We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

6,900
Open access books available

186,000
International authors and editors

200M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

BOOK CITATION INDEX
CLARIVATE ANALYTICS
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Treatment Resistant
Generalized Anxiety Disorder

Nesrin Dilbaz, Serçin Yalcın Cavus and Aslı Enez Darcin
Ankara Numune Research and Training Hospital 2, Psychiatry Clinic
Turkey

1. Introduction

The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text-Revision (DSM-IV-TR)* section on anxiety disorders includes several major disorders: generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder, specific phobia, social anxiety disorder (SAD), and posttraumatic stress disorder (PTSD) (DSM-IV-TR, 2000). Anxiety disorders are the most prevalent of all psychiatric disorders, with an estimated prevalence of 2% to 18% worldwide (Wittchen & Jacobi, 2005). Specific phobias have a lifetime prevalence of 12.5%; the lifetime prevalence for GAD, OCD, panic disorder, SAD, and PTSD are 5.7%, 1.6%, 4.7%, 12.1%, and 6.8%, respectively (Kessler et al., 2005).

Anxiety disorders mostly begin at an early age, significantly impair multiple areas of development and life, and are associated with numerous adverse consequences such as school failure, unemployment and underemployment, academic underachievement, interactional and marital problems, and excessive use of health care facilities (Demyttenaere et al., 2004; Wittchen & Jacobi, 2005). Although anxiety disorders are highly treatable disease the majority of the patients are underdiagnosed or do not receive adequate treatment.

The goal for the treatment of Anxiety disorders is achieving and sustaining remission complete resolution of symptoms and restoration of presymptomatic functioning level. However, a significant number of patients do not fully respond to an adequate trial of first line treatment with an serotonin reuptake inhibitors (SRIs) . For example, at least 40% to 60% of OCD patients still exhibit symptoms after treatment (Pallanti & Quercioli, 2006).

SRIs are currently the first-line pharmacotherapy for most anxiety disorders (Demyttenaere et al., 2004). Benzodiazepines are widely used for panic disorder, GAD, and SAD, but they are associated with unwanted cognitive side effects, a withdrawal syndrome, and potential for abuse. Use of tricyclic antidepressants and monoamine oxidase inhibitors is limited by their adverse side effect profiles. There are also new drugs that modify the γ-aminobutyric acid (GABA)-ergic, serotonergic, and glutamatergic receptor complexes and established drugs with anxiolytic properties such as antipsychotics and anticonvulsants. Approximately a few of the patients who receive treatment are fully symptomatic remitted (Wittchen & Jacobi, 2005; Craske et al., 2005).

Even in those who had response to treatment, remission cannot be achieved. There is no consensus on the operationalization of response, partial response, remission for each anxiety disorder (Ballenger, 2001). It remains important also to develop consensus on different

levels of non response ranging from failure respond to first line therapy to failure respond to complex procedures. The best definition for treatment resistance is still inadequate (Pallanti et al., 2002). A treatment-resistant patient could be defined as a patient who had a standard treatment with at least two antidepressants for a minimum of 6 weeks without response (Bandelow & Rüther, 2004).

This chapter presents a review of the current literature and issues related to GAD including definitions of response and remission, outcome measures and treatment strategies for treatment-resistant GAD.

2. Neurobiology of Generalized Anxiety Disorder (GAD)

Kessler and colleagues surveyed 5001 subjects and demonstrated that GAD and major depression are most likely to occur in the same year and this finding suggests that the disorders are probably linked in biologically, but certainly phenomenologically.(Kessler & Gruber 2008). The extensive overlap between depression and anxiety means that studying the neurobiology of GAD means also studying the neurobiology of depression. There is a variety of evidence implicating the dysfunction of GABA, noradrenergic and serotonerjic systems in the expression of GAD. (Ballenger,2001;Gorman and Hirschfeld, 2002).

Of all of the anxiety disorders, GAD has probably been the least well studied from a genetic perspective. In a recent study of more than 37000 twins from same-sex pairs examined the genetic interrelation among GAD, MDD, and neuroticism. The genetic correlation between major depression and GAD was very high, suggesting that the same genes influence major depression and GAD. The conclusion is that , genetically, MDD and GAD are strongly related and have a common connection to the personality trait neuroticism.(Kendler & Gardner, 2007)

Hettema and colleagues studied 2 subtypes of GAD genes, GAD1 and GAD2, and determined that variations in GAD1 account for a small proportion of the individual differences in neuroticism and may increase susceptibility for MDD and anxiety disorders. These preliminary findings are exciting, but replication is needed. (Hettema &An, 2006).

In neuroimaging studies of GAD, Mathew and colleagues compared GAD patients and the controls, the GAD subjects had higher ratios of N-acetylaspartate (NAA) to creatine in the right dorsolateral prefrontal cortex.(Mathew &Mao, 2004) In an other study, compared with the healthy subjects, individuals with GAD had increased activation in the right ventrolateral prefrontan cortex when viewing angry faces. (Monk &Nelson, 2006)

Available research has suggested that GAD is modestly heritable and shares substantial genetic variation with major depression and the personality trait neuroticism. Genetic association studies are starting to identify promising leads in the search for genes that may increase susceptibility to anxiety disorders. Neuroimaging studies in GAD suggest increased activity in the brain's fear circuitry, as well as increased activity in the prefrontal cortex, which appears to have a compansatory role in reducing GAD sypmtoms.

3. Assessment of GAD: Epidemiology, presentation, diagnosis and course

In the DSM-IV, the diagnostic features for GAD, include excessive anxiety and worry which is difficult to control and pertains to several events or activities. GAD is characterized by persistent and excessive anxiety and worry about a number of common events or situations (eg, finances, health of self or family, job performance or security) occurring on more days

for 6 months or more (DSM-IV). The degree of anxiety is in excess of what would be considered reasonably warranted by the reality of the situation. Difficulty controlling worry is the cardinal feature of GAD and is associated with at least 3 additional symptoms from a list including restlessness or tension, easy fatigability, difficulty concentrating, irritability, muscular tension and sleep disturbance. (APA 1980). There are some diagnostic difficulties like high rates of comorbidity, confusion in defining the term "excessive" worry and duration requirement of 6 months. Because subthreshold cases that meet all GAD diagnostic criteria except for duration of symptoms has demostrated in researches, it is suggested that perhaps the duration requirement of 6 months should be revised downward. (Kessler & Brandenburg, 2005).

The main tool used in the clinical setting to assess the severity of symptoms of GAD is the Hamilton Anxiety Scale (HAM-A).(Hamilton, 1959). However, the HAM-A isa 14-item, clinician-rated scale and is quite time consuming to perform. Recently, scales useful for all anxiety disorders as GAD have been developed, such as the Anxiety Sensitivity Index, *(ASI)* b (Reiss et al 1986) Anxiety Sensitivity refers to a person's tendency to fear anxiety-related symptoms due to the belief that there will be some negative outcome as a result of having those symptoms. the ASI is a widely used measure that has been translated into many languages. The validity and the reliability of the Turkish version was also studied and used in clinical researches. (Dilbaz 2005)

Generalized anxiety disorder (GAD) is a relatively common condition (lifetime prevalence 5.7%,and the 12-month prevalence rate was reported to be 3.1%) with chronic course which is associated with suicidality, significant distress and disability. GAD is an adult onset disorder with an oldest median age (estimated 31 years among US population) at onset of any anxiety disorder. Approximately 25% of cases of GAD have an age onset of 20 years and an additional 50% have an age at onset between 20 and 47. (Kessler &Berglund, 2005). Prevalance is higher among female gender ,(twice as often in voman as it does in men) , older age , white adults, widowed, separated or divorced with a low income. (Grant &Hasin, 2005)

Individuals with GAD has a high risk of recurrence. Harvard Research Anxiety Disorders project (HARP) the probability of recovery was 0.58 and probability of recurrence among patients who had recovered was 0.45 over 12 years. Primary Care Anxiety Project's probability of recovery was 0.39 over 2 years that is a some higher than HARP study. Average amount of time that patients were ill during 12 years was %74 in HARP study. Comorbid Axis I disorders,(Bruce &Yonkers, 2005) substance use disorders, cluster C personality disorders(Yonkers &Dyck, 2000) and female gender(Yonkers& Bruce, 2003) have been found to be less likely to remit.

4. GAD and medical illness

Patients with GAD often have medical comorbidities such as migraine, rheumatoid arthritis, peptic ulcer, irritable bowel syndrome, coronary heart disease, hiperthyroidism, diabetes, asthma and cronic obstructive pulmonary disease that may influence treatment choice. Activation of the HPA axis and sympathetic pathways can lead to cardiac and metabolik alteration and chronic activation of stres response may play a role in the vulnerability to chronic medical illnesses in inmay not be dividuals with GAD. (Habib&Gold, 2002; Charney, 2004)

When treating patients with GAD and medical illness, GAD should be treated as an independent problem. Controlling GAD may not only improve the patient's quality of life,

but may also improve the physical health which is mediated by the sympathetic nervous system and cortisol mechanism.

5. GAD and psychiatric comorbidities: Depression, bipolar disorder and substance abuse

GAD is frequently comorbid with several psychiatric disorders. 90% have likelihood of at least 1 psyhiatric disorder in their lifetime , 62.4% had a lifetime history of major depression, 37.6 % had a lifetime history of alcohol and substance use disorder   and 23.5% to 35.1% had at least one other anxiety disorder. The highest comorbidities were major depressive disorder (MDD) and dysthymia, while alcohol abuse, social anxiety disorder were also common ((Wittchen & Hoyer, 2001).

Comorbidity may complicate the diagnosis, treatment and outcome, resulting with greater disability and impairment. (Wittchen & Hoyer, 2001; Goodwin & Gorman, 2002). In a recent meta-analysis it is compared the impact of pure GAD and GAD comorbide depression on functioning and quality of life. Because patients with comorbidity has more impairment overall, it is suggested that clinicians should use clinical interview structured to diagnose for the presence of comorbid conditions. (Hoffman &Dukes, 2008) The presence of anxiety comorbidity in patients with MDD has also been demonstrated to interfere with the treatment response in Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study which eveluated 2,876 outpatients. Those who have comorbide anxiety and were given first-line pharmacotherapy treatment with citalopram had significantly lower remission rates (%22 versus %33) according to the Hamilton Rating Scale for Depression. (Fava & Rush, 2008)

As with MDD, anxiety comorbidity can worsen the course of bipolar disorder, having a greater lifetime risk of suicide attempts (with current GAD comorbidity it is reported %62; with lifetime GAD, %53) and greater risk of comorbide substance use disorder.(Simon &Otto, 2004) and higher impulsivity. (Taylor &Hisrshfeld, 2007).

Because patients with GAD and comorbid disorders are lekely to have more impairment, disability, suicidality, poorer functioning and quality of life, fort he best outcome careful treatment selection must be chosen. The choice of drug(s) will depend on the severity of GAD; other comorbidity; an assessment of the adverse effects; possible drug-drug interactions and other risks; and the need for an early onset of action

6. Treating GAD

6.1 First-line pharmacotherapy approaches for GAD

The aims of the treatment of GAD are to reduce the core symptoms of GAD (both the psychic and somatic), including restoration of sleep; to improve patient function and quality of life; to treat comorbid disorders—present at the time of diagnosis and those that appear over the long term; and to continue treatment for long enough to produce remission and, where possible, prevent relapse. Many patients with GAD do not receive adequate treatment. Benzodiazepines, selective serotonine reuptake inhibitors (SSRIs), serotonine-norepinephrine reuptake inhibitors (SNRIs) and cognitive therapy are consistantly effective as a first-line treatment. Dose ranges may need to be individualized according to the age, medical comorbidity , psychiatric comorbidity and other medications of the patients.

6.1.1 SSRIs

Several analyses have shown similar efficacy among antidepressant agents in the management of GAD.(Baldwin&Anderson,2005) Of these, SSRIs and SNRIs are generally preferred as first-line therapy, as the evidence supporting their efficacy is more robust, and they are usually better tolerated than the other classes of antidepressants. More recently, sertraline (Dahl &Ravindran, 2005) and paroxetine has been shown to be efficacious in GAD ,and citalopram has demonstrated efficacy in older patients ($\geq$ 60 years of age) with GAD (Lenze&Mulsant, 2005).Because of the prevalence of sexual dysfunction has been estimated to be as high as 40% during treatment with SSRIs, it is a common reason for treatment discontinuation.

The SSRIs escitalopram (10–20 mg/day) and paroxetine (20–50 mg/day) have also been shown to be effective in the long-term treatment of GAD. (Bielski & Bose, 2005) Relapse prevention studies have been reported for both drugs. (Allgulander & Florea, 2006; Stocchi &Nordera, 2003). Escitalopram reduced the risk of relapse compared with placebo during 24 to 72 weeks of randomized treatment following 12 weeks of open-label treatment. Similar results were found with paroxetine versus placebo in a shorter study.Essitalopram was also showen to exceed the effects of plasebo in an other study , and citalopram was effective in a geriatric population with GAD. (Goodman &Bose, 2005; Lenze &Mulsant,2005)

6.1.2 SNRIs (venlafaxine, duloksetin)

Venlafaxine, which affects both serotonin and norepinephrine systems, was the first drug that is approved fort he treatment of GAD and also has been showen to be effective in treating depression. Two placebo-controlled studies have demonstrated the efficacy of venlafaxine XR in GAD and have provided that both the psychic and somatic manifestations of anxiety can be controlled. One of these study compared venlafaxine (75 mg/da yor 150 mg/day fixed dose) with buspirone (30 mg7day) treatment for 8 weeks in 365 patients with GAD. A significantly higher response rate as measured on the CGI was seen for venlafaxine 75 mg/day, compared with either buspirone or placebo after week 1. The mean HAM-A anxious mood and tension scores were significantly lower for both doses of venlafaxine XR at week 8 compared with placebo , however, the mean total HAM-A scores for all the treatment groups compared with placebo were not significant. (Davidson&Dupont, 1999)

In the second study the efficacy of venlafaxine XR (75 to 225 mg/day) assessed by the HAM-A anxiety subscale was statistically higher than placeboin 238 patients with GAD, over a 28-week maintenance period.(Gelenberg& Lydiard, 2000) The results from these studies demonstrate the efficacy of venlafaxine XR in both the short- and long-term treatment of GAD, but the optimal dose was not defined. In an 8-week study of 349 patients with GAD , venlafaxine at 225 mg/doses was found to have more efficacy than placebo, in reducing HAM-A total scores. (Rickels &Pollack, 2000).

The efficacy of duloksetin, another SNRI, was approved in 2007 for the treatment of GAD. In two studies flexible doses of duloksetin (60-120 mg/day) was compared with placebo , found significantly greater improvement for both doses on HAM-A total scores.(Koponen&Allgulander, 2007). Duloxetine has also been shown to have long-term efficacy among patients with GAD who responded to 26 weeks of open-label treatment; administration of duloxetine for a further 26 weeks reduced the risk of relapse compared with placebo. (Davidson &Wittchen ,2008).

6.1.3 Benzodiazepines

Although benzodiazepines diazepam, alprazolam and lorazepam have showen efficacy in controlled trials and were commonly used in GAD; they must be used with caution because of modest abuse potential (Fraser, 1998) interactions with other drugs, including hypnotics sedating antidepressants, opiate analgesics, antihistamines, anticonvulsants and alcohol, particularly in older patients, falls, memory impaierment, incoordination, drowsiness and confusion (Petrovic & Mariman 2003)

Although benzodiazepines have a rapid onset of action on improving the core symptoms of GAD, they are not recommended as monotherapy for depression, dysthymia, obsessive-compulsive disorder, and posttraumatic stress disorder, which commonly occur with GAD.(Ballenger &Davidson,2001; Kessler &Chiu,2005).

Benzodiazepines are generally recommended only for short-term use and are not recommended for first-line long-term treatment of GAD,(Swinson & Anthony 2006) although they have a role in the management of acute anxiety (Bandelow B, Zohar,2008; Ballenger JC, Davidson,2001) and may have a role in some cases in which somatic symptoms are more prominent than psychic symptoms.

6.1.4 Nonpharmacological treatments (cognitive behavioral therapy-CBT)

CBT has been used in GAD as a psychological treatment strategy. However, comparisons between standard drugs for GAD and psychotherapy are lacking. Although CBT is the most effective of the psychological treatments available for GAD, clinical response occurs in less than 50% of people receiving this form of therapy (46% versus 14% for control), so unmet needs still remain (Hunot &Churchill R, 2007). When GAD is comorbid with depression, which is very common, pharmacotherapy with antidepressants is increasingly indicated (Ballenger et al., 2001).

6.2 Treatment comorbidity

Comorbidity is a critical factor that influence the treatment choice of GAD. Rickels and collegues found that, for GAD patients with significant depressive symptoms, an antidepressant drug is more useful than a benzodiazepine. In another study,MDD patients with a comorbidity of GAD, venlafaxine XR was found to be more effective than placebo and flouksetine.(Silverstone&Salinas, 2001). The data to support appropriate choices in the comorbide GAD and bipolar disorder is lacking. Risk of mania with an antidepressant and risk of SUD about using benzodiazepines are the likely reasons for inadequate treatments.

6.3 Treatment in children, adolescents and pregnancy

For children and adolescents, there are published studies of the treatment of GAD, evaluating the SSRIs sertraline, fluoxetine, fluvoxamine (Walkup & Labellarte 2001;Rynn & Siqueland 2001) and venlafaxine XR. (Sheehan & Keene 2008) These data suggest that these agents may be effective in treating the symptoms of GAD in children and adolescents. The SSRIs are generally well tolerated in this population. Guidelines from the British Association for Psychopharmacology recommend that, in children, pharmacologic treatments should be reserved for individuals who have not responded to psychological therapies and careful consideration of dosage is also necessary because of the adverse effects.

In addition, the risk of possible suicidal thoughts or behaviors should be considered and these potential adverse effects monitored when any antidepressants are administered in this age group.(FDA ,2008).

In pregnancy nonpharmacologic treatment such as cognitive-behavioral therapy or interpersonal psychotherapy should be employed whenever possible. But it is equally important to discuss the risks of the untreated illness to both mother and the infant. So if medication is required, the use of SSRIs in the lowest effective dosage for the minimum amount of time is preferable in the first-line treatment because of the data supporting their efficacy, minimal need for dose titration and favorable side effect profile. Paroxetine has been shown to be efficacious in GAD; however, the US Food and Drug Administration (FDA) labeling for its use in pregnancy was reclassified to category D due to possible risk of congenital malformations, especially septal defects, when used during the first trimester of pregnancy. Newer antidepressants such as venlafaxine XR and mirtazapine are options for patients unresponsive or intoleran to SSRIs. Benzodiazepines should be avoided because of physiological dependence and withdrawal in the newborn.

7. Other potentially effective agents

7.1 Bupropion
In a recent double-blind, randomized study, which performed on a small sample sizeof GAD patients , bupropion XL (150-300mg/day) compared with essitalopram (10-20 mg/day) for 12 weeks.The primary efficacy measures were the Clinical Global Impression of Improvement (CGI-I) and the Hamilton Anxiety Rating Scale (HARS).Bupropion XL is found to be demonstrated comparable anxiolytic efficacy to escitalopram in outpatients with GAD. These preliminary results needs to be improved further.

7.2 Atypical antipsychotics
Several preliminary reports of monotherapy trials of quetiapine versus placebo have described efficacy at doses in the range of 50–150 mg/day, (Chouinard & Ahokas A, 2008 ; Khan & Joyce 2008) but quetiapine cannot yet be recommended as a routine GAD treatment. However the use of quetiapine could be considered after other classes of drugs have proved ineffective orwhen certain types of symptoms are present. In the studies by Chouinard, quality of life was measured using the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)., and the highest score were seen with quetiapine XR 150 mg and paroxetine compared with placebo at week 8 (Chouinard et al 2008) . The efficacious application of quetiapine in MDD and GAD ranges from quetiapine monotherapy to adjunctive therapy with antidepressants for shortterm and maintenance treatment at a dose range between 50–300 mg/day. Despite the often benefi cial sedative effects of quetiapine on clinically relevant sleep problems in psychiatric patients, quetipaine is not recommended soley as a sleeping agent. Overall, the most recently available evidence on quetiapine suggests that it can play a signifi cant role in the management of MDD and GAD.For olanzapine or risperidone, it is suggested that the results have been obtained in partialresponders to antidepressants rather than as monotherapy in all patients (Pollack &Simon, 2006; Brawman& Knapp, 2005).

7.3 Antihistamines
Efficacy of the antihistamines in GAD was established in two studies. (Llorca& Spadone, 2002; Lader &Scotto, 1998).The antihistamine hydroxyzine appears to have higher anxiolytic efficacy than placebo in controlled studies. Because of the side effects (sedation,

anticholinergic effects) , slow onset of action, and lack of efficacy for comorbid disorders, hydroxyzine was not recommended to be used as first-line therapy in some guidelines. (IPAP,2008; Bandelow& Zohar,2008).

7.4 TCAs

The tricyclic drug imipramine is effective in GAD but is associated with the usual range of tricyclic antidepressant side effects, which limits its use for those who have not responded to an SSRI or SNRI.(Baldwin & Anderson ,2005 ; Ballenger &Davidson 2001). Another possible second-line antidepressant includes trazodone (Rickels & Downing ,1993).

7.5 Buspirone

The 5HT-1 receptor partial agonist buspirone is found to be effective in the treatment of GAD according to controlled studies (Goa &Ward 1986), but less effective than the benzodiazepines, (Laakmann & 1998) venlafaxine or hydroxyzine. Because of side effects like dizziness, drowsiness and nause, slow onset of action lack of effectivity on comorbid conditions, buspiron is not recommended as first-line treatment for GAD. (Bandelow&Zohar,2008)

7.6 $\alpha_2\delta$ Ca ++ channel modulators, pregabaline

The $\alpha_2\delta$ Ca++ channel modulator pregabalin was shown to have greater efficacy than placebo, nearly equal to benzodiazepines and venlafaxine both in the first week and maintenance of 6 months in several placebo controlled studies (Pande&Crockatt,2003; Montgomery,2006; Montgomery&Tobias, 2006; Owen,2007). The long-term efficacy of pregabalin has also been demonstrated in patients with GAD that it reduced the risk of relapse compared with placebo, during 24 weeks of randomized treatment following 8 weeks of open-label treatment. (Feltner & Wittchen, 2008)

7.7 Tiagabine

The selective GABA reuptake inhibitor tiagabin has been studied in 3 large placebo-controlled trials in 1830 patients with GAD and no significant difference from placebo was showen, moreover side effects were too high that %47 of patients were drop out. It seem hard to justify the use of tiagabine for GAD. (Pollack& Tiller ,2008)

7.8 Agomelatine

Agomelatine a novel agent that acts on melatonergic and serotonergic receptors was assessed on a randomized, double-blind, placebo-controlled trial on one hundred twenty-one patients with GAD with no comorbid disorders.The patients were randomized to agomelatine (25-50 mg/d) or placebo for 12 weeks. The primary outcome measure was the Hamilton Anxiety Rating Scale, whereas secondary outcome measures included the Clinical Global Impression scales. Analysis of covariance of change in the last Hamilton Anxiety Rating Scale total score from baseline demonstrated significant superiority of agomelatine 25 to 50 mg as compared with placebo.Safety analysis indicated that agomelatine was tolerated as well as placebo and was devoid of discontinuation emergent symptoms. This study suggests that agomelatine is effective in the treatment of GAD and is well tolerated (Stein & Ahokas,2008).

8. Adequate and poor response to pharmacotherapy: Switching medication and augmentation strategies

In most studies, response is commonly defined as a ≥50% reduction on the commonly used standard scales. This definition is also arbitrary, because that cannot be applied for all disorders. Assessment of changes on disease-specific rating scales and measures of global illness severity and improvement, social, occupational, and academic functioning, and quality of life should be performed. Remission implies not only the relief of symptoms but also restoration of patients to their premorbid high level of functioning, including resumption of family, social, and work-related role.

Treatment resistance patient could be defined as a patient who had a standard treatment for a minimum of 6 weeks without showing response. Before a treatment is considered as failure it should be ascertained that the diagnosis is correct, the patient is compliant with therapy, the dosage prescribed is therapeutic and there has been an adequate trial period. Comorbid personality disorders such as borderline personality disorder, depression and substance abuse may be associated with poor outcome. Coocurrence of GAD with medical disorders such as heart disease and gastrointestinal and chronic pain disorders causes an extended clinical course and poorer outcome than patients with GAD alone (Harter et al., 2003; Bowen et al., 2000; McWilliams et al., 2003; Roy-Byrne et al., 2008).

If partial response is not seen after 4–6 weeks, there is still a chance that the patient will respond after another 4–6 weeks of therapy with increased dose. When initial treatment fails,the psychiatrist can either *augment* the current treatment by adding another agent (in the case of pharmacotherapy) or another modality (i.e., add CBT if the patient is already receiving pharmacotherapy, or add pharmacotherapy if the patient is already receiving CBT) **,** or they can decide to *switch* to a different medication or therapeutic modality. Augmentation is generally a reasonable approach if some significant benefits were observed with the original treatment **.** On the other hand, if the original treatment failed to provide any significant alleviation of the patient's symptoms, a switch in treatment may be more useful. Treatment resistance are usually based on clinical judgment , "augmentation and switching studies" are lacking. Low doses of risperidone have been shown to improve in anxiety symptoms when added to initial treatment in patients who had not responded to first-line anxiolytic drugs. (Brawman& Knapp ,2005) A study of quetiapine augmentation of paroxetine did not provide evidence as an augmenting agent in GAD.(Simon & Connor,2008). Olanzapine has shown similar augmentation effects when added to fluoxetine in patients with refractory GAD, although this efficacy was achieved at the expense of substantial weight gain.(Pollack&Simon, 2006). Other augmentation strategies might include addition of a benzodiazepine or other GABAergic drug to an antidepressant. Augmentation of medication with cognitive-behavioral therapy (CBT) has not been studied meaningfully in GAD, and its benefit still awaits adequate evaluation.

9. Maintenance treatment

Because GAD is a chronic illness, maintenance treatment is required and it is showen that stopping acute treatment with anxiolytic after 4 weeks, %60 to 80 patients led to relapse within a year. (Rickels &Schweizer, 1990). In a study, even after 6 months of buspirone treatment for GAD, stopping treatment led to relapse of %25 within a month. (Rickels &Schweizer, 1988) After treating with essitalopram for 12 weeks, the patients randomized to essitalopram or placebo up to 76 weeks and the relapse rates were %19 and %56,

respectively. (Allgulander&Florea, 2006). Likely, After 8 weeks of treatment with paroxetine, the patients were randomized for 24 weeks and the relapse rates were%10,9 and %39,9. (Davidson&Wittchen, 2008). GAD requires long-term treatment that remission can take several moths and stopping medication increases the risk of relapse within the first year of initiating treatment.

10. Conclusion

It is recommended that the first-line treatment for patients with GAD should consist of an antidepressant, such as SSRI (paroxetine and essitalopram) or SNRI (venlafaxine and duloksetine). On the other hand they have efficacy limitations, including lack of response, lack of full remission, risk of relapse and adverse effects. This means that there is a need for alternative treatment options. Following the first-line treatment in case of inappropriate response; 1) increasing the dose of the SSRI/SNRI, 2)switching to a same class or different class agent or 3) augmentation therapy may be considered.The strategy of augmentation SSRIs/SNRIs with atypical antipsychotics may be useful in improving the rates of remission but randomized controlled studies are needed.

11. References

Allgulander C, Florea I, Huusom AK. Prevention of relapse in generalized anxiety disorder by escitalopram treatment. Int J Neuropsychopharmacol. 2006;9(5):495–505.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC:American Psyciatric Association;1994.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.Text revised. Washington, DC:American Psyciatric Association; 2000.

Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2005;19(6):567–596.

Ballenger JC. Overview of different pharmacotherapies for attaining remission in generalized anxiety disorder. J Clin Psychiatry 2001; 62 Suppl. 19; 11-9.

Ballenger JC, Davidson JRT, Lecrubier Y, et al. Consensus statement on generalized anxiety disorder from the international consensus group on depression and anxiety. *J Clin Psychiatry.* 2001;62(suppl 11):53-58.

Bandelow B, Rüther E. Treatment resistant panic disorder. *CNS Spectr. 2004;9(10):725-730, 732-739.*

Bandelow B, Zohar J, Hollander E, et al. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders: First Revision. World J Biol Psychiatry. 2008;9(4):248–312.

Bielski RJ, Bose A, Chang CC. A double-blind comparison of escitalopram and paroxetine in the long-term treatment of generalized anxiety disorder. Ann Clin Psychiatry. 2005;17(2):65–69.

Brawman-Mintzer O, Knapp RG, Nietert PJ. Adjunctive risperidone in generalized anxiety disorder: a double-blind, placebo-controlled study. J Clin Psychiatry. 2005;66(10):1321–1325

Bruce SE, Yonkers KA, Otto MW, et al. Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder:a 12 year prospective study. Am J Psychiatry. 2005;162:1179-1187.

Bystritsky A, Kerwin L, Feusner JD, Vapnik T.A Pilot Controlled Trial of Bupropion XL Versus Escitalopram in Generalized Anxiety Disorder. Psychopharmacol Bull. 2008;41(1):46-51.

Charney DS. Psycobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stres. Am J Psychiatry. 2004;161(2):195-216.

Chouinard G, Ahokas A, Bandelow B, et al. Extended release quetiapine fumarate (quetiapine XR) once-daily monotherapy in generalized anxiety disorder (GAD). Presented at the 27th Annual Meeting of the Anxiety Disorders Association of America; March 6–9, 2008; St Louis, MO.

Craske MG, Edlund MJ, Sullivan G, Roy-Byrne PP, Sherbourne CD, Bystritsky AS. M.B. Perceived unmet need for mental health and barriers to among care patients with panic disorder. Psychiatric Services 2005;56:988–94.

Dahl AA, Ravindran A, Allgulander C, et al. Sertraline in generalized anxiety disorder: efficacy in treating the psychic and somatic anxiety factors. *Acta Psychiatr Scand.* 2005;111(6):429–435.

Davidson JTR, Dupont RL, Hedges D, et al. Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder. J Clin Psychiatry 1999 ;60 :528-535.

Davidson JR, Wittchen HU, Llorca PM, et al. Duloxetine treatment for relapse prevention in adults with generalized anxiety disorder: a double-blind placebo-controlled trial. Eur Neuropsychopharmacol. 2008;18(9):673–681.

Demyttenaere K, Bruffaerts R, Posada-Villa J, et al. Prevalence, severity and unmet need for treatment of mental disorders in the World Health Organization World Mental Health (WMH) Surveys. Journal of the American Medical Association 2004;291:2581–90.

Dilbaz N. Turkish Anxiety Sensitivity Index: Psychometric properties. Presented at National Anxiety Disorders Congress in Tunusia, in 2005

Fava M, Rush AJ, Alpert JE, et al. Difference in treatment outcome in patients with anxious versus nonanxious depression: a STAR*D report. Am J Psychitry. 2008;165(3):342-351.

Feltner D, Wittchen HU, Kavoussi R, et al. Long-term efficacy of pregabalin in generalized anxiety disorder. Int Clin Psychopharmacol. 2008;23(1):18–28.

Fraser AD. Use and abuse of the benzodiazepines. Ther Drug Monit. 1998;20(5):481–489.

Food and Drug Administration. Revisions to product labeling: suicidality and antidepressant drugs; 2007. Accessed November 2008.

Gelenberg AJ, Lydiard RB, Rudolph RL, et al. Efficacy of venlafaxine extended-release capsules in nondepressed outpatients with generalized anxiety disorder: a 6-month randomized controlled trial. JAMA 2000;283:3082-3088.

Goa KL, Ward A. Buspirone: a preliminary review of its pharmacological properties and therapeutic efficacy as an anxiolytic. Drugs. 1986;32(2):114–129.

Gorman JM, Hirschfeld RM. Ninan PT. New developments in the neurobiological basis of anxiety disorders. Psychopharmacol Bull 2002; 36 Suppl. 2; 49-67
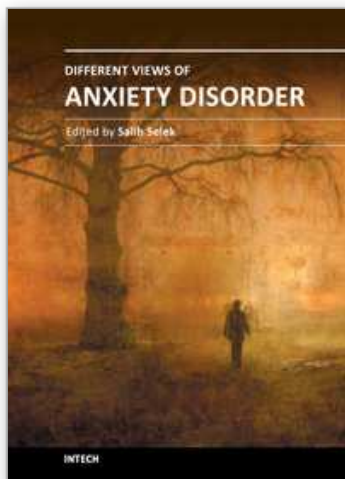
Goodman WK, Bose A, Wang Q. Treatment of generalized anxiety disorder with escitalopram: pooled results from double-blind, placebo-controlled trials. J Affect Disord. 2005;87(2-3):161-167.

Goodwin RD, Gorman JM. Psychopharmacologic treatment of generalized anxiety disorder and the risk of major depression. Am J Psychiatry. 2002;159(11):1935–1937.

Grant BF, Hasin DS, Stinson FS, et al. Prevalence, correlates, comorbidity, and comperative disability of DSM-IV generalized anxiety disorder in the USA:results from the National Epidemiologic Survey on Alcohol and Related Conditions. Psychol Med. 2005;35(12):747-759.

Habib KE, Gold PW, Chrousos GP. Neuroendocrinology of stres. Endocrinol Metab Clin North Am. 2001;30(3):695-728.

Hettema JM. What is the genetic relationship between anxiety and depression? Am J Med Genet C Semin Med Genet. 2008;148(2):140-146.

Hettema JM, An SS, Neale MC, et al. Association between glutamic acid decarboxylase genes and anxiety disorders, major depression, and neuroticism. Mol Psychiatry. 2006;11(8):752-762. Correction in 2006;11(8):794.

Hoffman DL, Dukes EM, Wittchen HU. Human and economic burden of generalized anxiety disorder. Depress Anxiety. 2008;25(1):72-90.

Hunot V, Churchill R, Silva de Lima M, et al. Psychological therapies for generalised anxiety disorder. Cochrane Database Syst Rev. 2007;(1):CD001848

International Psychopharmacology Algorithm Project. IPAP General Anxiety Disorder (GAD) Algorithm Notes. http://www.ipap.org/gad/index.php. Accessed November 2008.

Khan A, Joyce M, Eggens I, et al. Extended release quetiapine fumarate (quetiapine XR) monotherapy in the treatment of generalized anxiety disorder (GAD). Presented at the 27th Annual Meeting of the Anxiety Disorders Association of America; March 6–9, 2008; St Louis, MO.

Kendler KS, Gardner CO, Gatz M, et al. The sources of co-morbidity between major depression and generalized anxiety disorder in a Swedish national twin sample. Psychol Med. 2007;37(3):453-462.

Kessler RC, Brandenburg N, Lane M, et al. Rethinking the duration requirement for generalized anxiety disorder: evidence from the National Comorbidity Survey Replication. Psychol Med. 2005;35(7):1073-1082.

Kessler RC, Berglund P, Demler O, Jin R, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62:593-602.

Kessler RC, Chiu WT, Demler O, et al. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):617–627.

Koponen H, Allgulander C, Erikson J, et al. Efficacy of duloksetine fort he treatment of generalized anxiety disorder: implications for primary care phsicians. Prim Care Companion J Clin Psychiatry. 2007;9(2):100-107.

Laakmann G, Schule C, Lorkowski G, et al. Buspirone and lorazepam in the treatment of generalized anxiety disorder in outpatients. Psychopharmacology (Berl). 1998;136(4):357–366.

Lader M, Scotto JC. A multicentre double-blind comparison of hydroxyzine, buspirone, and placebo in patients with generalized anxiety disorder. Psychopharmacology (Berl):1998;139(4):402-406.

Lenze EJ, Mulsant BH, Shear MK, et al. Efficacy and tolerability of citalopram in the treatment of late-life anxiety disorder:results from an 8-week randomized, placebo-controllled trial. Am J Psychiatry. 2005;162(1):146-150.

Llorca PM, Spadone C, Sol O,et al. Efficacy and safety of hydroxyzine in the treatment of generalized anxiety disorder: a 3-month double-blind study. J Clin Psychiatry. 2002;63(11):102-1027.

Mathew SJ, Mao X, Coplan JD, et al. Dorsolateral prefrontal cortical pathology in generalized anxiety disorder:a proton magnetic resonance spectroscopic imaging study. Am J Psychiatry. 2004;161(6):1119-1121.

Monk CS, Nelson EE, McClure EB, et al. Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalized anxiety disorder. Am J Psychiatry. 2006;163(6):1091-1097.

Montgomery SA. Pregabaline fort he treatment of generalized anxiety disorder. Expert Opin Pharmacother. 2006;7(15):2139-2154.

Montgomery SA, Tobias K, Zomberg GL, et al. Efficacy and safety of pregabalin in the treatment of generalized anxiety disorder:a 6- week, multicenter, randomized, double-blind, placebo-controlled comparison of pregabalin and venlafaxine. J Clin Psychiatry. 2006;67(5):771-782.

Owen RT. Pregabalin:its efficacy, safety and tolerability profile in generalized anxiety disorder. Drugs Today (Barc). 2007;43(9):601-610.

Pallanti S, Hollander E, Bienstock C, et al. Treatment non-response in OCD: methodological issues and operational definitions. Int J Neuropsychopharmacol. 2002;5:181-191.

Pallanti S, Quercioli L. Treatment-refractory obsessive-compulsive disorder: methodological issues, operational definitions and therapeutic lines. Prog Neuropsychopharmacol Biol Psychiatry. 2006;30(3):400-412.

Pande AC, Crockatt JG, Feltner DE, et al.Pregabaline in generalized anxiety disorder: a placebo-controlled trial. Am J Psychiatry. 2003;160(3):533-540.

Petrovic M, Mariman A, Warie H, et al. Is there a rationale for prescription of benzodiazepines in the elderly? review of the literature. Acta Clin Belg. 2003;58(1):27–36.

Pollack MH, Simon NM, Zalta AK, et al. Olanzapine augmentation of fluoxetine for refractory generalized anxiety disorder: a placebo-controlled study. Biol Psychiatry. 2006;59(3):211–215. PubMed doi:10.1016/j.biopsych.2005.07.005.

Pollack MH, Tiller J, Xie F, et al. Tiagabine in adult patients with generalized anxiety disorder: results from 3 randomized, double-blind, placebo-controlled, parallel-group studies. J Clin Psychopharmacol. 2008;28(3):308–316

Pollack MH, Simon NM, Zalta AK, et al. Olanzapine augmentation of fluoxetine for refractory generalized anxiety disorder: a placebo-controlled study. *Biol Psychiatry.* 2006;59(3):211–215.

Rickels K, Pollack MH, Sheehan DV, et al. Efficacy of extended-release venlafaxine in nondepressed outpatients with generalized anxiety disorder. Am J Psychiatry. 2000;157(6):968-974.

Rickels K, Downing R, Schweizer E, et al. Antidepressants for the treatment of generalized anxiety disorder: a placebo-controlled comparison of imipramine, trazodone, and diazepam. Arch Gen Psychiatry. 1993;50(11):884–895

Rickels K, Schiweizer E. The clinical course and long-term management of generalized anxiety disorder. J Clin Psychopharmacol. 1990;10(suppl 3):101S-110S.

Rickels K, Schiweizer E, Csanalosi I, et al. Long-term treatment of anxiety and risk of withdrawal. Prospective comparison of clorazepate and buspirone. Arch Gen Psychiatry. 1988;45(5):444-450.

Rynn MA, Siqueland L, Rickels K. Placebo-controlled trial of sertraline in the treatment of children with generalized anxiety disorder. Am J Psychiatry. 2001;158(12):2008–2014.

Sheehan DV, Keene MS, Eaddy M, et al. Differences in medication adherence and healthcare resource utilization patterns: older versus newer antidepressant agents in patients with depression and/or anxiety disorders. CNS Drugs. 2008;22(11):963–973.

Silverstone PH, Salinas e. Efficacy of venlafaxine extended release in patients with major depressive disorder nd comorbid generalized anxiety disorder. J Clin Psychiatry.2001:62(7):523-529.

Simon NM, Connor KM, LeBeau RT, et al. Quetiapine augmentation of paroxetine CR for the treatment of refractory generalized anxiety disorder: preliminary findings. Psychopharmacology (Berl). 2008;197(4):675–681.

Simon NM, Otto MW, Wisniewski SR, et al. Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry. 2004;161(12):2222-2229.

Stein DJ, Ahokas AA, de Bodinat C. Efficacy of agomelatine in generalized anxiety disorder: a randomized, double-blind, placebo-controlled study. J Clin Psychopharmacol. 2008 Oct;28(5):561-6.

Stocchi F, Nordera G, Jokinen RH, et al. Efficacy and tolerability of paroxetine for the long-term treatment of generalized anxiety disorder. J Clin Psychiatry. 2003;64(3):250–258.

Swinson RP, Anthony MM, Bleau P, et al. Clinical practice guidelines: management of anxiety disorders. Can J Psychiatry. 2006;51(suppl 2):9S–91S

Taylor CT, Hirshfeld-Becker DR, Ostacher MJ, et al. Anxiety is associated with impulsivity in bipolar disorder. J Anxiety Disord. 2007;22(5):868-876.

Walkup JT, Labellarte MJ, Riddle MA, et al, for the Research Unit on Pediatric Psychopharmacology Anxiety Study Group. Fluvoxamine for the treatment of anxiety disorders in children and adolescents. N Engl J Med. 2001;344(17):1279–1285.

Wittchen HU, Hoyer J. Generalized anxiety disorder: nature and course. J Clin Psychiatry. 2001;62(suppl 11):15–19.

Wittchen H-U, Jacobi F. Size and burden of mental disorders in Europe: a critical review and appraisal of 27 studies. European Neuropsychopharmacology 2005;15(4):357–67.

Yonkers KA, Dyck IR, Warshaw M, et al. Factors predicting the clinical sourse of generalized anxiety disorder. Br J Psychiatry. 2000;176:544-549.

Yonkers KA, Bruce SE, Dyck IR, et al. Chronicity, relapse and illness:course of panic disorder, social phobia and generalized anxiety disorder: findings in men and women from 8 years of follow-up. Depress Anxiety. 2003;17(3):173-179.

Different Views of Anxiety Disorders

Edited by Dr. Salih Selek

Anxiety, whether an illness or emotion, is a term with historical roots even in the Bible, but it was not popular until the modern age. Today, we can group, diagnose and treat several anxiety disorders to an extent, but the assessment of symptoms and severity, dealing with resistant conditions, new treatment modalities and specific patient population, such as children, are still the challenging aspects of anxiety disorders. This book intends to present anxiety disorders from a different view and discuss a wide variety of topics in anxiety from a multidimensional approach. This Open Access book addresses not only psychiatrists but also a broad range of specialists, including psychologists, neuroscientists and other mental health professionals.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

INTECH

open science | open minds