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Review Article

Efficacy of benzodiazepines (BZD) in the treatment of anxiety disorders: a literature review

Eficácia dos benzodiazepínicos no tratamento de transtornos ansiosos: uma revisão de literatura

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ABSTRACT: With the increasing rate of anxiety disorders in the world population, there is a growing need for research on psychotropic drugs that provide treatment experience, safety, and sustainability to the patient. Thus, this research aims to conduct a systematic methodological review of the effectiveness of benzodiazepines (BZD) in the treatment of anxiety disorders (AD). The studies were searched in the PubMed and ScienceDirect databases, using the descriptors: "benzodiazepines" and "anxiety disorder". The Boolean operator "AND" will be used. Twenty-seven studies were reviewed, with a total sample of 120,418 patients from studies published between 2011 and 2021, including 15 systematic reviews, 5 systematic reviews with meta-analysis, 2 meta-analyses, 1 systematic review with the original study, 1 clinical trial, 1 clinical trial with a case-control study, 1 clinical trial with a prospective study and 1 double-blind clinical trial with placebo. BZD are effective in the treatment of anxiety disorders generalized anxiety and social phobia, but are impractical in terms of quality and safety related to their long-term dependence potential. New drugs have been considered as a possible replacement for BZD for AD. Studies considering other anxiety disorders are needed, in addition to those addressed in this research.

Keywords: Psychology; Psychiatry; Psychopharmacology; Benzodiazepines; Anxiety.

RESUMO: Com o crescente índice de transtornos ansiosos na população mundial, cresce a necessidade de se investigar psicofármacos que possibilitem experiências de tratamento, segurança e sustentabilidade ao paciente. Dessa forma, o objetivo desta pesquisa é realizar uma revisão sistemática metodológica acerca da eficácia dos benzodiazepínicos (BZ) para o tratamento de transtornos ansiosos (TA). Os estudos foram pesquisados nas bases de dados da PubMed e ScienceDirect, a partir dos descritores: "benzodiazepines" e "anxiety disorder". Será utilizado o operador booleano "AND". Foram revisados 27 artigos científicos, com amostra total de 120.418 pacientes de estudos publicados entre os anos de 2011 e 2021, sendo 15 revisões sistemáticas, 5 revisões sistemáticas com meta-análise, 2 meta-análises, 1 revisão sistemática com estudo original, 1 ensaio clínico, 1 ensaio clínico com caso controle, 1 ensaio clínico com estudo prospectivo e 1 estudo duplo cego com ensaio clínico utilizando placebo. Percebeu-se que os BZ se mostraram efetivos no tratamento de transtornos ansiosos (ansiedade generalizada e fobia social), mas inviável em termos de qualidade e seguridade em relação ao seu potencial de dependência a longo prazo. Novos medicamentos foram considerados como possível substituição do BZ para os TA. Novos estudos considerando outros transtornos ansiosos são necessários, além dos que foram abordados nesta pesquisa.

Palavras-chave: Psicologia; Psiquiatria; Psicofarmacologia; Benzodiazepínicos; Ansiedade.

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INTRODUCTION

Even as a consolidated drug for the treatment of anxiety disorders (AD), the prescription of benzodiazepines (BZD) has undergone a transformation in recent years with respect to new drugs that are considered in the literature to be the first line of treatment for AD. However, scientific support continuous to favor the use of BZD for psychiatric disorders, particularly panic and generalized anxiety[1].

These anxiety disorders are associated with a set of psychiatric conditions that share common features, such as anxiety and fear in large quantities, in addition to excessive disturbances on certain occasions when the person feels threatened. The body goes into a process of autonomic arousal, that produces fight-or-flight behavior, especially in environments of psychological stress[2].

However, when considering the BZD for anxiety disorders, some characteristics must be considered, such as the level of anxiety and the specific psychiatric disorder, identified from relevant anxiety scales that allow concise information to be integrated for drug prescription[3].

The use of BZD remains controversial in the scientific literature, precisely because of its positive and negative effects in relation to its primary use in cases of anxiety and its use as a long-term treatment, as well as its side effects[4].

While other antidepressant drugs require a few weeks of treatment to produce meaningful results, BZD start to be effective from the fourth week of use, mainly due to their sedative and anxiolytic effects. However, studies are still needed to support this evidence for the use of BZD in the treatment of anxiety disorders.

Although the efficacy of benzodiazepines in the treatment of AD has been scientifically proven, prolonged use of this drug makes it a poorly adaptive mechanism for patients, with a high risk of drug dependence. Furthermore, new first-line psychotropic drugs may provide a safer and more effective path to treatment. Therefore, the objective of this research is to discuss the effectiveness of benzodiazepines (BZD) in the treatment of anxiety disorders (AD).

METHOD

The purpose of this study was to conduct a systematic methodological review of the literature between the months of August and December 2021. For this investigation, the descriptors "benzodiazepines" and "anxiety disorder" were used – both present in the Medical Subject Heading (MeSH) – for searches in the PubMed and ScienceDirect databases. The Boolean operator "AND" was used.

As a selection criterion, only studies published in the last ten years (2011-2021) that contained any of the descriptors in the title or abstract were accepted. Following the eligibility criteria, only productions of the type: systematic review, meta-analysis, and clinical trials (or mixed studies). Cross-strategy references may be used throughout this review. To conduct the steps of this systematic review, the PRISMA literature review flowchart was followed, as shown in Figure 1.

Only for the description of terms and characteristics of the drug class of benzodiazepines, package inserts and updated technical references may be added during the development of the research.

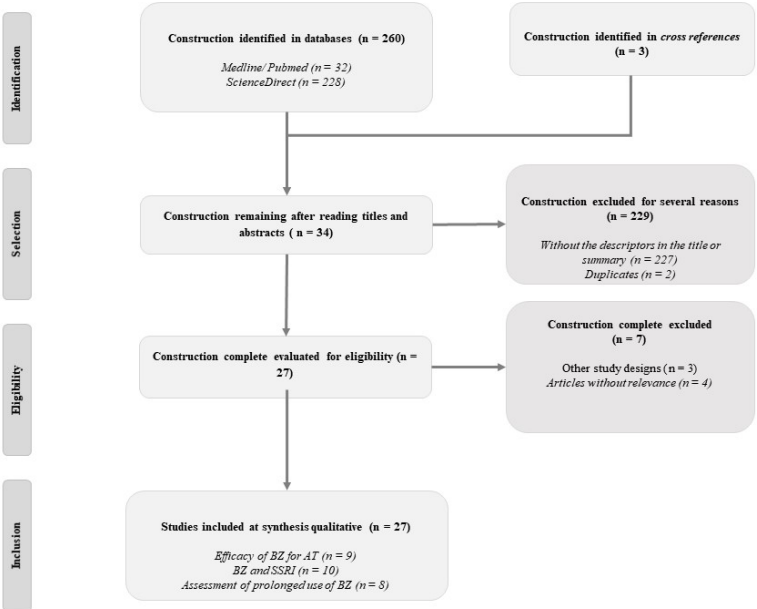

Figure 1. Research flowchart

RESULTS

A total of 27 scientific articles published between 2011 and 2021 were reviewed, including 15 systematic reviews, 5 systematic reviews with meta-analysis, 2 meta-analyses, 1 systematic review with original study, 1 clinical trial, 1 clinical trial with a case-control, 1 clinical trial with a prospective study and 1 double-blind study with a clinical trial using placebo, as shown in Table 1.

Table 1: Studies used in the research

AUTHOR/YEAR	TYPE OF STUDY	STUDY CHARACTERISTICS
Blanco et al., 2013	Systematic review	Reviews the pharmacological treatment of Social Phobia based on placebo-controlled studies and published meta-analyses.
Balon; Starcevic, 2020	Systematic review	Reviews the role of BZDs in the treatment of anxiety disorders, specifically panic disorder with or without agoraphobia, generalized anxiety disorder, and social phobia.
Choi et al., 2020	Systematic review	Presentation of clinical treatment distinctions for anxiety disorders and depressive disorders.
Bandelow, 2020	Systematic review	Reviews and recommends guidelines for the psychopharmacological treatment of anxiety disorders, based on comprehensive treatment guidelines.
Gomez et al., 2018	Meta-analysis	Reviews the effectiveness of SSRIs, BZDs, and SNRIs in treating adults with GAD.
Takeshima et al., 2021	Systematic review and meta-analysis	Investigates Cognitive-Behavioral Therapy for discontinuation of BZD anxiolytics in patients with anxiety disorders.
Hadley et al., 2012	Double blind study and clinical trial	Assesses the effectiveness of pregabalin in facilitating the reduction of benzodiazepines.
Starcevic, 2014	Systematic review	Reviews the BZDs and other pharmacotherapies for anxiety and related disorders and investigates long-term BZDs treatment guidelines for panic disorder, generalized anxiety disorder, and Social Phobia.
Lader, 2011	Systematic review	It re-examines aspects of BZD, widely prescribed 50 years ago, mainly to treat anxiety and insomnia.
De Mesmaeker et al., 2014	Systematic review	Investigates the place of benzodiazepines in the current treatment of anxiety disorders as opposed to antidepressants, neuroleptics and anticonvulsants.
Chen et al., 2019	Meta-analysis	It synthesizes direct and indirect evidence for alternative interventions for GAD.
Strawn et al., 2012	Systematic review	Summarizes functional characteristics, connectivity, and structural neuroimaging data in children and adolescents with GAD and synthesizes treatment guidelines.
Gale; Millichamp, 2016	Systematic review	It analyzes the effects of pharmacological treatment in children and adolescents with GAD.
Mesdrakis et al. 2013	Systematic review	Reviews pharmacological treatment for patients with Social Phobia.
Baldwin et al., 2011	Systematic review and meta-analysis	Efficacy of drug treatments for generalized anxiety disorder.
Reinhold; Rickels, 2015	Systematic review	Reviews the literature related to pharmacological treatment guidelines for GAD.
Strawn, 2018	Systematic review	Reviews pharmacotherapy for children and adult patients with GAD with specific comments on the efficacy and tolerability of selected agents in these age groups.
Weich et al., 2014.	Systematic review	Testing the hypothesis that people who take anxiolytics and hypnotics are at increased risk of premature mortality.
Mayo-Wilson et al., 2014	Systematic review and meta-analysis	Compare interventions and identify which are most effective for the acute treatment of Social Phobia in adults.
Slee et al., 2019	Systematic review and meta-analysis	Compare interventions and identify which are most effective for treating GAD.
Williams et al., 2017	Systematic review	Evaluates the effects of pharmacotherapy for Social Phobia in adults and identifies the main factors (methodological or clinical) for the response to treatment.
Berger et al., 2012	Systematic review	Examines usage patterns and health care costs in patients with anxiety disorder (GAD) who initiate treatment with benzodiazepine anxiolytics as adjunctive therapy.
Bernard et al., 2018	Systematic review and original study	Examines patterns of benzodiazepine use and long-term use.
Boggs et al., 2020	Clinical trial case control	Investigates the association between death by suicide and compliance with benzodiazepine guidelines.
Laurito et al., 2018	Clinical trial	Investigates the rates of current and past use of benzodiazepines seen in specialized clinics, especially in relation to panic, generalized anxiety and obsessive-compulsive disorders.
Langer et al., 2020	Systematic review and meta-analysis	Compares the effects of BZD and SSRIs in the treatment of anxiety disorders.
Pradeep et al., 2020	Clinical trial and prospective study	Investigates the relationship between gastroesophageal reflux disease and psychological symptoms, clinically diagnosed generalized anxiety and the effectiveness of sertraline and benzodiazepines in controlling these conditions.

Studies carried out in 8 countries were selected, including the United States, Canada, Taiwan, Israel, Africa, United Kingdom, Belgium, and Japan, with a total sample of 120,418 patients. In summary, the investigations were concerned with examining patterns in health care or nonspecific anxiety disorders using a BZD as pharmacological treatment, pharmacological evidence for Social Phobia and generalized anxiety. In addition to, comparative studies between benzodiazepines and other drugs, such as pregabalin and Selective Serotonin Reuptake Inhibition (SSRI), were also selected.

The Hamilton Anxiety Rating Scale (HAM)-A was the main instrument used to measure anxiety levels based on the mean difference (MD) in the change in patient scores on the scale in each of the investigations. Other assessment instruments such as GAD-7 and the Penn State Worry Questionnaire (PSWQ) were also used.

Benzodiazepines (BZD)

The chemical identification of the BZD class has a very similar structure. Its molecules consist of a 1,4-benzodiazepine ring. However, they differ in terms of the rest of the composition (2-keto; 3-hydroxy, 7-nitro, triazole, and imidazo benzodiazepines). Its action is associated with the potentiation of the action of gamma-aminobutyric acid (GABA), one of the main inhibitory neurotransmitters of the Central Nervous System (CNS)[5].

In the psychiatric clinic, benzodiazepines are used as potentiators for Selective Serotonin Reuptake Inhibition (SSRI). Recent clinical trials demonstrate the effectiveness of the drug in this proposal, complementing the need to focus on cognitive damage in older patients, potential abuse of BZD, in addition to withdrawal symptoms caused by the absence of the drug[6].

Far from being a new drug, BZD lead the ranking of psychotropic drugs used to treat anxiety disorders. By 2002, approximately 94% of North American patients with anxiety disorders were successfully treated with benzodiazepines[7].

Efficacy of BZD for the treatment of anxiety disorders

A review using metadata concluded that BZD was the most effective drug class in the treatment of AD in adults, but that the drug's effect size decreases over time[8]. Furthermore, the use of BZD for the treatment of long-term anxiety disorders is not recommended[9].

An Australian study suggested the use of BZD as a first-line drug that can be trusted for the treatment of anxiety disorders, especially panic, generalized anxiety, and social phobia. Long-term use was also considered positive, without considerable side effects other than those common to BZD[4].

Through a Polish study, it is possible to understand the controversy associated with the use of BZD for anxiety disorders. Belgium and France are the only European countries to adhere to BZD prescription rates different from those established by the National Institute for Health and care Excellence (NICE). However, the study concludes that it is precisely the existence of these controversies that make BZD irreplaceable for the treatment of anxiety disorders, at least at present, especially with the positive results of French and Belgian studies concerning the drug class[10].

A clinical trial compared the use of BZD versus placebo for the treatment of social phobia. It was demonstrated that most participants responded positively to treatment with BZD. However, the quality of the evidence proved to be low due to the limited number of patients participating in the study[11].

Comorbid anxiety disorders with gastroesophageal reflux resulted in an improvement in the quality of life of these patients, achieving high levels of efficacy in controlling the symptoms of reflux, anxiety, and panic[12].

BZD and SSRI for anxiety disorders

Although BZDs are among the oldest medications used to treat anxiety disorders, a study conducted in Taiwan did not recommend prescribing this class of substances as first-line treatment for GAD, considering the potential risk of dependence. It was also recommended that the use of SSRIs and SNRIs (Selective Serotonin and Norepinephrine Reuptake Inhibitors) be discontinued in cases of GAD[13].

A study using metadata found that SSRIs (such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) had higher efficacy rates as a pharmacological intervention for Social Phobia in adults, showing consistent evidence to be considered[14].

When investigated in the treatment of AD in children and adolescents, the scientific literature demonstrates evidence of positive effects of the use of BZD in the remission of symptoms, however, in relation specifically to GAD in children and adolescents, the literature strongly recommends SSRI drugs[15].

Furthermore, the relationship between the dosage and the biological response of BZDs for the treatment of anxiety disorders should be observed. Studies have already associated BZD with excessive sedation, confusion and increased mortality in specific cases[16].

An Israeli study using metadata concluded that the treatment effect of BZD was significantly associated with the dose used in the treatment. The opposite was observed in SSRI drugs, in which there was no statistical correlation between the amount of drug prescribed and its effect[17].

Assessment of long-term use of BZD

A literature review observed numerous adverse

effects concerning the use of BZD, such as cognitive and psychomotor alterations. In addition, dependence and abuse in the use of the drug continue to be some challenges. Despite existing prescribing guidelines, the use of these drugs remains at a high level[18].

A survey found that 88.4% of its respondents made long-term use of some BZD (more than 12 weeks). It was also found that although patients are aware of the effects related to the long-term use of a BZD, they continue to use the drug, which should be a factor to be identified by medical professionals to avoid drug dependence[19].

A Taiwanese study found that approximately 94% of the patients surveyed use BZD in the long term[20]. While in a Brazilian survey, this number rises to 95%[21].

Given the decrease in the drug effect of BZD and the non-recommendation of its long-term use, a control study suggested that switching from psychotropic drugs to pregabalin may be a safe intervention in cases of prolonged treatment with BZD[22].

Pregabalin proved to be a safe and effective drug for the treatment of anxiety disorders, especially GAD. It was found that the use of pregabalin significantly reduced anxiety signal points identified from the HAM-A. Nevertheless, it proved to be an effective treatment measure, especially for the replacement of BZD when used for an extended period[22].

Some studies show the need for attention to the prolonged use of BZD, which can lead to a series of side effects, such as depression, cognitive damage, especially in older patients, fatigue and others[7].

Other associations related to BZD

The association between the use of BZD and deaths by suicide maintains a great discussion in the scientific literature and outside it, with specialists. However, a North American study did not identify a statistically significant correlation between the variables[23].

Furthermore, Cognitive Behavioral Therapy (CBT) has been shown to be the most effective non-pharmacological treatment for anxiety disorders, especially when there is drug resistance in these conditions[13, 15, 20, 24]. However, studies still present impasses in relation to the existing scientific evidence that proves that the association between psychotropic drugs and psychotherapy is, in fact, beneficial for anxiety disorders, in relation to the exclusive use of only one psychotropic drug[16].

One study examined patterns in healthcare and healthcare costs among patients with AD who started pharmacologic treatment using BZD. It was found that the levels of care and health costs increased in the first six months after the beginning of anxiety treatment using a BZD[25].

DISCUSSION

This article promoted a discussion about the use of BZD for the treatment of anxiety disorders. It was noticed that BZD were effective in the treatment of symptoms related to AD in the reviewed studies, especially those of Generalized Anxiety and Social Phobia[26-30]. However, prolonged use of this drug is still a concern. This prolonged use has effects that are still poorly measured in the existing literature, from possible drug dependence to cognitive implications related to the mechanism of action of BZD[31,32].

The studies reviewed focused, for the most part, on pharmacological treatment guidelines for generalized anxiety disorders and Social Phobia, even in the face of data that show leaps in the care of patients with agoraphobia and obsessive- compulsive disorder[33].

BZDs were not considered first-line drugs for the treatment of AD. Research suggests that Selective Serotonin Reuptake Inhibitors (SSRIs) are safer and more effective, especially in cases of longer-term use of BZD[34-38].

The prolonged use of these drugs is still the main clinical concern of professionals in the field[39]. Since the use of BZD for AD was not recommended in the long term, it is necessary to stick to new drug proposals that replace the role of BZD in treatment. Pregabalin, for example, has obtained promising results as a strategy to replace BZD when used for long periods (over 12 weeks) aiming at patient safety and quality treatment[40,41].

The Selective Serotonin Reuptake Inhibitors (SSRI) show more promise in terms of treatment, in the short, medium and long term, without significant changes in patient safety or correlation with dosage and drug effect and, still, danger of dependency, the opposite of what happens in the BZD class.

CONCLUSIONS

Despite the reasonable sample size in this research, the evidence scored is not of high impact, given the concentration of the studies reviewed on specific anxiety disorders. It was found that even effective in the treatment of anxious symptoms, BZD are still reasons for many controversies in the literature due to the risk of dependence caused. Furthermore, studies have suggested that SSRI drugs are more indicated as first-line psychotropic drugs for the treatment of Generalized Anxiety Disorder and Social Phobia compared to benzodiazepines.

Limitation and recommendations

The limitations of this study should be considered as it was not possible to investigate the effectiveness of

BZD in all cases of anxiety disorders provided for in the diagnostic manuals, but focusing on Generalized Anxiety Disorder (GAD) and Social Phobia.

Cohort research and meta-analysis are recommended to make it possible to make comparisons between BZD and other SSRIs for the treatment of anxiety disorders, in addition to the metabolic side effects that these drug classes can cause on the Nervous System.

Authors and contributions: *Gabriel Luiz de Jesus Ribeiro:* final design of the research project, research execution, literature review and manuscript writing. *Josué da Silva Brito:* support in research design, review and writing of the manuscript.

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