

Pharmaceutical Management of General Anxiety Disorder

ABSTRACT

Generalized anxiety disorder (GAD) is a mental disorder defined as excessive worrying over little things. It is one of the most common types of anxiety disorders. A study stated that 1-5% of the general population suffers from GAD. The condition affects the quality of life of a patient negatively and activities in their everyday life. In this review article, we highlighted several studies that compared combined therapy of psychotherapy and pharmacotherapy to either therapy alone, results were conflicting and differ from one study to another. provide a thorough and comprehensive review of the different approaches of GAD management, several database websites were searched for articles discussing the pharmacological management of general anxiety disorder. Clinical trials, clinical guidelines, systematic reviews, meta-analyses and review articles were all reviewed and considered for inclusion. The review emphasizes the importance of taking the decision of therapy after counseling the patient, taking into account, the cost effectiveness of the treatment, patient's symptomatology, comorbidity, medical conditions, concomitant using medications, previous trials and preference. Accordingly, thorough assessment should be done before moving to management plan, and a trial of other group or other therapies should be taken if there is no response seen. However, generalized anxiety disorder is one of the most common types of anxiety disorders. It has a lifetime prevalence around 5%, it can include intolerable cognitive, emotional and physical symptoms. Thus, GAD can adversely affect the patient's life aspects, including personal, functional, social or educational. There are options to be taken among psychotherapy, pharmacotherapy or combined therapy

Keywords: Anxiety – Pharmaceutical – Cognitive behavioral therapy - Antidepressants

1. INTRODUCTION

Generalized anxiety disorder (GAD) is a mental disorder defined as excessive worrying over little things. Because of constant and excessive worrying about everyday life, a patient experiences fear, worry, and a constant feeling of being overwhelmed. The condition affects the quality of life of a patient negatively and activities in their everyday life. [1]. Generalized anxiety disorder is one of the most common types of anxiety disorders. A study stated that 1-5% of the general population suffers from GAD [2]. In the United States (US), it was found that the lifetime prevalence among the population was 5.7%, but the 12 months prevalence rate was 3.1% [3]. GAD affects some groups of people more than others. GAD is usually more common on females than males [2]. Also, it was found that GAD affects some races less than others, for example, Asian, Latino, and Black adults have a lower risk for GAD [3]. The disorder usually starts in population who are between 18-20 years old [2]. About 77% of people who suffered from GAD were diagnosed at adolescence and only 14% of the total population asked for medical care during their teens [4]. There are some factors that might increase the risk of developing GAD, such as trauma, low socioeconomic status, family history, and other concurrent psychiatric disorder. The genetic risk of GAD ranges between 1/3-2/3 of the patients [3]. As a part of anxiety disorders, GAD has a variable age of onset and a worldwide lifetime prevalence of 4-7% [5-6]. Anxiety disorders combined are the most common mental health disorder among children and adolescents and are ranked as the sixth largest contributor to non-fatal health loss globally [7].

General anxiety disorder is one of the most prevalent disorders in Saudi Arabia. Numerous studies concluded that anxiety is a condition with a significant effect on the Saudi population; especially among females, the young population (25-34 years old), students, not-working individuals, smokers, patients with chronic diseases (Hypersensitivity, rheumatoid arthritis, hypertension, and diabetes mellitus), and depressed people [8]. A recent study showed that the prevalence of anxiety symptoms among the general Saudi population during the pandemic of COVID-19 among youth varied according to the severity, 11% had mild GAD, 55.8% moderate GAD and 8.1% had severe GAD symptoms [8]. Another study assessed the prevalence of any degree of anxiety among medical students in Saudi Arabia, and it was found to be 68%. Most anxious students had one of the following factors: females, smokers, low income, and high GBA. About 10.4% of anxious students experience it daily. Female students and those with chronic diseases had higher anxiety levels than other students [9].

Approximately half of adults diagnosed with an anxiety disorder have been diagnosed with a prior disorder, most often an anxiety disorder, before the age of 15 years [10]. Relationship with parents is a potential risk factor. A study in the literature showed that the relationship with father might play a more decisive role in the etiology of adult anxiety disorders [11]. Another study showed greater association between maladaptive parenting and GAD [12]. It was reported that parental separation increases the risk for GAD [13]. On the other hand, parental overprotection as well increases the risk for anxiety disorders [14]. Male sex consistently emerges as a risk factor for the development of anxiety disorders gathered. Females are about twice as likely as males to develop each of the anxiety disorders [15-16]. However, sex differences in prevalence, if any, are small in childhood but they increase with age [17]. Other risk factors include low socioeconomic status [15], childhood sexual abuse [18] and smoking [19]. Physical activity is known to be a protective from GAD. A study showed physical activity as a protective factor in the development of anxiety disorders in a prospective cohort study [20]. Furthermore, coping skills were a protective according to a study that was done by Trumpf [21].

The symptoms of GAD are usually comprised of sleep disturbance (difficulty falling or staying asleep, restless and/or unsatisfying sleep), autonomic hyperactivity (e.g., palpitations, dry mouth, feelings of threat and sweating); these symptoms are considered as symptoms of the anxiety syndrome rather than single independent complaints. Irritability, restlessness, gastrointestinal symptoms, easy fatigability, chronic headaches, and muscle

tension causing pain in the neck, shoulders, and back were commonly reported as well [22-24].

The occurrence of other comorbid diseases with GAD is a very common observation. Epidemiological data collected from surveys have shown that anxiety disorders can present prior to other psychiatric disorders, which can be due to the fact that many of their major risk factors are the same [25]. Furthermore, according to a survey done in the US, GAD was accompanied by another disorder in 66% of adults [26]. Another study that was published in 2018 found that across all age groups there was a significant comorbidity between GAD and major depressive disorder. [27] In addition, poorer outcomes are associated with the co-occurrence of major depressive episodes with GAD [26]. Other anxiety disorders can also present as a comorbidity of GAD. An example of that is social phobia, specific phobias, and panic disorder with the former being the most common with GAD [26]. GAD can also be seen in cases of bipolar disorder with a lifetime rates ranging from 13% to 20%. Some studies have reported that the prevalence of bipolar occurring in cases of primary anxiety disorders is low. The rates of other psychiatric conditions such as post traumatic disorder, obsessive compulsive disorder, and substance abuse may be increased in the presence of GAD [26]. Chronic pathological diseases can also be associated with GAD. A study published in 2015 have reported that diabetes is associated with higher chances of developing GAD, this could be to the overwhelming of the new diagnosis of diabetes which may cause excessive worrying to the patient [28]. Another example is inflammatory bowel disease (IBD) in which there is a higher rate of GAD development [29]. Lastly, pain syndromes and chronic unexplained pain have a strong association with GAD [26, 30].

GAD may greatly affect the patients' quality of life and may cause impairment at work due to reduced productivity and control over tasks. In a study that was conducted to compare patients with GAD and non-anxious individuals, the results showed that persons with GAD had impairment at work and home responsibilities, lower quality of life and lower self-esteem. As regard to quality of life, patients with GAD reported some aspects such as life goals, values, money, learning and relationships with friends and family [31]. The management of GAD can lower the extent of comorbid diseases and improve the patients' quality of life. This review discusses the current and updated pharmacological management of GAD.

2. MATERIAL AND METHODS

Several database websites were searched for articles discussing the pharmacological management of general anxiety disorder. The search engines used included (PubMed, Medline, Ebsco, Google scholar and Cochrane). Various key words were used for the literature search of introduction to give a comprehensive idea about GAD (General anxiety disorder, prevalence, risk factors, symptoms, associated diseases, quality of life). As regard to the pharmaceutical management of GAD, the same database websites were used for articles including clinical trials, clinical guidelines, systematic reviews, meta-analyses and review articles were all reviewed and considered for inclusion in our review. Discussion part included brief parts about non-pharmacological management of GAD like cognitive behavioral therapy. Other parts of the discussion contain detailed description of the current available pharmacological options.

3. RESULTS AND DISCUSSION

3.1 Management approaches for GAD

Since anxiety disorders in general, and general anxiety disorder (GAD) specifically, has a wide prevalence worldwide, and a significant negative impact on the affected persons, it has been important to treat them appropriately, in a way that save the patient's life from falling apart, especially that their onset take a place in the most functioning years of life (31 years old). Over the last decades, different approaches were taken to treat GAD. Many studies were done to measure and compare the efficacy of psychotherapy, pharmacotherapy and combined therapy of both.

A randomized controlled comparisons of psychopharmacological and psychological treatments for anxiety disorders done in 2007, concluded that psychotherapy and pharmacotherapy generally demonstrate about equivalent efficacy for the treatment of most anxiety and related disorders [32]. A meta-analysis **has** demonstrated the efficacy of psychological treatments in group and individual formats in patients with GAD [33]. Cognitive Behavioral Therapy (CBT) in particular has shown a significant effect in reducing GAD symptoms, it has been more effective when compared to placebo or wait-list control group. While in the studies where it was compared to pharmacotherapy, both groups showed comparable effects [34]. It usually **combines** multiple interventions, including worry exposure (which thought to be the most important ingredient), psychoeducation, problem solving and cognitive restructuring. CBT is recommended as first line psychotherapy by anxiety and depression disorders association of America (ADAA) [35]. There are several other psychotherapies, that showed some positive effects in patients with GAD, such as relaxation therapy, whether with or without spa related treatment, acceptance-based behavior therapy, meta-cognitive therapy and adjunctive mind fullness based cognitive therapy (MBCT) [33, 36-37]. However, most of the studies done to assess the effectiveness of these therapies were done on small sample sizes, whether as an independent therapy or as adjunctive therapy. Therefore, further researches on larger sample size are needed. Many patients might prefer psychotherapy rather than pharmacotherapy, especially in mild to moderate cases, one of the reasons for such preference is the believe that psychotherapy is harmless and has no side effects in comparison to pharmacotherapy, where each medication has its own side effects. Unfortunately, this is not true, psychotherapy has unwanted and adverse reactions as well, which people are not familiar with due to the limited supporting evidence. There is a possibility of perceptual bias towards positive rather than negative effects, since the psychotherapist, who is the treatment producer is considered responsible of all the negative effects [38]. The side effects of psychotherapy include, treatment failure and deterioration of symptoms, emergence of new symptoms, suicidality, occupational problems or stigmatization, changes in the social network or strains in relationships, therapy dependence, or undermining of self-efficacy [38]. Psychotherapy is not free of side effects. Negative consequences can concern not only symptoms, like an increase in anxiety, or course of illness, like enduring false memories, but also negative changes in family, occupation or general adjustment in life. Consequences like job loss or divorce can be lasting, costly and detrimental for the patient and his/her environment" [38]. However, due to the limited data, this conclusion is based on psychotherapy for patients with post-traumatic stress disorders and substance abuse disorders.

3.2 Pharmacotherapy

3.2.1 Antidepressants

3.2.1.1 Selective serotonin re-uptake inhibitors (SSRI)

Among SSRI medications, only Paroxetine and Escitalopram are food and drug administration (FDA) approved to treat GAD, and **both** take a place in the first line pharmacotherapy in the Canadian Guideline and ADAA [35, 39]. Sertraline although not approved by FDA to treat GAD specifically, yet it is considered first line treatment by the Canadian guidelines, ADAA and National Institute for Health and Care Excellence (NICE) guidelines [35, 39, 40]. Fluoxetine also is considered a first line pharmacotherapy by ADAA [35], and third line pharmacotherapy in Canadian guidelines [39]. In general, all SSRIs showed a good effectiveness in treating GAD, supported by strong **evidence** and large RCTs, when compared to placebo, with a preference of one over another according to the patients' symptomatology, medical condition and other concomitant using drugs.

3.2.1.2 Serotonin-noradrenaline re-uptake inhibitors (SNRI)

Evidence from RCTs support the use of Venlafaxine XR and Duloxetine, which are FDA approved, and considered first line treatment in both ADAA and Canadian guideline [35, 39]. They are usually well **tolerable and** advised to be prescribed when patient does not have sufficient response to SSRI.

3.2.1.3 Side effects of SSRI and SNRI

The most common side effects seen with SSRIs and SNRIs include headache, irritability, gastrointestinal complaints, insomnia, sexual dysfunction, weight gain, increased anxiety, drowsiness, and tremor [41-42]. Most of these side effects are transient, that occur and resolve in the first two weeks of starting the medication, except for sexual dysfunction and weight gain, which might persist along the duration of treatment [41]. Knowing and identifying these side effects is important, as experiencing any of them might be the reason of poor compliance or abrupt discontinuation, which therefore, can lead to a discontinuation syndrome with gastrointestinal, psychiatric and vasomotor symptoms [43]. Other serious side effects include increased risk of upper gastrointestinal bleeding, particularly when used in combination with non-steroidal anti-inflammatory drugs (NSAIDs) **like Ibuprofen** [42]. SSRI also showed risk of hyponatremia [44], low bone mineral density [45], and subsequently increased risk of fractures [46]. Not to mention that Venlafaxine has a dose dependent effect in increasing the blood pressure [47], therefore, blood pressure should be monitored carefully. Moreover, risk of suicidal ideation and behavior in children and adolescents has been required by Health Canada and the US Food and Drug Administration (FDA) to be included as warning in the antidepressants [48]. The risk of suicide is increased in pediatric, and not in adults, in fact it may be decreased in adults [49]. However, careful monitoring for evidence of self-harming or suicidal thoughts or behaviors is important in both adult and pediatric patients [39]. To conclude, side effects of SSRIs and SNRIs should not significantly affect the decision making when prescribing a medication for GAD patients, as long as they are safe and suitable for them. It is worth mentioning, that these two groups are preferable over the other antidepressants, considering their safety and tolerability [50]. In addition to the fact of having **fewer** anticholinergic effects, toxicity, lethality, psychomotor and cognitive impairment compared to other classes of antidepressants [41].

3.2.1.4 Tricyclic Antidepressants (TCA)

Imipramine is indicated as a second line pharmacotherapy in Canadian guideline, as it showed a superior effect in treating GAD compared to placebo, and a similar effect to Paroxetine [51]. Side effects of imipramine include weight gain and anticholinergic effects, such as blurred vision, dry mouth, urinary retention and constipation, as well as anticholinergic induced cognitive impairment. Another concern regarding Imipramine is its toxicity in case of **overdose**. Therefore, TCA should not be prescribed if the patient has risk of suicide [51].

3.2.1.5 Trazodone

Trazodone (a serotonin antagonist and re-uptake inhibitor) and Mirtazapine (a noradrenaline and specific serotonergic antidepressant) are not FDA approved for GAD, yet they are recommended by Canadian Guidelines as a third line therapy [39]. Both medications have sedative effects, which can target the insomnia in certain patients, they are also less likely than SSRIs to cause sexual dysfunction [50]. In fact, Trazodone can be prescribed to manage erectile dysfunction, therefore, it has a risk of priapism, which the patient should be educated about. **Moreover**, it can cause significant orthostatic hypotension. While Mirtazapine is associated with increased appetite and weight gain [50].

3.2.2 Buspirone

Buspirone is chemically distinct from other psychotropic agents. It acts as an agonist or partial agonist on serotonin receptor (5-HT_{1A}) and acting as both an agonist and an antagonist on dopamine receptor (D). Although it is commonly prescribed for depression, Buspirone is only approved for GAD, as it has the anxiolytic effect of Benzodiazepine without possessing the anticonvulsant and muscle relaxant effect, it also showed no effect in other anxiety disorders, such as panic disorder, social phobia or **obsessive-compulsive** disorder (OCD). It is considered as second line therapy for GAD by both ADAA and Canadian guideline. It is less likely than SSRIs and SNRIs to cause weight gain or sexual dysfunction, which make it a preferable option for certain patients. Its common side effects include headache, nausea and dizziness [35, 39].

3.2.3 Benzodiazepine

GAD and other anxiety disorders are indications for Benzodiazepine, as they may be useful as adjunctive therapy early in treatment course, particularly for acute anxiety or agitation, to help patients in times of acute crises, or while waiting for onset of adequate efficacy of SSRIs or other antidepressants [52]. Alprazolam, Bromazepam, Diazepam and Lorazepam showed efficacy as treatment of GAD, and they are taking place in the second line therapy of Canadian guideline [39], while they are only considered as short-term crisis management in NICE guideline for GAD. However, considering their risk of dependency and other side effects, they should be prescribed as adjunctive therapy for short-term use [52]. Side effects include primarily sedation, fatigue, ataxia and weakness. Such effects may put the older patient at risk of fall and fractures [53]. Memory impairment has been identified as a side effect as well, especially in high-dose or high-potency benzodiazepines, particularly in older people [42]. Another concern regarding benzodiazepines is the risk of withdrawal reactions, rebound, and dependence, particularly with short and intermediate acting agents [54]. Therefore, they should be used with caution in patients who have substance use disorder [42].

3.2.4 Antipsychotics

Quetiapine is a second generation antipsychotic (serotonin- dopamine antagonist), it is not FDA approved for GAD, yet it showed to be more effective than placebo and may have similar effect to antidepressant in treating anxiety symptoms [55]. Thereby, it is considered as second line mono therapy and third line adjunctive therapy in Canadian guideline [39]. There is no sufficient data regarding other second generation antipsychotics, such as Aripiprazole, Olanzapine and Risperidone in treating GAD as mono therapy [55], they are considered as third line adjunctive therapy in Canadian guideline [39]. Antipsychotics have their own side effects profile, which include metabolic effect (e.g., weight gain, diabetes, increased lipid profile), extrapyramidal side effects (e.g., dystonia, tardive dyskinesia), hematological disturbance (e.g., neutropenia), hormonal disturbance (e.g., high prolactin level) and risk of QTc prolongation. Thus, careful assessment of patient's condition before prescribing and careful monitoring while using, should be done [56].

3.2.5 Non psychotropics

Pregabalin is an anticonvulsant that showed to be safe, tolerable and superior to placebo in treating GAD somatic and emotional symptoms in several RCTs [57-58], which make it a first line therapy in Canadian Guideline [39]. According to NICE guideline, it should be considered when the patient cannot tolerate SSRIs or SNRIs [40]. However, this indication is not FDA approved. As Pregabalin is a class C controlled substance and has a risk of misuse, careful evaluation of patient's past and current substance use should be done, as well as the observation of signs of dependence and abuse [40]. Hydroxyzine is an antagonist of histamine H1 receptor, that showed efficacy and safety in treating GAD and could be a safe alternative to benzodiazepine [59]. It is FDA approved for anxiety and considered a second line therapy in Canadian guideline [39]. Its side effects include daytime sleepiness and a negative effect on the mood [60].

3.3 Combined therapy

Several studies compared combined therapy of psychotherapy and pharmacotherapy to either therapy alone, results were conflicting and differ from one study to another. One meta-analysis concluded that "medication may be a useful strategy for enhancing acute-phase CBT outcomes, especially for panic disorder and generalized anxiety disorder. Findings to date do not support the use of this strategy for maximizing long-term CBT outcome" [61]. Unlike major depressive disorder, currently, no well-established evidence supports the routine combination of CBT and pharmacotherapy for GAD. However, if the patient did not show sufficient response to psychotherapy, a trial of pharmacotherapy should be considered, and vice versa.

3.4 Alternative therapies

Some GAD patients might tend to self-medicate themselves by herbal preparations, one of the common herbs used by people for anxiety symptoms is passionflower, which showed an improvement of anxiety symptoms to some extent [62]. However, data regarding alternative treatment for GAD are limited and preliminary to conclude regarding its effectiveness.

3.5 Treatment of resistant GAD

Resistant or refractory GAD is defined as failure to respond to at least one trial of antidepressant therapy at adequate dose and duration [63]. In such cases, if patient failed to respond to a first line treatment, he could be switched to another first line treatment, preferably from other category, e.g., if there is no response to SSRI, then SNRI should be considered. If different first line treatments failed, second and third line should be considered. Some cases might be refractory or still experiencing significant anxiety symptoms while using a mono therapy, thereby, adjunctive therapy is indicated. This could be GABA analogue agent, such as Pregabalin, as mentioned above, several RCTs concluded that Pregabalin as mono therapy has a good efficacy in treating different anxiety symptoms. It also showed to be effective as adjunctive therapy to antidepressants, in treating patients who have partial or poor response to antidepressant alone [63-64], and it is recommended as a second line adjunctive therapy by Canadian guideline [39]. However, several points should be noticed before prescribing pregabalin, first, if the patient has preexisting respiratory risk, pregabalin might cause further serious breathing difficulties, as warned by FDA [65]. Another point of consideration is the risk of dependence and misuse. Another class of medication that could be used as adjunctive therapy are second generation antipsychotics, although the results of related RCTs are inconsistent, yet few studies reported some efficacy of adding a small dose of Quetiapine, Aripiprazole, Olanzapine or Risperidone to antidepressant, in order to improve the anxiety outcomes [63, 66-67]. Aforementioned antipsychotics are considered third line adjunctive therapy by Canadian guidelines, except for Quetiapine, it is either second line mono therapy or second line adjunctive therapy [39].

4. CONCLUSION

GAD has a lifetime prevalence around 5%, it can include intolerable cognitive, emotional and physical symptoms, thus, can adversely affect the patient's life aspects, including personal, functional, social or educational. Therefore, a proper management of such disorder is crucial for the patient to maintain their functionality. There are options to be taken among psychotherapy, pharmacotherapy or combined therapy. Decision of therapy should be dual between the physician and the patient, taking into account, the cost effectiveness of the treatment, patient's symptomatology, comorbidity, medical conditions, concomitant using medications, previous trials and preference. Accordingly, thorough assessment should be done before moving to management plan, and a trial of other group or other therapy should be taken if there is no response seen. Careful psychoeducation, evaluation of symptoms and functionality improvement should be done, in addition to monitoring of possible side effects. Moreover, physicians should keep themselves updated regarding the recent trials and side effects reported.

Abbreviations:

- GAD: generalized anxiety disorder.
- CBT: cognitive behavioral therapy.
- ADAA: anxiety and depression disorders association of America.
- MBCT: mind fullness based cognitive therapy.
- SSRI: Selective serotonin re-uptake inhibitors.
- FDA: food and drug administration.
- NICE: National Institute for Health and Care Excellence.
- RCT: randomized controlled trial.
- SNRI: Serotonin-noradrenaline re-uptake inhibitors.

- NSAIDs: non-steroidal anti-inflammatory drugs.
- TCA: Tricyclic Antidepressants.
- OCD: obsessive compulsive disorder.

UNDER PEER REVIEW

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