IPAP GAD Algorithm Notes

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Introduction

Generalized anxiety disorder (GAD) is defined as excessive and uncontrollable worry and anxiety about everyday life situations. It is a chronic disorder, with lifetime prevalence estimates of around 5-6% in the USA[1] and elsewhere [2], and is associated with substantial somatization, high rates of comorbid depression and other anxiety disorders, and significant disability. The evidence base for pharmacotherapy and psychotherapy has continued to grow, and a wide range of drug choices for GAD now exists.

Current guidelines for GAD comprise those of (1) the British Association of Psychopharmacology (BAP) (www.BAP.org.uk) [3]; (2) the National Institute of Clinical Excellence (NICE) (www.nice.org.uk/CG022NICEguideline) and www.nice.org.uk/CG022quickrefguide); (3) the World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and posttraumatic stress disorders [4]; (4) Consensus Statement on Generalized Anxiety Disorder from the International Consensus Group on Depression and Anxiety [5]; (5) the Canadian guidelines [6]; and (6) the South African Primary Care Algorithms (http://www.mentalhealthsa.co.za/disclaimer.html).

These guidelines generally restrict themselves to presentation of the evidence for various treatments but do not offer detailed discussion or recommendation of strategies beyond the first level of treatment. Thus there is a lack of algorithm-based treatment guidelines for GAD. Our aim is therefore to present an algorithm for the psychopharmacologic management of GAD. It is important to recognize that two broad approaches are established, based on good evidence, for treating GAD - the pharmacological and the psychosocial methods of treatment. We are unaware of substantial evidence that the combination of the two adds any further benefit, but acknowledge that common clinical practice combines the two forms of treatment simultaneously or in sequence [7]

For decades, pharmacotherapy for generalized anxiety (previously called anxiety neurosis) was confined to the benzodiazepines, following the introduction of chlordiazepoxide and diazepam in the late 1950's-early 1960's. However, drug treatments expanded with the development of the serotonin $5HT1_a$ partial agonist buspirone in the 1980's. In the 1990's, the broad spectrum utility of the antidepressants became apparent, particularly the serotonergic agents, and these are now considered by many to be first line pharmacotherapy for GAD. Recent research is focusing on the development of drugs with novel mechanisms of action, as well on various pharmacologic augmentation strategies with other psychotropic drug classes.

In this algorithm, we provide a sequenced approach to the pharmacotherapy of GAD, taking into account salient symptomatology and comorbidity, levels of evidence (LOE, see appropriate nodes) and extent of response. We also cover special issues, including comorbidity, insomnia, suicidality, substance abuse, treatment adherence, pregnancy and lactation, cross-cultural issues, use of medication in the elderly, psychosocial treatment, and dosing issues. This approach is similar to one that we have previously taken with another anxiety disorder (PTSD) ([8] and www.ipap.org/ptsd/). In developing these algorithms, we have attempted to employ many of the methods that are thought essential to guideline development, as described, for example, by the Appraisal of Guidelines Research and Evaluation (AGREE) instrument [9] (e.g. defining scope and purpose, obtaining stakeholder involvement, rigorous development, clarity and presentation, applicability, and editorial independence).

Important: The GAD Algorithm Flowchart and Addenda are essential accompaniments to these notes. *They can be downloaded at www.ipap.org/gad/.*

Node 1: Diagnosis of GAD

No diagnostic category in psychiatry has changed as much over the past 25 years as GAD. The changes reflect, in part, the results of psychopharmacological studies designed to improve the specificity of treatments for this disorder [10]. These changes make GAD one of the more difficult disorders for making a psychopharmacology algorithm. It has been a moving target, and to interpret the studies we need to know which version of DSM was used for the particular study. An important change, from the standpoint of psychopharmacology, is the movement to the present criteria where the core problem is conceived to be chronic, excessive worrying that is difficult to control and causes impairment. This "psychic component" of the previous criteria responds better to antidepressants than BZDs [10]. GAD

used to be (in DSM-III) predominantly a disorder of autonomic, motor, and other somatic manifestations of anxiety. These symptoms respond better, in the short term (2 weeks) to BZDs than to antidepressants [10], though by week 8 the antidepressants (imipramine, trazodone) become as effective or almost as effective. Some patients previously diagnosed with GAD would now be classified as having somatoform disorders in DSM-IIIR or IV.

The concept of GAD was first described in DSM-III, as an anxiety condition. To make the diagnosis required patients to experience at least one month of symptoms from three out of four categories (motor tension often of the back or neck, tension headaches and muscle pains secondary to tension and making people reactive and jumpy to sudden events), autonomic hyperactivity (sweating, dry mouth, racing heart rate), apprehensive expectation (a sense of worry about everything in the future, predicting negative outcomes for future events and occurrences- when this occurs primarily at night, it can lead to insomnia) and vigilance/scanning (always looking for threats and problems). There were sweeping restrictions as to the allowable coexistence of other Axis I disorders, and GAD was believed to produce no more than mild impairment. With subsequent editions of the DSM, the criteria became simpler, shorter and the disorder is now acknowledged to result in significant impairment. The current DSM-IV-Text Revision (TR) criteria for GAD (American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision, Washington, DC, American Psychiatric Association, 2004) and the International Classification of Disease (ICD-10) criteria for GAD (International Statistical Classification of Diseases and Related Health Problems, 10th ed. Geneva: World Health Organization), which differs considerably from those of DSM-IV-TR (Text Revision), are given in Table 1. below.

Table 1. DSM-IV and ICD-10 Criteria for Generalized Anxiety Disorder

Diagnostic System	Diagnostic Code	Diagnostic Criteria
DSM-IV	300.02	a) Excessive anxiety and worry lasting at least 6 months b) Difficulty in controlling the worry c) Presence of 3 of the following 6 associated symptoms: restlessness, fatigability, difficulty concentrating, irritability, muscle tension, and sleep disturbance d) Focus of the anxiety and worry not confined to another anxiety or somatoform disorder e) Significant distress or functional impairment due to the symptoms f) Symptoms not due to a substance (eg, a drug of abuse, a medication) or a general medical condition (eg, hyperthyroidism)
ICD-10	F41.1	a) Generalized and persistent anxiety not restricted to any particular environment (ie, it is “free-floating”) b) Dominant symptoms including persistent nervousness, trembling, muscular tension, sweating, lightheadedness, palpitations, dizziness, epigastric discomfort, and fears of impending illness or an accident c) Exclusion of neurasthenia

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition;

ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th edition

While DSM-IV specifies the minimal duration of 6 months and at least 3 associated symptoms, ICD-10 does not require minimal duration or number of symptoms. ICD-10 criteria place greater emphasis on the presence of somatic symptoms. Because nearly all the evidence upon which our algorithms are based comes from studies which used

DSM-IV (or in some cases, DSM-III or IIIR), the algorithm recommendations are based on DSM, as the evidence is lacking for the creation of an algorithm based upon the ICD criteria. At the same time, we recognize that the diagnostic criteria for DSM-IV GAD may be overly conservative [11, 12], and that clinicians may therefore use their judgment in applying the current algorithm to patients who meet many, but not all, the relevant diagnostic criteria. Clinical judgment should also be used when applying the DSM criteria, as opposed to using it as checklist.

RELEVANT LITERATURE

The lifetime prevalence of GAD is estimated to be in the range of 4.1 to 6.6% among adults worldwide, and 12 month rates are in the range of 1.1 to 3.6% [2, 13-15]. The highest rates are often reported in the 45-55 year age group, with women twice as likely to have GAD as men [14-16]. In the elderly, one study found GAD to be the most common anxiety disorder, with a prevalence of 10.2% in this population [17].

In primary care practice, GAD is often diagnosed by the ICD criteria, and is the most common anxiety disorder, with an 8% prevalence rate [18]. Patients with GAD are in fact more likely to consult with gastroenterologists than psychiatrists [19], and a high proportion of difficult-to-treat high medical service utilizers of hospital medical services have GAD [20]. Generalized anxiety disorder is linked to the overuse of medical services: emergency department visits, hospitalizations, diagnostic and laboratory tests, pharmacy costs, and so on. Recognition of anxiety and depression in primary care is poor, with only 23% of pure anxiety cases being recognized compared with 56% of depression cases. The various stakeholders (patients, family members employers, and insurers) in a patient's outcome may act in such a way as to complicate treatment of anxiety [21].

GAD follows a chronic course in many cases and it is not uncommon to find that patients presenting for treatment have experienced active symptoms of the disorder for more than 10 years. While it can remit spontaneously, rates of spontaneous remission over 5 years are less than 40% in the case of DSM-IIIR criteria [22], and a waxing and waning course is more characteristic. Lifetime comorbidity with another Axis I disorder occurs in 90% of subjects with GAD, depression being found in over 60% [16]. When compared with chronic medical disorders, there is evidence that GAD is as disabling [23].

Node 2: Consider Diagnosis at Each Evaluation

With the extensive degree of psychiatric and medical comorbidity that is associated with GAD, it is important to keep in mind the possibility that ongoing symptoms could be attributable to either separate psychiatric or medical morbidity or a disorder which is comorbid with GAD. An initial evaluation needs to include assessment for all relevant comorbid conditions, with appropriate physical examination and laboratory testing, with attention to thyroid, parathyroid, glucose function, as well as assessment of current use of prescription and over-the-counter medications, intake of caffeine, alcohol, and other drugs.

GAD is often found in association with other medical conditions. For example, Castillo et al [24] noted clinically significant GAD-like symptoms in 40% of stroke patients, 27% of whom met full criteria for GAD. In people with migraine there was a 10.2% rate of GAD [25]. Subjects with GAD report a marked increase in the rate of peptic ulcer disease [26]. As noted by Stein [27], physical symptoms such as fatigue, palpitations, chest pain, hyperventilation, tension headache, insomnia, back pain, muscle tension, as well as hypertension, diabetes and heart disease all make it more likely that the patient with GAD will make frequent visits to the doctor.

Among the concomitant psychiatric disorders and symptoms to be included in the differential diagnosis are depression, bipolar disorder, alcohol and substance use disorders, other anxiety disorders, suicidal behavior, and attention deficit and hyperactivity disorder (ADHD). Posttraumatic stress disorder (PTSD) is often associated with extensive somatization [28], and hypervigilance is seen in both GAD and PTSD. One benefit of considering PTSD in the differential diagnosis is that it necessitates obtaining a trauma history, which may declare an aspect of the patient’s life which is important for the understanding of their anxiety, vulnerability or prognosis.

There is some evidence that pharmacotherapy for GAD may be associated with lower risk of developing secondary major depression, based on a large population study [29]. Although the two groups were only retrospectively randomized, the findings do suggest that pharmacotherapy for GAD can confer a preventive effect against depression. In the case of GAD and other comorbid disorders such as ADHD, Kessler et al have similarly raised for discussion the importance of adequately treating both conditions [30].

A. COMORBID DIAGNOSIS

Concomitant psychiatric or medical disorders can be present in patients who are being assessed for GAD and may complicate accurate diagnosis and treatment. Initially, the patient should have a full psychiatric and medical history with appropriate consideration or referral for laboratory and physical examination. As part of the initial diagnostic evaluation, and after a failed trial of treatment, the clinician should look for common coexisting conditions, such as depression, alcohol problems, bipolar disorder, and undiagnosed medical illness, e.g. endocrine (thyroid), pulmonary or cardiac disease. We would note here that according to the DSM-IV criterion F, if the GAD symptoms occur exclusively during the course of any mood disorder (unipolar or bipolar), a separate diagnosis of GAD is not made. However, Zimmerman found that this hierarchical relationship may not be supported by the evidence. Depressed patients with GAD (more severely ill) confined to the depressed periods and GAD not confined to the depressed periods were comparable on numerous parameters and different from a pure depression control group [31].

A number of newer antidepressants, e.g. some serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) have been shown to be effective in both GAD and major depression, suggesting that they be used first-line when there is overlap. Although anxiety decreases when such agents are used to treat major depression, and depression decreases when such agents are used to treat GAD, there are no prospectively designed trials published on the treatment of GAD with comorbid depression. A study utilizing post hoc analysis from large controlled trials has shown that venlafaxine-XR [32, 33] is superior to placebo in subgroups with dual diagnoses of GAD and a secondary diagnosis of major depression. Other relevant studies support the use of antidepressants, such as mirtazapine, in this context [34]. In one small placebo-controlled study of chromium picolinate in patients with atypical depression, 87% of whom had concomitant GAD, the drug was superior to placebo in the full sample and in the subsample with GAD [35].

For continuing depression, antidepressant therapy, if tolerated, should be titrated to its maximum dose. There may be some circumstances where the use of a BZD has intensified depression or promoted its emergence as a side-effect, most particularly in panic disorder treated with high dose clonazepam. If it should occur during treatment of GAD, the clinician is advised to withdraw the offending agent.

For ongoing, or emergent, hostility during the course of BZD therapy, assessment is recommended as to possible substance abuse or even abuse of the prescribed BZD, and appropriate action taken, which would normally be to either reduce the BZD dose or taper the drug towards discontinuation. In such a situation, SRI therapy is recommended if the symptoms are due to GAD or depression.

Although GAD with comorbid substance use disorder has not been well studied (see below), there is indirect, albeit mixed, evidence that a serotonergic antidepressant may be useful in either depressed or anxious patients with comorbid alcohol-related problems [36, 37]. It should be noted that anxiety in the context of substance abuse may reflect intoxication or withdrawal symptoms (see below).

For bipolar disorder, other approaches might be considered (see below in Node 11b). Before introducing a drug for GAD, it would be necessary to ensure adequate mood stabilization; since anxiety may reflect poor control of the mood disorder. No randomized controlled trials have been conducted in patients with bipolar disorder and any co-occurring anxiety disorder. Among agents with antimanic or mood-stabilizing effects, evidence of anxiolytic efficacy from placebo-controlled trials exists for valproate in the treatment of panic disorder [38, 39] (LOE 4); lamotrigine [40] (LOE 3), olanzapine [41, 42] (LOE 3), and risperidone [43, 44] (LOE 3) in posttraumatic stress disorder; olanzapine [45, 46] (LOE 1), quetiapine [47-49] (LOE 1) and risperidone [50-52] (LOE 1) as adjunctive treatment in selective serotonin reuptake inhibitor-refractory obsessive-compulsive disorder, and risperidone as augmentation to a SSRI in GAD [53] (LOE 2). Antidepressants from many classes have efficacy in the treatment of most anxiety disorders but present the challenge of minimizing switch risk when used in conjunction with a mood stabilizer. Among novel antiepileptic agents without proven thymoleptic properties, valproate with suggested efficacy in panic disorder might be a candidate for the treatment of GAD comorbid with bipolar disorder [54] (LOE 5). In one review, Freeman et al felt that antidepressants are best avoided for treating the anxiety disorders in these patients due to risk for “switch” to hypomania and mania, and preferred anxiolytic antimanics and atypical antipsychotics. However, as noted below (see node 11b), there are regional practice differences in respect of the role of antidepressants for patients with bipolar depression. For GAD, they made favorable comments about using benzodiazepines, in that these agents are efficacious, relatively safe and well-tolerated. However, they also caution that long-term use of benzodiazepine may be problematic due to tolerance, dependence, and withdrawal issues [55].

In summary, a careful evaluation for comorbidity is needed before initiating treatment, there is a limited evidence base specifically addressing comorbidity, and the choice of treatment in GAD patients with comorbidity needs to be formulated with appropriate clinical judgment.

B. SUICIDALITY

Although the National Comorbidity Survey (NCS) did not find GAD to be significantly associated with suicidal ideation or attempts [56], unless comorbidity was present, increased rates of attempted suicide or suicidal ideation are seen in GAD among young adults aged 14-24 year [57], as well as among an adult population in the Netherlands [58]. There is evidence that subthreshold depression associated with GAD may increase the rate of attempted suicide [59]. Suicide is certainly a potential risk when GAD patients have comorbid MDD. In cases where suicide risk is considered to be serious, the treatment of this component takes priority over treating GAD. Although suicidal patients are excluded from almost all GAD trials, we consider that rational treatment approach would be to institute an antidepressant drug and avoid the sole use of a benzodiazepine or other drug which is devoid of antidepressant effect, in this circumstance. General guidelines for assessment and treatment of suicide (e.g. APA guideline) should also be observed.

C. INSOMNIA

Insomnia is a common and troubling feature of GAD and may be the presenting complaint, particularly in the primary care setting. Sleep difficulty may persist even after an otherwise good response to SRI drugs. A careful assessment of whether the insomnia is a symptom of GAD, or a separate disorder, should be conducted early on. In addition, the initial assessment and treatment should include attention to sleep hygiene, lifestyle issues such as exercise (especially in the morning), diet, abstaining from products containing stimulants (coffee, OTC drugs with ephedra, supplements such as ginseng or Ma Huang, energy drinks, hoodia, myridia), as well as an evaluation of whether the sleep disturbance is caused or exacerbated by prescription medications such as some of the serotonergic antidepressants or stimulants. Some antidepressants have more immediate sleep promoting effects than others, these include the sedative tricyclic antidepressants plus trazodone and mirtazapine. In the longer term, the non-sedating agents including SSRIs and SNRIs often improve sleep as well, probably secondary to their anxiolytic actions. Discussion of ways in which antidepressants effect sleep appear in the review by Mayers and Baldwin [60].

In the event of continued poor response, it is important to consider the possibility of sleep-related breathing disorder, such as obstructive sleep apnea (OSA), or other sleep disorders, e.g., periodic limb movement disorder, restless leg syndrome (RLS), etc. In such circumstances, and if other symptoms are present to suggest these disorders, a polysomnogram can be obtained. If a sleep disorder is identified or diagnosed with a sleep study, then appropriate treatment (e.g. OSA- continuous positive airways pressure (CPAP), RLS- pharmacotherapy) can be instituted.

D. SUBSTANCE ABUSE

(i) Patients with Current or Recent Substance Dependence or Abuse

Individuals with GAD may misuse alcohol, cannabis, or other substances in an effort to ameliorate their anxiety. In time, such misuse may result in substance abuse or dependence. The patient is first required to undergo withdrawal from his or her substance(s) of abuse or dependence, and must make a commitment to abstain from future use of these substances. Of course, he or she may not succeed in achieving this goal, and compliance with the commitment to abstinence must be followed closely. As a general principle with these patients, conservative and less complicated regimens are recommended when possible. Although we are unaware of pharmacotherapy studies in GAD with comorbid alcohol use disorder, the evidence is mixed from studies of alcohol abuse with depression or PTSD [61-63], and there is a largely positive (but not on all measures) pilot study suggesting the benefit of paroxetine in subjects with social anxiety disorder and comorbid alcohol use disorder [64]. Thus, early use of SSRIs or other antidepressants may benefit these patients. For a comprehensive review of antidepressant use in dual diagnosis patients with depression and substance use disorder, see review by Nunes and Levin [36]. A possible role exists for buspirone in patients with GAD and alcohol use disorder [65], but benzodiazepines are generally contraindicated in this population, except for the initial period of detoxification. See also the BAP guidelines on the treatment of addiction [66].

Before beginning pharmacotherapy for comorbid GAD, it seems reasonable to recommend that the patient should have completed withdrawal from his or her drug of abuse or dependence and from any drug used for withdrawal, and be

abstinent for at least one additional week. This appears to be the minimum time after which drug-placebo differences have been demonstrated in the treatment of anxiety and depressive disorders that persist, for example, following alcohol withdrawal [65, 67]. Symptoms present after abstinence of less than one week may be due in part to the residual effects of the substance. If symptoms appear to be diminishing over the first week of sobriety, and there is no history of these symptoms prior to onset of the substance abuse/dependency or during previous periods of extended sobriety, it is reasonable to wait at least another week before initiating pharmacotherapy. However if this is not possible the initiation of treatment with an antidepressant e.g. an SSRI should be considered. Once the patient has shown a therapeutic response it may be easier for them to stop the other misused drugs.

Withdrawal from some substances can be prolonged, and the residual effects of their presence can affect subsequent medication that may be given. For example, methadone has a half-life of about two days and its effects as an inhibitor of cytochrome P450 2D6 could therefore persist for more than a week.

A group of patients not specifically addressed in this algorithm is individuals who use drugs of abuse but who do not meet DSM-IV criteria for abuse or dependency. Should the sequence of treatments for these "recreational" users be any different from the standard approach? These frequently encountered patients have received little research attention and a prudent treatment approach thus involves reasonable and appropriate clinical judgment in managing such cases. One important issue to consider in this group is the possible kindling effects of cocaine and amphetamine derivatives where the effect may be manifest as GAD symptoms. In this group, abstinence is important to achieve.

(ii) Patients with History of, But No Current, Substance Dependence or Abuse

If the patient is not actively abusing or dependent upon substances presently, but has a history of such abuse or dependence, the treatment approach may require relapse prevention treatment. The patient may have been recently detoxified, be under unusual stress, or may be experiencing strong cravings for his or her substance and therefore at high risk of relapse. This would suggest that management of this problem would be at least as high a priority for treatment compared with treating their GAD.

If the patient's problem is with alcohol, evidence-supported pharmacotherapy options could include naltrexone [68], acamprosate [69] or topiramate [70] (All LOE 1 for the index disorder; LOE 5 for GAD).

Disulfiram may be of value for prevention of relapse in cocaine-dependent individuals [71] (LOE 2 for index disorder. LOE 5 for GAD).

All pharmacotherapy options for substance abuse/dependence seem to work best in the context of ongoing intensive, structured psychotherapeutic treatment focused on abstinence, compliance and relapse-prevention [72]

If the patient with a history of substance abuse has been assessed and treated (if appropriate), the clinician may then return to the GAD algorithm. The clinician's vigilance towards detecting comorbid substance abuse needs to be continued throughout treatment.

E. TREATMENT NON-ADHERENCE

Clear explanation about the expected effects of medication and how to deal with problems which arise is essential at the initiation of pharmacotherapy, as well as with the addition of any new medication. Non-adherence rates to antidepressants in depression can be as high as 50% within the first three months [73, 74]. It is likely that similar rates might hold true for patients with GAD. Reasons for non-adherence are myriad, and include side effects, lack of efficacy, improvement of symptoms, as well as ambivalence about treatment and the stigma associated with taking psychotropic medication. Non-adherence to medication is higher in patients who view their symptoms from a non-medical perspective. Lin et al [73] have suggested a number of strategies to enhance treatment adherence in depression, all of which, in our view, also apply to GAD. The following educational messages to patients may prove helpful: (a) take medication daily; (b) antidepressants (but not benzodiazepines) may take some weeks to work; (c) continue taking medication even when feeling improved; (d) do not stop taking medication without checking with the prescribing physician; (e) instructions on how to deal with side effects or to resolve other questions about medication; (f) schedule pleasant activities. Wingerson et al [75] have reported that GAD subjects with impulsiveness, novelty seeking traits and who show dislike of regimentation are more likely to drop out of medication trials, and may therefore constitute a high risk group for treatment non-adherence.

Somatically focused patients are often reluctant to consider a psychiatric diagnosis and psychotropic medication. A strong treatment alliance and credible rationale are called for. The patient may require a detailed rationale about the relationship between physical symptoms and mode of action of the medication. The literature on somatic vigilance and selective attention is relevant in this regard, and provides one explanatory model by which the effects of psychotropic medication can be understood [76, 77].

F. ISSUES RELEVANT TO WOMEN OF CHILDBEARING POTENTIAL

Despite the prevalence of anxiety disorders in women, there is sparse information regarding the incidence and course of anxiety disorders during pregnancy and the postpartum period. In a large prospective longitudinal study of a community sample of 8323 pregnant women in England, 21.9% of the women had clinically significant symptoms of anxiety [78]. Most of the women (64%) who reported elevated levels of anxiety during pregnancy also reported elevated levels of anxiety after delivery. Furthermore, antenatal anxiety predicted postpartum depression at 8 weeks and 8 months, even after controlling for the presence of antenatal depression. The course of panic disorder during pregnancy has also received attention [79-82] with evidence of a either worsening or new onset in the postpartum period [80, 83, 84].

There is mounting evidence that maternal anxiety during pregnancy and the postpartum period potentially poses significant risk to the child. Maternal anxiety during pregnancy has been associated with behavioral problems at 4 and 6 years of age [85, 86]. Similarly, in older children ages 8-9 years of age there is a significant correlation between maternal antenatal anxiety (12-22 weeks gestation) with ADHD, self-reported anxiety and increased impulsivity as well as lower scores on the subtests of the WISC-R in 14-15 year old children [87, 88]. A recent prospective study demonstrated that maternal depression and anxiety during pregnancy predicted higher rates of conduct disorder in children [89].

As such, while the incidence and course of GAD is not well studied in women during pregnancy and the postpartum period, there is clear evidence that untreated anxiety may pose a significant risk for the mother in the postpartum period and potentially affect the developmental trajectory of the infant.

The primary issues in women of childbearing potential are best addressed at initial treatment planning. This includes: 1) Documentation of method of birth control for all women of reproductive capacity at all visits; 2) Treat women as if they are pregnant from the first visit. Clinicians seldom order routine pregnancy tests. Urine pregnancy tests do not rule out early pregnancy (1-3 weeks gestation) nor does a recent or current menses. In cases, where medications are indicated the treatment should be conducted with the medications with the majority of obstetrical outcome data (e.g. fluoxetine, sertraline, citalopram, paroxetine). The recent FDA pregnancy category change for paroxetine to category D, must be included in treatment decisions. Despite the B category rating – there is a dearth of information for buspirone during pregnancy and/or lactation. A review of the potential for pregnancy and/or urine pregnancy test should be considered at any juncture in the algorithm that adds adjunctive pharmacotherapy (node 9-17).

The primary and/or adjunctive use of BZDs is generally not recommended in treating GAD during pregnancy. Earlier reports with diazepam and chlordiazepoxide suggested a higher rate of cleft lip. While cohort studies have failed to demonstrate this increased risk, a meta-analysis [90] indicated a small but significant risk of birth defects with BZDs. Similarly, BZDs are considered "contra-indicated" in breast feeding according to American Academy of Pediatrics committee on medications in breast feeding report 2002. Should BZDs be required during pregnancy and/or lactation – the preferred agents would include clonazepam and lorazepam. Clonazepam has a better pregnancy rating (category C) relative to other BZDs. Similarly, lorazepam has the advantages of multiple routes of administration, a history of use in children with status epilepticus, and a pathway of metabolism that does not require the fetal/neonatal liver. Increased risk of pulmonary hypertension with SSRI in pregnancy has been reported and should be considered when advising patients about risk-benefit issues [91]. This information regarding the approach to women in their reproductive years should influence the algorithm at all points that include use of BZD.

G. GAD IN THE ELDERLY

GAD is more likely to be seen in the elderly than are other anxiety disorders, and has a reported prevalence rate which ranges from 0.7 to 10.2% [92-94]. About one half of all elderly subjects with GAD report that their condition is of recent onset, i.e. not simply the continuation of a long-standing problem [95]. In elderly patients who present with new onset anxiety, it is also important to consider relevant medical etiologies, as well as iatrogenic causes, e.g. medication side

effects or drug-drug interactions. Appropriate medical work-up is recommended when evidence suggests that other disorders may be present.

One study has found buspirone to show greater benefit than placebo in patients over age 65 with GAD [96] (LOE2). Retrospectively derived pooled data (LOE2) from 5 studies demonstrate efficacy of venlafaxine-extended release in patients with GAD who are age 65 and older [97]. A study which compared sertraline, cognitive behavioral therapy (CBT) and a waiting list control (WL) in a mixed anxiety population age 60 and older (LOE2 for aggregated diagnoses of anxiety, including GAD), found that both active treatments were superior to WL, with the pattern of results generally suggesting a more robust effect for sertraline over CBT [98]. Of all entered subjects, 35% met criteria for GAD, 45% for panic disorder and 20% other forms of anxiety. There is also a positive placebo-controlled study of citalopram in elderly patients with anxiety disorders, mainly GAD [99] (LOE 2 for the entire sample).

Side effects of antidepressants are of greater concern in the elderly, as for example the intolerance which was found in one study of venlafaxine extended-release in frail elderly subjects, as well as the greater risk of hyponatremia in response to SSRI drugs in older patients [100, 101].

Benzodiazepine (BZD) use in the elderly is problematic, given their higher incidence of falls, hip fracture, withdrawal difficulties, and increased risk of cognitive impairment [102, 103]. Also, there are pharmacokinetic and pharmacodynamic considerations to be kept in mind, in particular the greater likelihood of accumulation of those drugs which are metabolized by oxidation and which have longer half-lives. On the other hand, drugs with shorter half-lives may produce more severe withdrawal if used in the long-term. Elderly people are more likely to be taking other medications, often for long term treatment, and thus are at more risk for drug-drug interactions.

Cognitive therapy for GAD has been adapted to the elderly, with benefit (LOE 2) [98, 104].

H. CULTURAL ISSUES

There may be significant differences in reporting of GAD symptoms in different cultures [18, 105]. For example, an internet survey in Japan [106] found that the number of patients with GAD who sought medical treatment is less than 17% and that subjects tend to see their tension and excessive worry as being normal reactions to negative life events. There is a need to screen for GAD with appropriate questions, and to use standard diagnostic criteria and good clinical judgment, in order to ensure that a valid diagnosis is made. Although it has been argued that somatization varies in prevalence across different cultures, GAD is often accompanied by depression and somatization in different populations. In formulating a treatment plan, it is however useful to consider patients' explanatory model of their illness; this allows the clinician to understand the meaning of the symptoms for them, including any pertinent cultural aspects, and to negotiate an agreed upon treatment accordingly. Theories of illness are influenced by cultural factors and patients' beliefs should be discussed and carefully accommodated.

Node 3: Treatment

An initial treatment choice may be made as to whether medication, psychosocial treatment (PST) or both will be given.

Node 4: Psychosocial Treatment

Cognitive behavioral treatment is efficacious for GAD [107] (LOE 1). There is no evidence that combined use of CBT with drug therapy enhances CBT alone, but CBT in combination with a sub-therapeutic dose of diazepam produces a greater effect than the same dose of diazepam alone [108]. Psychotherapeutic treatments include CBT and relaxation therapy (although there is little evidence base for the latter), as well as social treatments include problem solving might also be helpful [109].

Node 5: Monotherapy with Selective Serotonin Reuptake Inhibitor (SSRI) or Serotonin Norepinephrine Reuptake Inhibitor (SNRI): 4-6 week evaluation with adequate dosing

Please refer to Table 3 for initial prescribing and dose titration strategies.

First Line Treatment–Antidepressants

Following a DSM-IV diagnosis of GAD, the recommended first line choice will be an SSRI or SNRI drug. Level 1 evidence supports the following SSRI drugs for DSM-IV diagnosed GAD: escitalopram [110]; paroxetine-immediate

release [111, 112]; sertraline [113]. Of the above 3 medications, sertraline would be the best option for women of reproductive years, from the perspective of the extent of safety data in pregnancy and lactation.

Level 1 evidence supports the SNRI drugs, venlafaxine-extended release and duloxetine, in patients who met DSM-IV criteria for GAD [114-118], including one long-term six month study of extended-release venlafaxine.

Other antidepressants (imipramine and trazodone) have been demonstrated to show greater efficacy than placebo in one study of DSM-III based GAD (level 2) [10], but these are not recommended as first choice treatments due to poorer tolerability and higher risk of potentially serious side effects.

Lower levels of evidence (LOE 4) support the use of mirtazapine in GAD [119], as well as in GAD with concomitant major depressive disorder [34]. Some evidence exists for citalopram (LOE 2) [99, 120, 121]; nefazodone (LOE 4) [122] and fluoxetine in children and adults (LOE 2 for children and for adults) [123, 124]. While the branded form of nefazodone (Serzone) has been discontinued, generic forms of this drug are still available, although we recommend that the drug should be generally avoided because of liver toxicity. In a head-to-head comparison trial of bupropion and escitalopram, bupropion was equivalent to escitalopram in treating GAD (LOE 3) [125].

Role of Non-Antidepressant Drugs in GAD

While it is acknowledged that many practitioners use the following drugs as first line treatment, we recommend their use only as a second line form of monotherapy after intolerance to a series of antidepressants. There is also a place for these drugs in augmentation (see below Nodes 9-17) or on occasion, early in treatment for marked agitation or severe sleep disturbances.

Benzodiazepines

A solid body of level 1 evidence supports the short-term efficacy of benzodiazepine (BZD) drugs for GAD, as reviewed by Mitte et al [126], and these data support BZD for all the recent DSM iterations of GAD, beginning with DSM-III. Their rapid onset of efficacy, reasonable side-effect profile and good tolerability make them appealing drugs for many clinicians. However, in other quarters, these medications are looked upon with disfavor because of their abuse potential and association with dependence. In general we recommend BZDs as second line treatments, to be chosen after intolerance has been established to antidepressants. However, Schweizer and Rickels [127] propose that BZD are appropriate first line choices in two circumstances: (1) short-duration GAD type reactions in response to stress and (2) where somatic symptoms are more prominent than psychic symptoms [10, 128]. In this regard, long-half life benzodiazepines may hold merits or advantages in anxiety disorders except in the elderly due to their relatively low risk of inter-dose rebound anxiety and withdrawal symptoms compared with those with short-half life. Nevertheless, although acknowledging that antidepressants typically have a greater benefit on psychic than somatic symptoms, we recommend the use of an SSRI or SNRI for treating the somatic symptoms of GAD, based upon their proven efficacy on this symptom cluster. While antidepressants may have a slower onset of action than BZDs, they are eventually as effective, if not more so, and a satisfactory effect is usually obtained. BZDs are not recommended where GAD is characterized by substantial hostility, impatience, irritability and impulsivity, which can sometimes be made worse by BZDs [129]. Rickels and Schweizer have noted that serotonergic drugs may be more effective in this situation (LOE 4) [130].

Many authorities suggest the use of BZDs in the early phases of treatment with SSRIs or other antidepressants in order to achieve some symptomatic relief until the antidepressant has had time to work (generally about 2-3 weeks) and to protect against the occasional early worsening of anxiety seen at the beginning of antidepressant therapy. This is perhaps more likely if comorbid panic disorder is also present. Fewer authorities advise that benzodiazepines should be avoided whenever possible [131], given that some patients benefit from and do not abuse them [132].

Antidepressants versus Benzodiazepines

In deciding upon the comparative merits of antidepressants and BZD, we note a limited literature (LOE 1 for imipramine; LOE 2 for paroxetine) which finds a superior effect for antidepressants [10, 133, 134]. Hoehn-Saric et al [133] (LOE2) noted that alprazolam was more effective for somatic symptoms, whereas imipramine was more effective for dysphoria and anticipatory thinking. BZDs are better for sleep and can be used as hypnotics. The large SSRI (e.g. escitalopram) and SNRI (e.g. venlafaxine-XR) databases suggest that the psychological components of the Hamilton Anxiety Scale are more responsive to each drug, but the somatic items do respond, albeit more slowly and to a lesser

degree, at least in the short term. Because of the chronic nature of GAD, some patients are used to benzodiazepines, buspirone or hydroxyzine, therefore previous medication experience should be taken into account.

Azapirones

Buspirone is a partial $5HT1_a$ agonist with short-term efficacy in GAD (LOE 1). There have been 10 studies referred to by Mitte et al [126], many of which were conducted in samples diagnosed with DSM-III or IIIR criteria, and of which the effect size relative to placebo was acceptable in 8. In patients with ICD-10 diagnosed, short-duration, mild symptoms of GAD, and not exposed to benzodiazepines, buspirone may have some role as an initial pharmacotherapy of GAD. However, due to its slow onset of action, variable tolerability and its overall lack of benefit against other comorbid disorders (except possibly for alcohol use disorder), and the lack of efficacy in recent BDZ users, (although not all findings are consistent in this respect [135] (LOE 2)), we in general do not recommend this drug as a first line treatment for DSM-IV GAD.

Tandospirone, which was launched in Japan in 1996, is widely used for mild anxious-depressive symptoms, especially among primary care physicians. The drug was approved for a wider indication mainly based on ICD-9 criteria of neurosis, but recently it was launched in China, and the results of a double-blind, randomized, non-placebo-controlled, trial of buspirone and tandospirone showed similar efficacy and safety for both treatments in GAD [136].

Antihistamines

The H_1 antihistaminic drug, hydroxyzine, is effective (LOE 1) in studies that have been conducted for as long as 12 weeks in DSM-IV GAD [137-139]. In some countries, hydroxyzine is a widely used anxiolytic, particularly among primary care doctors, but we recommend its use as a second line agent in view of its side effect profile, and lack of efficacy for comorbid disorders.

Other

The $\alpha_2\delta$ calcium channel antagonist, pregabalin, is also effective in the short-term treatment of GAD (LOE 1) [140-144]. The drug is available in some countries for treating epilepsy, as well as chronic pain associated with diabetes or herpes zoster. It is approved in some European countries, but not in the US, for GAD. We do not recommend it as a first-line agent in view of the relative lack of experience to date, and lack of efficacy for comorbid disorders.

Tiagabine (LOE 2) did not separate from placebo on the primary measure in a large GAD study, but on some secondary analyses there was separation in favor of drug [145].

Evidence for antipsychotic monotherapy in GAD is very meager. An open label trial suggested benefit for ziprasidone (LOE 4) [146]. In the United Kingdom, flupenthixol is approved for the use of depression but is widely used to treat GAD-like states. Most published evidence is limited to depression, there was one controlled study that showed flupenthixol was superior to amitriptyline, clotiazepam, or placebo among subjects with refractory GAD [147]. The latter drug may be useful in patients who have a mild paranoid element, e.g. a feeling that they are being observed (LOE5). Sulpiride is also used in similar situations [148, 149]. Although we are aware of ongoing interest in the use of atypical antipsychotics for GAD, at this point we remain sufficiently concerned about their tolerability and safety profile, that we would not recommend them as first-line agents.

Riluzole, a presynaptic glutamate release inhibitor, has shown promise in a small open label study (LOE 4) [150]. This was a proof-of-concept trial, and the drug has significant tolerability concerns.

Node 6: Assessment for Initial Response

Response to treatment after a trial period is described as remitted, improved, partial response or non-response after 4-6 weeks. Although reviews for schizophrenia and depression show that response often appears before 4 weeks, we do not know of any such reviews for GAD and would avoid recommending too short a treatment trial, in that many patients need longer to benefit. These response categories are generally defined as follows:

- Remission: at least 70% better or reduction in symptoms from baseline
- Improved: at least 50% better or reduction in symptoms from baseline
- Partial response: 25-49% better or reduction in symptom severity from baseline
- Non-response: Less than 25% better or reduction in symptoms from baseline

For antidepressants, while it may take over 12 weeks before remission occurs [151], if at least partial response (i.e. at least 25% symptom reduction from baseline) has occurred after 4-6 weeks of adequate trial, we recommend that the clinician re-evaluate according to Node 7 (see below). However, if there is no response or the response is less than 25%, we would recommend switch to a different treatment. We note that this is a clinical recommendation, and look forward to data that will help support it.

For other drug groups, such as BZD and antihistamine, there is little published data on time until remission, or even rate of remission, but Schweizer and Rickels [127] state that 3 to 4 weeks treatment at a diazepam equivalent dose of 40mg per day constitutes an adequate BZD trial. See node 5 for further information on definitions of response and remission.

In summary, for 1) Adequate trial and good response: go to node 7a; 2) Adequate trial and non-response: go to node 11; 3) Adequate trial and partial response: go to node 8; 4) Failure to give an adequate trial: go back up to node 5 for an adequate trial of an alternative agent.

Node 7: Remission and Relapse Prevention

After 8-12 weeks of treatment, many patients will experience improvement, with at least 50% reduction in symptoms. However, in GAD, there is evidence from two studies that response and remission rates continue to increase beyond two months, and even beyond 6 months in the case of remission [151-153].

Continued treatment over 8 months or longer is associated with a reduction in the risk of relapse (LOE 1) [153, 154]. Once a good response to SRI therapy has been determined, we recommend continuation of the therapy for at least a year in GAD, given the chronicity of symptoms, and randomized controlled trials showing relapse after short-term maintenance treatment. No data exist to our knowledge on the efficacy of continued treatment with a BZD or antihistamine in GAD.

Failure to achieve remission should constitute a signal for the clinicians to either increase the dose to maximal or supra-maximal levels, to augment or to switch to another drug class.

While data are not available, we recommend maintenance treatment at the same dose which it took to achieve response. An exception to this recommendation can be made where late emerging side effects occur, such as weight gain, sexual difficulty, sleep disruption, behavioral or other mental changes, such as hostility or impulsivity.. In these cases, the dose may be lowered, discontinued or antidote medicine used, according to clinical judgment. In primary care, it is possible that less severe cases of GAD are found as compared to psychiatric settings, and that the required dose may be lower, although data do not exist on this topic as far as we know. Because withdrawal from most anti-anxiety medications can be distressing, with the possible exception of azapirones and fluoxetine, we recommend a slow taper when the decision has been made to stop medication.

Node 8: Assessment for Partial Response

When there is only partial response to an initial trial after 4-6 weeks of adequate dosing, we recommend that the clinician re-evaluate and consider either (a) further increase of the dose, if the maximal dose had not been used, (b) augmentation where there has been some response to monotherapy (see below node 9, 10), or (c) switch to a different treatment (see below node 11),

The role of non-pharmacologically specific response may be considered in partial responders, where improvement can partly be due to the care, diagnostic process, time spent with the patient, empathic support, investigator bias, etc that are part of the interaction with the patient. If the physician determines that these factors are significant, then drug augmentation may be of very limited benefit.

Node 9: For Partial Response with Persistent Insomnia

While pharmacologic intervention may be indicated, it is also important to evaluate lifestyle issues which can impact on sleep (i.e., sleep hygiene, diet, excess caffeine usage especially late in the day, alcohol and other substance use, exercise) (see above, Node 2). When considering pharmacotherapeutic options, augmentation with proven non-benzodiazepine GABAergic hypnotic drugs (LOE 1), but which have unproven anxiolytic effects (LOE 5), can be used, e.g. zolpidem, zaleplon, or eszopiclone. BZD drugs can also be considered for sleep enhancement since they have beneficial effects in GAD. Other sedating anxiolytic or antidepressant drugs can be used, although their evidence

as hypnotics is weak and their side effects can be more problematic. Further studies of the dose/response/side effects relationships with antidepressants used as hypnotics are needed. Alternatively, a sedating antihistamine such as hydroxyzine can be added (LOE 1 for GAD), but its hypnotic effects are also unproven. The evidence is mixed, but the more recent studies of another antihistamine are not encouraging. Tolerance to the sedation from diphenhydramine 50 mg bid was complete by day 3 of a placebo-controlled study [155]. In elderly patients, major cognitive impairment was found in 426 patients given diphenhydramine [156]. It is also important to be mindful that in some instances, treatment of GAD may also exacerbate sleep disturbance.

Node 10: Augmentation Strategies for Partial Response with General Symptom Persistence

Almost all clinical trials of GAD have tested the efficacy of monotherapy, therefore our recommendations are largely extrapolations from monotherapy trials of the recommended product. Notable exception applies, however, to the atypical neuroleptics risperidone and olanzapine. For partial responders to an SSRI, who showed persistence of the full symptom complex, despite adequate treatment with a variety of antidepressant or non-antidepressant drugs for GAD, the addition of risperidone up to 1.5 mg per day was associated with further improvement (LOE 2) [53]. In a study by Pollock et al (LOE2) [124], augmentation of fluoxetine with olanzapine yielded better response than did augmentation with placebo on several measures. We consider that augmentation with an atypical antipsychotic drug has a good foundation based on short-term efficacy data (rather than long-term safety data). However, many clinicians may prefer to use drugs which are not associated with risks of metabolic changes or abnormal involuntary movements. In that case, we recommend the addition of a drug from other classes to the primary drug already being given to the patient. Thus, either a BZD, antihistamine, buspirone or tiagabine (LOE 5 each) could be added to an antidepressant. Tiagabine, whose effects in GAD are modest at best, should be used with caution in those with a seizure history or predisposition. An antidepressant could be added to any of the aforementioned drugs, in situations where the patient has been treated, for example, firstly with an antihistamine or BZD.

Cognitive-behavior therapy (CBT) could be added, although there is no current evidence to support a potentiating effect of CBT to ongoing pharmacotherapy in GAD (LOE5) [108].

Node 11: Switch Strategies for Partial Response or Non-response with General Symptom Persistence

An alternative strategy for partial response would be to switch to another antidepressant, either within the same class, or in a different one (e.g. SSRI to SSRI or SSRI to SNRI). No studies have examined the effects of this strategy in GAD, to our knowledge, but there are data in MDE that a second SSRI can be effective in around 50% of cases when there is failure on the first, and there is evidence that a SNRI can be effective in cases where patients have failed a number of prior medication trials. There is little systematic guidance as which strategy is preferable, and when, but there is arguably greater rationale for switching than for augmentation when response to the first medication is zero or below 25%.

We do not generally recommend switching from an SSRI/SNRI to a BZD on the grounds of non-response. If there has been intolerance to at least two different antidepressants, then switching to BZD seems reasonable (LOE 5). In addition, if there were two failed trials with SSRIs, we recommend switching to an SNRI. Imipramine (LOE 2) may also be a consideration for nonresponders to SSRI/SNRI, although no trials have been done to address this.

Node 12: Assessment for Response

See Node 6.

Node 13: Evaluate for comorbidity

If inadequate response is found to be associated with comorbid depression, stable bipolar disorder or other anxiety disorder (panic, social anxiety, PTSD, OCD, or specific phobia), then the following steps are recommended.

Node 14:

For persisting unipolar depression, we recommend use of maximum tolerated dose antidepressant drugs or augmentation of an SSRI or SNRI with buspirone [157, 158] (LOE 2 for augmentation of depression; LOE1 for GAD and MDD, each as monotherapy), bupropion [158] (LOE 1 for MDD as monotherapy and augmentation; LOE 3 for GAD) or

an atypical antipsychotic, such as risperidone or olanzapine (LOE 2 for GAD). In atypical major depression with comorbid GAD, chromium picolinate showed greater effect than placebo on symptoms of both conditions (LOE3) [35].

For severe depression with GAD, it is possible that ECT would be indicated for the depressive component (LOE 1 for depression; LOE 5 for GAD). Monoamine oxidase inhibitor (MAOI) therapy may also be tried at this stage (LOE 1 for depression and LOE 5 for GAD).

Node 15:

If the symptom picture suggests bipolar spectrum disorder which coexists with GAD, we would want to rule out uncontrolled mood instability. We might recommend addition of a drug with mood stabilizing properties such as an anticonvulsant (divalproex sodium, lithium) (LOE 1 for bipolar disorder, and LOE 5 for GAD) or atypical antipsychotic (LOE 1 for bipolar disorder; LOE 2 for SSRI augmentation in GAD). Of note, some mood stabilizers and antipsychotics may need periodic laboratory monitoring, e.g. blood levels of carbamazepine, valproic acid and lithium, and fasting lipid profile and fasting blood sugar for some antipsychotics. There are some regional differences in respect to the use of antidepressants in patients with bipolar depression, with US physicians preferring not to recommend their use. Those in Europe, however, utilize them more often in practice, backed by substantial long-term data of antidepressants being associated with lower mortality over 50 years' follow-up when used with a mood stabilizer or antipsychotic, as compared to treatment without an antidepressant [159]. Nevertheless, not all data is consistent, so in the event that an antidepressant is used, care should be taken that it does not exacerbate the bipolar disorder [160].

Node 16:

For GAD with other anxiety disorders, we recommend the use of treatments which are beneficial for both states. If monotherapy with, for example, an SRI or BZD, has failed to adequately treat the comorbid disorder, a second treatment can be added. Thus for all anxiety disorders, SSRIs (LOE 1) are effective, SNRI (LOE 1 for all anxiety disorders except OCD), TCA (LOE 1 for imipramine or clomipramine in PD; LOE 2 for imipramine in PTSD; LOE 1 for clomipramine, in OCD) may be beneficial. For panic disorder, a BZD (alprazolam or clonazepam) may be used (LOE 1). There is some evidence to support olanzapine monotherapy for SAD (LOE 3) [161], augmentation with risperidone or olanzapine in OCD (LOE 1) [45, 46, 50, 52, 162], and PTSD (LOE 1 or 2) [41-44, 163, 164]. There are data to support use of pregabalin (LOE 1) [165, 166] and levetiracetam (LOE 3) [167] in SAD.

Node 17: Inadequate response without Comorbidity

In the case of inadequate response (non-response or partial response) to the drug combination chosen at Node 9-11, without significant comorbidity, we recommend switching to another combination, of which one drug should be a serotonergic antidepressant (SSRI, SNRI, NaSSa or serotonergic TCA), or adding a third drug of a different class to the two already in use, although evidence from studies of triple therapy is lacking. Preliminary evidence (LOE 3) from a small trial in atypical depression, which was comorbid with GAD in the majority of subjects, found benefit for monotherapy with chromium picolinate (LOE 3) [35]. It is possible that in combination with established treatments, augmentation with this agent maybe useful (LOE 5) in refractory GAD. MAOI monotherapy could also be considered at this stage (LOE5).

Psychosocial treatment can also be added at this stage (LOE 5).

Node 18: Assessment for Response

See Node 6

Node 19: Diagnostic Re-evaluation

Non-response, or partial response at this stage would call for diagnostic re-evaluation.

IPAP GAD Addenda

General Principles

I. Initial and repeated evaluation.

A. GAD is common and often passes unrecognized.
B. The initial evaluation should adhere to DSM-IV or ICD-10 criteria. Given that the most research on GAD, and pharmacotherapy in particular, has used DSM-IV, these criteria may be especially useful.
C. The initial evaluation should include a thorough psychiatric assessment, medical history and, where appropriate, referral for laboratory or medical evaluation. Attention should also be added to sleep hygiene, lifestyle issues, as well as medication side effects.
D. Initially and at subsequent points of non-response, or when there is loss of previous response, assess for key symptoms that may change management (e.g. suicidality, psychotic or bipolar symptoms, substance use) introduction of other medications and treatment non-adherence.
E. Patients with bipolar disorder should already be stabilized before introducing antidepressant treatment for GAD. Latest data suggest avoiding antidepressants: only 16% respond and many experience a mood switch [160], although there are regional differences in the approach to using antidepressants for bipolar depression. Similarly, other comorbid disorders may need to be stabilized before attempting to treat GAD. On other occasions, treatment for both conditions can be instituted simultaneously.
F. Standardized rating scales for symptom severity, quality of life, function and resiliency (i.e., stress coping ability) can be useful.

II. Choice of treatment: medication, psychosocial or both.

A. The initial treatment of GAD can be either with medication or psychotherapy. Patient preference and therapist skill will be important determinants of the choice. Comorbidity and prior response to treatment are also important considerations.
B.Both approaches have been found efficacious for GAD.

III. Medications and adequacy of response

A. Patients with GAD who are going to be treated with medication should, in most cases, receive an SSRI or SNRI as first line monotherapy. Only if rapid response is needed, or if insomnia is a dominant symptom, would a concomitant BZD be recommended for brief treatment.
B. The response time to an antidepressant drug in GAD is generally 4-12 weeks. One expects at least partial response by 4-6 weeks with adequate dosing, and it is assumed that the clinician will progressively titrate the dose upwards according to tolerability of the drug. Response to BZDs is usually faster than for antidepressants, and if there has not been adequate response after 4-6 weeks, we do not believe that persistence with drug will produce greater improvement.
C. In our current state of knowledge, we cannot say whether it is better to increase dose, augment, switch or wait longer when there has been partial response. Clinicians may wish to keep their options open as to the preferred approach. We do, however, recommend switching treatment where an adequate trial has failed to elicit at least 25% improvement.
D. Occasionally patients with GAD experience exacerbation of anxiety or jitteriness with onset of SRI treatment. In such instances, we recommend either lowering of dose to minimal starting levels and then increase in small steps, or co-prescribe a BZD for a short period of time, e.g. at 5mg tid.
E. The patient who has shown an excellent response to pharmacotherapy should generally be treated for at least one year. Early withdrawal is associated with greater relapse risk.

IV. Managing Side Effects

A. Patients with an anxiety disorder are often more sensitive than other patients to medication side-effects and may need lower starting dose and incremental titration over a longer time than might be the case when treating depression.
B. When patients respond partially, or fail to respond, it is important to consider if this represents inadequate medication benefit, treatment non-adherence, the result of side effects, concomitant use of alcohol, substances, other anxiogenic prescription, over the counter treatments, or the need for diagnostic reevaluation.
C. Antipsychotic drugs are associated with metabolic and general cardiovascular side-effects. There may be greater risk of developing type II diabetes or worsening of previously controlled diabetes, weight gain, abdominal obesity, increased triglycerides, or total and LDL cholesterol. Appropriate monitoring of metabolic profile is recommended in accordance with current standards.
D. There is the possibility of untoward drug interactions brought about by the inhibitory properties of some antidepressant drugs on the CYP 450 isoenzyme system. With increased rates of comorbid medical illness, there is greater likelihood that a patient with GAD will be taking other medication over the long term. Clinicians are therefore encouraged to

familiarize themselves with the more common types of interactions that could occur with each psychotropic drug, e.g. as reviewed by Oesterheld J, Osser DN, and Sandson N at www.genelex.com.

E. Typical SSRI/SNRI discontinuation (or "withdrawal") symptoms include worsening of anxiety, irritability, depressed mood, and somatic symptoms such as headache, dizziness, nausea, tremor, paresthesia, vivid dreams, and insomnia [168]. As a general guide to management, we suggest the following 1) Educational material should be provided regarding the treatment to patients and their care-takers; 2) A gradual taper is recommended (with an even slower taper in the elderly and medically ill population) when a decision is made to discontinue a medication; 3) Liquid form, if available may be used for easier administering in the case of an unusually low dose or difficulty swallowing.

V. Placebo response

Sometimes an initial rapid response which fades may be indicative of a "placebo" or "non-specific" response, as has been suggested in the depression literature. We do not know to what extent this is the case for GAD, or how it would best be managed. Some hold that under these circumstances, a medication switch would be preferable to augmentation, although there are no data to inform on the matter. The role of the placebo response may be considered in partial responders, where improvement can partly be due to the care, diagnosis, time spent with the patient, empathic support, investigator bias, etc., that are part of the interaction with the patient. The implications for management remain somewhat unclear, but to the extent the placebo response is stronger for some patients than others, it may help explain why augmentation or switch strategies are not always successful.

VI. Cost-benefit considerations

Cost is often an important consideration in drug selection. However, cost of medication must be viewed more broadly as part of a cost-benefit equation, since "cheaper" drugs may have more problematic side-effects, which bring additional cost-burdens. Because of the variability in medication costs from one country to another, we do not make any specific recommendations about this issue. Related is the issue of risk-benefit, which should be a consideration in drug selection. However, taking into account what is available on the formulary in the country or locale of practice, if at any node in the algorithm there are two or more options of apparently equal efficacy, similar toxicity, and similar acceptability to the patient, and there is a big difference in cost, it is prudent for the clinician to prefer the less expensive product.

Table 2. Level of Evidence[1]

1 = More than one placebo-controlled trial having total sample sizes over 30
2 = One placebo-controlled trial (or active vs active drug comparison) with total sample size of 30 or greater
3 = One or more small (n<30) placebo-controlled trial(s)
4 = Case reports or open-label trials
5 = Expert clinical consensus without published evidence

[1] Treatment Guidelines for GAD include

(1) The British Association of Psychopharmacology (BAP) (www.BAP.org.uk) [3];

(2) The National Institute of Clinical Excellence (NICE) (NHS National Institute of Clinical Excellence. Anxiety: Management of anxiety (panic disorder, with or without agoraphobia, and generalized anxiety disorder) in adults in primary, secondary and community care (Clinical Guideline 22. December 2004. Available at www.nice.org.uk/CG022NICEguideline and www.nice.org.uk/CG022quickrefguide);

(3) The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and posttraumatic stress disorders [4];

(4) Consensus Statement on Generalized Anxiety Disorder from the International Consensus Group on Depression and Anxiety [5];

(5) The Canadian guidelines [6];

(6) The South African Primary Care Algorithms (http://www.mentalhealthsa.co.za/disclaimer.html).

Table 3. Medication Dosing Recommendations for Treating Generalized Anxiety Disorder

Drug	Starting dose (mg/day)	Maximum dose# (mg/day)	Dose increments
SSRI/SNRI			
Citalopram*	20	60	20 mg every 2 weeks
Escitalopram*	5-10	20	5-10 mg every 1-2 weeks
Fluoxetine*	10	60	10-20 mg every 2 weeks
Paroxetine-IR*	10-20	50	10-20 mg every 2 weeks
Paroxetine-CR	12.5	75	12.5-25 mg every 1-2 weeks
Sertraline*	25	200	Increase to 50 mg within 1 week, then increase by 25-50 mg every 1-2 weeks
Duloxetine	30	120	Increase by 30 mg after 1-2 weeks
Venlafaxine-XR	37.5-75	225	Increase to 75 mg within 1 week, then increase by 37.5-75 mg every 2 weeks
TCAs			
Imipramine	25 (HS)	300	25 mg every 4 days; when at 100 mg, may then increase in 50 mg increments
Other antidepressants			
Mirtazapine	15 (HS)	45	15 mg every 1-2 weeks
Trazodone	50 (HS)	400	50 mg every 3-4 days
Bupropion	100	400	100 mg every 4-7 days
Benzodiazepines			
Alprazolam	0.75-1.5 (0.25-0.5 TID)	4	0.5 mg every 3-4 days
Clonazepam	2 (1 BID)	6	1-2 mg every week
Diazepam	15 (5 TID)	40	5 mg after 4-7 days; 10 mg every week
Lorazepam	2 (1 BID)	6	1-2 mg every week
Azapirones			
Buspirone	10-15 (5 BID-TID)	60	5 mg every 3 days
Tandospirone	15-30 (5-10 TID)	60	15 mg every 2-4 weeks
Other anxiolytics			
Hydroxyzine	50 (25 BID)	100	50 mg every week
Pregabalin	150 (75 BID)	600	150 mg every 4-7 days
Anticonvulsants			
Tiagabine	4 (2 BID)	16	2-4 mg every week
Antipsychotics			
Fluphenthixol	0.5	1.5	0.5 mg every 1-2 weeks
Sulpiride	50	200	50 mg after 3-4 days; after 1 week, increase to 200 mg
Ziprasidone	40 (20 BID), with food	160	20 mg every 2-3 days
Other drugs			
Riluzole	50	100	50 mg after 1-3 days

@ U.S. Food and Drug Administration (FDA) approved for generalized anxiety disorder
* available in liquid formulation
# All maximum doses are according to US package insert, for approved indications (not necessary generalized anxiety disorder)

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