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

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

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 of Generalized Anxiety Disorders: Unmet Needs

Nesrin Dilbaz and Aslı Enez Darcin

Additional information is available at the end of the chapter

1. Introduction

Generalized anxiety disorder (GAD) is defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) as the presence of persistent, excessive anxiety and worry about a number of events and activities occurring on most of the days for at least 6 months. The patient must also experience at least three of the following six symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and sleep disturbance.

GAD has a 12-month prevalence of 1% – 2.1% and a lifetime prevalence of 2.8% – 4.1% in Europe and in the US (Grant et al., 2005), often occurs early in life with twice the number of women suffering from it compared to men (ESEMeD/MHEDEA Investigators, 2000). GAD is chronic and disabling, and is associated with high rates of psychiatric comorbidity and substantial personal, social and economic costs (Wittchen et al., 1994; Ballenger et al., 2001; Wittchen, 2002). Evidence shows GAD's impact on social functioning, distress levels, and utilization of medical care is equivalent to those of other major psychiatric disorders (Mennin et al. 2004). In the National Comorbidity Survey, Wittchen and colleagues found that ~38% of patients with GAD may have another anxiety disorder and 48% may have major depression in addition to GAD (Wittchen et al., 1994). In addition to psychiatric comorbidities, patients with anxiety disorders have a higher risk for developing medical diseases in the areas of cardiovascular, gastrointestinal and respiratory as compared with control groups (Bowen et al., 2000).

Remission criteria defined by Ballenger include no or minimal symptoms of anxiety (Hamilton Anxiety Scale score ≤7-10), no functional impairment (Sheehan Disability Scale score ≤1 on each item) and no or minimal symptoms of depression (Hamilton Depression Scale score ≤7) for generalized anxiety disorder (Ballenger, 1999). Remission rates are considerably low

in generalised anxiety disorder. Yonkers and colleagues have shown that the remission rates are only 15% and 25% among 164 patients after one and two years respectively (Yonkers et al., 1996). The probability of remission of GAD is only 38% at 5 years, and the probability of relapse after remission is 27-39% by 3 years (Yonkers et al., 2000).

GAD is often unrecognized or misdiagnosed as a physical condition due to the range of clinical presentations, including somatic symptoms, and the frequent occurrence of comorbid conditions. The main treatment approaches for GAD comprise pharmacotherapy or psychotherapy or a combination of both. The chronic and disabling nature of GAD often means that some individuals may fail to respond fully to first-line treatment (Bandelow et al., 2008; Goodwin et al., 2002; Altamura et al., 2008; Allgulander et al., 2002; Baldwin et al; 2005). Patients may therefore require a sequential trial of treatments or possibly a combination therapy (Davidson et al; 2010).

Research in the treatment of GAD has primarily focused on the efficacy of pharmacotherapy. Antidepressant and anxiolytic drugs are the two most commonly used pharmacological treatments for anxiety disorders. Newer anticonvulsant and sometimes antipsychotic drugs are also used in the treatment of some anxiety disorders including generalized anxiety disorder. More recently, there has been an increasing interest in the efficacy of psychotherapy. Of all the therapies, cognitive behavioral therapy (CBT) has established the most empirical support as an effective treatment for GAD (Gould et al. 2004).

In recent years, GAD-related disability (Wittchen, 2002) as well as impairment in quality of life and functioning has gain importance. Anxiety disorders result in considerable economic loss both decreasing working performance and increasing the number of applications for health care services (Wittchen, 2002; DuPont et al., 1996; Greenberg et al., 1999). GAD poses both personal and public substantial economic and social burden (Pollack et al., 2009).

According to the preliminary findings of our ongoing study on the evaluation of patient burden due to wrong diagnosis and treatment in patients with generalized anxiety disorder (GAD), the mean duration of GAD was 5.6±6.1 years, and the patients received initial treatment for their GAD 27.6±36.7 for months ago. It was noted that GAD was mostly accompanied by major depression (60.5%), followed by other anxiety disorders (31.6%). Of the patients diagnosed with GAD, 86.4% were using medication for GAD and 40.9% were admitted to an emergency service for any reason within the last 6 months. The mean number of emergency admissions was 3.1±3.7. Of the patients admitted to emergency services, 51.9% underwent analyses such as blood analysis, radiological examination, electrocardiography (ECG) and ultrasonography (USG), and 48.5% were referred to another specialist for consultation. The preliminary findings of the present study indicate that admissions of GAD patients to emergency services due to various complaints continue when these patients are not treated adequately and sufficiently, and that financial burden of this disorder increases incrementally due to laboratory analyses and imaging techniques, consultations and additional therapies performed during these admissions (Dilbaz and Karamustafalıoğlu 2012a).

This chapter presents the unmet needs in the treatment of generalised anxiety disorders and new strategies in treatment for GAD.

2. Treatment

The primary goal of treatment of GAD is to alleviate psychic and somatic complaints, promote sleep, improve patient's functioning and enhance patient quality of life. Besides, treating other concomitant medical conditions (psychiatric and/or medical co-morbidity) and consequently providing remission and preventing relapses are also aimed. The important requirements for the therapy drug include rapid action, broad spectrum, increasing remission rates, preventing relapses, absence of symptoms due to discontinuation of drug, minimum interaction with other drugs, and safety for elderly and children (Dilbaz et al., 2011; Davidson et al., 2010). Treatment of GAD comprises drug therapy together with behavioral therapy and psychotherapy. Characteristics and severity of symptoms, co-morbidities, presence of substance addiction and risk for suicide, results of previous therapies, costs, availability of drug and patient preference should be considered while planning GAD treatment (Davidson et al., 2010).

2.1. Pharmacological strategies

2.1.1. Benzodiazepines

Many randomized, double-blind trials have demonstrated the efficacy of benzodiazepines in the acute treatment of GAD (Greenblatt et al., 1983; Rickels et al., 1987; Hollister et al., 1993). However, there is evidence that more than a third of patients will not meet remission criteria in the treatments with benzodiazepines (Shader and Greenblatt, 1983).

The risks and benefits of using benzodiazepines should be carefully considered in each patient. Benzodiazepines have rapid onset, relatively low toxicity, and anxiolytic potency but these benefits should be weighed against for potential motor impairment, dependence and withdrawal symptoms esspecially when prescribed for >4 weeks (Rynn and Brawman-Mintzer, 2004).

Particularly in older people, benzodiazepine use can be problematic due to side effects such as falls, memory impairment, incoordination, drowsiness, and confusion (Petrovic et al., 2003). They can also disrupt sleep architecture, and rebound insomnia may occur after stopping treatment (Longo and Johnson, 2000).

2.1.2. Antidepressants

Selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenalin reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs, particularly imipramine), and, in a single controlled trial, trazodone have demonstrated efficacy in treatment of GAD compared to placebo (Rickels et al., 1993). Several analyses have shown similar efficacy among antidepressant agents in the management of GAD (Kapczinski et al, 2003).

2.1.2.1. SSRIs and SNRIs

Of these, SSRIs and SNRIs are the recommended first-line drugs for treatment of anxiety based on strength of evidence and acceptable tolerability. Antidepressants, particularly SSRI, may be associated with an initial worsening of anxiety symptoms in some patients. A retrospective cohort study defined characteristics of patients which developed emergent anxiety following an antidepressant intiation as young age, white and women sex (Li et al., 2011). Li et al. also found that receiving bupropion, fluoxetine or sertraline had lower risk of anxiety development than citalopram, paroxetine, venlafaxine and mirtazapine (Li et al, 2009). It is recommended to start on low doses and slowly titrate up to a therapeutic dose to reduce these "activation" symptoms (Sinclair et al., 2009). Patients should be advised of the potential for initial increase/worsening of symptoms and the likely delay of clinical effect (some response often seen by 4 weeks). Patient awareness of these factors when commencing SSRI treatment assists in reducing early discontinuation of treatment. Concomitant use of benzodiazepines during early treatment with SSRI may be useful in moderating these "activation effects" of SSRI early in treatment, although the potential for dependence must be considered. SSRI need to be taken for up to 12 weeks in order to assess a patient's response to treatment. Dosing requirements (like initiation in lower doses and reaching optimal doses by weekly increments) for antidepressants differ to that needed in the treatment of depression. All patients being treated with antidepressants (irrespective of diagnosis) should be monitored for worsening of their clinical condition and the emergence of suicidal ideation (Anxiety Disorders – Drug Treatment Guidelines, 2008)

According to Western Australian Psychotropic Drugs Committee; sertralin, escitalopram and venlafaxin have second line of evidence in treatment of generalized anxiety disorders whereas paroxetine has first line evidence (Hidalgo et al., 2007; Kapczinski et al., 2003; Anxiety Disorders – Drug Treatment Guidelines, 2008). There was a small statistically significance in favour of escitalopram compared with paroxetine based on a reduction in HAM-A scores. In addition, there was a 40% reduction in risk of non-response and lower risk (although not statistically significant) of discontinuation of treatment due to adverse events for escitalopram compared with paroxetine (Baldwin et al., 2006). There were no statistically significant differences found between paroxetine and sertraline on any outcomes (Ball et al., 2005).

There were no differences found on reduction of anxiety symptoms between escitalopram and venlafaxine while venlafaxine was associated with a greater risk of discontinuation (although this was not statistically significant) (Bose et al., 2008). Duloxetine was found to be effective in 60-120 mg/d doses in treatment of generalised anxiety disorder when compared to placebo (Rynn et al., 2008; Hartford et al., 2007). No difference was found between duloxetine and venlafaxine for reduction in anxiety and discontinuation due to adverse events (Nicolini et al; 2009).

2.1.2.2. Bupropion

Bystritsky and colleagues compared bupropion XL and escitalopram in 24 patients with generalised anxiety disorder in a 12-week, double-blind, randomized controlled trial and reported comparable efficacy between bupropion and escitalopram (2008).

2.1.2.3. Agomelatine

The efficacy of 25 to 50 mg/day agomelatine in generalised anxiety disorder (GAD) was assessed in a 12-week double-blind, placebo-controlled study of 121 patients with no comorbid disorders (Stein et al., 2008). Agomelatine was found more effective than placebo at reducing anxiety (based on Hamilton rating scale for Anxiety; p=0.04). Agomelatine also improved sleep symptoms, sleep latency (p≤0.001), quality of sleep (p=0.002) and awakenings (p≤0.0001).

2.1.3. Anticonvulsants

2.1.3.1. Valproate

Valproate has been investigated for the management of GAD in a double-blind, placebo-controlled randomized trial involving 80 male patients with GAD in a double-blind placebo-controlled design (Aliyev and Aliyev, 2008). 40 patients randomized to receive 500 mg valproate three times per day and 40 patients received mathed plasebo. At week 4, valproate separated from placebo by mean total HARS score, and at 6 weeks, the mean change in HARS score reached significance. The most common side effects in the valproate group were dizziness and nausea and further investigation is recommended.

2.1.3.2. Gabapentine

Pollack and colleagues reported two cases documenting improvements in patients with GAD, following addition of gabapentin to their treatment (Pollack et al., 1998).

2.1.3.3. Tiagabine

There are case series documenting patients with generalised anxiety disorder treated with tiagabine successfully (Schwarts, 2002; Crane et al., 2003; Schaller et al., 2004). Schwartz et al followed up 17 patients with GAD in an 8-week, open-label trial of tiagabine (mean dose 13 mg/d) augmentation to SSRIs or benzodiazepines. 76% of patients responded [≥ 50% reduction in anxiety symptoms (HARS)] and 59% achieved remission (HARS score ≤ 7) (Schwartz et al., 2005).

Pollack et al reported on 3 large 10-week, randomized, double-blind, placebo-controlled, parallel-group studies. In the fixed-dose study, 910 patients received 4, 8, or 12 mg/d of tiagabine and in two flexible-dose studies, a total of 920 participants were enrolled. The mean doses of tiagabine were 8.9 and 9.2 mg/d. Neither study found significant differences in anxiety symptoms (HARS used) when compared to placebo and investigators concluded that these studies do not support the efficacy of tiagabine in adult patients with GAD (Pollack et al., 2008).

2.1.3.4. Pregabaline

There have been several industry-sponsored, multicenter, outpatient, prospective, randomized, double-blind, placebo-controlled studies. Pande et al. showed a significant improvement with pregabalin compared to placebo, but no significant differences in response were observed when comparing pregabalin 50 mg tid to pregabalin 200 mg tid or lorazepam to pregabalin 200 mg tid. The most commonly associated adverse events with pregabalin were dizziness, somnolence, and headache (Pande et al., 2003). Feltner and colleagues also compared pregabalin (in different doses), lorazepam 2 mg tid, or placebo. They also found pregabalin 200 mg tid effective in treatment of GAD, however, pregabalin 50 mg tid wasn't effective and 200 mg tid was not significantly different from lorazepam (Feltner et al., 2003). Pohl et al. found pregabalin in 100 mg bid, 200 mg bid, and 150 mg tid doses significantly effective than in reducing anxiety symptoms (Pohl et al., 2005).

In another large study of 454 participants with GAD, Rickels et al. compared pregabaline (in different doses) with alprazolam and placebo. Investigators reported that of the 5 treatment groups, the 300-mg pregabalin group was the only medication group that differed statistically in global improvement at treatment end point not only from the placebo group but also from the alprazolam group (Rickels et al., 2005). Another study found pregabaline (400-600 mg/day) effective in treatment of GAD compared to placebo and safer than venlafaxine (Montgomery et al., 2006).

Lydiard et al combined data from 6 short-term, double-blind, placebo-controlled, fixed-dose trials of pregabalin for the treatment of GAD. They concluded that pregabalin had significant efficacy in treating both HARS psychic and somatic anxiety measures. Furthermore, they indicated that a dose-response effect was evident for pregabalin that appeared to reach a plateau at a dose of 300 mg/d (Lydiard et al., 2010).

Pregabalin is promising in both add-on and switch therapies in treatment-resistant GAD cases. Pregabalin rapidly (within days) relieves anxiety symptoms providing substantial advantage over SSRI and SNRIs (Dilbaz and Karamustafalıoğlu, 2012a).

2.1.3.5. Levetiracetam

One case with GAD reported by Pollack, had improved with levetiracetam 250 mg/d added to citalopram treatment (Pollack, 2002).

2.1.4. Atypical antipsychotics

Some first-generation antipsychotics were approved for a condition similar to GAD, and recent studies have suggested that atypical antipsychotics may also have a role in GAD. A Cochrane metaanalysis reported that nine studies investigated the effects of second-generation antipsychotics in generalised anxiety disorder. Seven of them investigated the effects of quetiapine. Participants with generalised anxiety disorder responded significantly better to quetiapine than to placebo (4 RCTs, N = 2265, OR = 2.21, 95% CI 1.10 to 4.45). However, patients on quetiapine arm were more likely to drop out due to adverse events, like gain weight or

sedation. When quetiapine was compared with antidepressants in GAD, there was no significant difference in efficacy-related outcomes, but more participants in the quetiapine groups dropped out due to adverse events.

2.1.4.1. Quetiapine

Several preliminary reports of monotherapy trials of quetiapine versus placebo have described efficacy at doses in the range of 50–150 mg/d (Chouinard et al., 2008; Khan et al., 2008; Joyce et al., 2008; Bandelow et al., 2009), but quetiapine cannot yet be recommended as a routine GAD treatment until a full description of efficacy and safety from these studies have been published. However, the use of quetiapine could be considered after other classes of drugs have proved ineffective or when certain types of symptoms are present like insomnia.

2.1.4.2. Olanzapine

Pollack investigated olanzapine augmentation to fluoxetine at a mean dose of 8.7 mg daily and reported that olanzapine may be helpful for patients who fail to respond to SSRIs alone, considering the advers events like wight gain (Pollack et al., 2006).

2.1.4.3. Aripiprazole

Two studies demonstrate that aripiprazole has promise in augmentation at dosages starting at 10 mg daily (Menza et al., 2007; Hoge et al., 2008).

2.1.4.4. Risperidone

Adjunctive risperidone could be tried in patients with poor response at titrated doses up to 3 mg daily (Brawman-Mintzer et al., 2005; Simon et al., 2006).

2.1.4.5. Ziprasidone

Ziprasidone at a daily dose range of 20 to 80 mg may be helpful for patients with GAD who did not have an adequate response to other medication treatment (Snyderman et al., 2005).

2.1.5. Other drugs

2.1.5.1. Azapirones

Buspirone was approved for the treatment of GAD more than 20 years ago. In recent years, multiple members of the azapirone class, which comprises the partial or full 5-HTIA agonists gepirone, zalospirone, and ipsapirone, have been studied. These molecules show anxiolytic properties but have limitations in terms of tolerability. In a recent brief report, Mathew *et al*. tested the short-term tolerability and efficacy of PRX-00023, a nonazapirone 5-HTIA selective partial agonist, in 23 outpatients with GAD (Mathew et al., 2008). This preliminary study indicated that PRX-00023 appeared to be generally well tolerated in patients with GAD. But further investigations needed.

2.1.5.2. Riluzole

Although double-blind, placebo-controlled trials are lacking, several open label trials have suggested that riluzole, either as monotherapy or as augmentation of standard therapy, reduces symptoms of some psychiatric disorders including generalized anxiety disorder (Grant et al., 2007; Mathew et al., 2005).

Mathew et al.,investigated the efficacy and safety of treatment with riluzole (100 mg/day): of the 15 patients who completed the trial, 12 had a rapid improvement of anxiety symptomatology (Mathew et al., 2005). Recently, Mathew et al. (2008), in an open-label trial, used proton magnetic resonance spectroscopic imaging (1H MRSI) to examine the effects of the glutamate-release inhibitor riluzole on hippocampal N-acetylaspartate (NAA), a neuronal marker, in 14 patients with GAD. Investigators demonstrated a relationship between hippocampal NAA and symptom alleviation after the administration of riluzole in patients for 8 weeks; this result suggested that riluzole might be efficacious for GAD (and subtypes of mood disorders) in part because of reduced glutamate excitotoxicity and enhancement of hippocampal neuroplasticity. In studies of psychiatrically ill patients conducted to date, the drug has been quite well tolerated; common adverse effects include nausea and sedation. Elevation of liver function tests is common and necessitates periodic monitoring. Riluzole may hold promise for the treatment of several psychiatric conditions, possibly through its ability to modulate pathologically dysregulated glutamate levels, and merits further investigation (Pittenger et al., 2008).

2.2. Nonpharmacological strategies; Psychotherapy

2.2.1. Cognitive behavioral therapy

One of the most successful psychosocial treatments for the treatment of GAD is cognitive-behavioral therapy (CBT). The components of this therapy may vary to include the following: education about the symptoms and causes of anxiety, cognitive restructuring, applied relaxation, increasing awareness, learning to monitor of anxious symptoms presenting as physical symptoms, and the automatic thoughts of worry created from situational and behavioral cues. Patients are taught to manage these symptoms through training in arousal reduction techniques such as pleasant imagery and diaphragmatic breathing; and imaginal and in vivo exposure to anxiety cues coupled with copings skill rehearsal (Roemer et al; 2002).

A Cochrane collaboration review concluded that current evidence demonstrates that CBT is effective for the short-term management of GAD relative to wait-list control but not active supportive therapy or supportive treatment (ie, active supportive therapies underpinned by humanistic principals). The most successful CBT treatment protocols have included motivational therapy, interpersonal psychotherapy, integrative CBT (ICBT) to treat GAD (Baer, 2003). Although CBT is the most effective of the psychological treatments available for GAD, available data indicate that a clinical response occurs in less than 50% of people receiving CBT, so unmet needs still remain (Hunot et al., 2007).

One promising form of psychotherapy emphasizes the promotion of positive emotional states and active coping behaviors, rather than focusing on how to reduce symptoms. This

resilience-building treatment is referred to as "well-being therapy" and appears to be superior to CBT on some measures in treatment-resistant GAD and other forms of anxiety (Fava et al., 2005).

2.2.2. Mindfulness based cognitive therapy

A number of approaches have integrated features of Buddhist mindfulness practices with CBT to treat a number of psychiatric disorders including GAD (Baer 2003). Mindfulness was conceptualized as being a set of skills that can be learned independently of any spiritual or cultural tradition and then applied to help manage psychiatric symptoms. These approaches have included mindfulness based stress reduction (MBSR) (Kabat-Zinn 1982, 2003), mindfulness based cognitive therapy (MBCT) (Segal et al. 2002), dialectical behavior therapy (DBT) for borderline personality disorders (Linehan 1993a, b), and acceptance and commitment therapy (ACT) mostly for anxiety and major mood disorders (Hayes et al. 1999).

There are two objectives associated with classical mindfulness (CM) skill training for treating GAD: (1) to achieve a level of sustained, detailed, non-conceptual divided attention and awareness (also known as bare attention or direct experience), and (2) develop the ability to carry out experiential based insight based on the way of experiencing as described in (1). These two objectives clearly imply that there are two major stages of mindfulness practice. The first stage is training in sustaining, detailed, nonconceptual divided attention and awareness which needs to be distinguished as significantly different from MBSR practice of mindfulness. The second stage involves the reinstatement of gradual application of discriminative processes informed by direct experience in order to enrich the process of knowing (Rapgay et al., 2011).

MBCT may be an acceptable and potentially effective treatment for reducing anxiety and mood symptoms and increasing awareness of everyday experiences in patients with GAD. Future directions include development of a randomized clinical trial of MBCT for GAD (Evans et al., 2008).

2.3. Combination strategies

CBT in combination with a sub-therapeutic dose of diazepam produces a greater effect than the same dose of diazepam alone (Power, et al., 1989). Given that GAD has a chronic course and is often comorbid with depression it may be that the combined treatment of medication and psychotherapy may provide an important treatment option that could lead to improved outcomes beyond monotherapy (Barlow, 2002). Unfortunately, at this time there is no data to support this conclusion.

3. Conclusion

GAD is a prevalent and disabling disorder that may appear with physical and psychiatric comorbitidies. SSRIs and SNRIs defined as first line treatment options in GAD, and there is

increasing interest in enhancement new strategies to deal with the disorder. Novel antidepressants agomelatine and bupropion, atypical antipsychotics and anticonvulsants are promising in the treatment of GAD but still far from expectations because the necessity of close monitoring and some adverse events. Pharmacological interventions are still the most effective interventions to manage the disorder while augmentation strategies promising. However clinicians still in need of more effective treatment options that have rapid effect and safe.

Author details

Nesrin Dilbaz and Aslı Enez Darcin

Üsküdar University, Neuropsychiatry (NP) Hospital. Istanbul, Turkey

References

[1] Aliyev NA, Aliyev ZN. Valproate (depakine-chrono) in the acute treatment of outpatients with generalized anxiety disorder without psychiatric comorbidity: randomized, double blind placebo-controlled study. *Eur Psychiatry* 2008;23:109-14.

[2] Allgulander C, Hirschfeld RM, Nutt DJ. Long-term treatment strategies in anxiety disorders. *Psychopharmacol Bull.* 2002;36(suppl 2):79–92.

[3] Altamura AC, Dell'osso B, D'Urso N, et al. Duration of untreated illness as a predictor of treatment response and clinical course in generalized anxiety disorder. *CNS Spectr.* 2008;13(5):415–422.

[4] *Anxiety Disorders – Drug Treatment Guidelines (August 2008).* Western Australian Therapeutics Advisory Group. Psychotropic Drugs Committee. http://www.watag.org.au/wapdc/guidelines.cfm#Anxiety

[5] Baer RA. Mindfulness training as a clinical intervention: A conceptual and empirical review. Clinical Psychology: Science and Practice 2003; 10(2), 125–143.

[6] 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.

[7] Baldwin DS, Huusom, A K T and Maehlum E. Escitalopram and paroxetine in the treatment of generalised anxiety disorder: randomised, placebo controlled, double-blind study. British Journal of Psychiatry, 2006;189, 264–272.

[8] Ball S, Kuhn A, Wall D et al. Selective serotonin reuptake inhibitor treatment for generalized anxiety disorder: a double-blind, prospective comparison between paroxetine and sertraline. Journal of Clinical Psychiatry, 2005;66, 94–99.

[9] Ballenger JC. Clinical guidelines for establishing remission in patients with depression and anxiety. J Clin Psychiatry 1999;60(suppl 22):29–34

[10] Ballenger JC, Davidson JR, Lecrubier Y, et al. Consensus statement on depression, anxiety, and oncology. J Clin Psychiatry 2001;62:64–67.

[11] Bandelow B, Chouinard G, Bobes J, et al. Extended-release quetiapine fumarate (quetiapine XR): a once-daily monotherapy effective in generalized anxiety disorder. Data from a randomized, double-blind, placebo- and active-controlled study. Int J Neuropsychopharmacol. 2009:1- 16.19691907

[12] 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.

[13] Barlow DH. Anxiety and Its Disorders. 2nd ed. New York, NY: Guilford; 2002.

[14] Bose A, Korotzer A, Gommoll C et al. Randomized placebo-controlled trial of escitalopram and venlafaxine XR in the treatment of generalized anxiety disorder. Depression and Anxiety, 2008; 25, 854–861.

[15] Bowen RC, Senthilselvan A, Barale A. Physical illness as an outcome of chronic anxiety disorders. Can J Psychiatry. 2000;45:459-464.

[16] 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.

[17] 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.

[18] Chambless DL and Gillis MM. Cognitive therapy for anxiety disorders. Journal of Consulting and Clinical Psychology, 1993;61, 248–260.

[19] Chouinard G, Ahokas A, Bandelow B, et al. St Louis, MO: 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.

[20] Crane D. Tiagabine for the treatment of anxiety. Depress Anxiety. 2003;18(1):51–52.

[21] Davidson JR, Feltner DE, Dugar A. Management of generalized anxiety disorder in primary care: identifying the challenges and unmet needs. Prim Care Companion J Clin Psychiatry. 2010;12(2):772.

[22] Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington DC, American Psychiatric Association; 1994.

[23] Dilbaz N, Yalcın Cavus S, Enez Darcin A. Treatment resistant generalized anxiety disorder. Selek S (ed), Different Views of Anxiety Disorders. InTech open access book, 2011, p.219-232.

[24] Dilbaz N, Karamustafalıoğlu KO. Unmet needs in the generalized anxiety disorder: pregabalin as a new option. Anatolia Journal Psychitary, 2012; 13(3): 232-238.

[25] Dilbaz N, Karamustafalıoğlu O. Burden due to misdiagnosis and mistreated patients with generalized anxiety disorder; preliminary findings (Anatolian Jounal of Psychiatry, 2012a)

[26] DuPont RL, Rice DP, Miller LS, Shiraki SS, Rowland CR, Harwood HJ. Economic costs of anxiety disorders. Anxiety 1996; 2:167-172.

[27] ESEMeD/MHEDEA 2000 Investigators. Prevalence of mental disorders in Europe: Results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand 2004;109:21–27.

[28] Evans S, Ferrando S, Findler M, Stowell C, Smart C, Haglin D. Mindfulness-based cognitive therapy for generalized anxiety disorder. J Anxiety Disord. 2008;22(4): 716-21.

[29] Fava GA, Ruini C, Rafanelli C, et al. Well-being therapy of generalized anxiety disorder. Psychother Psychosom. 2005;74(1):26–30.

[30] Feltner DE, Crockatt JG, Dubovsky SJ, et al. A randomized, double-blind, placebo-controlled, fixed-dose, multicenter study of pregabalin in patients with generalized anxiety disorder. J Clin Psychopharmacol. 2003;23(3):240–249.

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

[32] Gould RA, Safren SA, Washington D and Otto MW. A meta-analytic review of cognitive behavioral treatments. In RG Heimberg, CL Turk, & DS Mennin (Eds.), Generalized anxiety disorder: Advances in research and practice. New York: The Guilford Press 2004.

[33] Grant BF, Hasin DS, Stinson FS, et al. Prevalence, correlates, co-morbidity, and comparative disability of DSM-IV generalized anxiety disorder in the USA: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Psychol Med 2005;35:1747–1759.

[34] Grant P, Lougee L, Hirschtritt M, et al. An open-label trial of riluzole, a glutamate antagonist, in children with treatment- resistant obsessive-compulsive disorder. J Child Adolesc Psychopharmacol 2007; 17: 761-7

[35] Greenberg PE, Sisitsky T, Kessler RC, Finkelstein SN, Berndt ER, Davidson JR, et al. The economic burden of anxiety disorders in the 1990s. J Clin Psychiatry 1999; 60:427-435.

[36] Greenblatt DJ, Shader RI, Abernethy DR. Drug therapy. Current status of benzodiazepines. New Eng J Med. 1983;309:354-358.

[37] Hartford J. Komstein S. Liebowitz M, et al. Duloxetine as an SNRI treatment for generalized anxiety disorder: results from a placebo and active-controlled trial. Int Clin Psvchopharmacol 2007; 22 (3): 167-74.

[38] Hayes SC, Strosahl KD and Wilson KG. Acceptance and commitment therapy: An experiential approach to behavior change, 1999. New York: Guilford.

[39] Hidalgo RB, Tupler LA, Davidson JR. An effect-size analysis of pharmacologic treatments for generalized anxiety disorder. J Psychopharmacol 2007; 21(8):864-872.

[40] Hoge EA, Worthington JJ, 3rd, Kaufman RE, et al. Aripiprazole as augmentation treatment of refractory generalized anxiety disorder and panic disorder. CNS Spectr. 2008;13(6):522–527.

[41] Hollister LE, Muller-Oerlinghausen B, Rickels K, Shader RI. Clinical uses of benzodiazepines. J Clin Psychopharmacol. 1993;13(6 suppl 1):1S-169S.

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

[43] Joyce M, Khan A, Eggens I, et al. Efficacy and safety of extended release quetiapine fumarate (quetiapine XR) monotherapy in patients with generalized anxiety disorder (GAD). Poster presented at the 161st annual meeting of the American Psychiatric Association. May 3-8, 2008.

[44] Kabat-Zinn J. An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: Theoretical considerations and preliminary results. General Hospital Psychiatry,1982;4, 33–47.

[45] Kabat-Zinn J. Mindfulness-based interventions in context: Past, present, and future. Clinical Psychology: Science and Practice 2003;10, 144–156.

[46] Kapczinski F, Lima MS, Souza JS, Schmitt R. Antidepressants for generalized anxiety disorder. Cochrane Database Syst Rev 2003;(2):CD003592.

[47] Khan A, Joyce M, Eggens I, et al. St Louis, MO: 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.

[48] Li Z, Pfeiffer PN, Hoggatt KJ, Zivin K, Downing K, Ganoczy D, Valenstein M. Emergent anxiety after antidepressant initiation: a retrospective cohort study of Veterans Affairs Health System patients with depression. Clin Ther. 2011;33(12):1985-92.

[49] Li Z, Hoggatt K, Pfeiffer PN, Downing K, Kim HM, Zivin K, Valenstein M. Development of anxiety after antidepressant usage among depressed veterans. Annual Albert J. Silverman Conference, Ann Arbor, MI, June 2009.

[50] Linehan MM. Cognitive-behavioral treatment of borderline personality disorder, 1993a. New York: Guilford.

[51] Linehan MM. Skills training manual for cognitive behavioral treatment of borderline personality disorder, 1993b. New York: Guilford.

[52] Longo LP, Johnson B. Addiction, pt 1: benzodiazepines: side effects, abuse risk and alternatives. Am Fam Physician. 2000;61(7):2121–2128.

[53] Lydiard RB, Rickels K, Herman B, et al. Comparative efficacy of pregabalin and benzodiazepines in treating the psychic and somatic symptoms of generalized anxiety disorder. Int J Neuropsychopharmacol. 2010;13(2):229–241.

[54] Mathew SJ, Amiel JM, Coplan JD, Fitterling HA, Sackeim HA, Gorman JM. Open-label trial of riluzole in generalized anxiety disorder. *Am J Psychiatry* 2005;162:2379-81.

[55] Mathew SJ, Garakani A, Reinhard JF, Oshana S, Donahue S. Short-term tolerability of a nonazapirone selective serotonin 1A agonist in adults with generalized anxiety disorder: a 28-day, open-label study. Clin Ther 2008;30:9.

[56] Mathew SJ, Price RB, Mao X, Smith LP, Coplan JD, Charney DS, Shungu DC. Hippocampal N-acetylaspartate concentration and response to riluzole in generalized anxiety disorder. *Biol Psychiatry* 2008;63:891-8.

[57] Mennin DS, Heimberg RG and Turk CL. Clinical presentation and diagnostic features, 2004. In R. G. Heimberg, C. L. Turk, & D. S. Mennin (Eds.), Generalized anxiety disorder: Advances in research and practice. New York: The Guilford Press.

[58] Menza MA, Dobkin RD, Marin H. An open-label trial of aripiprazole augmentation for treatment-resistant generalized anxiety disorder. J Clin Psychopharmacol. 2007;27(2):207–210.

[59] Montgomery SA, Tobias K, Zornberg 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.

[60] Nicolini H, Bakish D, Duenas H et al. Improvement of psychic and somatic symptoms in adult patients with generalized anxiety disorder: examination from a duloxetine, venlafaxine extended-release and placebocontrolled trial. Psychological Medicine,2009; 39, 267–276.

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

[62] 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.

[63] Pittenger C, Coric V, Banasr M, Bloch M, Krystal JH, Sanacora G.Riluzole in the treatment of mood and anxiety disorders. CNS Drugs. 2008;22(9):761-86.

[64] Pohl RB, Feltner DE, Fieve RR, et al. Efficacy of pregabalin in the treatment of gener-alized anxiety disorder: double-blind, placebo-controlled comparison of BID versus TID dosing. J Clin Psychopharmacol. 2005;25(2):151–158.

[65] Pollack M. Levetiractam (Keppra) for anxiety. Curbside Consultant 2002; 1 (4): 4

[66] Pollack MH, Matthews J, Scott EL. Gabapentin as a potential treatment for anxiety disorders [letter]. Am J Psychiatry 1998;155 (7): 992-3

[67] 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.

[68] 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.

[69] Pollack MH. Refractory generalized anxiety disorder. J Clin Psychiatry 2009;70 (Suppl. 2):32-38.

[70] Power KG, Jerrom DWA, Simpson RJ. A controlled comparison of cognitive-behavio-ral therapy, diazepam and placebo in the management of generalized anxiety. Behav Psychother 1989;17: 1–14.

[71] Rapgay L, Bystritsky A, Dafter RE, Spearman M. New Strategies for Combining Mindfulness with Integrative Cognitive Behavioral Therapy for the Treatment of Generalized Anxiety Disorder. J Ration Emot Cogn Behav Ther. 2011;29(2):92-119.

[72] Rickels K, Downing R, Schweizer E, et al. Antidepressants for the treatment of gener-alized anxiety disorder: a placebo-controlled comparison of imipramine, trazodone, and diazepam. Arch Gen Psychiatry 1993; 50: 884-95

[73] Rickels K, Pollack MH, Feltner DE, et al. Pregabalin for treatment of generalized anxiety disorder: a 4-week, multicenter, double-blind, placebo-controlled trial of pre-gabalin and alprazolam. Arch Gen Psychiatry. 2005;62(9):1022–1030.

[74] Rickels K, Schweizer EE. Current pharmacotherapy of anxiety and panic. In: Meltzer HY, ed. Psychopharmacology: The Third Generation of Progress. New York, NY: Raven Press;1987:1193-1203.

[75] Roemer L, Orsillo SM, Barlow DH. Generalized anxiety disorder. In: Barlow DH, ed. Anxiety And Its Disorders. New York, NY: Guilford; 2002:477-515.

[76] Rynn M, Rüssell J, Erickson J. et al. Efficacy and safety of duloxeline in the treatment of generalized anxiety disorder: a flexible-dose, progressive-titration. placebo-con-trolled trial. Depress Anxiety 2008: 25 (3): 182-9

[77] Rynn M, Brawman-Mintzer O. Generalized anxiety disorder: acute and chronic treat-ment. CNS Spectr. 2004;9(10):716-23.

[78] Schaller JL, Thomas J, Rawlings D. Low-dose tiagabine effectiveness in anxiety disorders. MedGenMed. 2004;6(3):8.

[79] Schwartz TL, Azhar N, Husain J, et al. An open-label study of tiagabine as augmentation therapy for anxiety. Ann Clin Psychiatry. 2005;17(3):167–172.

[80] Schwartz TL. The use of tiagabine augmentation for treatment-resistant anxiety disorders: a case series. Psychopharmacol Bull. 2002;36(2):53–57.

[81] Segal ZV, Williams JMG and Teasdale JD. Mindfulness-based cognitive therapy for depression: A new approach to prevention relapse, 2002. New York: Guilford Press.

[82] Shader RI, Greenblatt DJ. Some current treatment options for symptoms of anxiety. J Clin Psychiatry. 1983;44:21-30.

[83] Simon NM, Hoge EA, Fischmann D, et al. An open-label trial of risperidone augmentation for refractory anxiety disorders. J Clin Psychiatry. 2006;67(3):381–385.

[84] Sinclair LI, Christmas DM, Hood SD, Potokar JP, Robertson A, Isaac A, Srivastava S, Nutt DJ, Davies SJ. Antidepressant-induced jitteriness/anxiety syndrome: systematic review. Br J Psychiatry. 2009;194(6):483-90.

[85] Snyderman SH, Rynn MA, Rickels K. Open-label pilot study of ziprasidone for refractory generalized anxiety disorder. J Clin Psychopharmacol. 2005;25(5):497–499.

[86] 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;28, 561-566.

[87] Wittchen HU, Zhao S, Kessler RC, et al. DSM-III-R generalized anxiety disorder in the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:355–364.

[88] Wittchen HU. Generalized anxiety disorder: prevalence, burden, and cost to society. Depress Anxiety 2002;16:162–171.

[89] Yonkers KA, Dyck IR, Warshaw MG and Keller MB. Factors predicting the clinical course of generalised anxiety disorder. Br J Psychiatry. 2000;176:544-49)

[90] Yonkers KA, Warshaw MG, Massion AO, Keller MB. Phenomenology and course of generalised anxiety disorder. Br J Psychiatry. 1996;168(3):308-13.