■ Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)

Addition of aerobic exercise to antidepressant drug monotherapy for major depressive disorder in adults

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Abstract

Introduction

Major depressive disorder is frequent and implies a high morbimortality. The addition of exercise has been proposed to improve the response rate to pharmacological monotherapy. However, this intervention is still controversial.

Methods

We searched Epistemonikos, the largest database of systematic reviews in health, maintained by screening multiple sources of information, including MEDLINE/PubMed, EMBASE, and Cochrane. We extracted data from the identified reviews, analyzed the data from the primary studies, performed a meta-analysis, and prepared a summary table of the results using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method.

Results and conclusions

We identified 20 systematic reviews that together included 14 primary studies. Of these, eight were randomized trials. We conclude that the addition of aerobic exercise to pharmacological monotherapy for patients with major depression could slightly decrease the severity of depressive symptoms with low certainty of evidence.

Problem

Depressive disorder is a psychiatric pathology that currently affects 264 million people worldwide. It is associated with disability, other comorbidities and, in severe cases, can lead to suicide [1]. The first line of pharmacological treatment for patients with depression is serotonin reuptake inhibitors, but only 28-33% of patients achieve remission. This means that about two-thirds of patients with depression require other antidepressants or combinations of drug families [2][3], adding higher costs and more adverse effects [4].

This problem encouraged the study and development of combination therapy strategies. This approach consists of combining two or more therapies with consolidated antidepressant action (adjuvant) and adding a therapy with unknown antidepressant effect to a known antidepressant (enhancer) [5]. There are pharmacological and non-pharmacological enhancers, including aerobic exercise, among the most relevant and widely studied strategies. Aerobic exercise decrease stress hormones (epinephrine and cortisol) [6], modulates norepinephrine, dopamine, and serotonin levels [7]. Moreover, it is beneficial for many organic diseases (e.g., diabetes,

hypertension, coronary heart disease) and improves self-concept and confidence. In addition, few adverse effects have been reported [8][9]. However, there are inconclusive results on the effectiveness, prescription mode, and safety of physical exercise for treating depressive disorder.

Main messages

- The addition of aerobic exercise to pharmacologic monotherapy for patients with depression might slightly decrease the severity of depressive symptoms (low certainty of evidence).
- The addition of aerobic exercise to pharmacologic monotherapy for patients with depression could result in little or no difference in patient-reported quality of life (low certainty of evidence).
- The severe adverse effects were not measured or reported by the evidence reviewed.

Methods

We searched Epistemonikos – the largest database of systematic reviews in health – which gathers information from multiple sources, including MEDLINE/PubMed, EMBASE, and Cochrane. We extracted data from the identified reviews and analyzed the primary studies (Table 1). We generated a structured summary called FRISBEE (Friendly Summaries of Body of Evidence using Epistemonikos) with this information. Following a pre-established format, we included main messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), a meta-analysis of all studies, if possible, a summary table of results with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method, and a section of other considerations for decision-making. (Tables 2, and *)

Table 1 About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found 20 systematic reviews [10-29] that which included 14 primary studies in 18 references [30-47], of which eight are randomized trials in 12 references [34-38][40-47]. This table and this summary are based on the latter, since the observational studies did not increase the certainty of the existing evidence, nor did they provide relevant information. One randomized trial [42] could not be included in the meta-analysis, as the necessary data were not reported within the systematic reviews.
What types of patients were included*	Five trials incorporated patients with a major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders-IV criteria [36-38][44],[47]. One trial used the International Classification of Diseases, 10th edition criteria for depression [36], and one trial included patients with a score equal to or greater than 18 on the 17-item Hamilton Depression Scale [46]. One trial included hospitalized patients with severe depression [38], and two trials included treatment-resistant patients [37][44]. One trial analyzed patients with mild to moderate depression [35]. One trial, extracting information directly from the primary study, incorporated patients with moderate depression [36]. The remaining three trials do not report severity as a diagnostic criterion [36][47][46]. Three trials included only female patients [36][37][47], while the other four trials included both sexes. [35][38][44][47]. Regarding population age among trials, patients older than 50 years [35], between 40 and 60 years of age [37], between 18 and 65 years [36], and 18 to 60 years [44] were included. Of note, it was necessary to extract information directly from the primary study for three trials. These trials included patients aged 18 to 60 years [38],

	between 65 and 85 years [46], and another trial that included patients with a mean age of 43.66 years [47].
What types of interventions were included*	Regarding the intervention, all trials evaluated the addition of aerobic exercise to drugs. Three trials evaluated aerobic exercise plus antidepressant drugs versus antidepressants alone from different pharmacological families [37][38][44], and two trials compared against a specific antidepressant (sertraline) [35][46]. We extracted information from the primary study for two trials that compared against the standard treatment, where 100% of participants were on antidepressant therapy of any type. One trial reported that the most frequently used serotonin reuptake inhibitor antidepressant was fluoxetine (66.7%), followed by escitalopram (22.2%) [35]. Another trial reported that the control and intervention groups used serotonin reuptake inhibitors (fluoxetine and paroxetine) and nonselective monoamine inhibitors (imipramine, amitriptyline, clomipramine) equally [47]. Regarding intervention fidelity, in five trials, aerobic exercise was performed in a supervised manner [35][36][37][38][47], and in one trial, only one weekly session was supervised [44]. Primary study data was extracted for one trial, where the exercise was supervised [46]. Regarding the delivery strategy of the intervention, three trials conducted aerobic exercise sessions in a group setting [35][37][46], while the other four trials conducted individual training [36][38][38][44][47]. In terms of training frequency, four trials had aerobic exercise sessions three times per week [35][36][38][47], two trials had a frequency of twice a week [37][47], and one trial had a frequency of five times per week [44]. In terms of training time, two trials used 45-minute aerobic exercise sessions [35][36], and two trials had 60-minute sessions [37][46], and in another, the training session was 30 to 40 minutes in duration [44]. We also extracted information directly from two trials. One trial had sessions of 50 minutes [4], while the other did not report a defined duration for the sessions and stated that patients should complete 16 kilocalories per kilogram per week [38]. In terms of assessing the cardiovascular response to exercise, three trials established a threshold for heart rate during physical activity as 70 to 80%, 65 to 75%, and from 60% of maximum heart rate [35][36][46], respectively. In the remaining four trials, no limiting heart rate was reported [37][38][44][47]. In two trials, patients could choose the exercise. The options were cycling, walking, and jogging [35], or stationary bicycle, treadmill, and elliptical [38]. While in the remaining five trials, the choice of aerobic exercise modality was not reported [36][37][44][44][46][47]. One trial based the exercise on cardio-fitness [37], one trial

	on walking [44], another trial on cycling [46], and finally, one trial on water aerobic exercise [47]. With information extracted directly from the primary study, one trial included traditional games, exercise circuits, jumping rope, exercise balls, brisk walking, and dancing as aerobic activity [36].
What types of outcomes were measured	The trials reported multiple outcomes, which were grouped by the systematic reviews as follows: • The severity of depressive symptoms, measured by the Beck Depression Inventory, Hamilton Depression Scale, Hamilton Depression Scale of 17 items, Global Cognitive Impression, and Global Assessment of Functioning. • Remission of illness. • Quality of life measured by the World Health Organization quality of life scale, Life Satisfaction Index. • Neurocognitive function. • Changes in body weight based on body mass index. • Impact on self-esteem measured with the Rosenberg self-esteem scale. • Changes in aerobic capacity measured by maximal oxygen consumption. • Discontinuation of treatment. Only the first four outcomes mentioned above were contemplated and analyzed within this FRISBEE. The average follow-up of the trials was 18 weeks, with a range between 12 and 40 weeks.

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

Summary of results

Information on the effects of adding exercise to monotherapy with antidepressant drugs is based on eight randomized trials involving 346 patients.

Seven trials measured severity of depressive symptoms (346 patients) [35][36][37][38][44][46][47], three trials measured remission (253 patients) [35][44][46] and two trials measured quality of life (133 patients) [35][37]. Regarding neurocognitive functions, no review allowed data extraction in a way that could be incorporated into a meta-analysis, so information on that outcome is presented as a narrative synthesis based on one trial (84 patients) [34].

No trials evaluated adverse effects, social isolation, or occupational functioning.

The summary of results is as follows:

• The addition of aerobic exercise may slightly decrease the severity of depressive symptoms (low certainty of evidence).
• The addition of aerobic exercise could result in little or no difference in disease remission and quality of life (low certainty of evidence).
• The addition of aerobic exercise may slightly increase neurocognitive function (low certainty of evidence).
• The evidence reviewed did not report "severe adverse effects", "social isolation", or "occupational functionality".

See Table 2

Table 2. Summary of findings.

Adding aerobic exercise to antidepressant drug monotherapy				
Patients	Adults (18 years or older)			
Intervention	Addition of aerobic exercise to antidepressant drug monotherapy			
Comparison	Antidepressant drugs alone			
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty in evidence (GRADE)*
	WITHOUT Aerobic exercise	WITH Aerobic exercise		
	Difference: Patients per 1000			
Severity of depressive symptoms**	The depression severity scale was on average 0.8 standard deviations lower in the group with the addition of aerobic exercise to antidepressant drug monotherapy.		--	$\oplus\oplus\bigcirc\bigcirc$[,1,2] Low
	SMD: 0.8 (Margin of error: 0.3 to -1.3)			
Remission***	520 per 1000	667 per 1000	RR 1.3 (0.8 to 2.4)	$\oplus\oplus\bigcirc\bigcirc$[1,2] Low
	Difference: 177 patients (Margin of error: -125 to 707)			
Quality of life****	The quality of life scale was on average 0.1 standard deviations lower in the intervention group compared to the control group.		--	$\oplus\oplus\bigcirc\bigcirc$[1,2] Low
	SMD: 0.1 (Margin of error: -0.5 to 0.3)			
Neurocognitive fuction	In one trial [34] (84 patients), some cognitive skills, executive processes, and memory improved in the intervention group compared to the control group.			$\oplus\oplus\bigcirc\bigcirc$[1,2] Low

Error margin: 95% confidence Interval (95% CI).
RR: relative risk.
SMD: standardized mean difference.
GRADE: Levels of evidence from the *GRADE Working Group* (see below).

* The risks **WITHOUT aerobic exercise** are based on the risks of the control group in the studies. The risk **WITH aerobic exercise** (and its margin of error) was calculated using the relative effect (and its margin of error).
* The standardized mean difference (SMD) is used when the outcome has been measured on different scales, and therefore, it is difficult to interpret clinically. It is commonly accepted that values close to 0.2 would have little clinical relevance, values of 0.5 would have moderate relevance (clinically recognized), and above 0.8 would have high relevance.
** The outcome severity of depressive symptoms was measured with the Hamilton Depression Scale (HAM-D) and Beck Depression Inventory (BDI). The higher the score, the greater the severity of depressive symptoms.
*** Remission is considered when patients do not meet the criteria for depression in a re-evaluation, with slight variations between studies.
**** The quality of life was measured with the World Health Organization Quality of Life Scale (WHO-QOL) and the Life Satisfaction Index. In both, the higher the score, the better the quality of life.
[1] A level of certainty of evidence was lowered due to serious risk of bias since most of the included trials do not comply with concealment and the generation of the randomization sequence is unclear [34][35][36][37][38][44][46][47].
[2] A level of certainty of evidence was decreased due to imprecision since there are different therapeutic decisions at each end of the confidence interval. It was decided to decrease one level of certainty of neurocognitive function outcome because it corresponds to a single study and is therefore expected to be imprecise [34].

Follow the link to access the interactive version of this table (*Interactive Summary of Findings - iSoF*)

Other considerations for decision-making

To whom this evidence does and does not apply

The findings of this summary can be applied to adult patients with major depressive disorder of mild-moderate and severe severity in inpatient and outpatient settings.

The results could be extrapolated to older adult patients with major depressive disorder.

The evidence described above cannot be extrapolated to patients under 18 years of age, patients with other types of affective disorders, or patients with other comorbidities that hinder an adequate implementation of aerobic exercise.

The evidence is limited to aerobic exercise, so it cannot be extrapolated to other physical activity modalities such as anaerobic exercise, stretching, or yoga, among others.

The evidence is limited in its application to other concomitant pathologies in patients with depressive symptoms since the biomedical characteristics of the intervened populations are not specified; therefore, this limits the generalization of the results. These comorbidities could be hypertension, diabetes, obesity, osteoarthritis, heart failure, and musculoskeletal sequelae, among others. We should note a high frequency of metabolic and cardiovascular, and psychiatric pathologies in the adult population, which may already be indicated to perform physical activity.

About the outcomes included in this summary

The selected outcomes are considered critical for decision-making. This is based on our opinion and is, for the most part, in line with the main systematic reviews included.

However, it is essential to note that most systematic reviews did not evaluate serious adverse events, aerobic capacity, or effects on neurocognitive function. Moreover, none evaluated outcomes related to other symptoms associated with this pathology, such as social isolation, demotivation, or occupational functionality.

Harm/benefit balance and certainty in evidence

Adding aerobic exercise to antidepressant drug monotherapy could improve the severity of depressive symptoms and neurocognitive function, but the certainty of the evidence is low.

On the other hand, the benefit of combining aerobic exercise with antidepressants could be similar to pharmacological monotherapy in terms of quality of life and disease remission.

Considering the above and the uncertainty of the evidence, it is not possible to balance risks and benefits.

Resource considerations

None of the identified systematic reviews included a cost-effectiveness analysis. However, with the evidence described, it is likely that interventions that do not lead to high costs, such as walking or jogging, without sports equipment or supervision, the cost-benefit balance leans towards therapy combined with aerobic exercise. Despite this, due to the diversity of aerobic exercise methods in each trial, the cost-benefit balance cannot be made until better quality evidence, including the risk of adverse events, is performed.

What patients and their caregivers think

Most treatment providers and patients would be inclined to favor the combined intervention. There is a possible improvement of symptoms without adding costs or another drug, reducing possible adverse effects of drug combinations and improving other aspects such as neurocognitive function

Differences between this summary and other sources

The conclusions of this summary are consistent with most of the systematic reviews included in the matrix, which favor the addition of aerobic exercise to an antidepressant drug.

The National Institute for Health and Care Excellence (NICE) guideline for depression in adults generally promotes exercise as a therapeutic strategy for subthreshold depressive symptoms and mild to moderate depression. However, it does not specify the type of exercise indicated and is not considered a possible addition to drug monotherapy [48].

The American Academy of Psychology guidelines for depression indicates insufficient evidence to recommend combined therapy with exercise (without specifying the type) and second-generation antidepressants [49].

The clinical practice guideline of the Anxiety and Depression Association of America indicates that exercise is not more effective than drug or psychotherapy but more effective than placebo [50].

A Spanish guideline on physical exercise indicates that patients with depression should include exercise as a healthy lifestyle habit. It is essential that patients are motivated and that the exercise is adjusted according to fitness and individual preferences. It also mentions that in moderate-severe depression, physical activity should be considered as a complement to antidepressants and/or psychotherapy [51].

The Canadian Mood and Anxiety Treatment Network's adult major depressive disorder management guideline recommends exercise as first-line monotherapy for mild to moderate depressive episodes and as second-line in addition to treatment in moderate to severe episodes. However, they point out a lack of long-term data and feasibility issues. The guidelines mention no clear evidence on the superiority of aerobic over anaerobic exercise. The administration should be at least 30 minutes of supervised moderate-intensity exercise at least three times a week for a minimum of nine weeks to be considered effective [52].

In the clinical guideline of the Explicit Health Guarantees for Depression in Chile, it is recommended to indicate a structured physical activity program to treat people with depression. However, it does not mention the type of exercise or combined therapy with drugs [53].

Could this evidence change in the future?

Future evidence is likely to change this summary's conclusions, as the evidence's certainty is low for all outcomes.

No ongoing trials or systematic reviews evaluating the addition of aerobic exercise to drug monotherapy with antidepressant effects for patients with major depressive disorder were found in the PROSPERO databases or the International Clinical Trials Registry Platform of the World Health Organization.

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database
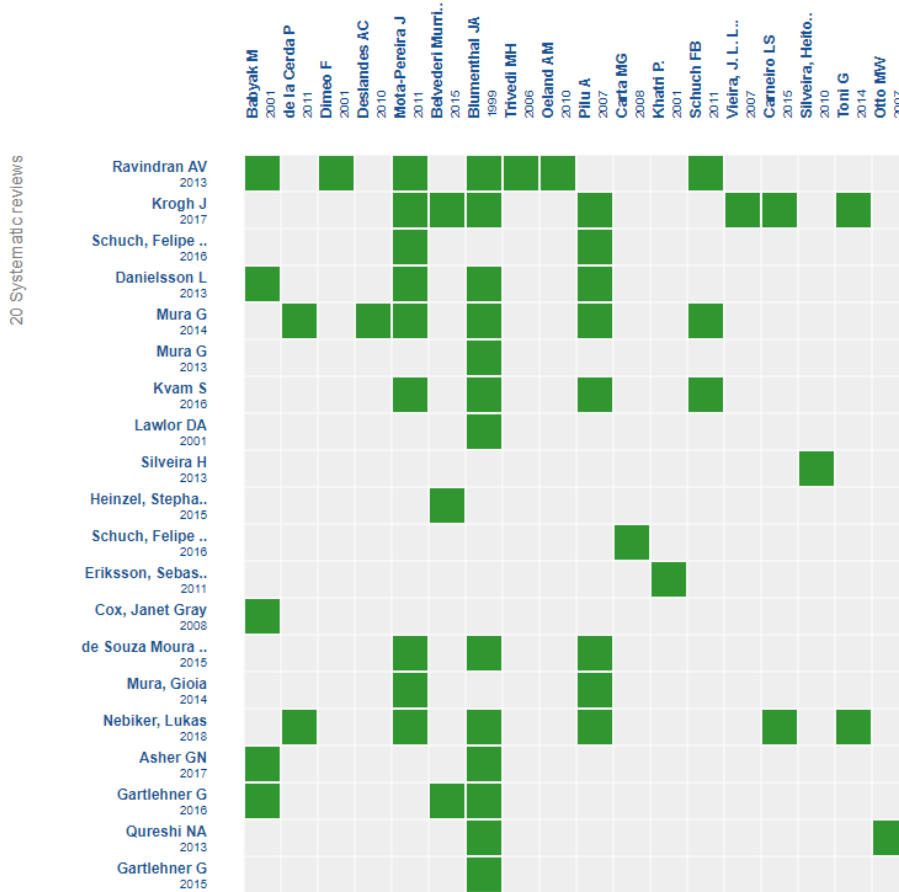
How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.

18 References (14 Primary studies) Studify ⑦   66.7% Randomized controlled trial (RCT) 12 / 18

Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version:** [Addition of aerobic exercise to antidepressant drug monotherapy for major depressive disorder in adults](#)

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