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Evidence from Cochrane systematic reviews on pharmacological treatment compared to placebo for panic disorder

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ABSTRACT. Panic disorder is an anxiety condition characterized by recurrent and unexpected panic attacks. The comparison between active treatment and placebo is essential to analyze an intervention's efficacy and safety. It is important to identify and summarize the studies with higher evidence to assist health professionals and public policy managers in clinical decision-making. **Objective:** The aim of this study was to identify and summarize all Cochrane systematic reviews (SRs) that compared the efficacy and safety of any drug treatment compared to placebo for panic disorder patients. **Methods:** SRs published in the Cochrane Library were included without date restriction. All outcomes presented were analyzed. The methodological quality of the SRs was evaluated using the AMSTAR-2 tool. **Results:** We included three Cochrane SRs of high methodological quality on the effects of antidepressants, benzodiazepines, and azapirones for panic disorder. All medications showed benefits in response to treatment, symptom improvement, and reduced panic attacks. Dropouts were lower with tricyclic antidepressants and benzodiazepines and higher with azapirones. The occurrence of adverse events was higher for drug groups. **Conclusions:** Very low to moderate certainty evidence (GRADE) showed that antidepressants and benzodiazepines seem to improve clinical symptoms in individuals with short-term panic disorder compared to placebo. In addition, the use of azapirones seems to have greater adherence by patients than placebo. However, there is insufficient evidence to support its clinical efficacy.

Keywords: Panic Disorder; Drug Therapy; Systematic Review; Evidence-Based Medicine.

EVIDÊNCIAS DAS REVISÕES SISTEMÁTICAS COCHRANE SOBRE O TRATAMENTO FARMACOLÓGICO COMPARADO AO PLACEBO PARA TRANSTORNO DE PÂNICO

RESUMO. O transtorno de pânico é uma condição de ansiedade caracterizada por ataques de pânico recorrentes e inesperados. A comparação entre tratamento ativo e placebo é essencial para analisar a eficácia e a segurança de uma intervenção. É importante identificar os estudos com maiores evidências para auxiliar os profissionais de saúde e gestores de políticas públicas nas decisões clínicas. **Objetivo:** Identificar e sumarizar todas as revisões sistemáticas (RS) publicadas na Cochrane que relatam a eficácia e a segurança de qualquer tratamento medicamentoso comparado ao placebo para pacientes com transtorno de pânico. **Métodos:** Foram selecionadas e analisadas todas as RS publicadas na base de dados Cochrane, sem restrição de data. A qualidade metodológica das RS foi avaliada utilizando a ferramenta AMSTAR-2. **Resultados:** Foram incluídas três RS Cochrane com alta qualidade metodológica que avaliaram os efeitos de antidepressivos, benzodiazepínicos e azapironas para transtorno de pânico. Todos os medicamentos mostraram benefícios na resposta ao tratamento, melhora dos sintomas e redução das crises de pânico. O número de desistências do tratamento foi baixo com antidepressivos tricíclicos e benzodiazepínicos e alto com azapironas. A ocorrência de eventos adversos foi elevada para os grupos das medicações analisadas. **Conclusões:** Evidências de certeza muito baixa a moderada (pela Classificação de Recomendações, Avaliação, Desenvolvimento e Análises — GRADE) mostraram que antidepressivos e benzodiazepínicos parecem melhorar os sintomas clínicos em indivíduos com transtorno de pânico em menor prazo, em comparação ao placebo. Além disso, o uso de azapironas parece ter maior adesão por parte dos pacientes do que o placebo. No entanto, não há evidências suficientes para comprovar sua eficácia clínica.

Palavras-chave: Transtorno de Pânico; Tratamento Farmacológico; Revisão Sistemática; Medicina Baseada em Evidências.

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INTRODUCTION

Panic disorder is an anxiety condition characterized by recurrent and unexpected panic attacks, leading to impaired functional capacity and a worse quality of life for the individual[1-3]. These are periods of fear, apprehension, or anxiety of rapid onset and with a typical duration of minutes, in which at least 4 of the 13 characteristic symptoms are experienced: fast heartbeat, sweat, tremor, feeling short of breath, chest pain, dizziness, a sensation of asphyxiation, paresthesia or tingling, choking, hot flashes, nausea or abdominal pain, feeling of detachment, feeling of losing control, and/or dying[1,4,5]. Data from the *World Mental Health Surveys* of 25 countries with 142,000 people showed that 13.2% had panic attacks at some point in their lives, and 12.8% met the criteria for diagnosing panic disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[6]. Estimates indicate that about 3.5% of the population will meet panic disorder criteria during life[5-7].

Most clinical studies assess the efficacy of panic disorder medications by changing the frequency of symptomatic attacks. However, panic attacks are only one component of this syndrome, and the reduction of attacks does not entirely represent a clinical improvement. Studies report that more than 50% of patients treated with placebo reduced the frequency of attacks but remained to show higher anticipatory anxiety, phobic distress, and depression[8-10].

The comparison between active treatment and placebo is essential to analyze an intervention's efficacy and safety[11]. Clinical studies on the treatment of panic disorder have increased significantly due to the higher diagnosis and/or incidence of the disease and, consequently, many available medications. Considering the clinical and economic relevance, it is important to identify and summarize the studies with higher evidence to assist health professionals and public policy managers in clinical decision-making regarding panic disorder medications' efficacy and safety.

Systematic reviews (SRs) are the appropriate studies to map the literature and summarize the available evidence, as they present a rigorous methodology to minimize the risk of bias. New methodological approaches were developed to synthesize this evidence to keep up with the growing volume of SRs. The overviews or reviews of SRs aim to gather, evaluate, and synthesize these studies' results on a given subject. The overviews have evolved to meet the need to filter the burden, improve access to information, and assist in health decision-making[12-14]. This review's objective was to identify and summarize all the SRs published in Cochrane that compared the efficacy and safety of any drug treatment compared to placebo for panic disorder patients.

METHODS

This overview of SRs followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[15], considering the sections for a review of SRs. In addition, the reporting was conducted according to the PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[16], with appropriate adaptations for an overview.

Criteria for inclusion of studies

Type of study

All SRs published in Cochrane (with and without meta-analysis) on pharmacological treatment compared to placebo in patients with panic disorder were included. There was no restriction on the date of publication of the SR. Protocols of Cochrane reviews and reviews withdrawals from the Cochrane Library were excluded.

Participants

Adults (18 years and older) were diagnosed with panic disorder according to the following criteria: Diagnostic and Statistical Manual of Mental Disorders (DSM)[5], International Statistical Classification of Diseases and Related Health Problems (ICD-10), Feighner criteria[17], or Research Diagnostic Criteria (RDC)[18].

Interventions

Any type of pharmacological treatment was compared to placebo, regardless of dose, duration, and frequency of treatment.

Outcomes

All the outcomes analyzed by the SRs were presented.

Search for studies

The systematized and sensitized search was performed in the Cochrane Database of Systematic Reviews – CDSR (via Wiley) on October 8, 2021, using the unique descriptor: "Panic Disorder" and its synonyms.

Selection of studies

The SRs identified were selected by two researchers independently. These researchers analyzed the eligibility of reviews by reading titles and abstracts. The eligible SRs were then evaluated in full text and classified as included or excluded. If there was disagreement regarding

the inclusion of the reviews, a consensus was made for inclusion or exclusion. The SRs were selected through the *Rayyan online* platform[19].

Data extraction and collection

The included SRs had their data extracted through a standardized form with information on methodological characteristics of the reviews, characteristics of the participants, and results of the outcomes evaluated. Two independent researchers extracted the data with disagreements resolved by consensus.

Methodological quality assessment

The SRs were evaluated for their methodological quality using the AMSTAR-2 tool *(Assessing the Methodological Quality of Systematic Reviews)*[20].

The AMSTAR-2 is a tool composed of 16 items:

1. Research question and inclusion criteria according to the components of PICO (Population, Intervention, Comparators, Outcomes);
2. Study planning protocol;
3. Justification for the selection of the study design for inclusion in the review;
4. Comprehensive literature search strategy;
5. Study selection in duplicate;
6. Data extraction in duplicate;
7. Report of excluded studies and justifications for exclusions;
8. Characteristics of the included studies described in adequate detail;
9. Methods to assess the risk of bias in the included studies;
10. Reporting of the funding sources of the included studies;
11. Methods for statistical combination of results (meta-analysis);
12. Potential impact of the risk of bias in meta-analyses;
13. Consideration of the risk of bias in the interpretation and discussion of the results;
14. Discussion and explanation of heterogeneity;
15. Investigation of publication bias; and
16. Conflict of interest report of the authors of the review. Each domain is classified as entirely suitable ("yes"), partially adequate ("partially yes"), or not applicable.

Some of these are considered critical (items 1, 4, 7, 9, 11, 13, and 15). The assessment classifies the SRs according to the following degrees of confidence: critically low (more than one critical failure), low (a critical failure), moderate (more than one noncritical failure), and high (none or one noncritical failure)[20]. The evidence set's confidence was generated through the *checklist* available on the AMSTAR-2 website (http://amstar.ca/Amstar_Checklist.php).

Data synthesis

The results of the included SRs were presented narratively, considering the methodological quality evaluated by AMSTAR-2. Identifying and analyzing overlapping primary studies were unnecessary since each SR considered a specific pharmacological treatment compared to placebo. Even if a randomized clinical trial (RCT) assessed more than one intervention arm, only the treatment of interest for each SR would be included.

RESULTS

The Cochrane Library database search identified eight SRs; three were considered eligible[21-23].

Characteristics of the included SRs

The included SRs were published between 2014 and 2019 and evaluated the effects of three classes of drugs to treat panic disorder compared to placebo: antidepressants, benzodiazepines, and azapirones. All SRs included only RCTs as a primary study, and total samples ranged from 170 to 8,252 participants. Table 1 presents the main characteristics of the included SRs.

Methodological quality assessment

The methodological quality of the included SRs was evaluated by the AMSTAR-2 tool, and all of them were classified as high quality. Table 2 presents the details of the evaluation.

Main results from the included SRs

Table 3 presents the main results from the meta-analyses of the primary outcomes assessed in the SRs. Most of the analyzed treatments showed benefits regarding treatment response compared to placebo. However, there were higher rates of dropouts due to any cause and losses due to adverse events. Regarding secondary outcomes, a possible benefit of antidepressants and benzodiazepines was also observed for disease remission, social interaction, panic symptoms, frequency of attacks, agoraphobia, anxiety, and depression. There was no observed difference in the quality of life improvement between groups.

It is important to note that the included studies did not assess the treatment's long-term effects and risks of dependence and abstinence symptoms.

Table 1. Main characteristics of the included systematic reviews.

Systematic review, year	Number of included RCTs	Participants	Intervention	Outcomes	Time points	Certainty of the evidence (GRADE)
Bighelli et al. (2018)[21]	41	n=8,525 30.6–61.2 years old	Antidepressants	Treatment response Dropouts Losses due to adverse events Disease remission Panic symptoms Frequency of panic attacks Quality of life	2–6 months	Very low to moderate
Breilmann et al. (2019)[22]	24	n=4,233 18 and 73 years old	Benzodiazepines	Treatment response Dropouts Losses due to adverse events Disease remission Social interaction Panic symptoms Frequency of panic attacks Agoraphobia, anxiety, and depression	1–6 months	Very low to low
Imai et al. (2014)[23]	3	n=170 Over 18 years old	Azapirones	Treatment response Dropouts Losses due to adverse events	2 months	Low to moderate

RCT: randomized clinical trial; GRADE: Grading of Recommendations Assessment, Development and Evaluation; n: number of participants.

Table 2. Main findings from the included systematic reviews.

AMSTAR-2 tool domains	Systematic reviews		
	Bighelli et al. (2018)[21]	Breilmann et al. (2019)[22]	Imai et al. (2014)[23]
1. Search question (PICO)	Yes	Yes	Yes
2. Study planning (protocol)	Yes	Yes	Yes
3. Justification for the selection of the study design	Yes	Yes	Yes
4. Search strategies	Yes	Yes	Yes
5. Selection of peer studies	Yes	Yes	Yes
6. Data extraction in pairs	Yes	Yes	Yes
7. Report of excluded studies	Yes	Yes	Yes
8. Characteristics of the studies included	Yes	Yes	Yes
9. Risk assessment of bias	Yes	Yes	Yes
10. Reporting of the sources of funding for the studies	Yes	Yes	Yes
11. Appropriate statistical methods	Yes	Yes	Yes
12. Assessment of the impact of the risk of bias in meta-analyses	Yes	Yes	Yes
13. Risk of bias in interpretation and results	Yes	Yes	Yes
14. Discussion and explanation of heterogeneity	Yes	Yes	Yes
15. Investigation of publication bias	Yes	Yes	Yes
16. Report of conflict of interest of the authors of the review	Yes	Yes	Yes
Total (quality)	High quality	High quality	High quality

Evaluated by the http://amstar.ca/Amstar_Checklist.php.

Table 3. Evaluation of the methodological quality of the included systematic reviews.

	Main results (95%CI)		
	Treatment response rate	**Number of dropouts (for any reason)**	**Losses from adverse events**
Antidepressants versus placebo			
Any class	RR 0.72 [0.66–0.79]* 30 RCT, n=6,500 Low-certainty evidence	RR 0.88 [0.81–0.97]* 38 RCT, n=7,850 Low-certainty evidence	RR 1.49 [1.25–1.78]* 33 RCT, n=7,688 Low-certainty evidence
Tricyclic antidepressants	RR 0.73 [0.63–0.86]* 9 RCT, n=829	RR 0.74 [0.63–0.86]* 17 RCT, n=1,906	RR 1.97 [1.33–2.91]* 10 RCT, n=1,641
Selective Serotonin Reuptake Inhibitors (SSRIs)	RR 0.75 [0.67–0.84]* 21 RCT, n=4,000	No difference with placebo	RR 1.45 [1.16–1.81]* 22 CT, n=4,131
Monoamine oxidase inhibitors (MAOIs)	RR 0.55 [0.34–0.88]* 1 RCT, n=29	NA	NA
Selective serotonin-norepinephrine reuptake inhibitors (ISRSN)	RR 0.61 [0.41–0.91]* 4 RCT, n=1,531	No difference with placebo	No difference with placebo
Noradrenergic resorption inhibitors	RR 0.71 [0.51–0.97]* 1 RCT, n=82	RR 0.50 [0.28–0.90]* 1 RCT, n=82	No difference with placebo
Benzodiazepines versus placebo	RR 1.65 [1.39–1.96]* 16 RCT, n=2,476 Low-certainty evidence	RR 0.50 [0.39–0.64]* 21 RCT, n=3,558 Low-certainty evidence	RR 1.58 [1.16–2.15]* 5 RCT, n=3,263 Low-certainty evidence
Azapirones versus placebo	NA	RR 2.13 [1.11–4.07]* 3 RCT, n=170 Moderate-certainty evidence	NA

95%CI: 95% confidence interval; RR: relative risk; RCT: randomized clinical trial; n: total number of participants; NA: not assessed. *Benefits in favor of the intervention.

DISCUSSION

The Cochrane SRs identified three classes of drugs compared to placebo: antidepressants, benzodiazepines, and azapirones. All SRs were evaluated by the AMSTAR-2 tool as of high methodological quality, which was expected given Cochrane's methodological rigor in the elaboration and conduction of the SRs.

According to the evaluation by the GRADE approach (The Grading of Recommendations Assessment, Development and Evaluation)[24], the certainty of the evidence varied from very low to moderate, which means that new RCTs are likely to modify the results found. All clinical trials included in the SRs presented methodological flaws, such as the risk of bias and inaccuracy in the results (wide confidence interval).

The absence of blind participants and outcome assessors may increase the risk of preventable biases such as subjective adverse events and treatment satisfaction[25]. Although most RCTs have been described as "double-blind" studies, many authors have not provided additional information on the blinding process used (e.g., using identical capsules and packaging to make it impossible to identify the placebo). This lack of information has limited the risk of bias assessment in the included SRs. For example, among the RCTs on antidepressants and benzodiazepines, only 39% and 54% were classified as low risk of bias for blinding domains. However, the three RCTs included in the review on azapirones were classified as low risk of bias, because they provided the necessary information on the blinding of participants. It is noteworthy that the meta-analysis of these three RCTs showed a higher rate of dropouts in the intervention group, reinforcing the uncertainty about the absence of the blind. Patients may give up treatment in the event of actual adverse events, for any other justifiable reason, or simply because they are aware of their allocation to the placebo group.

Few RCTs included in the SRs evaluated outcomes such as quality of life and cost-effectiveness analyses of the drugs studied. Furthermore, assessing clinical improvement of individuals with panic disorder is almost always subjective through scales and questionnaires. It does not always consider all aspects and the complexity of the disease[21], which may limit the applicability of RCT results. The patients' follow-up time was short-term, and it was impossible to determine these medications'

long-term effects. For this reason, the results of these SRs should be interpreted with caution, as the treatment choice should balance the benefits and harms of treatment from a long-term perspective.

There are no overview studies similar to the present work published in the literature. Therefore, the authors could not compare the results. The authors found no new reviews with high methodological quality on the drug treatment for panic disorder published after the publication of the SR included in this overview that could add to the results presented here. The authors chose to include only Cochrane SRs due to the rigorous methodology that gives greater confidence in the estimates of the interventions' effects. Besides, the included SRs were recently published and show the current clinical studies scenario on the drugs analyzed for panic disorder.

It is important to note that the choice for clinical practice is not between medicine and placebo but between the different drug therapies in terms of efficacy and safety. However, comparison with placebo in clinical studies allows for better proof of treatment effects beyond psychological or subjective outcomes, provided that the masking process is conducted correctly. New RCTs must be performed with appropriate methodology according to CONSORT[26], including evaluating outcomes and long-term follow-up of patients. Only this way can one determine the efficacy of panic disorder medications, the risk of adverse events, and the impact of their continued use.

In conclusion, evidence of very low to moderate certainty has shown that antidepressants and benzodiazepines seem to improve clinical symptoms in individuals with short-term panic disorder compared to placebo. The use of azapirones seems to have greater adherence by patients than placebo. However, there is insufficient evidence to support its clinical efficacy.

Authors' contributions. MMBR: conceptualization, methodology, project administration, software, validation; visualization; writing – original draft; and writing – review & editing. YDF: conceptualization, software, supervision, validation; visualization; writing – original draft; and writing – review & editing. ACLS: conceptualization, data curation, validation; visualization; writing – original draft; and writing – review & editing. GRC: conceptualization, data curation, validation; visualization; writing – original draft; and writing – review & editing. MESC: conceptualization, data curation, formal analysis, methodology, validation; visualization; writing – original draft; and writing – review & editing. ECM: conceptualization, resources, validation; visualization; writing – original draft; and writing – review & editing. ALCM: conceptualization, formal analysis, methodology, project administration, software, supervision, validation; visualization; writing – original draft; and writing – review & editing.

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