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Efficacy of Exercise on Depression: A Systematic Review

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Abstract

OBJECTIVES: in the last 30 years, a number of studies have shown that physical activity may reduce depressive symptoms both in healthy populations and in patients diagnosed with MDD. This systematic review of the literature aims to establish the new findings on the effectiveness of exercise on depression.

METHODS: the search of significant articles was carried out in PubMed/Medline with the following key words: “exercise”, “physical activity”, “physical fitness”, “depressive disorder”, “depression”, and “depressive symptoms”. Interval was set from January 2000 to December 2012.

RESULTS: 46 papers were retrieved by the search. Among the 14 included randomized controlled trials, treatment allocation was adequately conceived in 5 studies, intention-to-treat analysis was performed in 10 studies, and the main outcome assessment was blinded in all but three of the studies. We examined the results of all these trials, finding a small effect of exercise on depression, contaminated by the poor quality of the researches.

CONCLUSIONS: in the last 12 years, few progresses were done in showing the efficacy of exercise on depression, due in part to the persistent lack of high quality research, in part to the difficult to establish the real effectiveness of exercise on depressive symptoms. However, there are some promising findings on physical activity combined with antidepressants as an add-on strategy to manage depression, which may be probably more useful in clinical practice.

Key words: depression, exercise, physical activity.

Introduction

Major depressive disorder (MDD) is a significant cause of morbidity and mortality worldwide, with a lifetime prevalence of 15% to 20% (1, 2), and it is expected to be one of the three leading causes of burden of disease in 2030 (3). Antidepressant medication is currently the accepted treatment of choice for MDD (4): due the efficacy of these drugs, the favorable profile of side effects and the high prevalence of depression, antidepressants have become one of the most common drugs in the community in Western Countries, with 6% of utilizers in France (5) and 4.7% in Italy (6). However, the response rates of antidepressant monotherapy are only from 30% to 45% with single-action or dual-action antidepressant monotherapy (7).

These issues have stimulated the interest of researchers on the efficacy and safety of alternative or complementary therapies in depressed patients.

In the last 30 years, a large number of studies showed that physical activity may reduce depressive symptoms both in healthy populations (8-12) and in patients diagnosed with MDD (13-19).

It is noteworthy that the terms "physical activity" and "exercise" are frequently used interchangeably. To encourage investigators to carefully describe the type of activity under study, Caspersen et al. (20) proposed definitions to distinguish them: while physical activity is any bodily movement produced by skeletal muscles that results in energy expenditure (measured in kilocalories), and it can be categorized into occupational, sports, conditioning, household, or other activities, exercise is a subset of physical activity that is planned, structured, and repetitive, with a final or an intermediate objective of the improvement or maintenance of physical fitness.

The importance of exercise as a management strategy for depression has been highlighted by its inclusion in the latest guidelines from the National Institute for Health and Clinical Excellence (21), which recommended structured, supervised exercise programs, three times a week (45 min to 1 h) over 10–14 weeks, at low-intensity, as a Step 2 intervention for mild to moderate depression. Moreover, the guideline for promoting mental health recommended an accumulation each week of a minimum of 150 minutes of exercise at moderate intensity or a minimum of 75 minutes at vigorous intensity, in bouts of at least 25 minutes over 3 to 5 days per week (22).

Exercise may also improve the perceived physical Quality of Life in depressed patients (23, 24), with higher doses of exercise associated with larger improvements in mental and physical aspects of QOL (25). Patients' views on the specific effect of physical activity as treatment for depression stresses the importance of other cognitive mechanisms mediating subjective wellbeing include diversion from negative thinking, and a sense of purpose (26).

A series of review of literature and meta-analysis have been carried out in the recent past, showing overall a small effect of exercise on depressive disorders (24, 27-40).

Objective

We carried out a systematic review to establish the new findings on the effectiveness of exercise on depression. Thus, we will investigate exercise compared with stretching/flexibility, placebo, social contact, no treatment, in adjunction to antidepressants compared to antidepressants.

Method

Identification of the studies

The search of the significant articles was carried out in PubMed/Medline with the following key words: "exercise", "physical activity", "physical fitness", "depressive disorder", "depression", and "depressive symptoms". Only papers

published in English and conducted from June 2012 up to December 2012 with a search refined on January 2013 were preferentially reviewed. A manual search of additional references was performed in the references found in electronic databases.

Inclusion criteria

Studies were included in this review if they were randomized controlled trials, in which exercise was compared to standard treatments (including antidepressant drugs), no treatment or placebo-control, in people of all ages with depression (diagnosed by any method) as defined by trial authors. We excluded studies different from randomized controlled trials, those that compared different type of exercise, those that measured outcomes immediately before and after a single bout of exercise, samples with psychiatric and organic comorbidity, samples constituted by athletes.

Quality of studies

We assessed the quality of studies by noting the concealment of allocation, the intention to treat analysis, and the blinding. Trials were distinguished in adequately concealed (with central randomization; computerized allocation in which records are in a locked file; drawing of sealed and opaque sequentially numbered envelopes), or inadequately concealed (open list or tables of random numbers; open computer systems; drawing of non-opaque packages). Trials were defined as using intention to treat analysis if all the patients were analyzed in the groups to which they were randomly allocated. For blinding we distinguished between trials in which the main outcome was measured by a blinded assessor and those in which the main outcome was measured either by the participants themselves or by a non-blinded assessor. Moreover, we considered the duration of trials, if the sample had an adequate numerosity, and if it was performed a follow-up assessment. We also considered the quality of assessment (i.e. structured interview, self-report or observer-administered questionnaire), both at the baseline and at the end of trials.

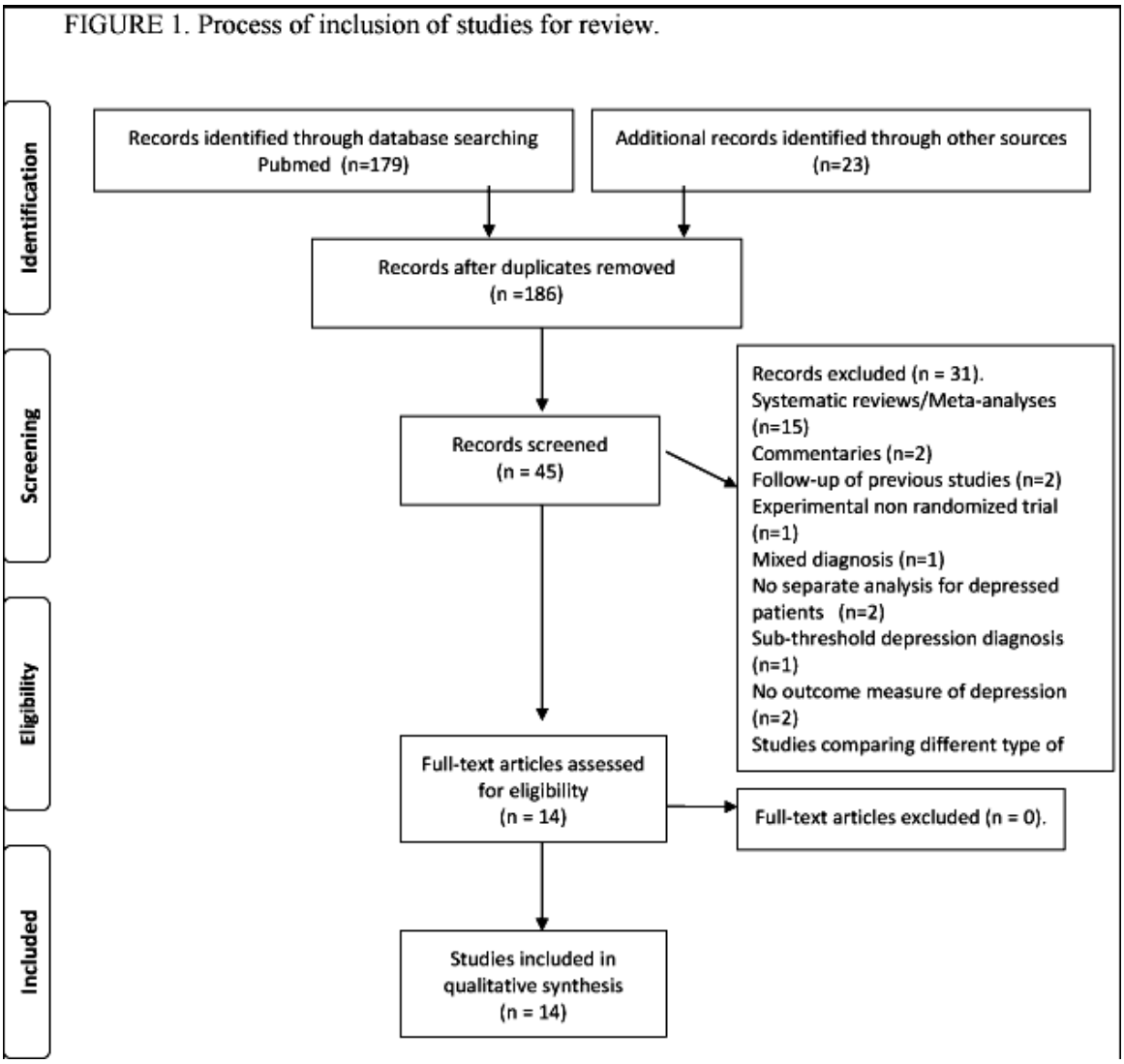
Outcome measures

We consider as outcome measure the main outcome declared by authors. Because the focus of this paper, we didn't consider secondary outcomes.

Results

Over 40 (n = 45) papers were retrieved by the search. Figure 1 shows the process of inclusion of studies for review.

FIGURE 1. Process of inclusion of studies for review.



Thirty-one papers were excluded because these didn't fulfill our criteria. The abstract of the extracted papers were read and the more pertinent ones (n =14) were obtained in full version and analyzed in deep. We also examined bibliographies.

Among the 31 papers excluded, 15 were systematic reviews (24, 27-40), most relevant of which we included in session "discussion". Two papers were commentaries (41, 42), two were studies on the outcomes or follow-up of previous papers (43, 44) one was an experimental non-randomized controlled trial (45), one was on psychiatric patients with mixed diagnoses (46), 2 had no separate analysis for depressed patients (47, 48), one was on the effect of exercise in a sub-threshold depressive sample (49), 2 did not have an outcome measure of depression (50, 51), and 5 compared different types of exercise but had no "non-exercising" control groups (52-56).
We found 14 studies that fulfilled our inclusion criteria (13, 57-69). Main characteristics of included studies are shown in Table 1.

Table 1. Main characteristics of included studies.

TRIAL	N	TREATMENT	CONTROL	DURATION	BLINDING	ASSESSMENT	ITT	RESULTS
Blumenthal et al. 2007	202	Supervised exercise Home-based exercise Sertraline	Placebo pills	16 weeks	yes	HAM-D 17	yes	p=0.057
Knubben et al. 2007	38	Treadmill walking	Stretching	10 days	no	BRMS CES-D	yes	p=0.01 p=0.003
Hua Chu et al. 2009	54	High intensity Low intensity aerobic	Stretching	10 weeks	no	BDI II	yes	p=0.009 (H p=0.583 (L
Dunn et al. 2005	80	High dose Low dose aerobic	Flexibility	12 weeks	yes	HAM-D17	yes	p=0.008 (HI p=0.38 (LD
Pilu et al. 2007	30	Supervised aerobic + Antidepressants	Antidepressants	8 months	no	HAM-D	no	p<0.0001
Mota-Pereira et al. 2011	33	Home-based aerobic + Antidepressants	Antidepressants	12 weeks	yes	HAM-D17	no	p=0.014
Chalder et al. 2012	361	Usual care + TREAD counselling	Usual care	16 weeks + follow-up 12 m	no	BDI	yes	p=0.68
Kerse et al. 2010	193 53.1 %*	Home-based exercise (+ antidepressants 28.8%)	Social visits (+antidepressants 24%)	12 months	yes	GDS	no	p=0.916
Krogh et al. 2009	165	Supervised aerobic	Relaxation	4 months + follow-up 12 m	yes	HAM-D17	yes	p=0.3
Krogh et al. 2012	115	Supervised aerobic	Stretching	3 months	yes	HAM-D17	yes	p=0.52
Singh et al. 2001	32	Weight lift	Health educ. lectures	20 weeks + follow-up 26 m	yes	BDI	yes	p<0.05
Mather et al. 2002	86	Aerobic supervised exercise+ Antidepressants	Health educ. talks + Antidepressants	10 weeks + follow-up 34 w	yes	HAM-D17	yes	p=0.05 (M-W p=0.2
Pakkala et al. 2008	624	Physical activity counselling	No counselling	24 months	yes	CES-D	yes	p>0.05
Nabkarson et al.	59	Jogging	Usual daily	8 weeks	no	CES-D	no	p=0.003

Of the studies, 4 were in USA (13, 57, 59, 65), 2 in UK (62, 66), 2 in Denmark (63, 64), and one each was in Germany (58), Italy (60), Portugal (61), Finland (67), Japan (68), and New Zealand (69).

Eight studies focused the treatment group on supervised aerobic exercise (13, 58, 59, 63-66, 68), one had a home-based exercise treatment group (69). Three had treatment groups with antidepressants plus: supervised aerobic

exercise (60), home-based physical activity (61), physical activity counselling (62). One had treatment group with exercise counseling alone (67); one had three active treatments, with supervised exercise, home-based exercise and sertraline (57). Among the studies that focused on active exercise treatment, 2 had two treatment groups, which exercised at low or high intensity (59) or at low or high dose (13).

Five studies compared the effect of exercise with stretching/flexibility control groups (13, 57, 58, 62, 63), three with usual antidepressant drugs (60-62), one with placebo pills (57), one with health educational lectures (65), one with health educational talks (66), one with social visits (69), and two with "no treatment" at all (67, 68).

Quality assessment

Treatment allocation was adequately conceived in 5 studies (13, 57, 65-67).

Intention to treat analysis was performed in 10 studies (13, 57, 58, 59, 62-67).

The main outcome assessment was blinded in all but four of the studies (59, 60, 62, 68). Nevertheless, a double-blinded assessment of the main outcome was performed in only one study (57).

Main outcome was a significant reduction compared to the baseline of HAM-D or HAM-D17 score in 7 studies (13, 57, 60, 61, 63, 64, 66), of GDS score in one study (69), of BDI score in 3 studies (59, 62, 65), of the CES-D score in 3 studies (58, 67, 68); Knubben et al. (58) assessed participants both with an observer-administered questionnaire (BRMS) and with CES-D.

Study populations

Six of the studies had populations of volunteers (57, 59, 65, 67-69) recruited through the media. Mather and colleagues (66) recruited both volunteers and clinical participants. One study reported financial incentives for participants (64).

Results

Exercise compared with stretching/flexibility

Among the five studies compared aerobic exercise with stretching or flexibility assumed as control (13, 58, 59, 63, 64), 3 showed a significant difference between treatment and control groups outcome (13, 58, 59).

The trial carried out by Knubben and colleagues (58) was focused on the short term (10 days) benefit of physical activity on a small sample of 38 depressed inpatients, undergoing antidepressant therapy, assessed both with an

observer-administered questionnaire, the Bech-Rafaelsen Melancholy Scale (BRMS), and with a self-administered

one, the Center for Epidemiologic Studies Depression scale (CES-D). Patients were randomly assigned either to an

exercise (daily walking on a treadmill) or a control (low-intensity stretching and relaxation exercises) group. The

exercise group had a substantially greater reduction in depression scores (BRMS and CES-D scores) than the control group ($p = 0.01$ and $p = 0.003$ respectively).

The study carried out by Hua Chu et al. in 2009 (59) tested the effect of two different exercise intensities (high or low) compared to stretching on depressive symptoms in 54 sedentary women during 10 weeks. Main outcome was considered a reduction of depressive symptoms (BDI-II) measured at baseline and at 5 and 10 weeks follow up. Participants in all groups had significant reductions in depressive symptoms at week 5 ($p < .001$) and week 10 ($p < .001$). The BDI-II change scores did not differ significantly among the groups ($p = .066$), but the high intensity group had significantly fewer depressive symptoms than the stretching control group ($p=0.009$), while the low intensity group didn't differ from controls ($p=0.583$).

Dunn et al. published a study with a similar design (13). Eighty mild to moderate depressed patients were randomized to one of four aerobic exercise treatment groups that varied total energy expenditure (7.0 kcal/kg/week: low dose, or 17.5 kcal/kg/week: high dose) and frequency (3 days/week or 5 days/week) or to exercise placebo control group (3 days/week flexibility exercise). After 12 weeks, the difference in HAM-D17 scores of the treatment "high dose" compared to placebo was significant ($p=0.008$), while the "low dose" didn't differ from placebo ($p=0.38$). As the 17.5-kcal/kg/week dose is consistent with public health recommendations for physical activity ("public health dose"), authors affirmed that aerobic exercise at a dose consistent with public health recommendations is an effective treatment for MDD of mild to moderate severity.

These three studies had smaller samples than the two carried out by Krogh et al., which found no effect.

The first one, DEMO-I (63), published in 2009, was a randomized pragmatic trial for patients with unipolar depression, in which 165 patients were allocated to supervised strength and aerobic exercise or relaxation training during a 4-month period. At the end of the trial, the mean change in HAM-D17 score was -1.3 ($p = .3$) and 0.4 ($p = .3$) for the strength and aerobic groups versus the relaxation group. At 12 months' follow-up, the mean differences in HAM-D17 score were -0.2 ($p = .8$) and 0.6 ($p = .6$) for the strength and aerobic group versus the relaxation group.

The second trial by Krogh and colleagues, DEMO II (64) was focused to establish the effect of a pragmatic exercise intervention on 115 patients affected by mild to moderate Major Depressive Disorder (assessed with HAM-D17), randomly assigned to the treatment (three times per week for three months aerobic supervised training) or to a control group (stretching). Post intervention, the mean difference between groups on the HAM-D17 was −0.78 points ($p = 0.52$), showing no effect of exercise on depression.

Exercise compared with placebo pills

Blumenthal and colleagues (57) carried out a prospective, randomized, double blinded controlled trial (SMILE study) with a sample of 202 depressed adults equally assigned randomly to one of four conditions: supervised exercise in a group setting; home-based exercise; antidepressant medication (sertraline, 50–200 mg daily); or placebo pills for 16 weeks. All groups showed a clinically and statistically significant decline ($p < .0001$) in HAM-D17 scores from baseline to 16 weeks, and 41% of participants achieved remission, defined as no longer meeting the criteria for major depressive disorder (MDD) and a HAM-D score of <8. Patients receiving active treatments tended to achieve higher remission rates compared with placebo ($p = .057$), without statistically significant differences between the two exercise groups and antidepressant medication, or between home-based and supervised exercise. Thus, the efficacy of exercise seemed to be comparable with sertraline, and both tended to be better than placebo.

Exercise compared to social contact

Two studies compared exercise to social contact, focusing on the effect of exercise in old aged samples, in which depressive symptoms are common and frequently associated with poor physical function (70).

Singh, Clements & Fiatarone Singh (65) carried out a randomized controlled trial on 32 community-dwelling patients (mean age 71,3 years), with major or minor depression or dysthymia. Participants were randomly assigned to the treatment (3 weekly for 10 weeks of supervised weight-lifting exercise plus 10 weeks of unsupervised exercise) or to the control group (2 weekly health education lectures and videos for 10 weeks), and assessed by BDI. The BDI score was found significantly reduced at 20 weeks in the treatment group compared to the control group ($p<0.05$), with a significant difference in the somatic subscale ($p= 0.001$) and a no-significant difference in the psychological subscale ($p= 0.09$); the difference was still significant at the 26-months follow-up.

Kerse and colleagues (69) carried out a trial aimed to establish the effectiveness of a home-based physical activity program (the Depression in Late Life Intervention Trial of Exercise: DeLLITE), in improving function, quality of life, and mood in older people with depressive symptoms. Participants (193 depressed people, aged 75 years and older, mean age 81 years) were randomly assigned either to an individualized physical activity program (home-based moderate-intensity balance retraining, progressive resistance lower limb-strengthening exercises, and walking) or social visits (without psychotherapeutic components) over 6 months, with a 12-month follow up. Among the participants, 53.1% had moderate to high levels of depression according to ICD-10, DSM-IV (from CIDI), or GDS-15 criteria, and 26.4% were taking antidepressants, as assessed at baseline. GDS-15 scores improved for all participants over the year of the trial ($p<0.001$), but there was no significant difference between the 2 groups ($p=0.916$). No differential effect was found when comparing GDS change in higher depression score participants between the groups over time ($p=0.269$).

Exercise compared to no treatment

A Finnish trial published by Pakkala et al. (67) analyzed data of the SCAMOB study, a 2-year single-blinded randomized controlled trial among 624 participants aged 75 years and older. Participants were assigned to either an intervention group (physical activity counseling) or to a control group (no counseling). Psychiatric assessment was performed at the baseline and after 24 months using the CES-D questionnaire. Among all the study participants, no effect of intervention was observed. However, among subgroup with minor depressive symptoms at baseline (CES-D score 16-20), a significant treatment effect was observed in the intervention group compared to the control group ($p< 0.05$).

A trial carried out by Nabkarson et al. (68) investigated the effect of physical exercise on depressive state in a sample of 59 adolescent females volunteers (mean age 18.8 ± 0.7 years) with mild-to-moderate depressive symptoms as measured by the Centre for Epidemiologic Studies Depression (CES-D) scale, randomly assigned to either an exercise regimen (5 weekly jogging training in 50 minutes session) or usual daily activities for 8 weeks. The subjects were then crossed over to the alternate regimen for an additional 8-week period. Because 10 participants dropped out, data analysis was performed on 49 subjects. Among subjects in the group A (training first) the total CES-D score decreased as the results of training ($p= 0.003$); during the subsequent daily activity phase, it gradually increased but was still significantly lower than baseline value ($p= 0.037$). The same result after training was also observed in the group B ($p= 0.008$). No significant changes were observed after the phase of usual daily routine.

Exercise in adjunction to antidepressants compared to antidepressants

Two studies compared exercise in adjunction to antidepressants with antidepressants alone, one study compared exercise plus antidepressants with health education talks plus antidepressants, and a fourth study compared physical counseling and usual therapy with usual therapy alone. Pilu et al. (60) performed a randomized trial with naturalistic control on a small sample of 30 depressed women undergoing and not responders to antidepressant therapy, randomized either to the treatment (one hour 2 weekly supervised aerobic exercise session plus usual antidepressant)

or control group (antidepressant alone) during 8 months, assessed with HAM-D. Only the treatment group showed significant reduction in HAM-D scores ($p<0.0001$), while controls didn't improve significantly ($p=0.28$). Another paper analyzing data from the same trial (23) found that exercise might also improve the perceived physical quality of life; the score of WHOQOL-Brief scale in the physical domain improved from T0 to T8 in the exercise plus antidepressants group, with statistically significant difference. WHOQOL-Brief physical remained the same in the control group, and, consequentially, the difference between T0 and T8 did not reach any statistical significance. The perceived Quality of Life in the other domains did not change during the treatment in both groups.

Mota-Pereira and colleagues (61) carried out a trial on 33 patients affected by treatment-resistant major depressive disorder. Participants were randomized to the treatment (5 weekly home-based aerobic exercise, consisting in 30-45 min/day walks, as an adjunction at the usual antidepressant treatment) or control group (usual antidepressant treatment alone) for 12 weeks. The treatment group showed lower HAM-D17 rates compared to the control group ($p < 0.014$). While in the control group none of participants showed response or remission, in the treatment group there were 21% of response and 26% of remission, although these data were not significant.

Mather et al. (66) performed a randomized controlled trial on the effectiveness of exercise as an adjunct to antidepressant therapy in a sample of 86 depressed patients aged 53 years or older. Participants were randomly assigned either to a treatment group (2 weekly exercise class, which contained elements of endurance, muscle strengthening and stretching) or a control group (twice-weekly health education talks) for 10 weeks. Patients were assessed on three occasions: baseline, 10 weeks and 34 weeks with HAM-D17; because the study focused on a particular population (treatment-resistant patients), the general convention in trials of antidepressant therapy to use a $\geq 50\%$ reduction in HAM-D17 score as definition of response was modified by authors, assuming that a $\geq 30\%$ reduction in HAM-D17 score associated with participation in exercise could reach clinical interest. At 10 weeks, the exercise group achieved a higher response compared to the control group ($p=0.05$). Further analysis using the Mann-Whitney test revealed no discernible difference between the two groups in overall effect on the HAM-D17 score ($p=0.28$).

Chalder et al., in a recently published paper (62), reported the findings of the TREAD-UK study (TREAtment of Depression with physical activity), a pragmatic, multicenter, two arm parallel randomized controlled trial (70), which investigated the effectiveness of a facilitated physical activity intervention in addition to usual care for the treatment of depression in adults presenting in primary care. 361 depressed participants were randomized to receive either usual care from their general practitioner or usual care plus the TREAD intervention, based on the assistance from a physical activity facilitator. The TREAD intervention was flexible and designed to encourage sustainable activity that could be easily incorporated into the participants' lifestyle as "moderate or vigorous activity for 150 minutes a week in bouts of at least 10 minutes, but if that seemed unrealistic, then the facilitator encouraged any increase in physical activity, whatever the intensity". Intervention group participants didn't reported significant improvement in mood at the 4-month assessment compared with those in the usual care group ($p=0.68$). Similarly, neither there was evidence that the intervention group reported a change in mood at the 8 and 12 month follow-up points, nor that the intervention reduced antidepressants use compared with usual care ($p=0.44$) over the duration of the trial. The proportion of participants reporting use of antidepressants was smaller in both groups at the end of the trial (33% antidepressants in intervention group and 42% in usual care group) compared with baseline (59% and 53% respectively). Authors said that there was no evidence to suggest any difference between the groups at either the four months' follow-up point (adjusted odds ratio 1.20, 95% confidence interval 0.69 to 2.08; $p=0.52$) or over the duration of the trial, and they didn't find any evidence in treatment effect across the three follow-up points (time by treatment interaction $p=0.22$). Concerning the specific objective of the present review, these data give poor information because: 1) the intervention group was not a physical activity protocol but rather a counseling treatment encouraging exercise, determining only some, not standardized, differences in the amount of different exercise practices in two groups; 2) no treatment effect was found, but a specific analysis comparing antidepressants plus intervention and antidepressant alone have not been carried out; due to the little percentage of subjects taking antidepressants as "usual care" in the overall sample (29% of participants at the end of the study) the no treatment effect may be found ever in

presence of a difference in the outcome measures between the two sub-sample taking antidepressant; 3) the study showed an higher drop-out rate at the end of the study in participants with antidepressant plus intervention (30%) than in antidepressants alone (20%), but no intention to treat analysis has been performed.

Discussion

The present paper focused on recent findings about the effectiveness of physical activity, consisting in both aerobic and anaerobic interventions, on depression. In the past, a large amount of studies were published on the topic; however, when analyzed in detail, many studies have had a variety of methodological limitations, such as the lack of randomized designs, failure to assess adequately the main psychiatric disorder and comorbidity, unblinding of assessors, use of self-report questionnaires of symptom severity rather than clinical interviews, and inadequate follow-up (29, 34, 36, 71). Comparisons between studies are often difficult, due to a wide variety in assessment or diagnosis of depression, level of severity of the condition, setting for delivery and size of the sample, type, frequency and duration of the intervention delivered, and outcomes (24).
In a meta-analysis published in 2001, Lawlor & Hopker (36), although they included only randomized controlled trials, found important methodological weakness in each of the 14 studies analyzed: allocation was adequately concealed in 3 out of 14 studies, intention to treat analysis in 2, assessment of outcome was blind only in 1 and the main outcome was measured by self-assessment in 12. Thus, authors concluded that "the effectiveness of exercise in reducing symptoms of depression cannot be determined because of a lack of good quality research on clinical populations with adequate follow up."

Despite the need of higher quality researches was called by a number of reviews on the topic, even recently published meta-analysis highlighted the poor quality of the trials analyzed: Krogh et al. (35) found 8 out of 13 trials with an adequate allocation concealment, 6 with a blinded outcome, and 5 which used intention-to-treat analyses; only 3 studies were assessed as high quality (adequately concealed random allocation, blinded outcome assessment, and intention-to-treat analysis). As recently, a Cochrane review (40) found randomization adequately concealed in 11 out of 32 studies examined, 12 performing intention-to-treat analyses and nine with blinded outcome assessors.
Overall considered, while exercise seems to improve depressive symptoms in people with a diagnosis of depression when compared with no treatment or control intervention (30, 33), this should be interpreted with caution since the positive effects of exercise were smaller in methodologically strong trials.

Out of 14 included trials, we found important methodological weaknesses in all but one (57), which performed adequate concealed random allocation, double-blinded outcome assessment, and intention-to-treat analysis. Blumenthal and colleagues (57) found that patients receiving active treatments (supervised or home-based exercise, or sertraline) tended to achieve higher remission rates compared with placebo ($p = 0.057$), without statistically significant differences between the exercise groups and antidepressant medication. However, exercise and sertraline were significantly superior to placebo only after exclusion of early responders, but such exclusion should introduced instability in the analysis (41). Moreover, the choice of the mean HAM-D score at baseline (17 in this study, compared to >20 in the majority of the treatment studies on major depressive disorder), the enrollment of volunteers, the lack of data on the inter-rater reliability of the assessments (which increased the risk of type II error), and the impossibility by the assessment to detect any other psychiatric comorbidity (above all, the presence of patients affected by Bipolar Disorder) make the translation of results into a clinical setting quite difficult (42).

Another important weakness in included studies seems to be the main outcome assessment, performed by self-administered reports in 5 trials (59, 62, 65, 67, 68). Among these, no effect of exercise on depressive symptoms compared to control treatment was found by the two trials with biggest samples, respectively $N=361$ with $p=0.68$ (62) and $N=624$ with $p>0.05$ (67).

Among included trials, only two (13, 59) focused on the effect of different intensities of exercise, and both showed high intensity/dose exercise superior compared to control treatment, with no effect for low intensity/dose. Trivedi and

colleagues (55), examining moderating variables, showed that while both high and low exercise doses appeared to yield a benefit with SSRI treatment, the higher dose appeared superior to the lower dose for men in general and in women with no family history of mental illness; conversely, the lower dose may be sufficient for women with a history of mental illness. Significantly, participants assigned to the low-dose exercise group showed a better compliance than those assigned to the high-dose exercise group, providing evidence that low-dose exercise may be both more tolerable and acceptable for depressed patients.

These last findings arise the problem of depressed patients' adherence to a physical activity intervention structured as vigorous, and the difficult to apply it in a naturalistic contest. The two trials aimed to establish if there is an effect dose for the efficacy of exercise both used structured interventions, without flexibility. Hua Chu et al. (59) had a drop-out rate of 30%, without significant difference among the groups; significantly, the main reasons for drop-out were "lack of time for exercise" and "low compliance with assigned exercise intensity and energy expenditure". Similarly, Dunn and colleagues (13) had a drop-out rate of 28% among exercising participants, with no significant difference among exercise condition. These drop-out rates are similar to that showed in trials with antidepressants (7), but the question about the extendibility of findings in a clinical setting remained unresolved. Interestingly, Callaghan and colleagues (54) affirmed the superiority of preferred intensity exercise in reducing depression, rather than prescribed intensity exercise.

An effect of exercise on mood as an adjunction to antidepressant therapy was detected in four of the included papers, with different findings: the largest trial, carried out by Chalder and colleagues (62), showing no effect, was performed with a treatment consisting in a counseling-based intervention rather than a physical treatment, and assessment was achieved by a self-administered questionnaire. Furthermore, a little percentage of participants took antidepressants as "usual care" in the overall sample, but a specific analysis comparing antidepressants plus intervention and antidepressant alone have not been carried out. The study published by Mather et al. (66) appears particularly interesting, because the clinical characteristics of the sample (elderly patients who failed to respond to antidepressants). The other two trials that showed a positive effect (60, 61) were also performed on treatment-resistant depressed patients, but were carried out on smaller samples than the Mather and colleagues' one.

Exercise has been supposed to act with a variety of neurobiological effects, such as increase of endorphin and monoamine levels or reduction in the levels of cortisol in the brain (72). It has been hypothesized that depressive disorders might be linked to decreased hippocampal neurogenesis (73). Laboratory researches have shown that exercise promotes adult hippocampal neurogenesis (74-76) and triggered dendritic remodeling (77), and such effect induced by exercise has been found to be much stronger than that determined by antidepressant drugs (78). Recently was shown that exercise-plus-antidepressant produced significant changes in the level of BDNF (Brain-derived neurotrophic factor) where antidepressant alone failed, and the combination between exercise and the antidepressant reboxetine led to both rapid (detectable at 2 days) and sustainable to 20 days increases in hippocampal BDNF mRNA expression (79), and this effect was demonstrated both in young and in aged rats (80).

Such a results may be of real interest on the light of the results of the present review and the findings of a systematic review of the literature on the efficacy of physical activity in depressed elderlies, that indicating should be drawn more attention on the problem of available adjunctive treatments, since depressed people in a naturalistic contest often undergoing and are resistant to antidepressants (81). While awaiting further higher methodological quality of trials, physical activity has been recommended in combination with other treatments (32), and, in a pilot study, it was proposed as a lower-cost augmentation strategy which may help to improve residual symptoms of depression and prevent relapse (82). The need for research lines more focused on the issue of combination therapy of exercise and antidepressant drugs is suggested given the great potential clinical relevance to treating depression with combination therapies without side effects, the above-mentioned findings on exercise as an add-on strategy, the finding of neurobiological research showing a potential interactive mechanism on hippocampal neurogenesis.

Conclusions

Despite the efforts of researchers, in the last 12 years few progress were done in showing the efficacy of exercise on depression. It was due in part to the persistent lack of high quality research, in part to the difficult to establish the real effectiveness of physical activity as a management for depressive symptoms, both from a qualitative and a quantitative view. A scientific evidence of exercise as an effective treatment for depression may be a "gold bullet", considering the low cost, the benefits on global health, and the acceptable risk. Despite these considerations, recommending exercise rather than usual care to a depressed patient may be nowadays at least a hazard, because the continuing ambiguous evidences of findings on the topic. However, there are some promising findings on physical activity combined with antidepressants, but further specific analyses need to be addressed in this direction.

COMPETING INTERESTS
Authors declare that they have no competing interests.

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