Brazilian Journal of Psychiatry
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Revista Brasileira de Psiquiatria
Brazilian Psychiatric Association
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BJP PRE-PROOF
(article published as accepted)

Special Article

Brazilian Psychiatric Association guidelines for the treatment of Social Anxiety Disorder

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http://doi.org/10.47626/1516-4446-2024-3878

Submitted: 11-Aug-2024

Accepted: 24-Oct-2024

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Abstract

Introduction: Social anxiety disorder (SAD) is one of the most prevalent anxiety disorders, often not well recognized. In most of the cases, SAD follows an unremitted and chronic course, affecting several areas of the individual functioning (i.e.: relationship, academic, work). Due to its relevance, there is a need for guideline-based treatments for SAD treatment adapted to the Brazilian social and economic reality. **Method:** A systematic review was produced by our group assessing several treatment modalities for SAD. The Medical Subject Headings term used was Social Anxiety Disorder or Social Phobia. PubMed, Cochrane, Scielo, ClinicalTrials.gov were searched resulting in 438 articles screened, of which 20 were selected. **Results:** Selective serotonin reuptake inhibitors are considered first line choices for the treatment of SAD, with great effects and a large database of evidence. Monoamine oxidase inhibitors (MAOIs), benzodiazepines and the anticonvulsants pregabalin and gabapentin are also effective. The serotonin noradrenaline reuptake inhibitor (SNRI) venlafaxine shows divergent results. With regards to psychological interventions, robust data offered evidence for cognitive behavioral therapy (CBT) as a first line option (individual, group and internet delivered). Psychodynamic psychotherapy, exposure and social skills therapy, self-help (with and without support) therapies, cognitive bias modification, virtual reality exposure therapy and mindfulness-based therapy are also effective techniques. Compared to pharmacological agents, psychological interventions are better tolerated and show evidence of long-term benefits. **Conclusion:** Patient's access to treatments (considering the Brazilian socioeconomic context), adherence, response rates (short and long-term treatment) and side effects must be considered when choosing the best strategy for the treatment of SAD.

Keywords: Social phobia; social anxiety disorder; phobic disorders

Introduction

Social anxiety disorder (SAD) is characterized by intense and disproportionate fear or anxiety associated with one or more social situations, such as social interactions, being observed while eating or drinking in public, or performing in front of others[1,2]. The individual expresses concern around potential negative evaluations from others regarding their behaviors, performance, or their display of anxiousness signs[1,2]. Significant social gatherings are frequently evaded or confronted with intense fear or anxiety. The symptoms must be sufficiently intense to result in significant distress or impairment in crucial domains of functioning, such as personal, family, social, educational, or occupational, and they must persist for a minimum of several months[1,2].

The prevalence of SAD ranges from 0.5 to 12% in adults [2-4]. Median age at onset of SAD in the United States is 13 years [2]. Among adults with SAD, an estimated 29.9% showed serious impairment, 38.8% had moderate impairment, and 31.3% had mild impairment, as per the results of a study analyzing functional impact in SAD [3,5]. Women diagnosed with SAD exhibit a higher prevalence of social fears and co-occurring major depressive disorder and other anxiety disorders. In contrast, males are more prone to the fear of dating, and are more likely to have comorbid oppositional defiant disorder, conduct disorder, or antisocial personality disorder, and are more likely to resort to alcohol and illicit drugs to alleviate symptoms of the disorder. In adolescents, SAD has been reported to increase the risk for active suicidal thoughts and suicide attempts [2].

Brazilians face a range of challenges in diagnosing and treating mental disorders. Some examples include the initial recognition of mental health issues (such as Social Anxiety Disorder, which is often diagnosed late), unequal and limited access to mental health services, the limited capacity of non-specialized healthcare services to identify and refer such patients, lack of integration among services, the influence of cultural and social factors that generate stigma and delay the search for care, as well as socioeconomic problems that restrict access to specialized treatment and care[6,7].

Different guidelines around the world have addressed the management of SAD, such as the Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines [8], the NICE guideline on the recognition, assessment and treatment of social anxiety disorder [4] and the Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorder [9]. In Brazil, the guidelines of the Brazilian Medical Association for the treatment of social anxiety disorder were published in 2010 [10]. However, after that date, there has been no further update on this topic. For this reason, the purpose of this article is to present an updated guideline for the pharmacologic and non-pharmacologic treatment of SAD.

Methods

Eligibility criteria: This is a systematic review that included the following types of studies: metanalysis, systematic reviews with inclusion of clinical trials, and clinical trials. Non-systematic reviews or government documents or other guidelines could be used if the information were essential for answer the main questions. Case reports, series of case reports, and editorials were excluded. There was no language or time limitation. There is no language or period restriction.

Subjects: Adults with a diagnosis of SAD (social phobia or social anxiety disorder), according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV and 5 or International Classification of Diseases (ICD) criteria (10th and 11th Revison). Male or female.

Types of interventions: pharmacological and/or psychotherapy approaches.

Information sources: PubMed, Cochrane, Scielo, ClinicalTrials.gov.

Selection criteria (screening)

Keywords were assessed by Medical Subject Heading (MeSH) terms in PubMed: “Social Anxiety Disorder” OR “Social Phobia” AND “Treatment”. The selection process was performed independently by two reviewers (TMA and DCS) using the Rayyan (https://www.rayyan.ai) selection platform (http://www.rayyan.ai).

The software was use to identify duplicates. In the screening for abstracts there were 4,860 results. From this 438 were selected.

Data collection process (eligibility)

TMA and DCS analyzed full-articles for eligibility. These articles were fully read and those that not met the inclusion criteria and presented higher risk of bias in all items were excluded. In this phase, 245 articles were excluded and 20 papers were selected.

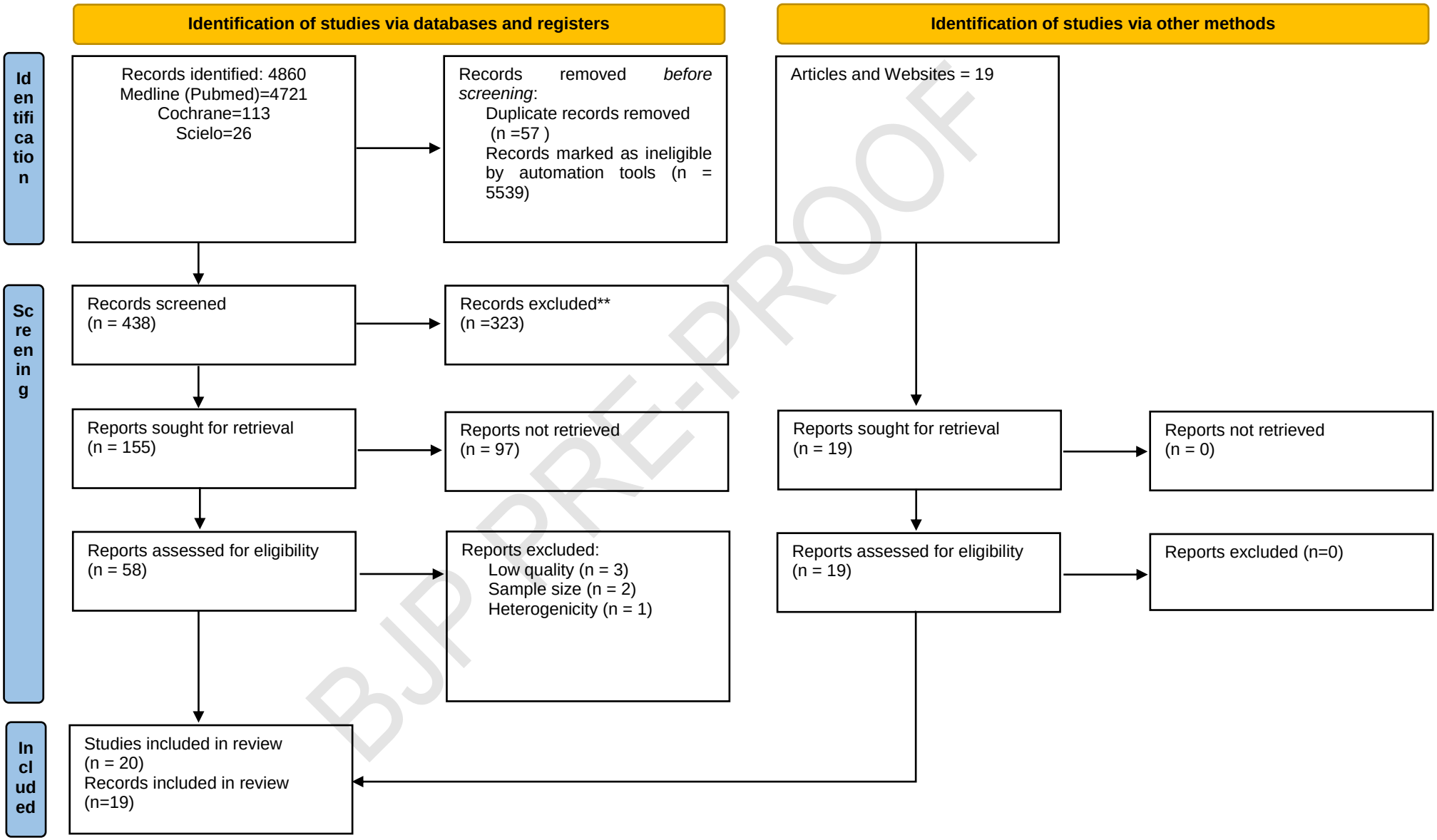
Data items (outcomes): Data were organized according to the PICO strategy with definition of Patient/Population of interest, Intervention/Exposure, Control/Comparison and Outcome. The main outcome assessed in most of the studies were the effectiveness of determined interventions in reducing SAD symptomatology measured by appropriate scale. Secondary outcomes varied according to each study methodology. The effectiveness of interventions was assessed mainly by odds ratio (OR), risk ratio (RR), and standardized mean differences (SMDs).

Other data items: A series of secondary measures were assessed in these articles. Improvements in the Clinical Global Impressions Scale (CGI), improvements in comorbidities, such as depression and other anxiety disorders, dropouts due to any reasons, dropouts due to side effects, and other measures.

Study risk of bias assessment: We used Robvis tool for Systematic Reviews and Metanalysis. For randomized trials we used RoB 2 tool. We considered the corresponding level of evidence for the study (Level 1 for SR or MT and Level 2 for RCT) only if the risk of bias was low. When the risk of bias was high or inconclusive, we downgraded the level of evidence by at least one point in the 2011 Oxford Classification.

Synthesis and evidence: In this process, all authors read the relevant articles in their entirety, then conduct a critical analysis of the evidence, extracted the results, and categorized the strength of the evidence. The levels of evidence and recommendation grades were chosen in accordance with the 2011 Oxford

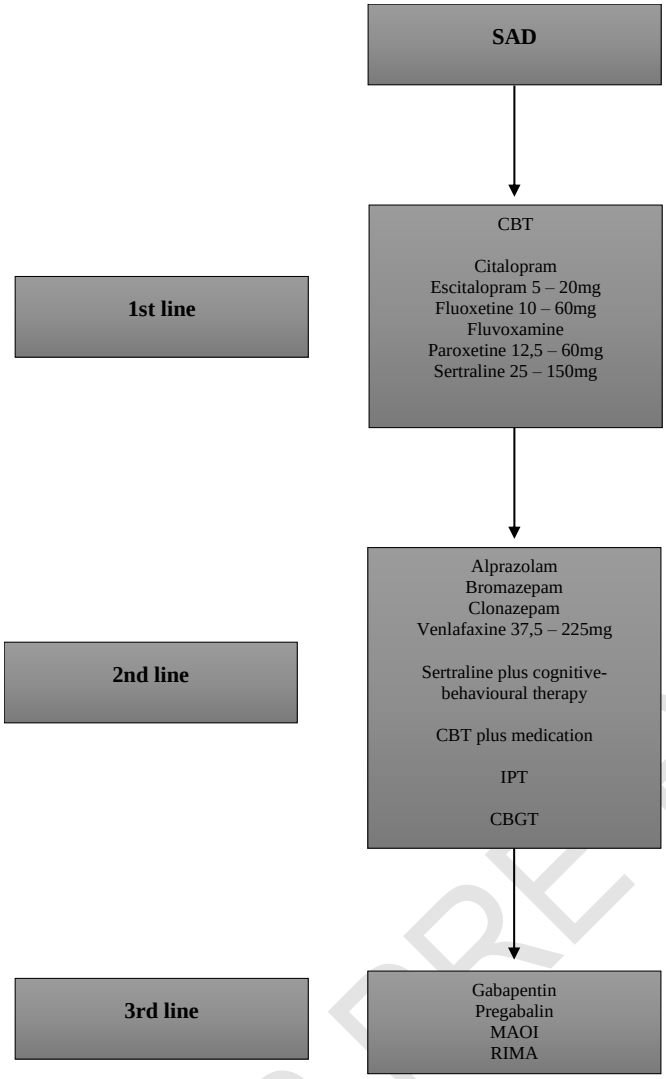
classification. For further information, see https://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf.



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Treatment



Pharmacological Treatment

Selective Serotonin Reuptake Inhibitors (SSRI's): SSRI's are the most extensively tested drug class in individuals with SAD. Citalopram [11], escitalopram [11-15], fluoxetine [11,14], fluvoxamine [11,12,14-16], paroxetine [11,12,14,15,17,18] and sertraline [11,12,14,15] were tested and demonstrated efficacy in reducing symptoms measured by scales. However, in one study, escitalopram, fluvoxamine, paroxetine, sertraline performed worse than placebo with regards to dropout rates due to side effects [15]. Nevertheless, the level of evidence for this group is 1.

Serotonin-Norepinephrine Reuptake Inhibitors (SNRI's): Venlafaxine is the only agent assessed in randomized controlled trials with positive results [11,14,15,19]. However, tolerance is not always satisfactory and there is a study that observed a

greater number of dropouts with venlafaxine compared to placebo [15]. Level of evidence is 2.

Monoamine Oxidase Inhibitors (MAOIs): Beside some evidence supporting its use in SAD [11], the quality of the available data regarding irreversible MAOIs (such as phenelzine and tranylcypromine) and reversible inhibitors of MAO-A (RIMAs) in SAD is rather low[15,19]. The level of evidence ranges from 3 to 1. For RIMAs the main medications tested were moclobemide and brofaromine with evidence ranging from 2 to 1[11,14,15,19]. In figure 2, we suggest an order in which medications should be chosen. Considering the side effects of this group, older studies and the need for strict dietary control for its prescription, we consider that they should be among the 3rd options.

Benzodiazepines: Alprazolam and clonazepam showed limited evidence compared to SSRIs and SNRIs [11]. In one study, bromazepam and clonazepam had superior response compared to placebo[15]. Because of risk of dependence and lack of studies addressing long-term treatment, we established its level of evidence as 2.

Anticonvulsivants: The use of antiepileptic drugs in SAD has been extensively reviewed [14]. Nonetheless, only two antiepileptic drugs showed distinct results in terms of efficacy [14]. Gabapentin and pregabalin are both ligands at the alpha-2 delta site on voltage-gated calcium channels. Functionally, both drugs reduce the release of a range of excitatory neurotransmitters through binding to that site. There are three positive RCT with alpha-2 delta ligands in the treatment of SAD [14]. The onset of anxiolytic effects is relatively rapid, occurring within the first week of treatment [14]. The anxiolytic dose-response has only been formally assessed for pregabalin, and efficacy was only evident at the maximum dose (600 mg/day), but not at lower doses [14]. This is in contrast with the effect of pregabalin in, other anxiety disorders, such as generalized anxiety disorder, where the anxiolytic dose-response is seen at much lower doses (150 mg/day)[14]. There are no data on long-term treatment or relapse prevention for alpha-2 delta ligands[14]. Level of evidence was rated as 3. Valproate, topiramate, levetiracetam, and tiagabine have also been studied, and all were associated with reductions in relevant social phobia rating scales. However, all studies analyzed small samples

(ranging from 17–54 subjects), and the magnitude of the change in symptom ratings was within the range that has been reported for placebo arms in other RCTs[14,15].

Other medications: No evidence supporting the use of 5HT1A partial agonists (buspirone), olanzapine, quetiapine, beta-blockers and norepinephrine reuptake inhibitors (NARIs) is currently available.

Duration of pharmacological treatment

The duration of intervention for SAD can vary depending on the individual's needs and the treatment plan recommended by psychiatrist. In some studies medications were tested by 6 to 28 weeks [11,13,14,16,17,19-21] This guideline recommended the treatment duration from 12 to 24 months.

Combined Therapy (pharmacological and psychological)

Few studies addressed the role of combined psychopharmacology interventions with psychotherapy. Based on the overall findings of the present review, though, combined treatment has been shown to be superior to isolated interventions[11,12,14,21]. In a meta-analysis aimed at identifying the best treatments for Social Anxiety Disorder (SAD), combined psychotherapy treatment (CBT/Exposure) with psychopharmacology was found to be superior to certain medication classes, including SSRIs (OR 0.83 [0.52, 1.33]), MAOIs (OR 0.46 [0.18, 1.18]), and BDZ (OR 0.30 [0.09, 0.97]). However, the sample size used in the combination analysis, comprising 230 participants, was small[14].

Following the same trend, in a meta-analysis addressing the acute treatment of SAD, combined treatment was found to be superior (SMD −1·30, 95% CrI −1·73 to −0·88) to isolated interventions, such as CBT (SMD –1·19 (–1·56 to –0·81), Group CBT (SMD –0·92 (–1·33 to –0·51) or psychopharmacology – SSRIs and SNRIs (SMD –0·91 (–1·23 to –0·60). Even though the findings indicated a good effect size, the sample was very small, just 156 individuals[11]. In this study, the combination was favorable for Group CBT with MAOIs and SSRIs (three

studies), psychodynamic therapy with BDZ and SSRIs with BDZs, one study each[11].

Moreover, in another meta-analysis with a more robust sample (1020 patients), the tendency towards the superiority of combined treatment was maintained (d = 2.15 [1.35-2.95]), compared with CBT alone (d = 1.10 [0.93-1.28]) and Group CBT alone (d = 1.01 [0.72-1.29])[11].

In an RCT of 102 participants, combined treatment of paroxetine with cognitive therapy (CT) resulted in significant improvements compared to placebo pill alone. It was also superior to medication and CT groups alone, but without statistically significant differences[18]. However, in the 12-month follow-up, combined treatment did not remain superior to CT alone, demonstrating superiority only to the placebo group, accompanied by higher relapse rates[18]. In a more recent RCT assessing the combined treatment of psychotherapy and sertraline in 146 participants, it sought to compare intervention groups with sertraline or placebo pill associated with Group CBT or Psychodynamic Therapy Group (GPT). The results demonstrated that combined treatment was superior to isolated psychotherapy and that sertraline enhanced the development of social skills and the improvement of specific symptoms of SAD[21].

Non Pharmacological Treatment - Psychotherapies

Several meta-analyses, conducted in recent years, have aimed at identifying psychological interventions with the most satisfactory effects for the treatment of SAD [11,14,20,22-25].Among the psychotherapeutic approaches evaluated, CBT showed better results compared to Group CBT, psychodynamic therapy and face-to-face therapies. Mindfulness showed better effects in the treatment of SAD than CBT[22]. However, it is important to emphasize that the authors, for purposes of the analysis, combined CBT and exposure in the same category; while exposure techniques can be part of the larger treatment protocol in CBT, individual exposure is just one intervention inside the CBT treatment protocol.

In another meta-analysis, the authors found CBT as having greater efficacy than Group CBT, followed by exposure with social skills training and a self-help

group with support. Psychodynamic psychotherapy and mindfulness had smaller effects in terms of effectiveness[20,23].

In another article, small to moderate effect sizes were found regarding the comparison of CBT with placebo psychotherapy group in the treatment of SAD. Despite the modest effects, the authors identified that the odds ratio of response to treatment was 3.51 for CBT compared to placebo[23]. Similar results were found in other previous meta-analyses in which the psychological comparison group was placebo[22].

In a more recent meta-analysis, group CBT was compared with waitlist, common factors group psychotherapy, pharmacotherapy, and individual CBT. Group CBT demonstrated a larger effect compared to the waitlist, and small effects compared to the group of common factors group psychotherapy and CBT, however, it was not superior to medication alone. Group CBT contributed to the relief of SAD symptoms but did not seem to bring about improvements in the general psychopathology outcome, which included symptoms of generalized anxiety and depression[18,20,21].

Another important aspect that must be considered is the heterogeneity of the studies with regards to duration of treatment, number of treatment sessions, and duration of sessions, all of which have a considerable impact on the number of hours of treatment given to participants, thus making it difficult to compare studies. Level of evidence was rated was 2.

Another important consideration is related to treatment effect persistence and risk of post-treatment relapse. A meta-analysis of nine CBT RCTs found significant effects at post-treatment (Cohen's *d* of 0.68 across all trials) that were maintained at follow-up, with no decrease in treatment effect size (0.76)[14]. CBT in maintenance demonstrated superiority in relation to medication, as it contributed to protection against relapses[14]. CT was the most effective treatment for SAD at both post-treatment and follow-up compared to paroxetine and better than combined treatment at 12-month follow-up on the Liebowitz Social Anxiety Scale[17].

CBT is associated with large effect sizes (SMD –1·19, 95% CrI –1·56 to –0·81)[11]. Therefore, it should be considered the best intervention for the initial treatment of SAD, as studies have described it as showing a lower risk of adverse

effects than pharmacotherapy. For individuals who refused psychological intervention, SSRIs demonstrated more consistent evidence of benefit[8]. CBT also had a greater effect than psychodynamic psychotherapy (SMD −0·56, 95% CrI −1·03 to −0 ·11) and interpersonal psychotherapy, mindfulness and supportive therapy (SMD −0·82, 95% CrI −1·41 to −0·24)[11]. The superiority of CBT has been maintained in other meta-analyses[22,23,26]. Level of evidence 1.

CBT has demonstrated strong evidence of effectiveness for the treatment of SAD, however a considerable number of patients who do not benefit from this intervention. In identified meta-analyses, important heterogeneity is observed between studies, which differ in relation to assessment instruments, treatment protocols, techniques utilized, total treatment time (number of sessions), treatment time for each session[18,22,23,26]. All these aspects make it difficult to compare treatment outcomes across different studies. Additional research, with more standardized outcome measurements and treatment description, as well as a specific attention to longitudinal monitoring, is necessary to identify the effects of treatment in the long term.

Based on the currently available evidence, CBT continues to be the psychological treatment of choice for SAD. However, considering the patient's preferences, the complexity of the condition, and the expertise of the professional responsible for the treatment, other psychotherapy approaches may be of benefit, even with less evidence supporting its use, such as psychodynamic psychotherapy, and interpersonal psychotherapy. Moreover, not all patients respond to CBT, therefore other options should be considered[11,12].

Duration of psychotherapeutic treatment

For CBT, treatment duration in clinical trials can range from 3 to 28 weekly sessions, with an average duration of 12 weeks. Each session varies from 60 minutes to 150 minutes depending on whether the intervention was CBT or group CBT. CBT for social anxiety often involves a structured program of sessions that focus on cognitive restructuring, exposure therapy, relaxation techniques, and social skills training[18,22-24].

Other therapies

Mindfulness-Based Interventions

In this guideline, mindfulness-based interventions (MBI) were included under perspective, since they comprise different intervention modalities and conceptual difficulties, as well as relationship and self-help therapies. An important difficulty associated with evaluating the effect of treatment refers to the need for patients to engage in the daily practice of mindfulness exercises. Therefore, it becomes complex to identify whether the treatment effect is due to the intervention itself or simply to the passage of time. In a meta-analysis comparing MBI with waiting list, MBI was found to have a high effect on relieving SAD symptoms (0.89 0.53 - 1.26), but when compared with active treatments, such as CBT or group CBT, it showed a smaller effect (-0.20, -0.42 - 0.03). An additional analysis of the five single-arm trials found that MBIs had a medium effect on relieving SAD symptoms (g =0.48) 21. MBIs are modalities that may hold promise but require more studies to conclude whether they are effective[12,27].

Cognitive bias modification

Cognitive bias modification (CBM) is a novel experimental technique, built on cognitive theories of SAD, aimed at reducing negative cognitions and thereby diminishing anxiety susceptibility and symptoms. Current findings broadly support cognitive theories of SAD that consider a bidirectional or mutually reinforcing relationship between symptoms and cognitions. However, the small therapeutic effect observed with CBM indicates that it is necessary to develop more reliable and efficient interventions, specifically taylored to address SAD[24]. Considering available evidence, the efficacy of CBM for the treatment of SAD is considered limited[26].

Internet delivered cognitive behavior therapy

There is evidence for ICBT indicating the potential of technology-assisted interventions for SAD[26]. An analysis of 21 trials showed significantly less SAD symptoms at post assessment than passive control conditions (g=0.84 and 0.82,

respectively). Compared to active control conditions, Internet-delivered cognitive behavior therapy (ICBT) had a small advantage (g=0.38)[26].

Virtual Reality Exposure Therapy

Virtual reality exposure therapies (VRET) have been shown an alternative for the development of social skills, aiming at reducing SAD symptoms. VRET enables the patient to face feared social situations through immersion in programmed scenes, gradually, mitigating possible difficulties such as the costs involved in exposing real situations, as well as the uncontrollability of real stimuli, which makes it difficult for the therapist to manage and grade the intensity of aversive stimuli[26,28-30]. The effectiveness of VRET for SAD has been found to be significant during post-intervention and longitudinal follow-up; however, when compared with In Vivo Exposure Therapy (iVET), the results were similar between the two interventions at post-treatment, although the VRET had a reduced effect at later follow-up times compared with iVET. No significant differences between both interventions were observed in dropout rates. Even though there are no differences significant between VRET and iVET, the low costs and flexibility of VRET may become a promising possibility for the rehabilitation of patients with SAD[26,28-30].

Exercises

The use of physical exercise as a treatment for mental disorders is still controversial. Additionally, few studies have been conducted specifically for Social Anxiety Disorder (SAD) with methodological limitations. Furthermore, data regarding exercises are sometimes presented for anxiety disorders and sometimes to alleviate anxiety. A meta-analysis concluded that exercise programs are a viable treatment option for anxiety. High-intensity exercise regimens were found to be more effective than low-intensity regimens[31]. The results suggest that may be implications for the use of exercise schemes in General Practice. However, there was no significant difference in outcomes between groups of patients with diagnosed anxiety disorders and patients who had raised anxiety on a rating scale. The authors concluded that they were limited by the small number of studies and the wide variation in the delivery of exercise interventions[31].

Discussion

This guideline aims at discussing evidence-based interventions for SAD treatment. When evaluating a patient, it is important to consider several aspects, including possible differential diagnoses, investigation of their psychiatric and medical history, presence of comorbid conditions, and history of treatment adherence, to formulate a correct diagnosis and, thereby, implement and appropriate and effective treatment modality.

Regarding pharmacological interventions, antidepressants (mainly SSRIs) are the most studied agents in the literature, with robust data available. Several metanalysis have shown that paroxetine, fluoxetine, sertraline, fluvoxamine and escitalopram are effective in SAD[11-14,16,17,21]

Paroxetine appears to be the most efficient medication when compared with other agents[11,14,17,18] SSRIs tend to separate from placebo during the acute phase, after 4-6 weeks, and higher doses may be necessary to achieve remission [19]. Considering long-term treatment, there is paucity of data available due to the methodological and financial difficulties in conducting a RCT during a long period of time. However, SSRIs are linked to decreases in relapse rates after 24 weeks of treatment[11,14,17-19]. Side effects are prevalent, mainly in the treatment beginning, and tend to decrease after the first month. The most common side effects are nausea, insomnia, sexual dysfunction, irritability, headache and diarrhea. Moreover, discontinuation symptoms may be relevant, mostly in patients who abruptly stop the medication and agents with short half-life (i.e paroxetine)[11,14,17-19].

Venlafaxine is the only SNRI agent assessed in RCTs and the data regarding its effectiveness is conflicting. While some metanalysis[14,1912] found evidence supporting the use of venlafaxine for SAD, with great response and improvements in anxiety symptoms, a systematic review and a metanalysis[15] conducted concluded that venlafaxine was not effective in the treatment of SAD. The poor performance may be related to the number of dropouts (due to side effects) and the presence of bias and heterogeneity in the RCT's methodology. Frequent side effects related to venlafaxine and other SNRI's agents are nausea, insomnia, irritability, diarrhea, increasing in the blood pressure, sexual dysfunction

and autonomic symptoms[15]. Additionally, venlafaxine is associated with one of the highest prevalence of withdrawal symptoms when compared to other antidepressants [15].

MAOIs are effective in the treatment of SAD, with great effect sizes described in previous systematic review and metanalysis[11,12,14] . Em um study phenelzine demonstrate low-quality of evidence[19] and moclobemide inconclusive[15].However, due its poor tolerability, need for dietary restrictions (risk of hypertensive crisis if ingestion of aliments containing tyramine associated with the blockage of monoamine oxidase), and potentially harmful interactions with serotonin/noradrenaline agents, the adherence to these medications may be limited[32,33]. Considering the side effects of this group, older studies and the need for strict dietary control for its prescription, we consider that they should be among the 3rd options.

Benzodiazepines are largely used in anxiety disorders[34] with most of data supporting response rates. Systematic review and metanalysis[11 15,19] found the effectiveness of benzodiazepines in SAD with great effect size and response rates. Moreover, these drugs appear to decrease the incidence of relapses after the acute phase of treatment [11 15,19] . However, the side effects profile should be weighted in the long-term due to the risk of tolerance, dependence, abstinence and cognitive impairments related to its chronic use[34,35].

The anticonvulsants pregabalin and gabapentin and pregabalin are associated with improvements in SAD symptoms, while in other studies levetiracetam, gabapentin and pregabalin showed limited effectiveness [12 11,14,15]. However, the data available assessing these agents are limited and further studies are necessary to offer more robust evidence. Prevalent side effects associated with anticonvulsants are sedation (specially in higher doses), dizziness, dry mouth, confusion and blurred vision[36].

Buspirone, norepinephrine reuptake inhibitors, beta blockers and mirtazapine were not associated with improvements in SAD according to the evidence available and should not be utilized in its treatment[15,19,37,38]. The second-generation antipsychotic (olanzapine, risperidone, and quetiapine) was not found to be effective for the treatment of SAD[15,19]. Moreover, it is important to weight the

risk of side effects when prescribing an antipsychotic such as metabolic syndrome, weight gain, sedation and extrapyramidal symptoms[37].

With respect to psychotherapy approaches, there are robust data supporting the use of CBT for the treatment of SAD. CBT following the Clark and Wells Model appears to be the most effective method[18,39], and individual CBT showed better results compared to group CBT[11,23]. Even so, group CBT is regarded as effective[22,23] and should be considered an option when available. To adapt to a new reality of appointments and personal relationships initiated during the COVID-19 pandemic, internet delivered CBT can also able considered an effective treatment option[26]. Thus, we recommend that investments are necessary for the training of physicians and psychologists to expand their expertise in this technique, specifically for anxiety disorders.

Mindfulness-based interventions has become largely popular in the last few years, and its efficacy has been assessed for several mental health disorders. While Mayo Wilson et al., 2014[11] found no evidence for mindfulness-based interventions, a later metanalysis with 11 studies[27] showed evidence assessing pre-post effect, comorbid symptoms and the maintenance of gains during the follow up. When compared to evidence-based treatment (ie. CBT) mindfulness-based interventions were less effective, indicating that further studies are required for purposes of a better characterization of its role in the treatment of SAD.

Other modalities such as psychodynamic psychotherapy, exposure and social skills therapy, and self-help groups (with and without support) therapy showed some evidence[11]. VRET treatment showed good evidence in the management of the core symptoms of SAD[26,28-30]. When compared to active control, however, VRET appeared to be less effective during the follow-up period. Few studies assessed the combination of medication and psychotherapy, and the available evidence is limited[12,14,18]. Further research is necessary and decisions regarding the potential benefits of this combination should be addressed by the practitioner along with the patient. In our group opinion, there is no strong evidence supporting the use of combined therapy in SAD.

Conclusion

SAD is a prevalent disorder resulting in great impact in quality of life following a chronic and unremitting course if untreated. The scope of this review was to offer evidence-based options for the pharmacological and non-pharmacological management of SAD. According to available literature findings, SSRIs are considered first-line agents. Moreover, benzodiazepines, MAOIs and the anticonvulsants pregabalin and gabapentin should be regarded as effective alternatives. Venlafaxine has shown controversial results in the literature, but is still an option, especially in patients who did not respond to SSRIs. With respect to psychological interventions, robust evidence for CBT as a first line option (individual, group and internet delivered) is available. Psychodynamic psychotherapy, exposure and social skills therapy, self-help groups (with and without support), and VRET are also effective techniques. Regarding mindfulness, additional data are necessary, although it appears to be a promising intervention in the treatment of SAD. Compared to pharmacological agents, psychological interventions have fewer side effects and evidence in long-term treatment. Considering the Brazilian reality and patients limited access to treatment (often provided in the primary care system), choosing the most appropriate treatment with regards to response rates, adverse effect profile, and adherence is of vital importance. To address heterogeneity of studies, we is recommended that various aspects for each patient be considered, such as the expertise of the physician prescribing the modality and the professional applying it (especially regarding psychotherapies), access to and the possibility of completing the therapy, and potential complications. In the absence of a response or the inability to use the chosen option, we advise following the other recommendations outlined in Figure 2.

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Edited by: Andre Brunoni

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Supplementary Table S1

Reference	Population	Instrument/ Intervention vs comparative	Study type	Primary efficacy outcome measure	Secondary outcome	Level of evidence
Bandelow B et al., 2015[1]	73 studies (n = 11066) assessing SAD	Pharmacological, psychological, and combined treatments vs Placebo	Metanalysis	Pre–post of scales results to measure anxiety symptoms for psychotherapy and medications compared to placebo.	Pre–post of scales results to measure SAD symptoms (i.e. HAD, GAD, and LSAS) for psychotherapy and medications compared to placebo.	2 Treatments with satisfactory effect size were (confidence intervals of two treatments do not overlap). Large: Individual and group exposure CBT, IPT, mindfulness, non-face-to-face therapies, and psychodynamic for psychological therapies. Moclobemide, phenelzine, pregabalin, venlafaxine, escitalopram, fluvoxamine, paroxetine, sertraline for medications. Other interventions: mindfulness and exercise. CBT + drug combinations had good effect size; however authors do not present which medications were tested.
Baldwin DS et al., 2016[2]	3RCTs (n=1596)	Escitalopram vs. Placebo	Metanalysis	Changes in the LSAS score at week 12 with different doses of escitalopram.	There is estimated difference from placebo in CGI-S score at week 12 and response to treatment	1 The overall difference in treatment effect was in favor of escitalopram versus placebo at all doses.
Barkowski S et al., 2016[3]	36 RCT's (n=2171 patients)	Group psychotherapy vs. Waitlist	Metanalysis	Improvements in specific symptomatology	Improvements in general psychopathology	1 Available studies used mainly cognitive-behavioral group therapies (CBGT); therefore,

						quantitative analyses were done for CBGT. Medium to large positive effects emerged for wait list-controlled trials for specific symptomatology: g = 0.84, 95% CI [0.72; 0.97] and general psychopathology: g = 0.62, 95% CI [0.36; 0.89]. Group psychotherapy was also superior to common factor control conditions in alleviating symptoms of SAD, but not in improving general psychopathology.
Bernik et al., 2018[4]	N=146	Sertraline +psychoteragpy vs. psychotherapy alone; group cognitive-behavioural therapy vs. psychodynamic therapy; sertraline + group cognitive-behavioural therapy or sertraline + group psychodinsamic therapy vs. placebo + group cognitive-behavioural therapy or placebo + group psychodynamic therapy	RCT	Remission rates assessed by the CGI-I and response rates assessed by the Scale of Avoidance and Distress Scale (SADS) and t Multidimensional Scale of Social Expression–Motor Part (M-MSSE	CGI-I, SADS and M-MESSE final score and other scales assessing depressive and anxiety symptoms	2 In overall, SER+psychotherapy was superior to psychotherapy alone. SER potentiated GCBT by enhancing social skills acquisition.
Canton J e tal., 2012.[5]	41 papers were selected on generalized social anxiety	Medications and psychotherapy vs. placebo	Metanalysis	Reduction of symptoms, odds ratio	-	1

		Paroxetine vs. placebo		OR=3.43 (CI 2.51-4.69)		1 In general, SSRIs showed separation from placebo by weeks 4–6 on a number of response or other outcome measures, however SSRI-placebo differences tended to increase out to 12 weeks of treatment. Robust effects of the SSRIs in preventing relapse of social phobia (pooled OR 0.25, 95% confidence interval [CI] 0.18–0.35).
		Sertraline vs. placebo		OR=2.48 (CI 1.82-3.37)		1
		Escitalopram vs. placebo		OR=2.05 (CI 1.47-2.86)		1
		Fluvoxamine vs. placebo		OR=1.98 (1.07-3.67)		1
		Fluoxetine vs. placebo		OR=2.73 (CI 1.67-4.48)		1
		Venlafaxine vs. placebo		OR=2.42 (CI 1.92-3.06)		1 The onset of response across all trials was evident at 4–6 weeks, although maximum separation from placebo continued out to 12 weeks.
		Irreversible MAOIs vs. placebo		OR=7.22 (CI 2.90-17.97)		3 The rationale for using monoamine oxidase inhibitors

						was because social phobia and atypical depression share the symptom of increased interpersonal sensitivity, and atypical depression is preferentially responsive to monoamine oxidase inhibitors. All four studies with this drug showed a significantly greater treatment response compared with placebo; however the pooled OR is heavily influenced by the results from one study. Exclusion of this study in a sensitivity analysis reduced the pooled OR from 7.22 to 4.58. There have also been positive open-label studies with tranylcypromine.
		RIMAs vs. placebo		OR=2.96 (95% CI 1.78-4.91)		2 High heterogeneity (I^2 = 69%) was noted in the analysis of this drug class. Exclusion of three studies of reversible selective inhibitors of monoamine oxidase A (two brofaromine, one moclobemide) reduced the heterogeneity to 0%, but also reduced the pooled OR from 2.96 to 1.88.
		Gabapentin and pregabalin vs. placebo		OR=3.11 (95% CI 1.92-5.04)		1 Gabapentin and pregabalin are

						both ligands at the alpha-2 delta site on voltage-gated calcium channels. Functionally, both drugs reduce the release of a range of excitatory neurotransmitters through binding to this site. There are three positive RCT with alpha-2 delta ligands. The onset of anxiolytic effects is relatively rapid, occurring within the first week of treatment. The anxiolytic dose-response has only been formally assessed for pregabalin, and efficacy is only evident at the maximum dose (600 mg/day), but not at lower doses. This is in contrast with the effect of pregabalin in, eg, generalized anxiety disorder, where the anxiolytic dose-response is seen at much lower doses (150 mg/day). There are no long-term treatment or relapse prevention data for alpha-2 delta ligands.
		SSRIs and MAOIs vs. psychotherapy		OR=1.86 (95% CI 0.94-3.69) favors to drugs		2 There are no significant differences in effectiveness between SSRIs and psychological treatments (CBT types). The meta-analysis of four monoamine oxidase inhibitor trials suggests that these drugs may be superior to

						psychological treatments, but this result is not statistically significant. It is also important to consider how these treatments compare over the longer term. Three studies have published follow-up data on outcomes after a treatment-free period. In all three trials, the psychological treatment showed greater maintenance of treatment gains or protection against relapse relative to the drug treatments.
		Medication vs. combined medication psychological treatment trials		OR=0.30 (95% 0.09-0.97). Favors to combination.		2 For response rates in the SSRI and monoamine oxidase inhibitor studies, there were nonsignificant trends in favor of combined medication-psychological treatments over medication alone. For the single benzodiazepine study, there was a statistically significant advantage in favor of combined treatment (Figure 7). It should be noted that all studies were relatively small in size and thus may not have been adequately powered statistically. For the pooled response rate in the SSRI studies, there was a nonsignificant trend in favor of combined medication-

						psychological treatments over psychological treatment alone. For the pooled response rate in the monoamine oxidase inhibitor studies, there was a significant trend in favour of combined medication psychological treatments over psychological treatment alone. It should be noted that all studies were relatively small in size and thus may not have been adequately powered statistically.
Caponnetto et al., 2021[6]	Patients diagnosed with social anxiety disorder and without further diagnosis of mental illness.	Immersive Virtual Reality Therapy using a head-mounted display (HMD) and a digitally recreated virtual environment. Comparison: symptoms before "VRET (Virtual Reality Exposure Therapy) with immersive virtual reality technologies" and "post-treatment" symptoms.	Systematic Review.	Post-treatment symptoms related to the disorder, whether or not there was the acquisition of social skills, and whether or not there was a greater adaptation to the social environment.	None	3 Virtual reality therapies proved to be a valid alternative to the acquisition of social skills suitable for improving the symptoms of SAD. Although there has not been a significant difference between VRET and iVET, the low costs and flexibility of VRET open up new scenarios for achieving greater psychophysical well-being.
Carl E et al., 2018[7]	30 studies (n= 1,057) 8 studies tested Virtual reality exposure therapy (VRET) for SAD.	VRET vs Placebo	Metanalysis	The efficacy of VRET compared to psychological placebo or waitlist conditions and in vivo exposure.	-	3 The pooled effect size for 7 studies comparing VRET to psychological placebo or waitlist conditions for SAD and performance anxiety showed a large effect size for VRET (g = 0.97, SE = 0.18, 95% CI: 0.62

						to 1.31). The pooled effect size for 6 studies comparing VRET to in vivo exposure for SAD and performance anxiety a small nonsignificant effect in favor of virtuo conditions (g = 0.06, SE = 0.22, 95% CI: -0.36 to 0.49). POTENTIAL
Carperter JK et al., 2018[8]	Patients were between ages 18 and 65 and met DSM-III-R, DSM-IV, or DSM-5 diagnostic criteria for acute stress disorder, GAD, OCD, PTSD, SAD or specific phobia as determined by a psychometrically sound and structured diagnostic instrument.	CBT vs placebo	Metanalysis	Effect sizes. Response rates.	Sample and study characteristics, including sample size, demographics, placebo type, CBT treatment type (exposure, cognitive or both; group vs. individual), number of sessions, type of analysis (completer vs. ITT), and year of publication.	1 Small to moderate effect sizes were found for SAD. Treatment response Odds ratio was 3.51 for CBT compared to placebo.
Cuijpers P et al., 2016[9]	Patiens with anxiety disorder, including SAD	CBT vs placebo and others	Metanalysis	Effect size indicating the difference between the two groups at post-test was calculated (Hedges's g).	Other effects related to scales scores and homogeneity.	2 More research is also needed to improve the effects of treatments, especially for GAD and SAD, because even if the effects of treatments are generally positive, there is still a considerable number of

						patients that do not benefit. There is great heterogeneity between studies.
Horigome et al., 2020[10]	14 out of 22 studies assessing SAD. 9 included studies did not have group control.	VRET	Metanalysis	SAD evaluation score change measured mainly by LSAS changes	RR for treatment discontinuation	2 The efficacy of VRET for SAD was significant and continued over a long-term follow-up period: Hedges' g for effect size at post-intervention, −0.86 (−1.04 to −0.68); three months post-intervention, −1.03 (−1.35 to −0.72); 6 months post-intervention, −1.14 (−1.39 to −0.89); and 12 months post-intervention, −0.74 (−1.05 to −0.43). When compared to in vivo exposure, the efficacy of VRET was similar at post-intervention but became inferior at later follow-up points. Participant dropout rates showed no significant difference compared to in vivo exposure.
Kampmanet al 2016[11]	37 studies (n=2991)	Technology-assisted interventions (ICBT, VRET, CBM) vs Placebo	Metanalysis	Self reported symptoms in postassesment and follow up	Depressive symptoms	2 Patients undergoing ICBT and VRET showed significantly less SAD symptoms at post assessment than passive control conditions.
Li et al. 2020[12]	13 RCTs (N = 2585)	Paroxetine vs placebo	SR	Changes in the LSAS total score and related subscales, Global	Tolerability	1 Mean changes in the LSAS total score and subscales were

				Impression Severity of Illness (CGI-S) scale score, the Social Avoidance and Distress Scale (SADS) and the Sheehan Disability Scale (SDS) for work, social, and family items.		all significantly greater in the active group. Response and remission rates were both significantly greater in the active group. Number of dropouts due to AEs were higher compared to placebo.
Liu 2021 et al.[13]	11 eligible randomized controlled trials (RCTs) and 5 single-arm trials	Mindfulness alone and associated versus other interventions	Metanalysis	The primary outcome was the severity of the SAD clinical symptoms	Secondary outcomes were depressive symptoms, mindfulness, quality of life and self-compassion.	2 The between-groups analysis of the 11 RCTs showed that Hedges' g =0.00, while the within-group analysis showed a large pre-post effect size (g =1.20). MBIs were superior to the no-treatment comparator (g =0.89), equivalent to specific active treatment (g = –0.19), and less effective than evidence-based treatment (i.e., cognitive behavioral therapies) (g= –0.29).MBIs significantly alleviated depressive symptoms and improved mindfulness, quality of life, and self-compassion. Meta-regression analysis showed a dose–response relationship between the alleviation of SAD symptoms and the duration of the MBIs (β =0.659). Follow-up analysis showed that the effects of MBIs on SAD persisted for 12 months (g =0.231). An analysis of the 5

						single-arm trials found that MBIs had a medium effect in alleviating SAD symptoms (g =0.48).
Liu H., et al 2017[14]	34 studies (n=2550)	Cognitive bias modification (CBM) vs Placebo	Metanalysis	Evaluate the degree to which certain variants of CBM improve SAD symptoms and cognitive behaviors (CBs).	Identify the potential moderators of the effectiveness of CBM on SAD.	2 There were small but significant effects of CBM on the primary symptoms of SAD , cognitive bias (CB) toward threat , and reactivity in stressful situations , but non-significant effects on secondary symptoms.
Liu X, et al. 2018[15]	5 RCT (N=1045)	Fluvoxamine vs Placebo	Metanalysis	Mean changes in LSAS total score and the CGI-S. The tolerability outcome was discontinuation rate due to AEs.	Response rate on the CGI-I scale and tolerability	1 Mean changes in LSAS total and CGI-S scores were both significantly greater in the active group.. Response rate was higher in the fluvoxamine group.. The discontinuation rate due to AEs was higher in patients that received fluvoxamine.
Mayo-Wilson et al 2014[16]	101 RCT's (n=13 164)	Psychological placebo and pharmacological vs placebo/waitlist	Systematic Review and Metanalysis	Assessed the severity of SAD symptoms mainly by the measure of the LSAS.	-	1 Greater effects on outcomes were found for IMAO, BZDs, SSRIs and SNRIs, and anticonvulsants. Effects for psychological interventions were found for individual CBT, group CBT, exposure and social skills, self-help with support, self-help without support and psychodynamic

						psychotherapy.
	6 studies (N= 490)	Maclobemide vs waitlist		–0·74 [–1·03 to –0·44]		1
	5 studies (N= 125)	Phenelzine vs waitlist		–1·28 [–1·57 to –0·98]		1
	1 study (N= 12)	Alprazolam vs waitlist		–0·85 [–1·40 to –0·30]		2 The largest effects were for MAOIs (class effect SMD −1·01, 95% CrI −1·56 to −0·45) and benzodiazepines (−0·96, −1·56 to −0·36), but the evidence for these effects was limited compared with evidence for SSRIs and SNRIs (−0·91, −1·23 to −0·60)
	4 studies (N= 100)	Clonazepam vs waitlist		–1·07 [–1·44 to –0·70]		2 The largest effects were for MAOIs (class effect SMD −1·01, 95% CrI −1·56 to −0·45) and benzodiazepines (−0·96, −1·56 to −0·36), but the evidence for these effects was limited compared with evidence for SSRIs and SNRIs (−0·91, −1·23 to −0·60)
	1 study (N= 34)	Gabapentin vs waitlist		–0·89 [–1·42 to –0·37]		Inconclusive
	1 study (N= 9)	Levetiracetam vs waitlist		–0·83 [–1·50 to –0·18]		Inconclusive
	3 studies (N= 199)	Pregabalin vs waitlist		–0·72 [–1·07 to –0·37]		Inconclusive

	2 studies (N= 18)	Citalopram vs waitlist		–0·83 [–1·28 to –0·39]		1
	2 studies (N=675)	Escitalopram vs waitlist		–0·88 [–1·20 to –0·56]		1
	3 studies (N=107)	Fluoxetine vs waitlist		–0·87 [–1·16 to –0·57]		1
	5 studies (N=500)	Fluvoxamine vs waitlist		–0·94 [–1·25 to –0·63]		1
	12 studies (N=1449)	Paroxetine vs waitlist		-0.99 [-1.26;-0.73]		1
	3 studies (N=535)	Sertraline vs waitlist		–0·92 [–1·23 to –0·61]		1
	5 studies (N=759)	Venlafaxine vs waitlist		–0·96 [–1·25 to –0·67]		1
	1 study (N=30)	Mirtazapine vs waitlist		–0·81 [–1·45 to –0·16]		1 Mirtazapine, a noradrenergic and sepcific serotonergic antidepressant, was the only pharmacological intervention in a class by itself; its effect was not greater than that for waitlist (class effect SMD −0·80, 95% CrI −1·64 to 0·01), but only 30 people received the intervention.
Nordahl et al., 2016[17]	N = 102	paroxetine vs CT vs paroxetine + CT and placebo	RCT	symptoms measured by the e Fear of Negative Evaluation Questionnaire (FNE)	anxiety symptoms assessed by the LSAS and BAI	2 Recovery rates were higher in the CT group compared to the Sgroup. CT was also superior to paroxetine alone and pill

						placebo at 12 month follow up.
Williams T et al 2020[18]	67 RCT's	Pharmacotherapy vs placebo and head to head comparisons	Metanalysis	Efficacy and acceptability measured by the LSAS and number of dropouts	Response and tolerability measured by the CGI-I and number of dropouts due to AEs	2 Response was found for paroxetine, brofaromine, bromazepam, clonazepam, escitalopram, fluvoxamine phenelzin, and sertraline. Olanzapine achieved the greatest result for treatment response efficacy and buspirone the worse. Brofaromine, escitalopram, fluvoxamine, paroxetine, pregabalin, sertraline and venlafaxine performed worse than placebo for dropouts due to side effects.
		Olanzapine		MD -37.8 (-87.24;11.64)		Inconclusive.
		Bromazepam		MD -31..60 (-66.64;3.44)		2 Superior response to treatment was also observed for paroxetine, brofaromine, bromazepam, clonazepam, escitalopram, fluvoxamine, phenelzine, and sertraline.
		Clonazepam		MD -23.70 (-58.87;11.67)		2 Superior response to treatment was also observed for paroxetine, brofaromine, bromazepam, clonazepam, escitalopram, fluvoxamine, phenelzine, and sertraline.

		Sertraline		MD -17.45 (-43.76;8.88)		2 Superior response to treatment was also observed for paroxetine, brofaromine, bromazepam, clonazepam, escitalopram, fluvoxamine, phenelzine, and sertraline.
		Paroxetine		MD -15.89 (-29.94;-1.84)		2 Superior response to treatment was also observed for paroxetine, brofaromine, bromazepam, clonazepam, escitalopram, fluvoxamine, phenelzine, and sertraline.
		Mirtazapine		MD -14.53 (-38.87;9.82)		Inconclusive.
		Gabapentin		MD -11.50 (-47.62; 24.62)		Inconclusive.
		Phenelzine		MD -8.65 (-28.65; 11.38)		2 Superior response to treatment was also observed for paroxetine, brofaromine, bromazepam, clonazepam, escitalopram, fluvoxamine, phenelzine, and sertraline.
		Moclobemide		MD -8.51 (-25.87; 8.86)		Inconclusive.
		Brofaromine		MD - 8.10 (-43.29; 27.09)		2 Superior response to treatment was also observed for paroxetine, brofaromine, bromazepam, clonazepam, escitalopram, fluvoxamine, phenelzine, and sertraline.

		Escitalopram		MD -8.05 (-41.81;25.71)		2 Superior response to treatment was also observed for paroxetine, brofaromine, bromazepam, clonazepam, escitalopram, fluvoxamine, phenelzine, and sertraline.
		Levetiracetam		MD -3.82 (-31.80;24.15)		Non significant.
		Fluvoxamine		MD -2.12 (-21.88;17.64)		2 Superior response to treatment was also observed for paroxetine, brofaromine, bromazepam, clonazepam, escitalopram, fluvoxamine, phenelzine, and sertraline.
		Atomoxetine		MD 2.60 (-35.38; 40.58)		Non significant.
		Vilazodone		MD 15.60 (-22.05;53.25)		Non significant.
		Venlafaxine		MD 30.47 (7.76;53.18)		Inconclusive.
Williams T et al 2017[19]	66 RCTs (n= 11,597)	Pharmacotherapy vs Placebo	Systematic Review	Reduction in SAD symptoms using the LSAS, Reduction in depressive symptoms, functional disability, and dropout rates	For the secondary outcome of SAnD symptom severity, there was benefit for the SSRIs, the SNRI venlafaxine, MAOIs, RIMAs, benzodiazepines, the antipsychotic olanzapine, and the noradrenergic and specific serotonergic antidepressant (NaSSA) atomoxetine in the	1 Found very low-quality evidence of treatment response for SSRIs. There was also evidence of benefit for MAOIs, RIMAs, BZD, pregabalin and gabapentin. The SSRIs were the only medication proving effective in reducing relapse based on moderate-quality evidence.

					reduction of SAnD symptoms, but most of the evidence was of very low quality.	
	1 study (N=30 15 active/15 placebo	5HT1A partial agonists (Buspirone) vs Placebo		1.00 [0.07 to 14.55]		Non significant.
	3 studies (N=532 (369 active / 163 placebo)	Anticonvulsivants GABAs (gabapentin and pregabalin) vs Placebo		1.60 [1.16 to 2.20]		Non significant.
	2 studies (N=228 (118 active /110 placebo)	Levetiracetam vs placebo		0.98 [0.70 to 1.37]		Non significant.
	2 studies (N=132 (67 active/65 placebo)	BZDs vs Placebo		4.03 [2.45 to 6.65]		Non significant.
	2 trials	Antipsychotics (olanzapine and quetiapine)		1.07 [0.27 to 4.23]		Non significant.
		Quetiapine				
	2 studies (N=97 (49 active/ 48 placebo)	Beta-blockers vs placebo		1.09 [0.63 to 1.88]		Non significant.
	4 studies (N=235 (121 active/ 114 placebo)	MAOI (phenelzine) vs placebo		2.36 [1.48, 3.75]		3 MAOIs was reported with very low-quality evidence.
	1 study (n=60)	Mirtazapine vs placebo		1.00 [0.28, 3.63]		Difference was not significant

	(30 active/30 control					
	8 studies (N=1270) 632 active / 638 placebo	RIMAs vs Placebo		1.83 [1.32 to 2.55]		3 There was evidence that this medication was eficacious compared to placebo (k = 5, RR 1.32;95% CI 1.14 to 1.52, N = 1063; P < 0.001). Furthermore, there was moderate-quality evidence of a long-term eFect for moclobemide on treatment eFicacy in participants with SAnD compared to placebo (k = 1, RR 1.50; 95% CI 1.12 to 2.00, N = 90. Comparisons between medication classes revealed that response to the RIMAs was smaller than that observed for the benzodiazepines (Chi2 = 6.63, df = 1, P = 0.01; I2 = 84.9%).
	4 studies (N=1173) 630 active / 543 placebo	Venlafaxine vs placebo		1.30 [0.85 to 1.99]		2 Venlafaxine on the basis of treatment withdrawal; this was higher for medication than placebo (SSRIs: k = 24, RR 2.59; 95% CI 1.97 to 3.39, N = 5131, low-quality evidence; venlafaxine: k = 4, RR 3.23; 95% CI 2.15 to 4.86, N = 1213, moderate-quality evidence), but there were low absolute rates of withdrawal for both these

						medications classes compared to placebo.
	24 studies (N=4984) 2767 active/ 2217 placebo	SSRIs vs Placebo		1.65 [1.48 to 1.85]		1 The SSRIs were the only medication proving effective in reducing relapse based on moderate-quality evidence.
Yang L et al., 2019[20]	17 RCT's (n= 1134)	Psychological interventions for children and adolescents	Metanalysis	Change scores on anxiety symptoms measured by anxiety rating scales and acceptability (dropout due to any reason)	Remission, quality of life/functional improvement and depressive symptoms	1 PI's were more affective than control (SMD -1.13; RR 8.99 and NNT=3.3). PI's were also superior to control in improving quality of life and reducing depressive symptoms.

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Supplementary Table S2 Risk of bias of systematic reviews with or without metanalysis for pharmacological approach

Study	Study eligibility criteria	Identification and selection of studies	Data collection and study appraisal	Synthesis and findings	Risk of bias in the review
Bandelow B et al. 2015	Low	Low	Low	Low	Low
Baldwin DS, et al. 2016	Low	Low	Low	Low	Low
Barkowski S et al., 2016	Low	Low	Low	Low	Low
Canton J e tal., 2012	Low	Low	Low	Low	Low
Caponnetto et al. 2021	High	High	High	High	High
Carl E et al., 2018	High	High	High	High	High
Carperter JK et al., 2018	Low	Low	Low	Low	Low
Cuijpers P et al., 2016	Low	Low	Unclear	High	Unclear
Horigome et al., 2020	Low	Low	Low	Low	Low
Jakubovski et al. 2019	High	High	High	High	High
Kampmann IL et al 2016	Low	Low	Low	Low	Low
Li et al. 2020	Low	Low	Low	Low	Low
Liu X et al. 2021	Low	Low	Low	Low	Low
Liu H et al. 2017	Low	Low	Low	Low	Low
Liu X et al. 2018	Low	Low	Low	Low	Low
Mayo-Wilson et al. 2014	Low	Low	Low	Low	Low
Nordahl et al. 2016	Low	Low	Low	Low	Low
Van Dis et al. 2019	Low	Low	Low	Low	Low
Scaini et al. 2016	Low	Low	Low	Low	Low
Williams et al. 2017	Low	Low	Low	Low	Low
Williams et al. 2020	Low	Low	Low	Low	Low
Yang L et al., 2019	Low	Low	Low	Low	Low

Supplementary Table S3 Risk of bias of randomized clinical trials for pharmacological approach

Authors	Randomization process	Risk of bias arising from the timing of identification or recruitment of participants	Deviations from intended interventions	Mising outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
Bernik et al., 2018	Low	Low		Low	Low	Low	Low
Nordahl et al., 2016	Low	Unclear	Low	High	Low	Low	Unclear