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SPECIAL ARTICLE

Brazilian Psychiatric Association treatment guidelines for generalized anxiety disorder: perspectives on pharmacological and psychotherapeutic approaches

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Generalized anxiety disorder is a highly prevalent mental disorder. Previous data indicate that more than 18 million Brazilians suffer from this condition. Traditionally, generalized anxiety disorder has been considered a mild mental health disorder, despite its links to lower life expectancy, cardiovascular disease, and suicide. The aim of this article is to combine elements of systematic and critical reviews to produce a synthesis of the best evidence about generalized anxiety disorder treatment. Systematic reviews, meta-analyses, and randomized controlled trials were included. The descriptor used in the search was "generalized anxiety disorder," which resulted in 4,860 articles and seven other studies, of which 59 were selected. Antidepressants and benzodiazepines were indicated, as was pregabalin, and atypical antipsychotics, such as quetiapine, have been studied. Individual cognitive behavior therapy (third wave) has proven effective. There is extensive literature on many effective treatments for generalized anxiety disorder. The present review summarizes the therapeutic possibilities, emphasizing those available in Brazil. Further studies are needed to compare other available medications, assess psychotherapies and new treatments in greater depth, as well as to assess the ideal duration of therapy.
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Keywords: Generalized anxiety disorder; mental health; anxiety disorders; treatment

Introduction

Anxiety is a normal response to stressful situations, but it is diagnosed as a pathological problem when it becomes severe and uncontrollable. Generalized anxiety disorder (GAD) is a group of anxiety or fear-related disorders characterized by persistent anxiety symptoms lasting $\geqslant$ 6 months, manifesting as general apprehension (i.e., "free-floating anxiety") or excessive worry about routine activities.[1,2] Most often, anxiety is focused on academic or professional performance, family, health, finances, school or work, and can involve additional symptoms, such as muscle tension, restlessness, sympathetic autonomic hyperactivity, nervousness, difficulty maintaining concentration, irritability, fatigue, and sleep disturbances.[1,2] These symptoms are neither a sign of another health condition nor the result of a chemical or drug that affects the central nervous system. GAD may co-occur with other mental illnesses, including different forms of anxiety, unipolar depression, drug use disorders, behavior disorder, psychosis, and neurodevelopmental and neurocognitive abnormalities.[1,2]

The overall GAD prevalence has been reported at 4.5%, being lower in low- and middle-income countries (2.8%) than high-income countries (5.3%); 34.6% of respondents with lifetime GAD reported receiving

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treatment, with lower proportions in low- and middle-income countries (19.2%) than high-income countries (38.4%). The World Health Organization considers GAD a public health issue in Brazil. GAD affects 18 million Brazilians, or 9.3% of the population. Between 55 and 60% of GAD patients are women.[3] Anxiety symptoms are also a risk factor for myocardial infarction and other illnesses.[4] Additionally, there is a significant correlation between GAD and suicidal behavior.[5]

Previous guidelines on GAD treatment include Hurtado et al. (Spain, 2020),[6] Katzman et al. (Canada, 2014),[7] and by Bandelow et al.[8] (Germany, 2014). In 2008, the Brazilian Psychiatric Association published general guidelines on anxiety disorders, including GAD, in association with the Associação Médica Brasileira and the Conselho Federal de Medicina.[9]

Due to the disorder's importance in Brazil and the availability of several treatment options with varying efficacy and side effects, there is a need for evidence-based GAD management recommendations tailored for Brazil. Thus, the purpose of this guideline is to evaluate evidence on GAD therapies that target the Brazilian context.

Methods

Search strategy (identification)

We used the PICO (''patient/population,'' ''intervention/exposure,'' ''control/comparison,'' and ''result'') search strategy to identify studies for inclusion. Men, women, and children with GAD (participants) who were treated with pharmacotherapy or psychotherapy (interventions), using different comparators (placebo or other interventions), were eligible for inclusion. The outcome was a reduction in anxiety symptoms. MEDLINE (via PubMed), SciELO, and the Cochrane Database of Systematic Reviews were searched for relevant articles. No language or time restrictions were made. Non-systematic reviews or government documents were used if the data were essential for answering the main questions. Case reports, case series, and editorials were excluded, as were studies with mixed samples. Studies with a high risk of bias that impaired interpretation of the results were also excluded.

Keywords were determined using Medical Subject Headings in PubMed. We searched for articles published in any language using the keywords ''generalized anxiety disorder'' AND ''treatment,'' which resulted in 4,860 articles and another seven studies. We used efficacy (i.e., symptom reduction) as the main outcome. We removed the publication time criterion, accepting older studies in order to assess important treatment strategies not addressed in more recent publications. Other publications were used to support the Introduction, Methods, and Discussion. This process was performed by two authors (ABP and AFP). In case of disagreement, a third party (LR) performed a new evaluation.

We included meta-analyses or systematic reviews that analyzed randomized clinical trials focusing on GAD treatment among male and female patients. We used RCT and other study types only when there was inconclusive data from meta-analyses or systematic reviews. The exclusion criteria were observational studies, case reports and series, editorials, non-systematic reviews, studies with fewer than 20 participants, insufficient data, and poor statistical analysis, as well as studies with selection bias, insufficient sample size, statistical bias, or risk of bias in the synthesis or the review that compromised interpretation of the data. Studies with high or unclear bias according to Risk of Bias VISualisation (for systematic reviews)[10-12] and the Cochrane Bias Risk Assessment (RoB 2) tool[12-14] were also excluded.

Information sources

MEDLINE (via PubMed), SciELO, and the Cochrane Database of Systematic Reviews were searched.

Selection criteria (screening)

The selection process was performed independently by two reviewers (ABP and AFP) using the Rayyan (https://www.rayyan.ai) selection platform (http://www.rayyan.ai). There were some difficulties evaluating the results, especially assesseing GAD when diagnosed using different sets of criteria, assessing and monitoring GAD in different contexts with different criteria and instruments, and some studies analyzed interventions in a small number of patients. As a result, the following criteria were established: 1) GAD studies in children, adolescents, adults, or older adults; 2) male or female samples only; and 3) objective response assessment, either according to symptom reduction or an objective scale. Of the 438 initially selected abstracts, 323 were rejected, leaving 155 reports for retrieval (Figure 1 presents the study selection flowchart).

Data collection process (eligibility)

ABP and AFP analyzed 52 full-text articles and another seven manuscripts for eligibility. The selected articles were read in full; only those fulfilling the inclusion/exclusion criteria and without significant bias were included.

Data items (outcomes)

The main outcome was treatment efficacy (symptom reduction $\geqslant$ 50% according to the scale used during treatment). The most common instrument was the Hamilton Anxiety Scale in adults and older adults, with post-treatment score reduction being the response criterion. Other instruments included the Hospital Anxiety and Depression Scale and the Clinical Global Impression Severity Scale. Several scales were used for children, including the Pediatric Anxiety Rating Scale, the Hamilton Anxiety Scale, the Social Anxiety Scale for Children, the Social Phobia and Anxiety Inventory, and the Kiddie Schedule for Affective Disorders and Schizophrenia.

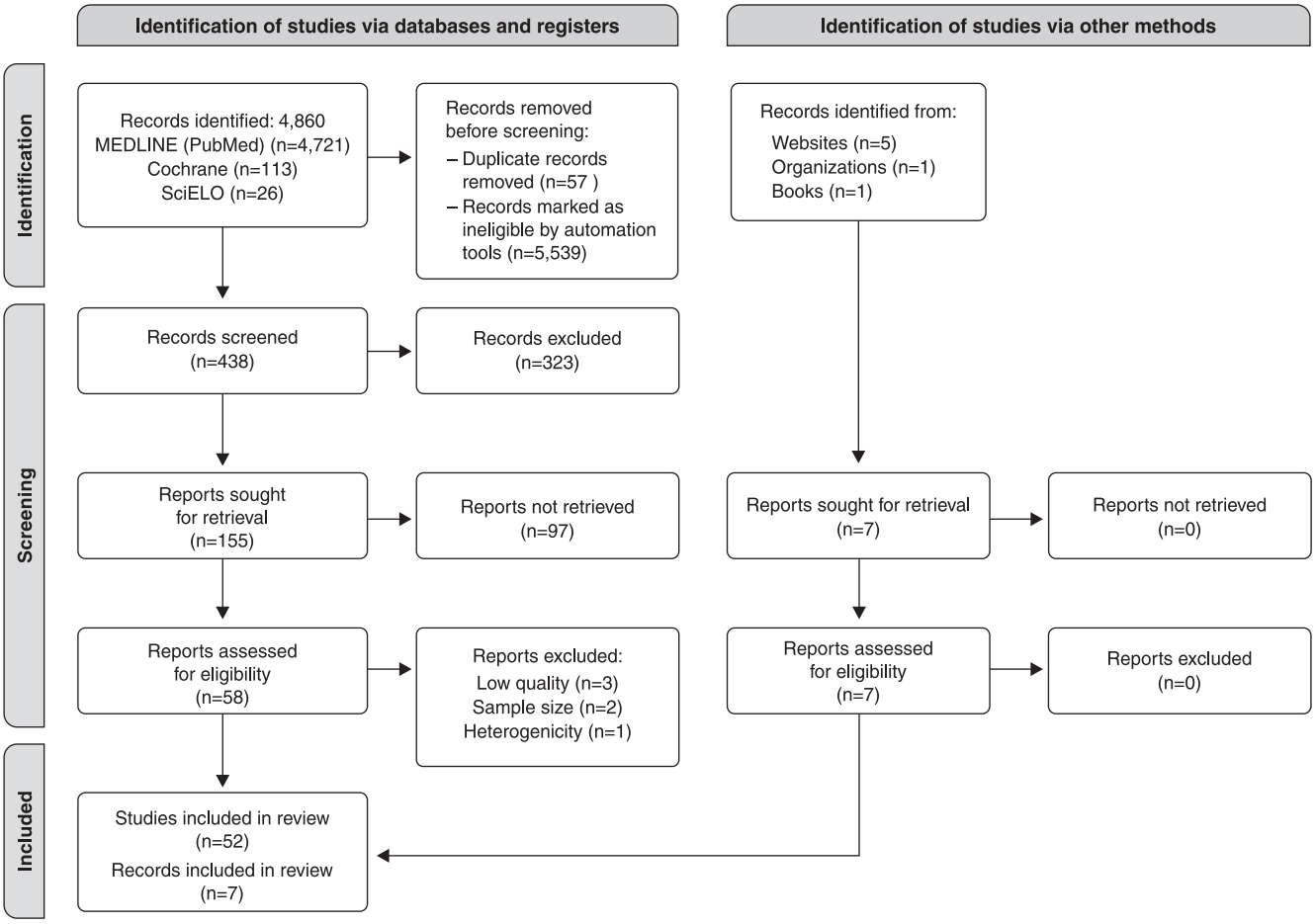

Figure 1 Study selection flowchart [15]

Study risk of bias assessment

To determine risk of bias in the included studies, we used the RoB 2 tool and other above-mentioned instruments.

Synthesis and evidence

In the evidence synthesis process, all authors read the relevant articles in full, then critically analyzed the evidence, extracted the results, and categorized the strength of the evidence. The levels of evidence and recommendation grades were chosen in accordance with Oxford Centre for Evidence-Based Medicine 2011 criteria (see https://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf).

Results

Tables 1 and 2 show the main recommendations for pharmacological treatment (Table 1) and psychotherapy (Table 2). Figure 2 shows the main recommendations of this guideline. Risk of bias tables were inserted as supplemental material in Tables S1, S2, and S3, and the summary of all results based on the PICO framework and level of evidence is shown in the supplemental material (Tables S4 and S5 – all available online-only).

Pharmacological treatment: antidepressants

Selective serotonin reuptake inhibitors

Adults. Medications considered efficacious were sertraline,[16,17] paroxetine,[16-18] and escitalopram (level 1 evidence).[16-19] There was insufficient evidence about fluoxetine, citalopram, and fluvoxamine.

Children and adolescents. Although fewer studies focused on these age groups, sertraline (5-17 years of age; level 2 evidence),[20] fluoxetine (7-17 years of age; level 3 evidence), and paroxetine (for 8 to 17 years of age; level 3 evidence) were found efficacious.[20] No evidence could be found about fluvoxamine, citalopram, or escitalopram in this age group.

Older adults. Despite having a high risk of bias, Balasubramaniam et al.[21] was included due to the scarcity of data on pharmacological GAD treatment in older adults. Level 3 evidence was found for sertraline, paroxetine, citalopram, and escitalopram.[21] Two studies provided level 3 evidence on escitalopram,[22,23] while two others provided level 3 evidence specifically for patients aged 60 to 65 years,[18,19] although all of these studies had a high risk of bias. However, these medications cause few side effects, have a simple dosage, and have been

Table 1 Recommendations for pharmacological GAD treatment

Class/medication	Level	Daily dose (mg)	Group (years)	Alert
Anticonvulsants				
Pregabalin	1	75.0-600.0	Adults	†
Antidepressants				
Atypical antidepressants				
Agomelatine	3	25.0-50.0	Adults	‡
SSRIs				
Citalopram	3	10.0-30.0	Older adults	§ ‖
Escitalopram	1	10.0-20.0	Adults	§
	3	10.0-20.0	Older adults	§ ‖ ¶
Fluoxetine	1	10.0-60.0	Adults	§ ‖
	3	For patients < 10 years of age, recommendation: 0.2 mg/kg for 1 week, then 0.4 mg/kg for 1 week, then 0.6 mg/kg for 10 weeks	7-17	§ ‖ ¶
Paroxetine	1	10.0-50.0	Adults	§
	3	10.0-60.0	8-17	§ ‖ ¶
	3	10.0-40.0	Older adults	§ ‖
Sertraline	1	25.0-200.0	Adults	§ ‖
	2	25.0-200.0	5-17	§ ‖
	3	25.0-150.0	Older adults	§ ‖
SNRIS				
Duloxetine	1	30.0-120.0	Adults	§ ‖
	2	30.0-120.0	7-17	§ ‖
	3	30.0-120.0	Older adults	§ ‖
Venlafaxine extended release	1	75.0-225.0	Adults	§ ‖
	2	37.5-225.0	6-17	§ ‖
	3	37.5-225.0	Older adults	§ ‖
TCA				
Imipramine	3	25.0-200.0	Adults	
Antipsychotics				
Quetiapine extended release	1	50.0-300.0	Adults	† †† ‡‡
Benzodiazepines				
Suggestions: alprazolam, bromazepam, clobazam, clonazepam, diazepam, lorazepam	1	-	Adults	‡ §§

GAD = generalized anxiety disorder; SSRIs = selective serotonin reuptake inhibitors; SNRIS = serotonin and norepinephrine reuptake inhibitors; TCA = tricyclic antidepressants.
† Somnolence.
‡ Limited data on remission and long-term use.
§ Discontinuation symptoms may occur when abruptly washed out.
‖ Age should be considered in dose adjustment; dose progression should be gradual.
¶ Better response when associated with cognitive behavioral therapy.
†† Patients reported lower tolerance to side effects.
‡‡ Risk of extrapyramidal effects.
§§ Risk of dependence and withdrawal syndrome.

studied for several years in this age group. The prescribing physician should begin with low doses and should be aware of possible drug interactions, side effects (more intense in this group) and, especially, the cost-effectiveness of the treatment.

Serotonin and norepinephrine reuptake inhibitors

Adults. Level 1 evidence was found for duloxetine. This medication, along with escitalopram, had larger effect sizes (-3.1 [-4 to -2.2] and -3.2 [-4.2 to -2.2], respectively) than paroxetine, sertraline, fluoxetine, or venlafaxine in a study lasting at least 4 weeks.[16] Although the results were comparable to placebo in previous studies,[24] duloxetine has been considered a first-line treatment for GAD.[25] Duloxetine was assessed in short-term treatment, resulting in improved psychic anxiety and somatic symptoms. Level 1 evidence was found for venlafaxine ER. Two meta-analyses found venlafaxine efficacious in 3,622 adults with GAD in interventions ranging from 6 to 12 weeks.[23,26] The extended-release formulation was effective and well tolerated (odds ratio = 1.83, 95%CI 1.58- 2.12).[26]

Children and adolescents. A meta-analysis of 1,673 patients found duloxetine superior to placebo in interventions $\geqslant$ 12 weeks[20] (effect size 17.3 [SD, 2.2]). Another study with a 10-week intervention corroborates this data[27] (7 to 17 years of age; level 2 evidence). Level 2 evidence was found for venlafaxine ER among 6- to 17-year-olds.[20]

Older adults. Among older adults, level 3 evidence was found for duloxetine and venlafaxine ER due to the study's high risk of bias.[21]

Table 2 Psychotherapeutic recommendations for GAD

Type	Level	Group
CBT, individual	1	Adults
	1	3 to 18 years of age
	1	Older adults
CBT, individual, exposure	2	Adults
CBT, group	2	Adults
CT	3	Adults
iCBT	3	Adults
Psychodynamic therapy	2	Adults
Applied relaxation	2	Adults
Biofeedback	2	Adults
Supportive psychotherapy	2	Adults

CBT = cognitive behavioral therapy; CT = cognitive therapy; GAD = generalized anxiety disorder; iCBT = internet cognitive behavioral therapy.

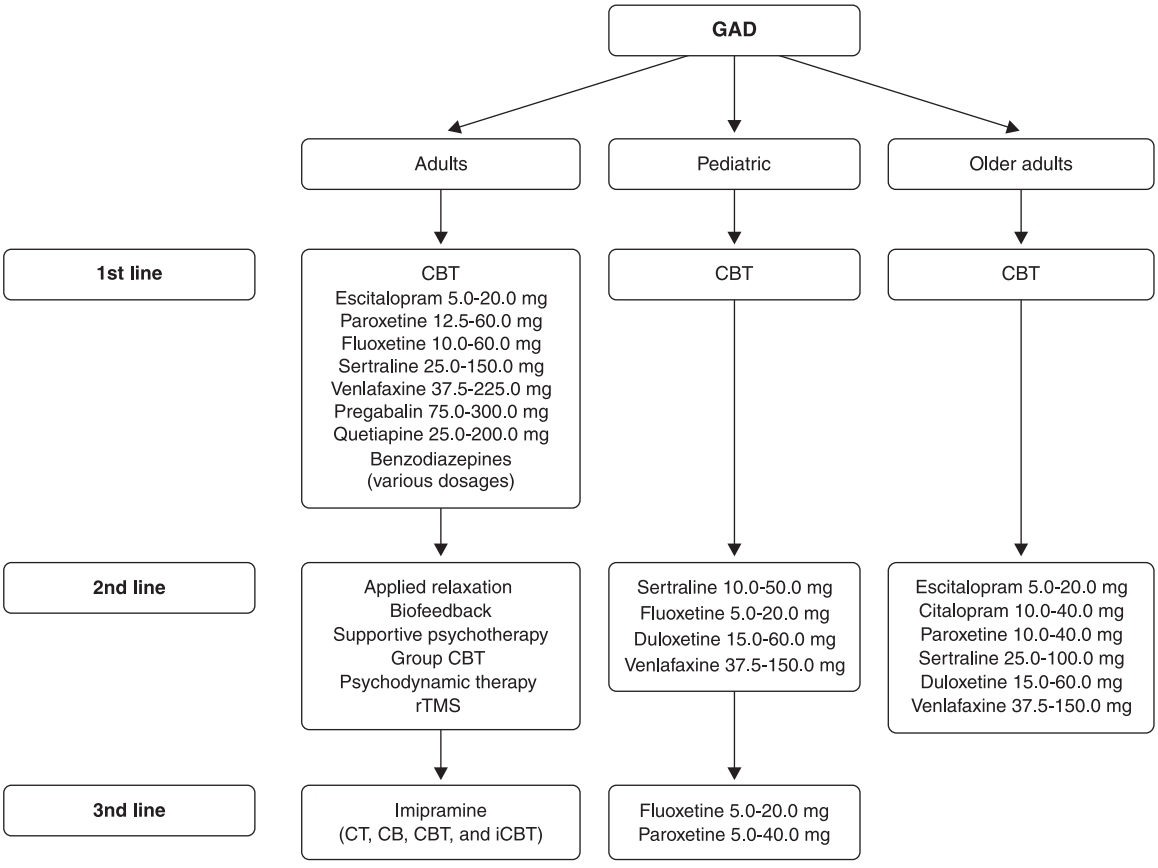

Figure 2 Recommendations for GAD treatment. CB = cognitive therapy; CBT = cognitive behavioral therapy; CT = cognitive therapy; GAD = generalized anxiety disorder; iCBT = internet cognitive behavioral therapy; rTMS = repetitive transcranial magnetic stimulation.

Tricyclic antidepressants

Despite being an older antidepressant with several potential adverse effects, this drug class is well-known and inexpensive. A comprehensive evaluation of three trials comparing tricyclic antidepressants and benzodiazepines (BZDs) indicated that imipramine was superior to BZD for reducing GAD symptoms. As measured by pre- to post-treatment improvement in Hamilton Anxiety Scale scores, alprazolam was substantially more efficacious than imipramine for lowering somatic symptoms of anxiety.[28]

In contrast, the benefits of imipramine were greater than alprazolam for psychiatric symptoms of anxiety and depression, including interpersonal sensitivity, anger, and paranoid ideation. Compared to diazepam, imipramine had a greater anxiolytic impact on psychological symptoms and a similar effect on physical symptoms. Another investigation confirmed these findings.[29] Level 3 evidence was found for imipramine, but only for adults.

Nevertheless, tolerance for imipramine is generally lower than for BZD.

Atypical antidepressants

Agomelatine. The results for agomelatine were similar to escitalopram.[30] Stein et al.[30] found agomelatine to be effective in short-term therapy, reducing the relapse risk over 6 months. Although the incidence of most adverse events was similar to placebo, agomelatine cannot be widely recommended for long-term GAD treatment due to concerns about liver injury[23] (adults; level 2 evidence).

Precautions with antidepressants and side effects at the beginning of treatment

Selective serotonin reuptake inhibitors. Owing to increased serotonin levels in the central nervous system and other areas, such as the gastrointestinal tract, the onset of side effects may be quick. It is important to point out that the majority of adverse effects diminish or vanish after the 1st month of medication use. The most common adverse reactions are nausea, diarrhea, appetite loss, dry mouth (gastrointestinal side effect), sleeplessness, tremors, headache, dizziness, and sexual dysfunction. Episodes of mania, bleeding (usually when associated with anti-inflammatory drugs), and excessive perspiration are also possible. Gradual dose progression should be recommended due to adverse effects and somatic symptoms. Patients can tolerate these effects with reassurance and guidance about their transient nature. Nevertheless, it should be pointed out that selective serotonin reuptake inhibitors are generally safe and well tolerated.

Selective norepinephrine reuptake inhibitors. The adverse effects of selective norepinephrine reuptake inhibitors are similar to those of selective serotonin reuptake inhibitors. In addition, owing to their noradrenergic activity, dry mouth and constipation are possible. There is also a risk of cardiac arrhythmias and seizures with selective norepinephrine reuptake inhibitors.

Tricyclic antidepressants. Due to the anticholinergic properties of tricyclic antidepressants, diarrhea, constipation, drowsiness, dry mouth, and impaired vision are frequent side effects. Sedation and weight gain are also possible due to their antihistamine characteristics. Blockade of alpha-adrenergic receptors frequently results in hypotension and vertigo, whereas the blockade of ionic channels can lead to fatal conditions, such as cardiac arrhythmias and seizures.

Agomelatine. Agomelatine acts on melatonergic and 5HT2C receptors, which can cause nausea, dizziness, drowsiness, fatigue, insomnia, headache, anxiety, abdominal pain, risk of liver injury, and hypertension.

Precautions for antidepressant discontinuation

When discontinuing antidepressants, symptoms usually subside within a few days and continue to decrease gradually over a few weeks. The most prevalent side effects are headaches, nausea, sweating, loss of balance, and hyperarousal. These side effects are more severe with venlafaxine than other antidepressants.

Pharmacological treatment: benzodiazepines

According to a meta-analysis of 56 trials (n=12,655), BZDs are more effective for GAD than selective serotonin reuptake inhibitors or selective norepinephrine reuptake inhibitors.[31] A second meta-analysis found that patients with severe baseline symptoms who received short-term therapy had the greatest response (alprazolam [p = 0.001], clobazam [p = 0.01], diazepam [p = 0.003], estazolam [p = 0.001], lorazepam [p = 0.0004], and zopiclone [p = 0.007]).[32] However, the possibility of long-term negative effects and dependency must be considered prior to prescription. The Canadian Study of Health and Aging reported that deteriorating cognitive function was a possibility, but no correlation was found between dementia diagnosis and BZD use.[33] No long-term relationships were found between BZD use and dementia diagnosis in a second trial with 235,465 participants.[34] BZDs are effective and generally safe, and should be prescribed with the same caution as any other psychiatric medicine (level 1 evidence: adults only).

Precautions and side effects

Sedation, tiredness, dizziness, weakness, ataxia, hyperarousal, and irritability are common with BZDs. Since GAD is a chronic disorder, chronic BZD use increases the risk of dependence and tolerance, possibly resulting in a paradoxical consequence. No information exists on the minimum or maximum duration of BZD therapy in GAD.

Pharmacological treatment: pregabalin

In a meta-analysis (n = 2,299) by Generoso et al.[35] (Hedges' g = 0.37; 95%CI 0.30-0.44), pregabalin was superior to placebo for GAD treatment (0.30-0.44). Other meta-analyses have found similar efficacy in long-term therapy (CI -2.61 [-3.21-2.01]; Hedges' g = 0.364, respectively).[23,36,37] A randomized controlled trial of 1-12 weeks suggested that pregabalin may be a safe choice for terminating chronic BZD use (51.4% $\times$ 37.6%, respectively).[38] Level 1 evidence was found for adults only.

Precautions and side effects

Blocking calcium channels in the central nervous system may cause sedation, dizziness, ataxia, lethargy, disorientation, and mood swings. Nausea, dry mouth, increased hunger, change in body weight, and impaired eyesight may occur.

Pharmacological treatment: quetiapine

Three previous meta-analyses and a systematic review found evidence supporting the efficacy of quetiapine as monotherapy[39-41] and in long-term maintenance. Zhornitsky et al.[42] reported that quetiapine was more efficacious than paroxetine and placebo in a

comprehensive analysis of two studies that spanned 8-52 weeks.[23] Level 1 evidence was found for extended-release quetiapine in adults only.

Precautions and side effects

Quetiapine can cause sedation, weight gain, dizziness, dry mouth, constipation, metabolic dysfunction, and an increased risk of diabetes and dyslipidemia.

Treatment-resistant generalized anxiety disorder

The number of articles discussing instances of treatment-resistant anxiety has increased in recent years. Nevertheless, this idea is often ambiguous or poorly described. Determining the parameters of a sufficient trial (e.g., the number and duration of prior trials) is heterogeneous and imprecise in the majority of studies. Response and remission analysis should include anxiety symptoms, functional impairment, and comorbidities.[43]

Pollack et al.[44] proposed considering response to anxiety disorder treatment in terms of remission or significant response in core anxious symptoms, functional impairment, and comorbid depressive symptoms. A systematic review found that combining olanzapine or risperidone with selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, or BZDs was effective for treatment-resistant GAD.[45] Since relevant studies were few and had small effect sizes, we will not provide a level of evidence; psychiatrists should determine the best individualized therapy in cases of treatment-resistant GAD.

Pharmacological treatment duration

The proper length of pharmacological therapy was a very pressing issue that our investigation could not answer. Patients who responded to the same course of therapy with a particular medicine and were subsequently randomized to placebo or continuous blind treatment with the drug for 6 to 18 months and subsequently participated in relapse prevention trials for at least one anxiety disorder.[17] All of these studies found that remaining in active therapy was far more beneficial than switching to placebo. According to the findings of these clinical experiments on relapse prevention, pharmaceutical treatment should be maintained for at least 1 year after remission. Given the chronic nature of anxiety disorders, it is curious that almost no controlled studies have examined treatment durations $>$ 1 year.[17] To minimize withdrawal symptoms, the dose should be progressively reduced over 2 weeks after therapy is completed.[17]

Since studies are inconclusive about the time-dependent risks or benefits of BZDs, doctors and their patients should determine treatment duration, always bearing in mind the risk of dependence.

Psychotherapies

Psychotherapies involve great heterogeneity of variables and are difficult to execute in clinical trials due to limitations enrolling a sufficient number of patients with the same diagnosis, precisely reproducing the technique within the same group by different professionals, and even to choosing a comparator (which may be a psychological placebo or a drug).

Adults

Level 1 evidence was found for cognitive behavioral therapy (CBT) in the short term. CBT was more effective than other psychotherapies, including psychodynamic and supportive therapies.[46,47] A review found that none of the studies comparing CBT with treatment as usual or wait-listing assessed the long-term efficacy of CBT.[46] Level 2 evidence was found for group psychodynamic therapy and CBT.[17]

The evidence for applied relaxation, biofeedback, and supportive psychotherapy was also considered level 2.[47]

Children and adolescents

Compared to wait-listing or no treatment, CBT significantly improved primary anxiety symptoms, remission, and response. CBT led to a greater reduction in primary anxiety symptoms than fluoxetine and a higher remission rate than sertraline. Combining sertraline and CBT led to a significantly greater reduction in clinician-reported primary anxiety symptoms and response than either treatment alone[48] (level 1 evidence). However, this study involved several anxiety disorders and did not limit its evaluation to anxiety reduction in GAD alone. Until further reviews can be conducted, we support these authors' recommendations.

Older adults

At the end of treatment and at 6 months of follow-up, significant treatment effects were found for CBT in older adults compared to wait-listing or treatment as usual. Compared to active controls, CBT led to a small nonsignificant advantage at the end of treatment, although the outcomes were equivalent at follow-up. CBT's treatment effect size for GAD was significantly associated with attrition rates and depression outcomes[49] (level 1 evidence).

Psychotherapy duration

The minimum treatment duration necessary to maintain the effects of psychotherapy was not described in the literature. Due to the chronic nature of GAD symptoms, new studies are needed to describe the required frequency and duration of sessions for each approach to produce psychotherapeutic effects in GAD. However, according to the included literature, the average duration of psychotherapy is longer than drug treatments since its effects may not be immediately apparent. Thus, duration is unfeasible as a moderator. Drug studies were significantly shorter (9.2 [SD, 4.4] weeks on average) than psychotherapy studies (12.4 [SD, 5.5] weeks).[17] The mean treatment duration of psychotherapeutic interventions was between 8 and 12 weeks.[5,50-52]

Thus, since the literature does not include clear recommendations about the length of psychotherapeutic interventions, in addition to the subjectivity of treatment, we recommend individualizing the treatment duration regardless of the approach.

Combined therapy

A network meta-analysis[5] observed that most pharmacological interventions had larger effect sizes than psychological interventions, and most psychological interventions had larger effect sizes than self-help interventions. According to one author, many experts recommended combined treatment despite insufficient evidence that combined therapy is more effective than monotherapy for GAD.[53] Although both of these studies focused on monotherapy, we have presented what we could find in the literature, i.e., studies on combined therapy for patients with GAD are scarce. Only one RCT could be found, which compared the efficacy of CBT plus venlafaxine XR to venlafaxine monotherapy and found similar treatment outcomes.[54]

Perspectives

Neurostimulation

A meta-analysis with 61 participants found that transcranial magnetic stimulation was efficacious for treating GAD symptoms.[55] The overall effect size was -2.06 (95%CI -2.64 to -1.48) in favor of active repetitive transcranial magnetic stimulation treatment (level 2 evidence; adults only). A systematic review with 475 participants found that transcranial direct current stimulation reduced the severity of GAD symptoms.[56] Nevertheless, there is still insufficient evidence to recommend this intervention as a first-line treatment due to the low number of studies.

Mindfulness

Although we decided to mention mindfulness therapy in this guideline, it involves several modalities and conceptual difficulties, as well as a relationship with self-help therapies. This modality may be promising but requires further research to determine its efficacy.[57,58]

Exercise

A recent meta-analysis with 13,574 participants found that exercise alone could reduce GAD symptoms.[59] Another meta-analysis in university students with GAD (49 students:75% female; age: 20.68 [SD, 5.8] years) concluded exercise significantly reduced GAD symptoms.[60] It should be pointed out that exercise programs, which are widely available and have no side effects, may be an alternative to pharmacological treatment or cognitive-behavioral therapy[61] (level 5 evidence).

Kava-kava (*Piper methysticum*), chamomile, nutritional supplements, lavender oil (*Lavandula angustifolia*), and probiotics

The literature includes inconclusive data and a low level of evidence regarding these supplement-based treatments; further research is required for safer conclusions.

Discussion

A previous Brazilian guideline on the diagnosis and treatment of anxiety disorders proposed venlafaxine and sertraline as first-line treatments, paroxetine as a second-line treatment, and short-term BZD as a third-line treatment. At least 6 months of treatment was recommended.[9]

The present review found the following the medications efficacious for GAD: sertraline, paroxetine, escitalopram, duloxetine, venlafaxine, imipramine, pregabalin, BZD, and quetiapine. Buspirone may be an option, despite weak effects and a lower level of evidence. In pediatric patients, fluoxetine, fluvoxamine, paroxetine, sertraline, duloxetine, and venlafaxine were efficacious. In older adults, citalopram, escitalopram, paroxetine, sertraline, duloxetine, and venlafaxine were efficacious. At least 12 months of treatment is recommended. For treatment-resistant GAD, a systematic review found that risperidone and olanzapine to be effective when used as adjunctive treatment with selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, and BZDs.[45]

BZDs are an effective option for GAD. Their effects are almost immediate, and they have muscle relaxant and hypnotic effects. However, there is a risk of dependence in individuals previously diagnosed with a substance use disorder. Another problem is that neither a maximum nor a minimum dose has been recommend in the literature. Thus, the decision must be left up to the psychiatrist and patient.

It is important to point out that in the studies used to develop this guideline, there was no consensus on the ideal duration of psychotherapy or pharmacological treatment. It is known that treatment response is individual, and continuous follow-up with a professional capable of evaluating improvement in GAD symptoms is recommended. Although some patients may relapse, others will not and may avoid side effects. Given that GAD is often a chronic condition, if a pharmaceutical benefit seems likely, maintenance treatment of at least 1 year has been reasonably well-established and is endorsed by most evidence-based guidelines.[37]

These guidelines aimed to discuss the various therapeutic approaches to GAD in a manner adapted to the Brazilian context, offering evidence-based recommendations for health professionals. Some limitations should be mentioned. The samples were heterogeneous, response was assessed at various times, and different outcome measures were used. However, the studies were well selected regarding diagnosis, which is a strong point.

The pharmaceutical industry has supported a number of trials involving GAD to present new medications. Because this guideline focused only on GAD, many studies were excluded because they did not separate interventions according to anxiety disorder subtype. There was great difficulty in determining the technique used in psychotherapeutic interventions, in addition to the

fact that they involve other biases that cannot always be resolved.

The efficacy of many GAD treatments was assessed. Antidepressants (with some exceptions) and BZDs are recommended, as are pregabalin (an anticonvulsant) and quetiapine (atypical antipsychotic). CBT and psychodynamic therapy were found effective. Treatment access and side effects must be considered when selecting the best therapeutic strategy. There was insufficient evidence regarding neuromodulation, mindfulness, exercise, kava-kava (*Piper methysticum*), chamomile, nutritional supplements, lavender oil (*Lavandula angustifolia*), or probiotics to make any recommendations; further studies are needed to determine their efficacy.

Disclosure

The authors report no conflicts of interest.

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