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Exercise or antidepressants as first choice for the treatment of depression: a systematic review

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Exercise or antidepressants as first choice for the treatment of depression: a systematic review

Artigo de Revisão

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RESUMO

Background: A depressão é uma das maiores causas de morbilidade no mundo. O tratamento é complexo e profissionais de saúde devem estar conscientes e informados sobre outras estratégias que possam ser usadas como tratamento de primeira linha. Tendo isto em conta, a atividade física pode ter um papel importante no tratamento da depressão, tanto como adjuvante ou até mesmo como primeira linha, sendo que se trata de uma alternativa válida aos antidepressivos.

Objetivo: Fazer uma revisão sistemática e avaliar o impacto da atividade física na qualidade de vida e nos sintomas de doentes com diagnóstico clínico de depressão. Assim como comparar os efeitos com os resultados da terapêutica com antidepressivos.

Método: Esta revisão sistemática foi conduzida de acordo com a PRISMA checklist para revisões sistemáticas e meta-análises. Foi feita uma pesquisa recorrendo às bases de dados do PubMed e EMBASE. Critérios de inclusão: (1) *população*- adultos com depressão clínica de qualquer tipo; (2) *intervenção*- atividade física (estratégias motivacionais ou psicológicas podem ser incluídas); (3) *controlo*- antidepressivos (ou tratamento farmacológico habitual); (4) *resultados*- qualidade de vida e sintomas de depressão.

Resultados: De 121 estudos, só 4 foram incluídos. Em última análise, os quatro artigos constataram que não havia diferença estatística em usar exercício ou medicação como primeira linha para reduzir os sintomas de depressão e melhorar a qualidade de vida. Foram utilizadas estratégias diferentes para avaliar o impacto da atividade física como primeira linha no tratamento da depressão. A diversidade clínica e disparidade da metodologia impossibilitaram a realização de uma análise quantitativa de todos os dados.

Conclusão: Relativamente ao uso de atividade física como tratamento de primeira linha, a evidência existente não demonstra nenhuma diferença estatística significativa em comparação com o grupo de controlo (antidepressivos). Como qualquer outro estudo, este apresenta algumas limitações: o tamanho da amostra e a heterogeneidade, assim como viabilidade da intervenção levantaram questões significativas, já que não há certezas de que os resultados obtidos possam ser aplicados a toda a população.

Palavras-chave: Qualidade de vida; antidepressivos; depressão; atividade física; exercício.

ABSTRACT

Background: Depression is one of the biggest causes of morbidity worldwide. The treatment is complex and healthcare practitioners should be aware of the availability of other strategies that could be used as primary treatment and can have an effective outcome without the side effects that antidepressants can cause. Bearing this in mind, physical activity can have a very important role in treating depression, both as adjuvant or first line, being a valid alternative to antidepressants.

Objective: To systematically review and assess the impact of physical activity on quality of life and depression symptoms of people with a depression diagnosis, and to compare such effects with the results achieved by treatment with antidepressants.

Methods: This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines for systematic reviews and meta-analysis. Comprehensive systematic online searches were conducted on PubMed and EMBASE databases. Inclusion criteria: (1) *population*- adults with clinical depression of any type; (2) *intervention*- physical activity (motivational or psychological strategies can be included); (3) *control*- antidepressants (or pharmacological treatment as usual); (4) *outcomes*- quality of life and depression symptoms.

Results: From 121 studies screened, only 4 were included. In the end the four articles found that there was no significantly statistical difference in reducing depressive symptoms or improving quality of life when using exercise vs drugs as first line. Different strategies were used to assess the impact of physical activity as a first-line treatment of depression and clinical diversity and disparity of methodology made impossible to perform a quantitative analysis of all data.

Conclusion: Regarding the use of physical activity as a first-line treatment, existing evidence doesn't show any significant statistical difference to the control group (antidepressants). Like any other study, our presented a few limitations: two out of four studies had "unclear risk" concerning the overall score, one was labelled as "high risk", and one as "low risk" (as described in Methods). Matters such as sample size and heterogeneity, as well as feasibility of the intervention raise major concern because we are not certain that results obtained can be applied to the entire population. Further studies should try to find the best way to obtain positive outcomes from a wider a more diverse sample. Also it would be interesting to know if there is a specific type of physical activity that could get better results in reducing symptoms of depression and improving quality of life.

Keywords: Quality of life; antidepressants; depression; physical activity; exercise.

ÍNDICE

1. INTRODUCTION

Depression is one of the biggest causes of morbidity worldwide[1]. It's characterized by persistent sadness, loss of interest in daily activities and an inability to solve problems and deal with adverse events. It can easily be triggered by other diseases and have an impact not only in psychological but also physical domains[2].

The proportion of people worldwide with depression in 2015 was estimated to be 4.4% according with data collected by World Health Organization. The total number of people living with depression in the world is around 322 million. The total estimated number of people living with depression increased by 18.4% between 2005 and 2015[3].

Even though there isn't a common ground around the scientific community concerning the best strategy to address depression, the vast majority of times, physicians choose to initiate treatment with antidepressants[4,5] as soon as someone starts to show depressive symptoms.

The treatment of depression is complex and healthcare practitioners should be aware of the availability of other strategies that could be used as primary treatment for people with depression[6] and that can have an effective outcome without the side effects that antidepressants[7, 8] can cause.

Its well-documented that physical activity can have a very important role[9, 10] in treating depression, however is still unclear which populations would benefit more in terms of long term remission and improvement in quality of life[11] of a long term program of physical activity[12] and also if this is a realistic strategy to be used solo in treatment of depression[13]. Some aspects have to be accounted for, such as the adherence to treatment and obviously long term effects in maintaining remission as well as comparing this type of therapy to antidepressants.

As a consequence, the aim of this review is to assess the impact of physical activity on quality of life and depression symptoms of people with a depression diagnosis, and to compare such effects with the results achieved by treatment with antidepressants.

2. METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines for systematic reviews and meta-analysis (Appendix 1 - PRISMA 2009 Checklist).

2.1 Eligibility criteria:

In the present systematic review, we included randomized controlled trials that met the following inclusion criteria: (1) *population*- adults with clinical depression of any type; (2) *intervention*- physical activity (motivational or psychological strategies can be included); (3) *control*- antidepressants (or pharmacological treatment as usual); (4) *predefined outcomes*- quality of life and depression symptoms.

Exclusion criteria were: RCTs with children as target population as well as RCTs that apply physical activity as an add-on strategy or a secondary intervention to treat depression or depressive symptoms.

2.2 Information Sources and search strategy:

Comprehensive systematic online searches were conducted on PubMed and EMBASE databases in October 2018 to identify relevant studies.

The search strategy words used were: (“Antidepressants” AND “Depression” AND “Physical Activity” AND “Quality of life”).

The search was restricted to articles written in either English, Portuguese, Spanish or French; no other limits were placed during this phase of the study.

2.3 Data extraction and quality assessment

Two reviewers (FF and IR) independently screened the titles and abstracts obtained. Together they assessed which did not comply with the inclusion criteria and after some debate reached consensus concerning which studies should move on to the next phase. In order to complete the study an additional analysis and extraction was done by searching throughout the references of the articles previously selected. In the end, the same two

researchers read the full texts of the remaining articles individually and reached a consensus, with no need for any dispute to be settled by a third party.

The risk of bias tool provided by the Cochrane Collaboration[14] was used to estimate the quality of the selected articles chosen by the two reviewers and both classified them independently according to different parameters: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; other sources of bias. Each parameter was given a value of high, unclear or low. The level of risk for each study was then classified as low (all key domains presenting low risk), unclear (one or more key domains with unclear risk), and high (high risk for one or more key domains).

Our key domains were: “Random Sequence Generation”, “Blinding of the outcome assessors” and “Selective outcome report”.

Data and records management throughout the review were conducted in Covidence, the standard production platform for Cochrane reviews selected by Cochrane.

2.4 Outcomes and statistical analysis

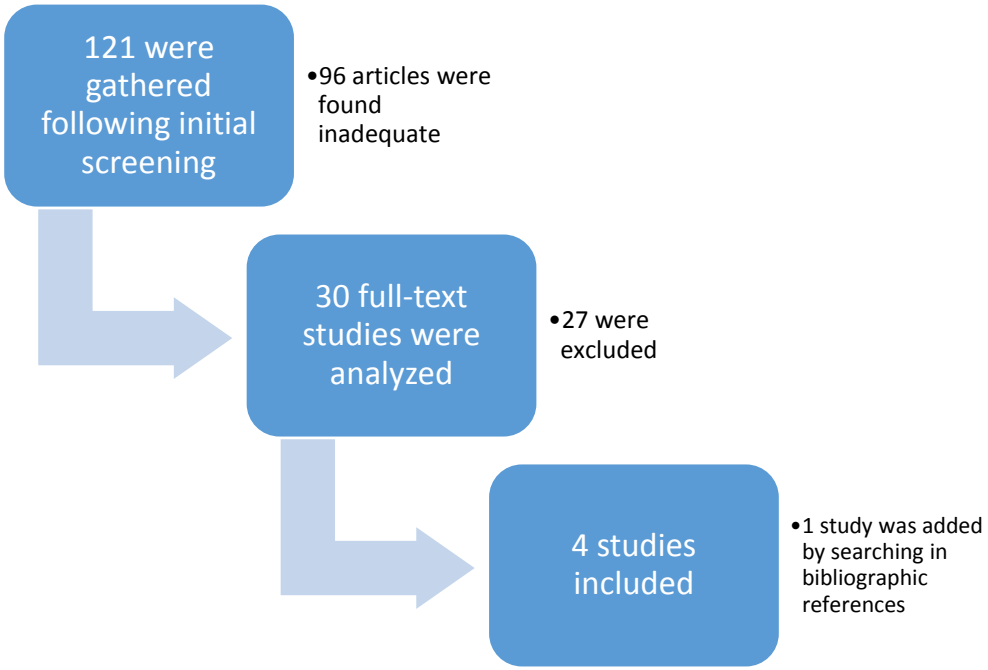
The main and primary outcomes evaluated were the impact of such intervention on quality of life and levels of depression in people with depression.

Outcomes were described narratively, as due to clinical diversity and disparity of methodology, it was not possible to perform a quantitative analysis (meta-analysis).

3. RESULTS

3.1 Study selection

Our search throughout the PubMed and EMBASE electronic databases resulted in 121 references. By reading the abstract and title of all of them, 91 were found inadequate and were therefore excluded. After the first review, both researchers did a thorough analysis of the full text of the remaining 30 articles: 27 were put aside due to inadequate population. The look for additional papers in the bibliographic references of the 3 studies already chosen found another 1[15] more. So, in the end, 4 studies were included.



Flowchart 1 *– Literature search and selection process for included studies.*

3.2 Study characteristics and quality

The main characteristics and outcomes of interest of the included studies were extracted for the purpose of this systematic review, and are summarized in **Table 1.**

Authors and year	Country	Number of	Interventions	Control	Assessment method	Results of intervention
Brenes *et al.*[16]2007	United states of America	37	A sixteen week facility-based exercise regimen with three sessions per week and each session lasting 60 min (n= 14)	Open-label sertraline. Treatment response and side effects were assessed by a physician at weeks 2, 6, 10 and 14 (n=11)	ANOVA and ANCOVAs were conducted to examine differences between groups prior and after treatment.	HAM-D: **pre-treatment:** exercise= 12.7, medication= 13.7 **Posttreatment:** exercise= 7.8, medication= 7.4 SF-36: **Pre-treatment:** exercise= 54.1; medication= 61.2 **Posttreatment:** exercise= 31.3, medication= 43.2
Haller *et al.*[17], 2018	Germany	20	An 8 week web-based exercise intervention. The plan of physical activity was based on heart rate and had a duration of 30-60 min a day	Participants that were assigned to the medication group.	ANCOVA compared the intervention to the control group for each outcome using T2 (outcome) as dependent variables and T0 as covariantes.	QIDS-SR (median change: -5; IQR: -2 to -10; P=.001) and QIDS-C (median change: -5; IQR: -2 to -7; P=.02). ANCOVA revealed a positive influence of the intervention in the total quality of life score (P=.07) and on SF-36 ("social functioning" with P=.04 and "emotional well -being with P.02)
Blumenthal *et al.*[18], 1999	United states of America	156	A 16-week supervised exercise routine (n=53). Included 3 supervised exercise sessions a week. The training regimen was based on their maximum heart rate (reached during the treadmill test).	The medical group received sertraline (n= 48). A staff psychiatrist evaluated side effects and treatment response at weeks 0, 2, 6, 10, 14 and 16. Starting dose was 50mg, maximum dose was 200mg.	A 1-way multivariate analysis of variance, with posttreatment HAM-D and BDI scores serving as dependent variables. ANCOVA was performed.	1 way-multivariate analysis of variance revealed no statistically significant difference among the groups on the HAM-D or BDI (Wilks $\lambda_{4,64}$=0.98; P=.67) as well as the ANCOVA models to HAM-D ($F_2'_{152}$=0.61; P=.55) or BDI ($F_2'_{152}$=1.01; P=.37).
Blumenthal *et al.*[15], 2007	United States of America	202	A 16 week personalized program (n=104)	Sertraline (n=49) once a day. Starting dose was 50 mg (one pill) and was increased until a maximum of 200 mg (four pills).	Effect of interventions was evaluated using generalized linear models.	All groups showed a statistically significant decline (p<.0001) in the HAM-D scores. No differences between the exercise groups and medication (p= .514).

***Table 1**- Summary of study's characteristics*

HAM-D- Hamilton depression rating scale[19]; SF-36[20]- Short-form 36; BDI[21]-Beck Depression Inventory; QIDS[22]-SR- Quick Inventory of depressive Symptomatology self-reported;

The four final studies included in our systematic review were published between the year of 1999 and 2018. All of them took place in the United States of America with the exception of one that was performed in Germany (Mainz)[17]. Sample sizes ranged from 37 to 202 participants. One of them used people aged more than 65[16], another people 40 or older[15], one between 20 and 65 years[17], and another with 50 or more[18].

Concerning the intervention, all of them included at least one group that underwent a physical activity program of variable duration. One of the RCTs had two intervention arms[16] (exercise and sertraline) and two RCTs had three intervention arms[15,18].

About the control group, in both studies of Blumenthal *et al.*[15,18], the participants taking sertraline were considered the control group on the present review. Concerning the trial of Haller *et al.*[17], the group who underwent 'treatment as usual' was considered to be the control. We considered that all of them were doing any kind of psychopharmacotherapy for depression. Finally, Brenes *et al*.[16] study used a control group that received open-label sertraline.

The main outcome measured and evaluated in the four studies was the impact of the intervention in depressive symptoms and quality of life of the participants. Other outcomes were assessed: in two of the studies[15,18] the researchers try to understand if after the treatment there was any improvement in aerobic capacity of the participants. Also adherence to physical exercise programs was an outcome of three RCTs[15,17,18]. Finally one of the studies evaluated also the side effects[15] of the intervention and another the psychological variables[17] that could have a negative impact in the participants quality of life.

All studies had different strategies to rate the impact of exercise in depressive symptoms in the intervention group. HAM-D[19] (Hamilton Depression Rating scale) was the main tool used by 3 of the studies[15,16,18]. Haller *et al.*[17] used QIDS[22] (Quick Inventory of Depressive Symptomatology) to assess depressive symptoms, and SF-36 (Short Form-36)[20] to assess quality of life. Brenes *et al*.[16] also used SF-36 to score the outcome "Quality of life".

The results of quality assessment, performed such as described in Methods, are presented in **Table 2.**

Table 2 - *Risk of bias summary for studies whose outcome was "quality of life and depression symptoms" review authors' judgements about each risk of bias item. Underlined domains refer to key domains used to assess overall level of risk (see Methods).*

Author	Brenes *et al.*[16]	Haller *et al.*[17]	Blumenthal *et al.*[18] (1999)	Blumenthal *et al.*[15] (2007)
Random Sequence generation	+	+	?	+
Allocation concealment	+	+	?	+
Blinding of the outcome assessors	+	+	?	+
Blinding of participants and personnel	?	?	?	?
Selective outcome report	?	-	+	+
Other sources of bias	+	+	+	+
Overall level of risk	?	-	?	+

3.3 Results of studies

3.3.1. Outcome- Symptoms of depression

In the 1999 study of Blumenthal *et al.*[18] the appliance of both scores[19,21] at the beginning and 16-weeks after found that, there wasn't any significant difference between the groups, either on baseline or after the intervention [HAM-D (F2.153=0.96; p=0.39) BDI (F2.153= 0.90; p=0.67)]. ANCOVA also didn't find any significant differences in the response to treatment using HAM-D (F2.152= 0.61; p=0.55) or BDI (F2.152=1.01; p=0.37). Still concerning the study of Blumenthal *et al.*[18], according to DSM-IV criteria for MDD[23], the percentage of patients who improved their status and were no longer considered clinically depressed was very similar across the interventions: 32 patients (60.4%) in the exercise group, 33 (68.8%) in the medication group and 36 (65.5%) (χ^2_2= 0.79; p=0.67) -this criteria were applied by a physician.

In the second, and more recent study of Blumenthal *et al.*[15], they found that the three interventions, home based exercise, supervised exercise, and medication had higher remission rates (no longer meeting MDD criteria[24]) when compared to placebo (p=.057). However there was no statistically significant difference between the interventions concerning remission rates: supervised exercise= 45 %; home-based exercise=40%; medication 47%. When applying the HAM-D score they found very positive results across the groups from baseline to 16 weeks: *(1) supervised exercise:*-7.2 (SD= 6.9); *(2) home-based exercise*: -7.1 (SD =6.7); *(3) medication:* -6.1 (SD= 6.7); *(4) placebo:* -6.1 (SD = 7.3). Again, there were no differences between the exercise groups and medication (p=0.514) or between the two exercise groups (p=0.510). Also they found no differences between treatments in different levels of depression (ranging from mild to severe).

In another study, published in 2018 (Haller N. *et al.*[17]), researchers confirmed that the intervention group had a remarkable decrease in self-reported and clinician rated scores. Even though this is a good achievement, there was no difference between the intervention group and the controls (group received pharmacological treatment for depression): QIDS-SR (median change: -5; IQR: -2 to -10: p=0.001) and QIDS-C (median change: -5; IQR: -2 to -7; p=0.2). The intervention group also showed a marked decrease in symptoms (≥50%) evaluated through the QIDS-SR score (36% reported decline) and in the QIDS-C score (21%). Finally ANCOVA found no statistically significant difference between the intervention group and the control group.

The last study included in the present systematic review (Brenes *et al.*[16]) found that there were no significant statistical difference among the participants that took the study and were assigned either to “Medication” or the “Exercise” condition. The participants who took part of the exercise and sertraline groups had improvements in the HRDS[19] (Hamilton Rating Depression Scale) and the GDS-15[25], another score used during this RCT demonstrated a decrease in self-reported depressive symptoms. Concerning the Hamilton Rating Depression Scale (HRDS), the values of pre and post treatment for exercise and medication are as follows: exercise pre=12.7, post=7.8; medication pre=13.7, post=7.4. GDS-15: exercise pre=7.0, post=4.5; medication pre=6.5, post=6.1. Statistical analysis using ANCOVAs showed that the main effect of the intervention condition (“exercise”) wasn’t significant (p=0.13), however there was a trend for both exercise and sertraline to have a similar effect in reducing depression severity (exercise: *p=0.09,* effect size (ES)= 0.96; sertraline: *p=0.06,* ES= 1.56).

3.3.2. Outcome- Quality of life

Two of the studies included addressed the issue of quality of life, one of which was Brenes *et al.*[16] that reported similar effects obtained in both "Exercise" and "Medication" groups: SF-36[20] mental health component: exercise pre= 54.1, post=31.3; medication pre= 61.2, post=43.2.

Concerning Haller *et al.*[17] paper, the results (ANCOVA was used to perform statistical analysis) revealed that the intervention was successful in improving the items concerning life quality on SF-36[20]: *"emotional well-being"*- p=0.02, Eta^2=0.29; *"social functioning"*- p=0.04, Eta^2= 0.23; *"mental health"*-p=0.08; total quality of life score (p=0.07).

4. DISCUSSION

The four studies included in the present systematic review allowed us to do a qualitative analysis of the strategies used to treat depression. They all use exercise as a tool, however, the strategy implemented is different as well as the population to which is administered.

4.1 Outcome- Quality of life and symptoms of depression

According to Blumenthal *et al.*[18] study from 1999 the use of a supervised and structured aerobic training schedule is feasible in the treatment of MDD in older adults. Among the 156 patients who entered the trial, 60.4% of participants in the exercise condition, 68.8% of patients in the medical condition and 65.5% of patients in the combined condition, no longer met the criteria for MDD[26]. Adding up to this, also HAM-D and BDI scores were significantly reduced in vast majority of participants, meaning less symptoms.

The team was very impressed and excited with this findings and even one of the big worries demonstrated in the beginning of the study was dissipated. They were afraid of a significant drop-out rate in the exercise group that didn't happen (20% dropped-out).

This promising results, however, should be looked with an appropriate criticism. This trial was conducted during a period of 16 weeks, a small amount of time, when we're talking about chronic disease with very high relapsing course[27], also the sample was small and homogeneous, giving small power to this study. Finally, the fact that people included in the exercise group had social interaction[28,29] with each other may be an important factor involved in the remission of symptoms.

In the 2007 Blumenthal *et al.*[15] study there is a peremptory conclusion: "exercise is as effective as antidepressant medications".

By looking at the remission rates, both exercise and medication achieved better results than placebo: 45% for participants of the supervise exercise group and 47% for those who took medication over the 16 weeks of treatment. The placebo group got 31% of remission. This results where even more pronounced when the team removed the patients who showed an "early response to treatment" (≥50% reduction in BDI after only the first week): 46% for supervised exercise group, 38% in home-base exercise, and 46% from the sertraline group were in remission after 16 weeks. Again, no major differences between exercise and medication.

However, like the former study of Blumenthal *et al.*, there is a very big doubt about the dissemination of this findings to the entire population. The main worry is the fact that the sample is mostly composed of volunteers. The sample presented some heterogeneity concerning the range of severity attributed to the clinical depression. This fact makes the data obtained from this trial more generalized. This happens because it proves that exercise is beneficial to patients with mild depression but also to patients with moderately to severe depression.

Concerning Brenes *et al*.[16] trial, minor depression is addressed. They concluded that both exercise and sertraline were equally effective in the treatment of minor depression. Their results showed that both approaches are equally able to improve mental health and symptoms of depression. There is also some issues related with the improvement of aerobic capacity and the potentially impact in psychological domains, more specifically related with the improvement of self-efficacy and quality of life.

The study, however, raises a few problems: very weak statistical power (small sample), the fact that diagnosis of minor depression was solely done by self-reported symptoms and a full clinical interview was completely putted aside and last, the setting of the intervention.

The RCT by Haller *et al*.[17] tries to find alternatives to medication in the treatment of depression. They address an alternative, not only as effective in reducing depression symptoms as pharmacological treatment, but also cheaper and with less side effects.

The team noticed that exercise had an impact in both clinician and self-rating depression following the 8 weeks of treatment. On top of that, there're also improvements in self-efficacy and quality of life. They also noticed that during the first two weeks of treatment there were already signs of a reduction in QIDS-SR and QIDS-C scores (36% and 21% respectively). Results are comparable to pharmacotherapy[30].

Even though this results occurred in a group that performed physical exercise, is very unlikely they were the result of a physiological adaptation. The researchers conclude that, the likely cause for this early change is the placebo effect. However, this should not undermine the results and the use of exercise as an alternative strategy. Also antidepressants, like SRSIs, have a very powerful placebo effect, both in early stages and during the course of the treatment[31,32].

LIMITATIONS

The present systematic review, like any other study, presents a few limitations.

Starting with overall risk of bias, one[15] out of four included studies had low risk of bias, this happened due to low risk of bias in key domains for this review's authors (described in "Methods"). The study of Haller *et al.*[17] which scored high risk concerning the item "Selective outcome report" as disparity between the proposed and reported outcomes was found. About the trial of Blumenthal *et al*.[18], we considered to have an overall risk of bias of unclear because two of the key domains presented "unclear risk" ("random sequence generation" and "blinding of the outcome assessors").

Concerning the study of Brenes *et al*.[16], we gave a score of "unclear risk" because no public protocol was found that allowed us to understand if the reported outcomes were in accordance with the previously defined goals. Major domains such "blinding of the outcome assessors" and "selective outcome report" scored "unclear risk".

Secondly, and even though the studies had a similar outcome measured (depressive symptoms), the results obtained included other variables (besides medication and exercise) or there was missing data, giving them lack of homogeneity that didn't allow us to do a quantitative analyses. Also there was a study[17] that presented a different methodology when measuring the symptoms of depression.

Thirdly, and even though both depressive symptoms (across the four studies[15–18]) and quality of life (in two[16,17] out of four studies) showed an improvement after the implementation of the intervention (exercise), doubts still remain concerning the feasibility and implementation of a long-term exercise program in a random sample of people with clinical diagnosed depression.

Finally, the four studies[15–18] shared in common the fact that the patient's databases were rather small, giving this trials weak power and questioning the possibility of disseminating the findings to the entire population.

CONCLUSION

Regarding the use of physical activity as a first-line treatment, we found that there isn't any significant statistical difference to the control group. Although some improvement could be seen in depressive symptoms and quality of life. This allows us to conclude that, regarding the most recent evidence, a short-term intervention strategy based on exercise is equally effective to antidepressants in the improvement of quality of life and in reducing symptoms in people with depression. Also, the setting of the intervention appears to be a factor that doesn't influence the outcomes.

The findings of this studies are indeed promising, but still there's a lot of ground to cover. As we talked before, there are a few limitations that should be addressed in order to give a higher clinical relevance to future studies. Due to the chronicity of depression, bigger and more diverse sample sizes and longer time periods are critical to understand if physical activity is really an alternative strategy to the use of antidepressants and if there're specific stratums of the population with specific types of depressive symptoms who would benefit more from this type of intervention. Also, reporting of randomization and blinding strategies and a public study protocol would be relevant to understand bias in these studies.

Also it would be interesting to understand the biological and physiological mechanisms behind the reduction of symptoms and improvement of life quality in order to design specific programs of physical activity and add-on therapies that could maximize the beneficial effects of it.

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APPENDIX 1- PRISMA 2009 Guidelines

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1-2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6,7,8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6,7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8,9,10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11,12,13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14,15,16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

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