Studies demonstrated superior efficacy of SNRIs compared with placebo in the reduction of anxiety symptoms both in the short and long-term, with 70 percent response rates. In studies comparing venlafaxine and paroxetine, no difference was found in the HAM-A scores. Compared with escitalopram, venlafaxine XR was superior in improving HAM-A scores while escitalopram was better tolerated. Studies have shown that duloxetine and venlafaxine demonstrated similar response rates, with both drugs improving psychiatric and somatic symptoms.

  Benzodiazepines – Recent studies suggest that antidepressants (ADs) may not be superior to benzodiazepines in terms of efficacy and tolerability and "the guidance and paradigm shift to prefer the newer ADs was premature and without an adequate evidence base" (Reinhold and Rickels, p. 1673). Results from studies have demonstrated that benzodiazepines induce an earlier response than antidepressants that tends to be sustained throughout treatment. Studies have also shown that benzodiazepines are associated with sedation, cognitive impairment and interference with psychomotor function, but authors note that these generally occur only with initiation of therapy and on an increase in dosage. Authors suggested that since SSRIs and SNRIs are associated with a discontinuation syndrome mimicking that of a benzodiazepine withdrawal syndrome, no legitimate advantage over benzodiazepines exists.
- Pregabalin – A recent study evaluating the efficacy of pregabalin after a partial response to an SSRI or SNRI found the pregabalin-treated group had greater reduction in HAM-A score than placebo. Authors noted that the "relative efficacy and early onset of effect of pregabalin versus commonly used benzodiazepines has been established and this may represent a new therapeutic intervention for GAD" (Reinhold and Rickels, p.1675). However, there is a risk of weight gain that is clinically significant.
- Newer or Novel Treatments: agomelatine, vilazodone and vortioxetine – Authors indicated that due to the lack of consistent efficacy data in trials, agomelatine, vortioxetine and vilazodone are not considered to be appropriate treatments for GAD at the present time.
- Atypical Antipsychotics – Authors noted that atypical antipsychotics have primarily been evaluated in short term studies as adjunctive therapies in treatment resistant GAD and the evidence is sparse and inconsistent. They indicated that the majority of studies of quetiapine XR do not support its efficacy over placebo.
- Conclusions – Authors noted that SSRIs and SNRIs are appropriate as first-line therapy in patients tolerating adverse effects. However, they recommended that benzodiazepines be considered as a possible first-line therapy for patients with GAD, based on physician's clinical judgment, as they are generally better tolerated than SSRIs and SNRIs. They recommended discontinuation (by taper) of the medication if there is no significant improvement. They further suggested that atypical antipsychotics should only be used to treat patients with GAD

with a concurrent psychotic condition.

Drug choice should be made based on several factors, i.e., efficacy, possible side effects, contraindications and interactions (Bandelow et al., 2015). In a meta-analysis of the efficacy of treatments, authors reported that benzodiazepines are not recommended for routine use as they may cause dependency, and in direct comparisons, tricyclic antidepressants have more adverse events than SSRIs. They also cautioned that pregabalin has been associated with both withdrawal symptoms and abuse in patients with substance abuse, and antipsychotics, i.e., quetiapine, has been associated with risk of metabolic abnormalities (Bandelow et al., 2015).

A recent meta-analysis of randomized controlled trials including adults (n = 2248) with GAD investigated the outcomes, i.e., efficacy, acceptability and tolerability, of treatment with quetiapine monotherapy (Maneeton et al., 2016). Efficacy outcomes were measured by scores of rating scales for anxiety (HAM-A) and response rate [Clinical Global Impression (CGI), CGI-Severity (CGI-S), Pittsburgh Sleep Quality Index (PSQI), Montgomery-Asberg Depression Rating Scale (MADRS)]. Quetiapine as monotherapy was compared with placebo or SSRIs in adults with GAD. Results of the meta-analysis showed that low dosage (50 and 150 mg/day) quetiapine-XR is effective in treating GAD. PSQI scores indicated greater improvement of quality of sleep in those treated with quetiapine compared with placebo while acceptability and tolerability was less than placebo. Response rates of quetiapine and SSRIs in this meta-analysis were similar at approximately 61 percent and remission rates of each were 35.5 equally. Although the study found quetiapine has better sleep promoting quality compared to SSRI, its sedative effect may hinder daytime functioning. Authors concluded that low dose quetiapine is comparable to SSRIs in both acceptability and tolerability and may be considered as an alternative treatment for GAD. However, they also cautioned that its use should be cautiously carried out due to adverse events and further studies are needed to confirm the results of this study (Maneeton et al., 2016).

A recent literature review of quetiapine for GAD evaluated the efficacy and tolerability of quetiapine for the treatment of generalized anxiety disorder (Kreys and Phan, 2015). This review included studies evaluating the use of quetiapine monotherapy as well as studies of quetiapine adjunct therapy. Results of the monotherapy trials demonstrated significant improvement in HAM-A scores “as early as day four or week one of treatment and at week eight study end point compared with placebo” (Kreys and Phan, p. 183). Improvement in anxiety symptoms generally takes two to four weeks with standard antidepressant treatment. Results of the quetiapine augmentation trials showed response and remission rates comparable with placebo while not as robust as for quetiapine monotherapy. Authors concluded that these studies demonstrated both efficacy and tolerability of quetiapine monotherapy or adjunct therapy to antidepressants for treatment of acute GAD. They further suggested a careful benefit-risk analysis of the use of quetiapine when patients fail to respond to conventional antidepressant treatment and recommended close monitoring of metabolic side effects.

Combined Treatment

In a recent meta-analysis comparing the effects of treatment with antidepressant medications to the effects of combined antidepressant medications and psychotherapy in adults with depressive or anxiety disorder, researchers found evidence that the combined treatment was more effective in major depression, panic disorder and OCD,

but there was insufficient evidence for GAD (Cuijpers et al., 2014).

A later meta-analysis compared the efficacy of pharmacological, psychological and combined treatment in patients (n = 37333) with GAD, panic disorder and social phobia (Bandelow et al., 2015). In rationalizing the combination of all three disorders in this study, researchers explained the high comorbidity among the disorders and the lack of evidence suggesting differential efficacy of treatment for different anxiety disorders. This meta-analysis, including 234 studies, found that most psychopharmacological medications used in treating anxiety disorders have significantly higher effect sizes than psychological therapies, with the improvements achieved in a shorter time period. Among drugs, the SSRIs, SNRIs and pregabalin had the highest effect sizes. Researchers cautioned that side effects must be considered in the choice of drug. Among psychological treatments, CBT was found to be more effective than waiting list, psychological placebo and pill placebo. Group CBT, however, was not superior to psychological placebo conditions in direct comparisons. Researchers suggested CBT has an advantage over drug treatment as gains from CBT are maintained after termination of treatment. After stopping medications, patients generally experience a recurrence of anxiety symptoms. Researchers also noted the lack of combination studies of CBT with currently recommended medications. They also emphasized that patients should be involved in the selection of treatment, whether psychotherapy, medications or a combination of the two (Bandelow et al., 2015).

A recent randomized, comparative, partial crossover study evaluated the relationships between psychophysiological and clinical measures during venlafaxine ER treatment compared with relaxation therapy in patients with GAD (Zullino et al., 2015). In Phase I of this trial patients (n = 58) were randomly assigned to eight weeks of venlafaxine ER (75 mg/day for one week, increased to 150 mg/day and after two weeks increased to 300 mg/day) or to eight weeks of relaxation treatment (individual 45-minute sessions). Patients (n = 32) who did not remit to treatment (from both groups) received combined venlafaxine ER and applied relaxation for another eight weeks (Phase II). In the second eight-week period, remitted patients continued treatment with venlafaxine XR (those who had been allocated to this treatment) or continued home practice of relaxation. Results showed no group differences in treatment responses. However, when venlafaxine ER was added to applied relaxation therapy and vice versa for patients who had not remitted in Phase I, the number of responses was increased. Researchers suggested that venlafaxine and applied relaxation combined enhances treatment response in the case of initial failure (Zullino et al., 2015).

Alternative Treatments

Complementary and alternative treatments GAD lack sufficient evidence (Locke et al., 2015). Botanicals and supplements are sometimes used to treat anxiety disorder and panic disorder, but most must be used with caution in combination with SSRIs due to an increased risk of serotonin syndrome. Although music therapy, aromatherapy, acupuncture, and massage may be helpful for anxiety associated with GAD, authors reported that they have not been evaluated specifically for GAD.

A recent pilot study examined the potential efficacy of Kundalini Yoga-enhanced CBT (Y-CBT) in the treatment of treatment resistant GAD in adult participants (n=32) at a community health clinic (Khalsa et al., 2015). Y-CBT was conducted in weekly one-hour sessions during a period of six weeks that included low impact yoga/meditation, instruction and experiential cognitive restructuring using traditional as well as

alternative CBT interventions, and group discussion. Authors described "alternative CBT interventions" as teaching participants to "restructure their relation to their thoughts, as well as their physiologic interaction with the thought" (Khalsa et al., p. 5). Out of the 32 participants, 22 completed the six-week intervention. Self-report measures, i.e., the *State Trait Anxiety Inventory* and the *Treatment Outcome Package* were administered before and after the six-week treatment. The results of this small pilot study indicated that treatment resistant outpatient mental health patients experienced significant improvement in anxiety levels as well as in reported symptoms of comorbid depression and panic after Y-CBT compared with before treatment. Authors suggested the need of future research to investigate ways to decrease the drop-out rate, while acknowledging that Y-CBT "appears to be a promising new treatment for those suffering from GAD" (Khalsa et al., p. 10).

Prediction, Learning and Feedback

White et al (2017) suggest that individuals with GAD have impairments in their ability to predict outcomes, to take the consequences of those outcomes and to make corresponding behavior changes as compared to those without GAD. In White's study, patients with generalized anxiety disorder and healthy comparison participants were given tasks requiring decisions. The decisions made were associated with different probabilities of reward and punishment. Compared to healthy subjects, individuals with GAD failed to learn as well from the rewards and punishments associated with the choices they made. They maintained a persistently high error rate whereas the healthy subjects progressively decreased their errors. These findings suggest that the impairments in learning in learning were due to inadequate experience of prediction errors and thus inefficient updating of value. Consequently, individuals with GAD are hampered when making choices about which stimulus may lead to a reward or punishment.

Generalized Anxiety Disorder in Adults:

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	
	RECOMMENDATIONS
Introduction Epidemiology Comorbidities Assessment	Epidemiologic surveys show the prevalence of GAD is 5.7 percent during a patient's lifetime and 3.1 percent in the previous year, with higher prevalence among women than men. Most cases of GAD begin in early adulthood, and often in the context of chronic physical health conditions (Stein and Sareen, 2015). Its prevalence is greater in the primary care setting at 7-8 percent of patients, but it is not always detected or recognized because anxiety symptoms are not often the presenting complaints. Most patients with GAD present with complaints of physical symptoms offering a significant challenge to practitioners (Baldwin et al, 2014). The age of onset of GAD differs from that of other anxiety disorders, with the majority of cases presenting between 35 to 45 years of age. Peaking in middle age, the prevalence of the diagnosis declines across the later years of life, although GAD may be the most common anxiety disorder among the older population (aged 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 to 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 patients with GAD are high users of primary care resources. GAD is diagnosed twice as often in women as in men; in clinical settings, 55-60 percent of those with GAD are women (APA, 2013). Prevalence rates are higher in white and Native American persons than in black, Asian and Hispanic individuals (Newman et al., 2013). 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). According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5™)* published by the American Psychiatric Association in 2013, GAD is an anxiety disorder characterized by persistent, excessive and difficult-to-control

anxiety and worry about a number of activities or events (APA, 2013). The worry and anxiety are out of proportion to the actual likelihood or impact of the anticipated events, its focus often shifting from one concern to another during the course of the disorder. Having difficulty in controlling the worry, the individual's worrisome thoughts may interfere with attention to tasks at hand. Worries may be about every day, routine life circumstances, e.g., job responsibilities, health and finances, health of family members, their children's misfortunes or minor matters, e.g., chores around the house or tardiness in meeting appointments.

DSM-5 did not adopt the considered term, "generalized worry disorder" although chronic and excessive worry that interferes significantly with psychosocial functioning is a core and defining feature of generalized anxiety disorder (GAD) (Stein and Sareen, 2015). According to the DSM-5, the worries occur for at least six months, often occurring without precipitants. Three or more of the following symptoms are associated with GAD: restlessness/being on edge, being easily fatigued, trouble concentrating, irritability, muscle tension and disturbed sleep (APA, 2013). Comorbidities often include major depression, panic disorder and obsessive-compulsive disorder.

GAD is distinguished from non-pathological anxiety as worries associated with GAD are excessive and usually interfere significantly with psychosocial functioning. They may occur without precipitants, and are more pervasive, distressing and pronounced with longer duration. Worries associated with GAD are much more likely to be accompanied by physical symptoms, e.g., restlessness or feeling keyed up or on edge. Constant worry and related impairment in social, occupational or other important areas of functioning lead to subjective stress (APA, 2013). GAD may be accompanied by several psychic and somatic symptoms including suicidality. Other features supporting diagnosis of GAD include muscle tension, and somatic symptoms, e.g., nausea, diarrhea, sweating, irritable bowel syndrome, headaches and exaggerated startle response.

Clinical presentations often include somatic illness, pain, fatigue, depression and problems with sleeping. Diagnosis of GAD must meet the following DSM-5 criteria:

- Persistent and excessive anxiety and worry about common events or activities occur on more days than not, for six 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.
- Difficulty controlling worry is associated with at least three of the following six symptoms: 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).

- Clinically significant distress or impairment in social, occupational or other important areas of functioning are caused by the anxiety, worry or physical symptoms. Diagnosis of GAD should be made only when the focus of anxiety or worry is unrelated to disorders, 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) or having a serious illness (as in hypochondriasis). Also, in GAD, the worry does not occur exclusively during post-traumatic stress disorder. Anxiety, worry or physical symptoms cause clinically significant distress or impairment in social, occupational or other important area of function.
- 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.
- The disturbance is not better explained by another mental disorder, e.g., panic disorder, social phobia, obsessive-compulsive disorder, separation anxiety disorder, posttraumatic stress disorder, body dysmorphic disorder, illness anxiety disorder, schizophrenia or delusional disorder (APA, 2013).
- Patients with GAD may present with symptoms other than anxiety, e.g., pain or sleep disturbance, leading to a misdiagnosis.

Assessment Scales – Evidence from a criterion-standard study found 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; Kroenke et al., 2010). Two other symptom severity measurement instruments have been developed and tested for GAD. The Generalized Anxiety Disorder Severity Scale (DGSS) is comprised of eight 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).

A new computerized adaptive test for GAD, CAT-ANX, based on multidimensional item response theory, allows the specific items administered and the number of items to vary from individual to individual, leading to a dramatic decrease in the number of items required for a fixed level of measurement uncertainty. Items are selected for each patient from a large bank of test items based on prior item responses (Gibbons et al., 2013).

A later study focused on the development of the Computerized Adaptive test for Anxiety (CAT-ANX) (Gibbons et al., 2014). Authors reported on the analysis of data from psychiatric participants (n=798) and non-psychiatric community comparison subjects (n=816). The computerized adaptive testing allowed the selection of only a small set of items for each patient from a large bank of test items based on prior item responses. Results of this study showed CAT-ANX scores strongly related to generalized anxiety disorder diagnosis. Authors stated, "The resulting increase in measurement efficiency permits anxiety screening of large populations for epidemiologic studies and determining phenotypes for large-scale molecular genetic studies. The scientific contribution of this study lies in our demonstration that the use of computerized adaptive testing based on multidimensional item response theory generalizes to the measurement of other psychopathologic conditions beyond depression" (Gibbons et al., p. 192). They further noted how routine anxiety screening of patients in primary care is improved by CAT-ANX and is administered in minutes using the internet, without clinician assistance.

Epidemiological Data – Data from the U.S. National Comorbidity Survey Replication (NCS-R) showed that GAD prevalence rates changed when using a broader definition of episode from the required six months. Community epidemiological data for the range of 1-12 months showed that *lifetime prevalence* changed from 6.1 percent to 4.2-12.7 percent; *12 month prevalence* changed from 2.9 percent to 2.2-5.5 percent; and *30 day prevalence* changed from 1.8 percent to 1.6-2.6 percent. Cases with episodes of 1-5 months did not differ greatly from those with episodes greater than or equal to six months in onset, persistence, impairment, comorbidity, 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 six months duration and question the basis for excluding these people from a diagnosis of GAD (Kessler, Brandenburg, et al. 2005). DSM-5 continues to include excessive anxiety and worry (apprehensive expectation) occurring for at least six months as part of the diagnostic criteria for GAD (APA, 2013).

Risk Factors – One study found that GAD (comorbid 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 (Moffit, Caspi, et al. 2007). Although childhood adversities and parental overprotection have been shown to be associated with GAD, DSM-5 notes that these factors have not been identified as specific to GAD and are not sufficient for making a diagnosis of GAD (APA, 2013). Temperamental factors, e.g., behavioral inhibition, neuroticism and harm avoidance, are associated with GAD, as are genetic and physiological factors. According to DSM-5, one-third of the risk of experiencing GAD is genetic. Although there is cultural variation in the expression of GAD, there is a lack of information about whether the propensity for excessive worrying is related to culture (APA, 2013).

Comorbid Psychiatric Conditions – Individuals meeting the criteria for GAD are most likely to have met the criteria for other anxiety disorders and unipolar depressive disorders which share the same risk factors, although independent pathways are also possible (APA. 2013). Other less common comorbidities include substance use, conduct, psychotic, neurodevelopmental and neurocognitive disorders (APA, 2013). The comorbidity rate with major depression is about 59 percent and 56 percent 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) comorbidity 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 percent of depression cases, but depression began before or concurrently in 32 percent of anxiety cases. Also, cumulatively, 72 percent of lifetime anxiety cases had a history of depression, but 48 percent of lifetime depression cases 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 percent of subjects with bipolar disorder had a lifetime occurrence of GAD (somewhat higher for bipolar I than for bipolar II disorder) and 51 percent of bipolar patients had at least one type of lifetime anxiety disorder (Simon, 2009).

A more recent study addressed the symptom overlap of participants (n=1218) meeting diagnostic criteria for GAD, MDD, or both, to investigate whether comorbidity may be explained by

overlapping diagnostic criteria. Data in the study included symptom profiles of participants with GAD, MDD, and comorbid GAD/MDD. DSM-5 diagnostic criteria for GAD and MDD share four symptoms: difficulty sleeping, difficulty concentrating, being easily fatigued and psychomotor agitation. Authors reviewed data from the Mini International Neuropsychiatric Interview (MINI) to determine whether the comorbid GAD/MDD group endorsed the overlapping symptoms more than the non-overlapping symptoms, and whether the comorbid GAD/MDD group endorsed the overlapping symptoms more than GAD only or MDD only groups. Results showed that the GAD/MDD group endorsed the overlapping symptoms more that the MDD group but not the GAD group and the comorbid group endorsed the overlapping symptoms more than the non-overlapping symptoms. Findings suggested that symptom overlap may inflate rates of comorbidity between GAD and MDD; alternatively it may represent the shared psychopathology underlying the conditions (Zbozinek et al., 2012).

Comorbid Physical Conditions – 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 disorders, the presence of an anxiety disorder was significantly associated with thyroid disease, respiratory disease, gastrointestinal disease, arthritis, migraine headaches and allergic conditions. Comorbidity was also shown to be significantly associated with poor quality of life and disability (Sareen, Jacobi, et al. 2006).

Suicide Ideation and Suicide Attempt – 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 comorbidity 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 percent 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). A more recent study explored independent association between specific anxiety disorders (including GAD) and suicide attempts and ideation using

	a process that simulated a case-control study and made use of the National Comorbidity Survey Replication and the National Epidemiologic Survey on Alcohol and Related Conditions. This study presented evidence that each anxiety disorder, e.g., GAD, is associated with suicide ideation and suicide attempts beyond the effects of co-occurring mental disorders (Thibodeau et al., 2013).
Diagnosis and Planning	The British Association of Psychopharmacology's revised guidelines for the evidence-based pharmacological treatment of anxiety disorders include recommendations in the detection and diagnosis of GAD including (Baldwin et al., 2014): • Recognition of the symptoms/signs of GAD • Assessment of coexisting depressive symptoms • Inquiring about long-standing anxiety symptoms in patients with unexplained physical symptoms • Assessment of comorbid physical illness. It is important to identify the diagnosis of GAD as early as possible in order to plan and begin treatment.
Management of Patient Including Patient/Family Education	All patients who are suspected of having GAD should receive a comprehensive assessment, not relying solely on the number, severity and duration of symptoms, but also considering the degree of distress and functional impairment (National Institute for Health and Clinical Excellence (NICE), 2011). Patients should receive education from their physician about the nature of GAD, options for treatment, and general prognosis. Physicians should identify alleviating and aggravating factors as well as signs of relapse for each patient. In addition, information on local self-help and support 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). Along with educating the patient, the individual's symptoms and functioning should be actively monitored. Education and active monitoring may have the effect of improving less severe presentations and may avoid the need for further interventions (NICE, 2011). Management of care may include the following: (Baldwin et al., 2014) o Education of patient and family (lifestyle changes, strategies including exercise and yoga, and minimization of alcohol use) while monitoring patient's progress o Low intensity psychological interventions, e.g., individual self-help, educational groups, computer-assisted cognitive behavioral therapy o Choice of high-intensity psychological intervention, i.e.,

	individual or group-based cognitive behavioral therapy, or first-line pharmacological treatment, i.e., selective serotonin-reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs), based on patient's preference o Specialized care by mental health professions including other first-line pharmacologic treatments or adjunctive treatments with other medications, e.g., benzodiazepine (avoid in elderly patients and in those receiving opioids), buspirone, pregabalin or quetiapine, and more intensive cognitive behavioral therapy or other psychotherapy.
Psychotherapy Treatments	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 *Consensus Statement on Generalized Anxiety Disorder from the International Consensus Group on Depression and Anxiety* (Ballenger, 2001). Additionally, the *Canadian Psychiatric Association Clinical Practice Guidelines on the Management of Anxiety Disorders* (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 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 six months to two 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). A recent meta-analysis examining the effects of psychological treatment of GAD included 41 randomized studies and adults (n=2132) with a diagnosis of GAD (Cuijpers et al., 2014). Trials compared psychotherapy, e.g., CBT, with untreated controls, with pharmacotherapy, and with other psychotherapies. Results suggested that CBT is more effective than applied relaxation as a first line treatment of GAD and it may have longer-lasting effects compared to usual care. Internet-based treatments and face-to-face therapies had comparable outcomes. Studies comparing psychological treatment to medication suggested psychological treatment to be at least as effective as medication. Authors concluded that these results, demonstrating large and clinically relevant effects of psychotherapy, suggests that psychological treatment, especially CBT, is as effective as medication in treating GAD in adults and may be the treatment of choice (Cuijpers et al., 2014). Important research findings on psychotherapy for the treatment of

GAD include studies on CBT, Worry Exposure, Applied Relaxation, Muscle Relaxation, Short-term Psychodynamic Psychotherapy, Mindfulness-based Therapy and Motivational Interviewing summarized as follows:

- A recent randomized trial examined the impact of integrating motivational interviewing (MI) and CBT for treatment of GAD (Westra et al., 2015). Adults with GAD (n=85) who scored above the high severity cutoff on the Penn State Worry Questionnaire (PSWQ) were randomized to 15 weekly sessions of CBT alone or to four weekly sessions of MI followed by 11 weekly CBT sessions integrated with MI (MI-CBT). The primary outcome measure was the PSWQ. Results found no effect of treatment group on worry level or rate of change at session 15, but at 6-month and 12-month follow-up, patients receiving MI-CBT had a steeper rate both of worry decline and of distress reduction. Additionally, twice as many drop-outs occurred in the CBT group compared with the MI-CBT group. Researchers concluded, "These findings suggest that explicit training in empathy, i.e., MI-CBT therapists, greatly improves performance on this vital dimension compared to standard CBT training (CBT alone group)" (Westra et al., p. 11). They indicated that this is consistent with recommendations to "include guidance in systematic process observation and ongoing identification of motivational markers that indicate the need for responsive intervention using MI spirit and skills" (Westra et al., p. 11).
- Worry outcome monitoring is considered one of many cognitive behavioral components of cognitive behavioral therapy (LaFreniere and Newman, 2016). In a recent randomized controlled trial evaluating the efficacy of worry outcome monitoring in the treatment of GAD, participants (n = 51) with GAD and over age 18 years were randomized to a treatment, Worry Outcome Journal (WOJ) or to a control condition, Thought Log (TL) for a period of 10 days. Worry outcome monitoring asked the participants to record on paper their worry content and predictions about the future, as well as to rate the degree of distress caused by the worry. Participants tracked outcomes in a "worry outcome diary." Paper contents were entered online each night. Twenty days after the 10-day period of worry recording, participants reviewed each of the entries in the journal and indicated whether the worries came true and whether they were as expected in terms of distress. Participants in the Thought Log condition recorded on paper thoughts, not worries, and rated any distress related to the thought and recorded these online each night. Twenty days after the period of thought recording, they reviewed their entries without indicating whether outcomes came true. Outcome measures including the PSWQ showed a significant reduction in worry during the 10 day intervention period which was maintained for 20 days following the trial in the

WOJ group compared to the TL group. Researchers suggested, "Repeated present moment awareness of the content, distress, and interference created by even a few emotions can have positive effects on mental and physical health"… and that "writing about thoughts and emotions can have positive effects on mental and physical health" (LaFreniere and Newman, p. 9). They concluded that the WOJ may be a first line treatment for patients with GAD before more intensive therapist-dependent treatment.

- A recent randomized clinical trial compared two therapist-delivered treatments, telephone-delivered CBT (CBT-T) and telephone-delivered non-directive supportive therapy (NST-T), in the treatment of rural adults (n = 141) aged 60 years and older with GAD (Brenes et al., 2015). The comparison included the effects of CBT-T and NST-T on anxiety, worry, GAD symptoms and depressive symptoms at four-month randomization. Primary outcome measures were the Hamilton Anxiety Rating Scale (HAMA) and the Penn State Worry Questionnaire-Abbreviated (PWSQ-A). CBT-T included 9-11 weekly 50-minute telephone therapy sessions with CBT techniques, while NST-T included 10 weekly 50-minute therapy sessions with supportive and reflective communications (no advice, suggestions or coping methods). Results showed that both CBT-T and NST-T reduced symptoms of GAD, worry and depression, although the decline in each was significantly greater among the participants in CBT-T. A recent study performed secondary data analyses of a randomized controlled trial of CBT for late-life GAD compared with usual care (UC) in a combined sample of community and Veteran participants (Barrera et al, 2014). The results showed significant improvements in GAD severity and anxiety in participants treated with CBT relative to UC. The secondary analyses were performed in the Barrera et al. study to further evaluate the outcomes for CBT within the community vs. the Veteran group and to examine predictors of outcomes in the Veterans sample. Results suggested that treatment effects with a standard CBT package were larger in community participants than in Veterans. Analyses in Veterans found that poorer outcomes were associated with poorer perceived social support. Researchers emphasized the complexity of treating Veterans with anxiety, and suggested particular attention to social support to improve the efficacy of CBT for Veterans (Barrera et al., 2014).
- A recent review of literature and clinical synthesis focused on structured internet-delivered cognitive behavioral therapy (iCBT) for anxiety disorders and depression (Titov et al., 2014). Authors noted the variation between iCBT interventions, e.g., number or lessons/modules, organization of modules, and duration of intervention (generally over 4-16 weeks). More than 150 clinical trials evaluating iCBT for GAD generally have

reported the efficacy of iCBT while also finding that superior clinical outcomes result from therapist-guided iCBT compared with self-guided CBT. Authors emphasized the assumption in psychotherapy that "the therapist is essential for effective treatment, and that therapist training, expertise and skill are the most important predictors of clinical outcomes" (Titov et al., p. 303). They concluded that blended mental health services, e.g., internet-delivered psychological treatment along with face-to-face services, will increase access to evidence-based care for patients who might not otherwise either receive or seek treatment.

- 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).

- Previous studies have suggested that transdiagnostic CBT for anxiety disorders reduces symptoms of anxiety. A randomized clinical trial by Norton and Barrera investigated the efficacy of a 12-week transdiagnostic CBT group treatment compared with a 12-week well-established diagnosis-specific group CBT treatment for panic disorder, social anxiety disorder and GAD. Participants (n=46) with the above disorders were randomized either to the transdiagnostic CBT group or the diagnosis-specific CBT group. Participants in the transdiagnostic CBT condition received treatment that deemphasized diagnostic labels and focused on challenging and confronting feared stimulation. It included psychoeducation, cognitive restructuring and exposure therapy. Participants in the diagnosis-specific CBT group received group CBT treatment specifically targeting individual diagnoses of panic disorder, social anxiety disorder and GAD. The results of this trial showed effects of transdiagnostic CBT at least as strong as those of diagnosis-specific CBT on most outcome measures. Researchers noted the shared clinical features and underlying processes among the anxiety disorders and suggested that a single transdiagnostic CBT applicable to more than one anxiety disorder may increase the adoption rate of evidence-based CBT by mental health practitioners. They concluded that the almost identical outcomes across transdiagnostic and diagnosis-specific groups provides preliminary evidence supporting the efficacy of transdiagnostic CBT in the treatment of social anxiety disorder, GAD and panic disorder, suggesting that transdiagnostic treatments may be extended to include other anxiety disorders (Norton et al., 2012).
- CBT is considered the cornerstone of treatment of adults with GAD with the goal of helping patients identify distressing/ dysfunctional beliefs and thought patterns with more rational and realistic views (Patel et al., 2013). Authors noted other nondrug therapies which can augment or replace CBT if it is not effective, e.g., relaxation training, worry exposure or exposure therapy, short-term psychodynamic psychotherapy.
- Internet and computer-based CBT delivery formats continue to be developed in an effort to increase patient access to this type of therapy. One large meta-analysis studied the effects of 22 studies of computerized CBT models against a control condition for patients with the following disorders: major depression, panic disorder, social phobia or GAD. The mean effect size superiority for the four diagnostic groups (Hedges g) was 0.88 and specifically for GAD was 1.12 (two studies; n=198) showing short- and long-term benefits, good patient adherence and satisfaction with computerized CBT despite decreased clinician contact (Andrews et al., 2010). Similarly, a randomized controlled trial of eight-week internet-delivered

CBT (n=89) consisting of a self-help program based on CBT principles and applied relaxation along with therapist guidance revealed significant improvement compared with the control group on measures of worry, anxiety and depression at both the one- and three-year follow up (Paxling et al., 2011).

- An exploratory study addressed the content of therapist e-mails in therapist-guided internet-based cognitive behavioral therapy (iCBT) for GAD (Paxling et al., 2013). Authors examined almost 500 e-mails from three therapists providing support to patients (n=44) diagnosed with GAD in a randomized controlled trial. Online text modules, e.g., applied relaxation, worry exposure, problem solving and cognitive restructuring, communicated CBT strategies to the participants in order to reduce problems related to excessive worrying. Homework assignments were included and at the end of each week the patient responded by providing information about their progress and related problems. The therapist replied to the e-mail with feedback and answers to any patient questions. In this study, the therapist e-mails to patients were analyzed and therapist behaviors were coded as follows: deadline flexibility, task reinforcement, alliance bolstering, task prompting, psychoeducation, self-disclosure, self-efficacy shaping, and empathetic utterance. Investigators indicated that distinct therapist behavior exists in online therapy. Lenience regarding deadlines was negatively associated with treatment outcome, and task reinforcement correlated with module completion and positive outcomes. Investigators suggested further studies with a larger sample size are needed along with studies addressing the impact of e-mail support given in addition to traditional face-to-face therapy (Paxling et al., 2013). Bandelow et al. suggested that internet-based CBT should not be recommended for the treatment of GAD as trials have not compared it to traditional CBT in which the patient and therapist are in personal contact (Bandelow et al., 2013).
- A systematic review of 27 clinical trials (total n=2,373) evaluating both pharmacological (14 studies using various agents, i.e., antidepressants, anticonvulsants, buspirone, piperazine/azapirone anxiolytic or quetiapine) and psychotherapeutic interventions (13 studies – 12 studies using CBT in at least one study arm and one study comparing community treatment vs. modular psychotherapy) for GAD in adults aged 55 and over demonstrated that pooled treatment effects were similar for either type of intervention and that patients benefited from the active intervention when compared to waiting list, usual care or minimal contact conditions. These effects however, were lost for psychotherapeutic interventions when other active conditions were employed as comparators, i.e., discussion group, medical management, (Goncalves et al., 2011).

- 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, i.e., 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 CBT treatment (Covin, 2007).
- 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 six month and one 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 three 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 later study examined the psychometric properties of the Pittsburgh Sleep Quality Index (PSQI, a comprehensive self-report measure of sleep quality and impairment, comparing the component scores of older adults (n=134) with GAD to those (n=82) without GAD (Bush et al, 2012). PSQI scores showed that participants with GAD experienced greater sleep difficulties than those without GAD. Researchers then used the PSQI as an outcome measure in a trial examining the response to CBT compared to enhanced usual care (EUC) in older adults (n=134) with principal or co-principal GAD. Participants were randomized to receive either CBT (consisting of 10 individual sessions including psychoeducation, motivational interviewing, relaxation training, cognitive restructuring, exposure, problem-solving skills training and behavioral sleep management) or EUC (consisting of biweekly telephone conversations with a therapist, focusing on safety

monitoring and providing support). At posttreatment (three months) and over a 12 month interval, the Pittsburgh Sleep Quality Index (PSQI), a comprehensive self-report measure of sleep quality and impairment, was administered to each group. Participants who received CBT for anxiety experienced greater reductions (improvement) on scores of sleep quality, sleep latency and sleep disturbances than those who received enhanced usual care. Researchers noted that although CBT for anxiety alleviated some aspects of sleep difficulty over time, it did not improve improvement in sleep duration, daily functioning or use of sleep medications (Bush et al., 2013).

- Another study examined the effects of cognitive behavioral therapy delivered by telephone (CBT-T) to older adults diagnosed with a diagnosis of GAD, panic disorder, combined GAD and panic disorder, or anxiety disorder not otherwise specified (Brenes et al., 2012). Participants (n=60) were randomized to CBT-T or information-only comparison. CBT-T was comprised of telephone therapy sessions and a treatment workbook. After the participant received a workbook chapter addressing a specific topic, e.g., treatment rationale, relaxation techniques, problem-solving, behavioral activation and relapse prevention, a telephone therapy session was conducted during which the content of the chapter was reviewed and the participant could ask questions. Homework was reviewed and discussed along with recommendations by the therapist. Participants randomized to information-only received written information on anxiety disorders and a list of referral options. This study found that participants who received CBT demonstrated greater improvement in self-report and clinician-rated worry and anxiety symptoms than participants in information only. They also experienced greater reductions in insomnia and anxiety sensitivity. Follow-up data (six months after treatment completion) indicated no significant differences in the reductions in anxiety sensitivity and insomnia between the two conditions, suggesting that a longer intervention or more intense follow-up may be needed. Researchers suggested that CBT-T may be useful in a stepped care to late-life anxiety as older adults often prefer psychotherapy to pharmacotherapy and many are unable to attend regular face-to-face therapy sessions. They also suggested that more follow-up sessions should be integrated into telephone treatment (Brenes et al., 2012).
- 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 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. According to investigators, these findings remained stable at the 12-month follow-up. 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; Salzer et al. 2011).
- Mindfulness-based therapy (MBT) was developed to help individuals counter experiential avoidance strategies by use of a mental state characterized by nonjudgmental awareness of present moment experiences using techniques derived from Buddhist meditation and traditional yoga practices (Hofmann et al., 2010). A meta-analytic review of 39 studies of 1,140 patients was conducted on patients who received this treatment (including both mindfulness-based cognitive therapy and stress reduction) for a range of conditions, e.g., GAD, cancer, depression and other medical or psychiatric disorders. Overall findings showed that in patients with anxiety and mood disorders, MBT was associated with effect sizes of 0.97 and 0.95 (Hedge's g) for improving anxiety and mood symptoms, respectively. Results from the seven studies that evaluated anxiety disorders specifically, i.e., GAD, GAD comorbid with panic disorder or social anxiety disorder) significant treatment effects were found for reducing anxiety symptoms (Hedge's g=0.97) and depressive symptoms (Hedge's g=0.75) in those patients who demonstrated elevated level of depressive symptoms at pre-treatment (Hofmann et al., 2010).
- In a later trial, participants aged 18 or older (n=93) with GAD were randomized to an eight-week program of manualized Mindfulness-Based Stress Reduction (MBSR) or to an attention control, Stress Management Education (SME) to compare the effects of the two treatments (Hoge et al., 2013). MBSR was comprised of group in class practices, e.g., breath-awareness, gentle Hatha yoga and Body-Scan exercises, which focused on present experience and treating the body gently. Participates were also instructed in daily home practice, e.g., present-

	focused awareness while eating, bathing or cleaning. SME, which did not include any mindfulness components, was taught in a didactic format comprising both class and home activities, e.g., stress physiology, time management techniques, sleep physiology, nutrition and factors that buffer the impact of stress. Findings showed that both MBSR and SME led to significant reductions in anxiety symptoms as measured by the Hamilton Anxiety Scale (HAM-A). Anxiety symptoms as measured by the Clinical Global Impression of Severity and Improvement (CGI-S and CGI-I) the Beck Anxiety Inventory (BAI), and the pre- and post-treatment Trier Social Stress Tests were significantly reduced in the MBSR group compared to the SME group. Researchers suggested that MBSR, which may result in increased resilience to stressful psychological challenges and reduce anxiety symptoms in patients with GAD, should be studied further in larger trials (Hoge et al., 2013). • 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).
Pharmacology Treatments	A recent literature search was conducted to provide an update of pharmacological treatments for the treatment of GAD in adults (Reinhold and Rickels, 2015). Authors noted the difficulty in recognizing and treating GAD in primary care as clinical presentation is variable among patients. They estimated that the rate of correct recognition and diagnosis is 34 percent in primary care with somatic concerns often obscuring the psychiatric symptoms. Additionally, they noted that 90 percent of patients with GAD also have a comorbid psychiatric illness, e.g., depressive disorder. Authors reviewed trials that established specific drugs as first- or second-line therapies and also reviewed some new pharmacologic treatment modalities. A recent resurgence of interest in the role of benzodiazepines in the treatment of GAD led the authors to evaluate published comparisons of benzodiazepines with antidepressants in the treatment of GAD (Reinhold and Rickels, 2015). Following is a summary of highlights of the study follows:

- SSRIs – Paroxetine has demonstrated significant improvement in HAM-A scores compared to placebo with response rates as high as 80 percent for those completing an eight-week study. Studies demonstrated that sertraline was superior to placebo in improving the Hamilton Rating Scale for Anxiety (HAM-A) score, and escitalopram demonstrated superior efficacy compared to placebo in the long-term treatment of GAD and prevention of relapse. SSRIs were also associated with adverse events, e.g., weight gain, sexual dysfunction, agitation/jitteriness in acute phase of treatment, and discontinuation syndrome on abrupt cessation (authors suggested that this discontinuation syndrome parallels that of the benzodiazepines).
- SNRIs – Studies demonstrated superiority efficacy compared with placebo in the reduction of anxiety symptoms both in the short and long-term, with 70 percent response rates. In studies comparing venlafaxine and paroxetine, no difference was found in the HAM-A scores. Compared with escitalopram, venlafaxine XR was superior in improving HAM-A scores while escitalopram was better tolerated. Studies have shown that duloxetine and venlafaxine demonstrated similar response rates, with both drugs improving psychiatric and somatic symptoms.
- Benzodiazepines – Recent studies suggest that antidepressants (ADs) may not be superior to benzodiazepines in terms of efficacy and tolerability and "the guidance and paradigm shift to prefer the newer ADs was premature and without an adequate evidence base" (Reinhold and Rickels, p. 1673). Results from studies have demonstrated that benzodiazepines induce an earlier response than antidepressants that tends to be sustained throughout treatment. Studies have also shown that benzodiazepines are associated with sedation, cognitive impairment and interference with psychomotor function, but authors note that these generally occur only with initiation of therapy and on an increase in dosage. Authors suggested that since SSRIs and SNRIs are associated with a discontinuation syndrome mimicking that of a benzodiazepine withdrawal syndrome, no legitimate advantage over benzodiazepine exists.
- Pregabalin – A recent study evaluating the efficacy of pregabalin after a partial response to an SSRI or SNRI found the pregabalin-treated group had greater reduction in HAM-A score than placebo. Authors noted that the "relative efficacy and early onset of effect of pregabalin versus commonly used benzodiazepines has been established and this may represent a new therapeutic intervention for GAD" (Reinhold and Rickels, p. 1675). However, there is a risk of weight gain that is clinically significant.

- Newer or Novel Treatments: agomelatine, vilazodone and vortioxetine – Authors indicated that due to the lack of consistent efficacy data in trials, agomelatine, vortioxetine, and vilazodone are not considered to be appropriate treatments for GAD at the present time.
- Atypical Antipsychotics – Authors note that atypical antipsychotics have primarily been evaluated in short term studies as adjunctive therapies in treatment resistant GAD and the evidence is sparse and inconsistent. The majority of studies of quetiapine XR do not support its efficacy over placebo.
- Conclusions – Authors noted that SSRIs and SNRIs are appropriate as first-line therapy in patients tolerating adverse effects. However, they recommended that benzodiazepines be considered as a possible first-line therapy for patients with GAD, based on physician's clinical judgment, as they are generally better tolerated than SSRIs and SNRIs. They recommended discontinuation (by taper) of the medication if there is no significant improvement. They further suggested that atypical antipsychotics should only be used to treat patients with GAD with a concurrent psychotic condition.

Drug choice should be made based on several factors, i.e., efficacy, possible side effects, contraindications and interactions (Bandelow et al., 2015). In a meta-analysis of the efficacy of treatments, authors reported that benzodiazepines are not recommended for routine use as they may cause dependency and in direct comparisons, tricyclic antidepressants have more adverse events than SSRIs. They also cautioned that pregabalin has been associated with both withdrawal symptoms and abuse in patients with substance abuse, and antipsychotics, i.e., quetiapine, has been associated with risk of metabolic abnormalities (Bandelow et al., 2015).

In 2008, the *World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders--Revised* 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. Strong evidence of clinical efficacy in the treatment of GAD was found for first-line pharmacological treatments for GAD, i.e., SSRIs – escitalopram, paroxetine, sertraline; SNRIs – venlafaxine and duloxetine; and the calcium channel modulator – pregabalin. Second-line treatment options include buspirone (for augmentation), benzodiazepines, i.e., alprazolam and diazepam, and the antihistamine hydroxyzine. An atypical antipsychotic, i.e., quetiapine may be used as

monotherapy in GAD and is reserved for treatment-refractory cases (Patel et al., 2013, Bandelow et al., 2012, Bandelow et al., 2013). Only when all other drugs or CBT have failed, benzodiazepines, i.e., diazepam and lorazepam, can be used for long-term treatment (Allgulander 2010; Bandelow et al., 2008, Bandelow et al., 2012).

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 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 (Allgulander 2010; Bandelow et al., 2008).

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 percent 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).

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 Re-uptake 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).

The U.S. Food and Drug Administration (FDA) 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 six 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 (Allgulander, 2009).

In 2010, *The International Psychopharmacology Algorithm Project (IPAP)* 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 comorbidities 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 that stabilization of comorbid disorders should be attempted prior to treatment of GAD (Davidson et al., 2010).

Proposed Treatment Steps: Several conditions, e.g., patient's preference, severity of illness, comorbidity, concomitant medical illnesses, substance use disorders, risk of suicide, history of prior treatments, cost issues and availability of types of treatment, may affect the development of the treatment plan (Bandelow et al., 2012). Information and support should be provided to individuals with GAD, their families and caregivers.

The following summarizes important clinical information from the decision points and action steps conveyed in the IPAP review and treatment algorithm for GAD: (Davidson et al., 2010; IPAP GAD Algorithm Flowchart, 2009).

- Expert consensus indicates that an SSRI or SNRI monotherapy may be the initial choice of medication of a treatment-naive patient presenting with GAD. Other antidepressants, e.g., 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, in order to reduce the risk of relapse. 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 percent symptom improvement from baseline using a valid clinical measurement scale.
    - 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 comorbid disorder. Recommended drugs are as follows:
    - Comorbid depression – adequate dose of an antidepressant or augmentation with bupropion, buspirone, atypical antipsychotic, or the nutritional supplement, chromium picolinate. Severe depression may need ECT.
    - Comorbid stable bipolar disorder – add mood stabilizer, anticonvulsant or atypical antipsychotic drug. May need laboratory monitoring.
    - Comorbid panic disorder – add TCA or SSRI/SNRI or benzodiazepine.
    - Comorbid social anxiety disorder – add benzodiazepine, serotonin-reuptake inhibitor (SRI), atypical antipsychotic, pregabalin or anticonvulsant agent, levetiracetam.
    - Comorbid obsessive-compulsive disorder – add SSRI or clomipramine.

- Comorbid posttraumatic stress disorder – add SSRI, SNRI, atypical antipsychotic or sympatholytic drug, prazosin.

If there is no comorbid 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. Other important research findings on recommended drugs to treat GAD are summarized below:

Benzodiazepines – 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 comorbid depression (Baldwin, 2005). Baldwin et al. concluded that treatment with benzodiazepines should be for a short-term duration (up to four 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).

Another study compared healthcare costs of patients with GAD who received treatment with a benzodiazepine adjunctive to antidepressants with costs of those who did not receive concomitant therapy. Researchers found that healthcare costs increased in patients following benzodiazepine treatment and noted that approximately half of the increase in costs was associated with known sequelae of long-term treatment with benzodiazepines, e.g., care associated with accidents (Berger et al., 2012).

In a later study, Offidani et al. performed a systematic review and meta-analysis to analyze whether controlled comparisons support the current prescribing pattern favoring newer antidepressants (SSRIs, SNRIs) over benzodiazepines (Offidani et al., 2013). In one study comparing the efficacy of benzodiazepines to venlafaxine XR and placebo in patients with GAD (n=540), results showed no significant differences in response rates between groups. Discontinuations of treatment, due to adverse events, occurred more often in patients taking venlafaxine XR than in those treated with benzodiapepines. In another study, researchers evaluated the efficacy of treatment with lorazepam, paroxetine or placebo in patients with GAD (n=169) over four weeks. Results showed that

both lorazepam and paroxetine treatments were effective in reducing anxiety-related psychiatric symptoms. Somatic features improved significantly only in those taking lorazepam. Researchers noted serious and bothersome side effects of treatment with SSRIs, e.g., high rates of sexual dysfunction, weight gain, osteoporosis, hyponatremia, gastrointestinal bleeding and potential for drug interactions. Researchers suggested that the only potential advantage of SSRI versus benzodiazepines is the associated lower impairment in cognitive and psychomotor skills. They concluded that literature lends no support to the pattern favoring newer antidepressants over benzodiazepines in the treatment of anxiety disorders (Offidani et al., 2013).

Azapirones – Two meta-analyses have shown that buspirone (an azapirone anxiolytic with partial agonist properties at 5-HT1A 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 (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 comorbid disorders (Davidson et al., 2010; Pollack, 2009).

Selective Serotonin Reuptake Inhibitors (SSRIs) – 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:

- A published review of research findings from paroxetine clinical trials (three short-term and one 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 comorbid with it (Rickels, 2006).

- Study findings support the clinical efficacy of short-term treatment with sertraline, resulting in significant improvement in both psychic and somatic anxiety symptoms, including quality of life and work productivity (Allgulander, 2004).
- 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).
- A randomized, single-blind trial comparing sertraline (50-100mg./day) and buspirone (10-15 mg./day) in elderly patients (n=46) showed that they were both efficacious and well tolerated for the treatment of GAD in this population (Mokhber et al., 2010).
- 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 percent) compared with placebo (51 percent). 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).
- In a review of literature, Bandelow et al. reported the results of randomized trials including various treatments of GAD. They reported a number of controlled trials demonstrating the efficacy of the SSRIs escitalopram, paroxetine, and sertraline. Although SSRIs are generally well tolerated they noted adverse effects that may impair compliance and suggested that they should be taken in the morning to avoid nocturnal restlessness and insomnia at beginning of treatment (Bandelow et al., 2013).

Selective Serotonin and Norepinephrine Re-uptake Inhibitors (SNRIs) – Venlafaxine extended release (XR) was the first SNRI

antidepressant to receive FDA approval for the treatment of GAD followed by duloxetine (Collins et al., 2009; Davidson 2009; Baldwin, 2005).

- An open trial demonstrated equal efficacy and tolerability during eight 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 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-tern duloxetine treatments were associated with improvement in painful physical 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).
- 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 percent

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).

- A systematic review of studies in the use of duloxetine substantiated the drug's effectiveness for anxiety disorders with or without concomitant major depression. Specifically, the GAD studies confirmed duloxetine's short-term effectiveness, long-term efficacy, early response to treatment at first and second weeks of therapy and efficacy/tolerability in the elderly (Mancini et al., 2010).
- A review of literature reported the results of randomized trials demonstrating the efficacy of SNRIs (Bandelow et al., 2013). In all but one trial, venlafaxine was effective against GAD. Duloxetine was also found to be effective against GAD in controlled trials. Researchers cautioned that adverse effects, e.g., nausea, sleep problems, agitation, may impair compliance (Bandelow et al., 2013).

Tricyclics (TCAs) – 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 (Kapczinski, 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).

Noradrenergic and specific serotonergic antidepressant (NaSSA) – 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).

Antipsychotics – A published literature review on the efficacy of typical and atypical antipsychotics for primary and comorbid 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).Using annual data from the 1996-2007 National Ambulatory Medical Care Survey, a study reported that across this 12-year period, antipsychotic prescriptions in visits for anxiety disorders increased from 10.6 percent to 21.3 percent particularly among new patients (Comer et al., 2011). The investigators noted the availability of SGA drugs with improved anxiolytic prosperities and fewer short-term anticholinergic and extrapyramidal effects than first generation agents while offering less sedation have contributed to this trend. In addition, authors reported that "across drug classes, antipsychotic medications ranked near the top in off-label use, drug safety concerns and inadequate supporting evidence" (p. 1064, Comer et al., 2011).

- A recent meta-analysis of randomized controlled trials including adults (n = 2248) with GAD investigated the outcomes, i.e., efficacy, acceptability and tolerability, of treatment with quetiapine monotherapy (Maneeton et al., 2016). Efficacy outcomes were measured by scores of rating scales for anxiety (HAM-A) and response rate (Clinical Global Impression (CGI), CGI-Severity (CGI-S), Pittsburgh Sleep Quality Index (PSQI), Montgomery-Asberg Depression Rating Scale (MADRS). Quetiapine as monotherapy was compared with placebo or SSRIs and SNRIs. Results of the meta-analysis showed that 50 and 150 mg/day of quetiapine-XR is effective in treating GAD and one out of every nine patients with GAD will benefit from the treatment. PSQI scores indicated greater improvement of quality of sleep in those treated with quetiapine compared with placebo while acceptability and tolerability was less than placebo. Response rates of quetiapine and SSRIs in this meta-analysis were similar at approximately 61 percent and remission rates of each were 35.5 equally. The study found quetiapine has better sleep promoting quality compared to SSRI, but its sedative effect may hinder daytime functioning. Authors concluded that low dose quetiapine is comparable to SSRIs in both acceptability and tolerability and may be considered as an alternative treatment for GAD. However, they also warned that its use should be cautiously carried out due to adverse events, and further studies are needed to confirm the results of this study (Maneeton et al., 2016).

- A recent literature review of quetiapine for GAD evaluated

the efficacy and tolerability of quetiapine for the treatment of generalized anxiety disorder (Kreys and Phan, 2015). This review included studies evaluating the use of quetiapine monotherapy as well as studies of quetiapine adjunct therapy. Results of the monotherapy trials demonstrated significant improvement in HAM-A scores "as early as day four or week one of treatment and at week eight study end point compared with placebo (Kreys and Phan, p. 183). Improvement in anxiety symptoms generally takes two-four weeks with standard antidepressant treatment. Results of the quetiapine augmentation trials showed response and remission rates comparable with placebo while not as robust as for quetiapine monotherapy. Authors concluded that these studies demonstrated both efficacy and tolerability of quetiapine monotherapy or adjunct therapy to antidepressants for treatment of acute GAD. They further suggested a careful benefit-risk analysis of the use of quetiapine when patients fail to respond to conventional antidepressant treatment and recommended close monitoring of metabolic side effects.

- 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).
- 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 comorbid with GAD. Patients (n=111) with bipolar disorder comorbid with GAD (88 percent) or panic disorder (59 percent) were randomly assigned to receive risperidone 0.5 mg.-4 mg./day or placebo monotherapy for eight 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).

- A meta-analysis on the treatment of GAD with atypical antipsychotics (SGAs) suggests that existing data do not support their usage as augmentation therapy for refractory GAD. Five studies (n=912) demonstrated that SGA augmentation (using olanzapine, risperidone or quetiapine) did not demonstrate superiority against placebo for clinical response or remission and showed that these patients were 43 percent more likely to discontinue treatment. Conversely, four studies (n=1383) that examined quetiapine XR monotherapy (150 mg.) demonstrated that patients were 31 percent more likely to respond, and 44 percent more likely to achieve remission than the placebo group. In addition, patients in the quetiapine group were 30 percent more likely to leave the study before completion. Investigators stressed that while quetiapine monotherapy may be efficacious, issues with adverse effects and tolerability must be considered in clinical practice (Lalonde et al. 2011). In addition, two other systematic reviews on the use of SGAs for the treatment of refractory GAD emphasized the need for both larger and more rigorous clinical trials on safety and efficacy in order to recommend their usage (Samuel et al, 2010; Lorenz et al., 2010).
- With a lifetime prevalence of 6 percent in older patients, GAD is both undertreated and under investigated (Mezhebovsky et al., 2012). In a large study, researchers evaluated the efficacy and tolerability of quetiapine XR monotherapy in older patients (n=450), aged 66 and greater) with GAD. Patients were randomized to quetiapine XR (50-300 mg/day) or placebo during a nine-week treatment period and a two-week drug-discontinuation period. Treatment was initiated at 50 mg/day with dose adjustment made on the basis of efficacy and/or tolerability. Efficacy evaluations were based on the changes in the Hamilton Anxiety Rating Scale (HAM-A), Clinical Global Impressions-Severity of Illness (CGI-S), and the Montgomery Asberg Depression Rating Scale (MADRS). Results showed significantly reduced HAM-A scores at week nine with quetiapine XR versus placebo. Significant improvements were also seen with quetiapine XR as early as week one, suggesting the reduction of anxiety symptoms within a timeframe similar to benzodiazepines. In patient-reported outcomes, quetiapine XR was associated with significant improvements versus placebo. Researcher concluded that quetiapine XR monotherapy is an effective short-term treatment in older patients with GAD, improving anxiety symptoms, psychic and somatic symptoms, health-related quality of life, sleep quality and pain versus placebo

(Mezhebovsky et al., 2013).

- A small study evaluated the feasibility of augmenting antidepressant treatment with quetiapine XR in patients with either a primary anxiety disorder or a mood disorder with comorbid anxiety symptoms (Chen et al., 2012). Patients receiving treatment with an antidepressant, i.e., escitalopram, paroxetin, venlafaxine, duloxetine, and mirtazapine, were randomized to quetiapine (50-300 mg/day) or placebo for eight weeks. Although efficacy evaluations based on changes in the HAM-A and CGI-S showed no significant differences between the quetiapine XR and placebo groups at eight weeks, treatment with quetiapine XR as an adjunct to treatment with an antidepressant provided a short-term benefit at four weeks. Researchers cautioned that the results should be considered preliminary due to the small sample size, recommending further studies (Chen et al., 2012).

As noted in the Assessment section, GAD may be the most common anxiety disorder in the elderly. Clinicians should be aware of a FDA Alert that was issued notifying healthcare professionals that both conventional and atypical antipsychotics are associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis (FDA Alert 6/16/08).

Non-benzodiazepine hypnotics – Zolpidem extended-release co-administered with escitalopram in patients' insomnia and comorbid 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).

Anticonvulsants – As noted earlier, the *World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders-Revised* 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 comorbid 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).

- 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 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-analysis and replicated randomized controlled trials) was for pregabalin in GAD with or without comorbidity (Mula, 2007).
- 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 600 mg./day groups where pregabalin 300-450 mg./day dosage demonstrated the most beneficial response (Stein, Baldwin et al., 2009).
- A meta-analysis examined seven trials of GAD patients (n=1,352) using pregabalin compared to placebo and calculated an overall effect size of 0.364 (Hedge's g), an effect size of 0.349 on psychic anxiety symptoms, and 0.239 on somatic anxiety symptoms. Investigators concluded that while pregabalin is an effective treatment for GAD, they also noted these effect sizes are smaller than earlier studies even though their findings were based on participants taking the largest doses of the drug during the clinical trial (Boschen 2011).
- A review summarized the results of clinical trials and pooled analyses providing data on pregabalin's effect on sleep disturbance in patients with GAD (Holsboer-Trachsler and Prieto, 2013). Sleep disturbance, i.e., difficulty falling or staying asleep, or restless, unsatisfying sleep, is a symptom

of GAD in DSM-5. Hiksbier-Trachsler and Prieto noted that insomnia, associated with impairment in both functioning and quality of life, is an important target for effective treatment of GAD. A review of the results of seven randomized controlled trials found that treatment with pregabalin is associated with improvement in sleep among patients with GAD as well as improved functioning and quality of life. Adverse events were mild to moderate and limited to the first 2-3 weeks of treatment. One of these, sedation, occurs in some patients but the incidence is lower compared to benzodiazepines. Authors concluded that pregabalin is a treatment option for patients with GAD who present with insomnia (Holsboer-Trachsler and Prieto, 2013).

- 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).

Novel Agents - 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, the 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 clinical trial. An eight-week, open-label, fixed-dose trial of riluzole in 18 outpatients with GAD resulted in a significant reduction in anxiety symptoms where 67 percent of patients responded and 44 percent entered remission by the end of the study (Pollack, 2009; Gao et al., 2009). Another novel agent, the corticotropin-releasing factor receptor-1 antagonist (CRF), pexacerfont (100mg./day) was studied in patients (n=294) with GAD (after receiving a one week loading dose of 300 mg./day) in a randomized trial comparing it to placebo or escitalopram (20 mg./day) in a 2:2:1 ratio, i.e., a half-powered comparator arm. Response rates for pexacerfont, placebo and escitalopram were 42, 42, and 53 percent respectively, leading researchers to conclude that the novel agent did not demonstrate anxiolytic properties (Coric et al., 2010).

The novel antidepressant, agomelatine, which has both a serotonergic and a melatonergic mechanism of action (Stein, 2012), has been considered to be a promising option for treatment-resistant GAD. Authors reviewed two studies that investigated the efficacy of agomelatine in the treatment of GAD. In a 12-week, randomized, controlled trial examining the efficacy of agomelatine

in patients (n=121) with GAD, researchers found that in a 12-week treatment period, agomelatine demonstrated higher rates of response and anxiety remission than placebo. Another trial evaluating the efficacy of agomelatine in preventing relapses in patients with GAD over six months, found that patients randomized to continue agomelatine after week 16 showed a lower incidence of relapse at the endpoint than the placebo group (Levitan et al., 2012). A literature search and review noted that although preliminary data indicate agomelatine as a promising option for both acute and long-term treatment of GAD, caution is needed when prescribing and using it in patients with psychiatric or medical comorbidities, due to potential interactions with a number of compounds. They suggest studies are needed, especially in special populations such as elderly patient with GAD (Buoli et al., 2014).

Complementary and Alternative Medicine (CAM) –

Complementary and alternative treatments GAD lack sufficient evidence (Locke et al., 2015). Botanicals and supplements are sometimes used to treat anxiety disorder and panic disorder, but most must be used with caution in combination with SSRIs due to an increased risk of serotonin syndrome. Although music therapy, aromatherapy, acupuncture, and massage may be helpful for anxiety associated with GAD, authors reported that they have not been evaluated specifically for GAD.

A recent pilot study examined the potential efficacy of Kundalini Yoga-enhanced CBT (Y-CBT) in the treatment of treatment resistant GAD in adult participants (n=32) at a community health clinic (Khalsa et al., 2015). Y-CBT was conducted in weekly one-hour sessions during a period of six weeks that included low impact yoga/meditation, instruction and experiential cognitive restructuring using traditional as well as alternative CBT interventions, and group discussion. Authors described "alternative CBT interventions" as teaching participants to "restructure their relation to their thoughts, as well as their physiologic interaction with the thought" (Khalsa et al., p. 5). Out of the 32 participants, 22 completed the six-week intervention Self-report measures, i.e., the *State Trait Anxiety Inventory* and the *Treatment Outcome Package* were administered before and after the 6-week treatment. The results of this small pilot study indicated that treatment resistant outpatient mental health patients experienced significant improvement in anxiety levels as well as in reported symptoms of comorbid depression and panic after Y-CBT compared with before treatment. Authors suggested the need of future research to investigate ways to decrease the drop-out rate, while acknowledging that Y-CBT "appears to be a promising new treatment for those suffering from GAD" (Khalsa et al., p. 10).

Piper methysticum (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 some countries due to concerns about hepatoxicity 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).

- The first randomized, double-blind, placebo-controlled efficacy and tolerability trial of *Matricaria recutita* (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 two tablets daily during the second week. Patients with a 50 percent reduction or less in HAM-A scores from baseline were increased one tablet each week up to week five if they still continued to have a 50 percent reduction or less in symptom improvement (up to five capsules daily during week five-eight of therapy). Results showed that patients had a significantly greater reduction in mean total HAM-A scores with chamomile versus placebo treatment (Amsterdam et al., 2009).
- A comprehensive review of plant-based medicines assessed in human clinical trials revealed evidence for anxiolytic effects for 21 plants (Sarris et al., 2013). This review reported evidence supporting the use of the following plant-based anxiolytics: piper methysticum (kava), matricaria recutita (chamomile), ginkgo biloba, scutellaria lateriflora (skullcap), silybum marianum (milk thistle), passiflora incarnata (passionflower), withania somniferum (ashwaghanda), galphimia glauca (galphimia), centella asiatica (gotu cola), rhodiola rosea (roseroot), echinacea spp (purple cone flower), melissa officinalis (lemon balm), and echium amoenum (Iranian borage). In one 15-week, controlled, double blind randomized trial, patients (n=191) with GAD were randomized to one of the following treatments: 1) 2-4 capsules of dried galphimia (350 or 700 mg/day) or 2) lorazepam in capsule form (1 -2 mg). Anxiety scores on Hamilton Anxiety Scale were significantly reduced for galphimia treatment compared with lorazepam during the course of the 15 week period. Authors cautioned that some anxiolytic plants may have mild adverse effects, e.g., digestive disturbance, headaches and skin reactions. Serious adverse effects may include liver toxicity associated with kava (Sarris et al., 2013).

Combined Treatments	In a recent meta-analysis comparing the effects of treatment with antidepressant medications to the effects of combined pharmacotherapy and psychotherapy in adults with depressive or anxiety disorder, researchers found evidence that the combined treatment was more effective in major depression, panic disorder, and OCD, but there was insufficient evidence for GAD (Cuijpers et al., 2014). A later meta-analysis compared the efficacy of pharmacological, psychological and combined treatment in patients (n = 37333) with GAD, panic disorder, and social phobia (Bandelow et al., 2015). In rationalizing the combination of all three disorders in this study, researchers explained the high comorbidity among the disorders and the lack of evidence suggesting differential efficacy of treatment for different anxiety disorders. This meta-analysis, including 234 studies, found that most psychopharmacological medications used in treating anxiety disorders have significantly higher effect sizes than psychological therapies, with the improvements achieved in a shorter time period. Among drugs, the SSRIs, SNRIs, and pregabalin had the highest effect sizes. Researchers cautioned that side effects must be considered in the choice of drug. Among psychological treatments, CBT was found to be more effective than waiting list, psychological placebo and pill placebo. Group CBT, however, was not superior to psychological placebo conditions in direct comparisons. Researchers suggested CBT has an advantage over drug treatment as gains from CBT are maintained after termination of treatment. After stopping medications, patients generally experience a recurrence of anxiety symptoms. Researchers also note the lack of combination studies of CBT with currently recommended medications. They also emphasized that patients should be involved in the selection of treatment, whether psychotherapy, medications, or a combination of the two (Bandelow et al., 2015). A recent randomized, comparative, partial crossover study evaluated the relationships between psychophysiological and clinical measures during venlafaxine ER treatment compared with relaxation therapy in patients with GAD (Zullino et al., 2015). In Phase I of this trial patients (n = 58) were randomly assigned to 8 weeks of venlafaxine ER (75 mg/day for one week, increased to 150 mg/day and after two weeks increased to 300 mg/day) or to 8 weeks of relaxation treatment (individual 45-minute sessions). Patients (n = 32) who did not remit to treatment (from both groups) received combined venlafaxine ER and applied relaxation for another 8 weeks (Phase II). In the second 8-week period, remitted patients continued treatment with venlafaxine XR (those who had been allocated to this treatment) or continued home practice of relaxation. Results showed no group differences in treatment responses. However, when venlafaxine ER was added to applied relaxation therapy and vice versa for patients who had not

remitted in Phase I, the number of responses was increased. Researchers suggested that venlafaxine and applied relaxation combined enhances treatment response in the case of initial failure (Zullino et al., 2015).

Both the *Canadian Psychiatric Association Clinical Practice Guidelines on the Management of Anxiety Disorders* (2006) and *The International Psychopharmacology Algorithm Project (IPAP)* 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).

A later study assessed the efficacy of combined treatment including CBT and venlafaxine XR in patients with GAD. Patients (n=117) were randomly offered or not offered an option of adding CBT (12-weeks) in addition to venlafaxine XR (Crits-Christoph et al., 2011). Only one-third of those offered CBT chose to receive the therapy including techniques such as applied relaxation/self-control desensitization; training in self-monitoring of environmental, somatic, affective, imaginal and thought cues; slowed diaphragmatic breathing; and development of coping self-statement to respond to cues. Results of the study showed no evidence of additional benefit for the combined CBT and venlafaxine XR compared to venlafaxine XR alone in treating patients with GAD (Crits-Christoph et al., 2011).

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.

- 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 percent to 37 percent), 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).
- A large randomized controlled trial (n=1004) of adults being treated in 17 primary care clinics for anxiety disorders (panic, generalized anxiety, social anxiety, and posttraumatic stress disorder) were treated with Coordinated Anxiety Learning and Management (CALM) or usual care (UC) for three to 12 months. Usual care consisted of treatment by a patient's physician with limited familiarity with evidenced-based psychotherapy, or referral to a mental health specialist. The CALM intervention was designed to allow patient choice of CBT, medication or both; it also included real-time web-based outcomes monitoring to optimize treatment decisions and care management to promote medication adherence. Investigators reported that CALM compared with UC resulted in greater improvement in anxiety symptoms, depression symptoms, functional disability and quality of care during the 18 months of follow-up (Roy-Byrne et al, 2010).
- A study examined sequenced treatment with escitalopram and CBT to learn whether this treatment boosts acute response and prevents relapse in adults aged 60 and older with GAD (Wetherell et al., 2013). Participants with GAD (n=73) were treated with escitalopram over 12 weeks followed by randomization to one of four conditions: 1) 16 weeks of escitalopram (10-20 mg/day) combined with 16 sessions of CBT followed by 28 weeks of maintenance escitalopram, 2) 16 weeks of escitalopram (10-20 mg/day) alone followed by 28 weeks of maintenance escitalopram, 3) 16 weeks of escitalopram (10-20 mg/day) combined with 16 sessions of CBT followed by 28 weeks of pill placebo, or 4)16 weeks of escitalopram (10-20 mg/day) alone followed by 28 weeks of pill placebo. This study showed that a sequence of escitalopram followed by augmentation with CBT resulted in greater improvement in pathological worry as measured by the Penn State Worry Questionnaire than those on escitalopram alone. However, escitalopram followed by augmentation with CBT did

	not lead to higher rates of response on a measure of anxiety symptoms. Participants receiving maintenance escitalopram had a significantly lower relapse rate than those receiving placebo. In addition, among participants taking maintenance placebo, those who received escitalopram augmented with CBT had lower rates of relapse than those who had escitalopram without CBT. Researchers concluded that antidepressant medication augmented with CBT reduces pathological worrying and relapse risk in older patients with GAD, even when antidepressant treatment is stopped after augmentation. They suggested that for older patients who prefer to discontinue antidepressants, CBT could be an option. Further they noted that CBT could be an alternative to augmentation with antipsychotic medications which are increasingly used in treating anxiety disorders (Wetherell et al., 2013).
Monitor Progress and Address Sub-optimal Recovery	1. Psychiatric Comorbidity 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 percent 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 studies showing significant impairment across multiple domains. For those patients suffering with major depressive disorder comorbid 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 9 and summarization of the IPAP psychopharmacological treatment algorithm on page 10,11 for strategies to manage treatment resistance and meta-analysis findings on SGA augmentation efficacy for refractory GAD on page 15). 3. Standard Tools to Assess Response – The *Canadian Psychiatric*

Association's Clinical Practice Guidelines on the Management of Anxiety Disorders (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 percent 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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