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Review Article

Generalized Anxiety Disorder in Adults

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Abstract

Introduction: Generalized anxiety disorder (GAD) is commonly encountered psychiatric condition. It is one of the most common psychiatric disorders leading to seek of medical care. About 5 - 12 percent of the general population are affected in the United States alone. Patients with GAD have excessive, persistent, and hard to control worrying; leading to significant distress. The symptoms occur on more days than not for at least six months. Generalized anxiety disorder is associated with comorbidity in most patients. In the United State, it is estimated that 66 percent of individuals with GAD had at least one concurrent disorder. Commonly co-occurred conditions include social phobia, specific phobia, and panic disorder.

Aim of Work: In this review, we will discuss different angle of generalized anxiety disorder including clinical manifestation, assessment and diagnosis, and commonly used medication

Methodology: A comprehensive and systematic search was conducted regarding generalized anxiety disorder in adults, epidemiology, clinical picture and managements. PubMed search engine and Google Scholar search were the mainly used database for search process. All relevant available and accessible articles of all types were reviewed and included.

Conclusion: Excessive and persistent worrying is considered as the pathognomic feature of generalized anxiety disorder (GAD). However, most patients present with other symptoms as autonomic hyperactivity, muscle tension, and/or hyperarousal. Careful history and evaluation is the backbone of GAD diagnosis. This include symptoms as well as co-occurring medical conditions such as psychiatric disorders. For screening, the generalized anxiety disorder seven-item (GAD-7) scale can be used. The scale has acceptable reliability and validity. Nevertheless, the scale could be used for follow-up as it has a good sensitivity to changes over time. Another instrument is Hospital Anxiety and Depression Scale (HADS).

Serotonin reuptake inhibitors (SRIs) are widely used in the setting of generalized anxiety disorder (GAD) managements. Benzodiazepines is evidenced to be effective in the treatment of GAD. They have the advantage of rapid onset. Buspirone agents have been shown to be effective in reducing symptoms of anxiety

Keywords: *Hospital Anxiety and Depression Scale (HADS); Serotonin Reuptake Inhibitors (SRIs); Generalized Anxiety Disorder (GAD)*

Introduction

Generalized anxiety disorder (GAD) is commonly encountered psychiatric condition as well as in the community. It is one of the most common psychiatric disorders leading to seek of medical care [1]. In epidemiological studies, about 5 - 12 percent of the general population are affected in the United States alone [2-4]. In Europe, a review found fewer prevalence; about 4 - 6 percent [5,6]. Women are affected twice as men [2-4]. It is also the most common mental problem in elderly people [5,7].

Patients with GAD have excessive, persistent, and hard to control worrying; leading to significant distress. The symptoms occur on more days than not for at least six months. Other manifestations include apprehensiveness, irritability, and increased fatigue and muscular tension. Similar to major depression, GAD may cause significant degree of functional impairment [8,9]. Generalized anxiety disorder is associated with comorbidity in most patients [5]. In the United State, it is estimated that 66 percent of individuals with GAD had at least one concurrent disorder [3]. Commonly co-occurred conditions include social phobia, specific phobia, and panic disorder [3,10].

Effective treatments for generalized anxiety disorder include cognitive-behavioral therapy (CBT) and medications. Commonly used drugs are selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).

In this review, we will discuss different angle of generalized anxiety disorder including clinical manifestation, assessment and diagnosis, and commonly used medication.

Methodology

A comprehensive and systematic search was conducted regarding generalized anxiety disorder in adults, epidemiology, clinical picture and managements. PubMed search engine and Google Scholar search were the mainly used database for search process. All relevant available and accessible articles of all types were reviewed and included. Studies about cognitive and behavioral therapy was not analyzed as this review is focusing on the pharmacological management of the disease. In addition, other types of anxiety disorder and GAD in children were not discussed as well. The term used in search were generalized anxiety disorder, adults, presentation, and pharmacologic management.

Clinical picture

Excessive and persistent worrying is considered as the pathognomic feature of generalized anxiety disorder (GAD). However, most patients present with other symptoms as autonomic hyperactivity, muscle tension, and/or hyperarousal. Poor sleep and fatigue, headaches, neck and shoulder pain are also common complaint.

Few evidence is available about the nature of worrying. GAD patients have reported a greater attack of worries, but their concerns about health, family and relationships, work and finances are similar to normal controls [11]. It is suggested that patients with GAD may differ by greater worry about trivial problems [11]. Patients with GAD admit that they excessively worry about minor situation, denial of such worries should rule out the diagnosis [12].

Generalized anxiety disorder (GAD) is usually of gradual onset, chronic course, fluctuating severity, and relapsing after recovery [13]. In a cohort study, approximately 60 percent of patients with GAD recovered over 12 years, but 50 percent of recovered patients subsequently relapsed during the follow-up period [14].

The gradual onset of GAD is slower than some anxiety disorders [13]. Some symptoms may appear before the age of 20 years [15]. Early age of onset is associated with prolonged illness and higher prevalence of comorbid mental disorders; particularly depression [16]. On the other hand, late-onset is usually associated with certain demographic, clinical, and environmental risk factors [17,18]. In a prospective study of adults aged 65 years or elder, 8.4 percent experienced an episode of GAD during the subsequent 12 years [18]. The

majority of diagnosed patients had never experienced such symptoms before. Factors that are associated with this late-onset GAD include female, poverty, chronic physical and/or mental disorders, and recent undesirable life events as parental loss or separation.

Assessment and diagnosis

Careful history and evaluation is the backbone of GAD diagnosis. This include symptoms as well as co-occurring medical conditions such as psychiatric disorders. Those who have findings suggesting a possible physical cause of anxiety symptoms should undergo a physical and laboratory studies to rule out organic causes of anxiety. Psychiatric evaluation should also focus on the history of substance abuse, medical history of possible medical condition or medication side effects, psychiatric history of the family, and the history of recent stressful undesired life events.

For screening, the generalized anxiety disorder seven-item (GAD-7) scale can be used. The scale has acceptable reliability and validity [19]. Nevertheless, the scale could be used for follow-up as it has a good sensitivity to changes over time [20]. Another instrument is Hospital Anxiety and Depression Scale (HADS). HADS is widely used instruments to assess the severity of symptoms of anxiety and depression. It is sensitive and specific in identifying pathological anxiety and could be used to distinguish symptoms of GAD from anxiety caused by other medical conditions [21].

The diagnosis of GAD differ among adults and children. In adults, DSM-5 has set the following diagnostic criteria to diagnose generalized anxiety disorder [22]: (1) anxiety and worry occurring more days than not for at least six months; (2) difficulty to control the worry by the patient; (3) the presence of at least 3 of the following 6 (Restlessness, irritability, easily fatigued, difficulty concentrating, muscle tension and/or sleep disturbance; (4) clinically significant impairment caused by the symptoms; (5) symptoms not explained by physiological effects; (6) Symptoms are not explained by another mental. Because the majority of the anxiety symptoms are not specific to GAD, it is important to exclude the other anxiety disorders before making the diagnosis.

GAD in elderly is challenging to diagnose due to the common co-occurrence of physical illnesses, chronic insomnia, cognitive impairment, and the side effects of prescribed medication.

Other mental condition to be differentiated from GAD include depression. The two conditions have many similar characteristics as gradual onset, protracted course, prominent dysphoria and anxiety symptoms. Hence, it is of great challenge to differentiate primary GAD with secondary depressive symptoms from major depressive disorder or persistent depressive disorder.

Another condition to be bore in mind as a differential diagnosis is hypochondriasis. In both conditions the patients may have concern about medically unexplained symptoms, however, GAD is usually characterized by worries about multiple different things, while patients with hypochondriasis worry principally about their health. Panic attacks can occur in GAD, arising out of uncontrollable worry. However, unexpected panic attacks is unusual in GAD in contrast to panic disorder. Patients with panic disorder tend to have episodic attacks of thoughts about life-threatening life conditions, whereas patients with GAD usually focus on general chronic matter. Generalized anxiety disorder should also be distinguished from adjustment disorder. In the latter, worries and other symptoms are encountered within three months of known stressors.

Managements

Generalized anxiety disorder can be effectively managed with cognitive-behavioral therapy (CBT), medication, or a combination of the two modalities. In this review, however, we will focus on the medication could be used to manage GAD.

Serotonin reuptake inhibitors (SRIs) include Selective-serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), these agents are widely used in the setting of generalized anxiety disorder (GAD) managements. SSRIs can be very

effective choice in managing co-occurring GAD and depression. Few data are available about direct comparison between different types of SRIs and SSRIS versus SNRIs for GAD [23,24]. Clinical trials have generally demonstrated that all SRIs may have the same degree of effectiveness with approximately 60 to 70 percent response rate versus 40 percent for placebo. Hence, the choice between types of SRIs agents could be determined by side effect profile, drug-drug interactions, and/or patient treatment history/preference.

SSRIs agents that have been shown by randomized clinical trials to be effective for GAD include paroxetine [25-27], sertraline [28,29], citalopram, and escitalopram [30-32]. Other less powerful trials and experts suggest that other SSRIs such as fluoxetine and fluvoxamine are also effective for GAD management. The number need to treat (NNT) as calculated by meta-analysis was 5; this means that 1 of 5 patients treated with SSRIs will achieve the clinical response compared with placebo [33]. In the largest randomized control trial (RCT) compared two dosed of paroxetine (20 and 40 mg/day) with placebo, both doses resulted in a greater reduction of anxiety symptoms. Similarly, was the rates of remission for patients receiving either dose of paroxetine compared with placebo (30, 36 and 20 percent of remission respectively) [26]. It is suggested that the efficacy of SSRIs may be maintained for at least six months [34]. Some experts believe that the efficacy is much extended than this.

SSRIs have many side effects as they may interfere with the quality of life (QoL) and medication adherence. The clinician plays essential role in recognizing and managing these side effect as early as they appears. The side effects vary among individuals hence the term side effect profile was given for each individual. However, common side effects include sexual dysfunction, nausea, diarrhea, insomnia, and withdrawal on discontinuation. SSRIs may interact with many other agents and may cause weight gain and agitation.

Serotonin-norepinephrine reuptake inhibitors (SNRIs) produce their effects by inhibiting serotonin and norepinephrine reuptake. Regarding their usage in GAD, it is acceptable to say that they are as effective as SSRIs. SNRIs also have the same pattern of tolerability and hence their use follows the same general guidelines. Venlafaxine (extended-release XR SNRIs) [35-37] and duloxetine [38,39] have been demonstrated to be efficacious in patients with GAD by many RCTs. In one trial including 541 outpatients with GAD, venlafaxine XR was more effective than placebo on all primary outcome measures at 8 and 24 weeks [40]. Additionally, four clinical trials have examined duloxetine and found it effective in 60 and 120 mg daily doses though it is typically started at 30 mg per day. Longer follow-up showed similar results for up to 6 months, however, experts believes the efficacy is much of a longer-term [38,41]. Nausea, constipation, dizziness, insomnia, sedation, and sweating are common side effects of all SNRIs. Venlafaxine may slightly increase blood pressure. Rates of 3 to 7 percent increase have been seen at daily doses of 100 - 300 mg; higher increase by about 13 percent was associated with doses higher than 300 mg/day [42].

Benzodiazepines is evidenced to be effective in the treatment of generalized anxiety disorder (GAD). They have the advantage decreasing emotional and somatic symptoms within minutes to hours, depending on the specific medication [43,44]. However, due to risks of dependence and tolerance a decline in their use has occurred [25,36]. It is estimated by a large observational study that between 1989 - 1991 and 1996, use of benzodiazepine in treating GAD was declined in the US with concomitant increase in antidepressant use [45]. Benzodiazepines should be used with caution as all controlled substance, and should be avoided in patients with a history of a substance misuse or substance use disorders. They may be used for acute, maintenance, or long-term treatment of GAD, either as monotherapy or, more commonly, as an adjunct to antidepressant treatment. Due its rapid onset of action, benzodiazepines are usually used for acute management of anxiety and worry in GAD patients during the period before selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors take effect. In addition, adjunct use of benzodiazepines has the advantage of counteracting the initial agitation often caused by the SSRI. Once the patient responds to the SSRI, the benzodiazepine can be tapered off gradually. Antidepressants are preferred over benzodiazepines in patients with concomitant depression because antidepressants are effective treatments for both conditions. In patients with chronic GAD without a history of a substance use disorder can be managed by long-term, low-dose of benzodiazepine if antidepressants are ineffective or poorly tolerated [46]. Some patients respond well to chronic

treatment with benzodiazepines, do not develop tolerance to their anxiolytic effects. Patients who develop rapid tolerance, increasing benzodiazepine doses against medical advice, or exhibit withdrawal symptoms between doses are not good candidates for chronic benzodiazepine treatment.

A meta-analysis have included 23 trials that met their inclusion criteria; benzodiazepine was shown to be efficacious in the treatment of GAD compared with placebo. It is suggested by another meta-analysis of three clinical trials that efficacy of benzodiazepines is comparable to SSRIs and SNRIs antidepressant. One major limitation of these trials is that they were conducted in patients diagnosed with the previous DSM-III definition of GAD, an old definition that differs significantly from the newly used DSM-5. In our clinical experience, however, the efficacy of benzodiazepines in patients diagnosed with DSM-5 GAD is evident within minutes of taking a more-rapid onset benzodiazepine.

Benzodiazepines exert their main effect via central nervous system GABA receptors, increasing the effects of endogenous GABA, the main inhibitory neurotransmitter. GABA receptors are divided into three subtypes, A, B, and C receptors. Type A receptors are composed of five subunits that together form the chloride channel, which primarily mediates neuronal excitability (seizures), rapid mood changes, clinical anxiety, and sleep. GABAB receptors mediate memory, mood, and analgesia. The role of the GABAC receptors remains unclear [47]. Flumazenil is a benzodiazepine antagonist that interacts with type A GABA receptors [48] and is used clinically to rapidly reverse the effects of benzodiazepine overdoses [49].

Benzodiazepines classes have same general effect however, unique properties of individual benzodiazepines have clinical significance. Pharmacologic differences between classes include the rapidity of onset (distributional half-life), persistence of active drug and/or metabolite in the body (elimination half-life), major metabolic breakdown pathways (conjugation versus oxidation), and specific molecular structure [49,50]. In addition, elimination half-life of a benzodiazepine or its active metabolite from the body determine the timing of withdrawal onset in patients who have used benzodiazepines every day for prolonged periods. Benzodiazepines with shorter elimination half-lives (alprazolam, lorazepam, and oxazepam) are more likely to produce acute withdrawal on abrupt cessation after prolonged use. Benzodiazepines with longer elimination half-lives (clorazepate, diazepam, and clonazepam) usually produce more delayed and relatively attenuated withdrawal symptoms.

Side effects of benzodiazepines include psychomotor impairment, amnesia, dependence and withdrawal symptoms after long-term treatment and rebound anxiety after short-term treatment [51]. Withdrawal and cognitive or learning impairment are more likely for persons taking higher doses. Tapering off benzodiazepines should be done very slowly, at approximately a 10 percent dose reduction every 1 - 2 weeks. It is the clinician role to monitor the patient for symptoms of benzodiazepine withdrawal or relapse of GAD and slow the rate of dose reduction accordingly. Early signs of withdrawal include anxiety, dysphoria, and tremor; advanced manifestations include perceptual disturbances, psychosis, and seizures.

Buspirone agents (azapirone buspirone) have been shown to be effective in reducing symptoms of anxiety in patients with generalized anxiety disorder (GAD) by clinical trials; offering similar efficacy to benzodiazepines without the risk of dependence. The mechanism of action of buspirone is believed to be through the serotonergic system via blockade of 5HT1A autoreceptors. One trial has compared buspirone with placebo in 44 patients with GAD after 5 weeks of lorazepam (benzodiazepine), with tapering off of the benzodiazepine; buspirone was more effective than placebo, similarly effective to lorazepam, and had a fewer side effects [52]. In a systematic review and meta-analysis of 8 trials involving patients with GAD; buspirone effectively reduced anxiety symptoms compared with placebo [53].

One drawback of buspirone is longer onset of action compared benzodiazepine. Similar to the antidepressant, buspirone time to action may take up to 4 weeks. Some experts believe that buspirone is weaker anxiolytic than benzodiazepines. These factors have limited its use to treat GAD by psychiatrists compared in favor of SSRIs, though it remains a popular treatment for GAD among primary care

practitioners. Typical side effects can include insomnia, agitation, and nausea. Buspirone should not be used as monotherapy in case of concomitant depression.

Conclusion

Generalized anxiety disorder (GAD) is commonly encountered psychiatric condition**.** It is one of the most common psychiatric disorders leading to seek of medical care. About 5 - 12 percent of the general population are affected in the United States alone**.** Patients with GAD have excessive, persistent and hard to control worrying; leading to significant distress. The symptoms occur on more days than not for at least six months. Generalized anxiety disorder is associated with comorbidity in most patients. In the United State, it is estimated that 66 percent of individuals with GAD had at least one concurrent disorder. Commonly co-occurred conditions include social phobia, specific phobia, and panic disorder.

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