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Review article

Exercise in bipolar patients: A systematic review

Matias Carvalho Aguiar Melo [a,*], Elizabeth De Francesco Daher [a], Saulo Giovanni Castor Albuquerque [b], Veralice Meireles Sales de Bruin [a]

[a] Department of Medical Sciences, Universidade Federal do Ceará, Brazil
[b] Hospital de Saúde Mental Professor Frota Pinto, Brazil

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ABSTRACT

Background: Sedentary lifestyle is frequent in psychiatric disorders, however the directions of this association and benefits of physical activity are unclear. This is a systematic review about exercise in patients with bipolar disorder.

Methods: We performed a systematic literature search of studies published in English (1995 Jan to 2016 Jan) in PubMed, and Cochrane Library combining the medical terms 'physical activity' or 'sedentary' or 'physical exercise' with 'bipolar disorder' or 'mania' or 'bipolar depression'.

Results: Thirty-one studies were selected and included 15,587 patients with bipolar disorder. Sedentary lifestyle varied from 40% to 64.9%. Physical activity was associated with less depressive symptoms, better quality of life and increased functioning. Some evidence indicates a relationship between vigorous exercises and mania. Three prospective cohorts were reported; and no prospective randomized controlled trial was identified. Three studies focused on biomarkers in bipolar patients; and one reported the relationship between exercise and sleep in this group. Two assessed physical exercise in adolescents.

Limitations: (1) Differences between studies preventing a unified analysis; (2) most studies were cross-sectional; (3) motivation for exercising is a selection bias in most studies; (4) no intervention study assessing only physical exercise; (5) lack of studies comparing exercise across mood states.

Conclusion: Generally, exercise was associated with improved health measures including depressive symptoms, functioning and quality of life. Evidence was insufficient to establish a cause-effect relationship between mood and physical exercise. Future research including randomized trials is needed to clarify the role of physical activity in bipolar patients.

Contents

* Correspondence to: Department of Medical Sciences, Universidade Federal do Ceará, Av. Sargento Hermínio, 880 Quadra A. Bloco 5. Ap 201, Bairro: Monte Castelo, Fortaleza, CE CEP 60326-348, Brazil.
E-mail address: matcarv01@yahoo.com.br (M.C.A. Melo).

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1. Background

Bipolar disorder is a chronic psychiatric condition associated with severe disability, high mortality rates and increased demand for health services (Anderson et al., 2012; Price and Marzani-Nissen, 2012) whose therapy generally is based on pharmacological and non-pharmacological interventions (Geddes and Miklowitz, 2013; Kendall et al., 2014; McCormick et al., 2015).

Physical activity is frequently indicated for the prevention and treatment of various mental disorders (Moylan et al., 2013; Ten Have et al., 2011). The anti-inflammatory properties of exercise and the high comorbidity with obesity, diabetes, hypertension and cardiovascular disease (increased by psychotropic action) support this recommendation (Morriss and Mohammed, 2005; Petersen and Pedersen, 2005).

Exercise is a good non-pharmacological option to treat depressive disorders (Josefsson et al., 2014; Stanton and Reaburn, 2014; Stubbs et al., in press; Wegner et al., 2014). It is also associated with better cardiorespiratory performance, physical fitness, metabolic syndrome in depressive patients (Kerling et al., 2015; Stubbs et al., 2016b). Studies show that exercise training reduces depressive symptoms in people with cardiovascular and neurological conditions (Adamson et al., 2015; Ensari et al., 2014; Tu et al., 2014). Furthermore, it has been suggested that physical activity increased hippocampal brain-derived neurotrophic factor (BDNF) levels and stimulates neurogenesis, similarly to anti-depressant medications. It can be a neurophysiologic mechanism that can explain the antidepressant properties of exercise (Carek et al., 2011; Lopresti et al., 2013).

Nevertheless, the effect of physical activity on bipolar disorder is unclear. Whereas bipolar disorder may be understood as an inflammatory disease (Drago et al., 2015; Leboyer et al., 2012), it is interesting to consider whether the anti-inflammatory properties of exercise are particularly important for bipolar disorder and could be a specific pathway to improve all its mood states (Kucyi et al., 2010). Conversely, physical activity increases body energy and has be associated with manic episodes (Sylvia et al., 2013a; Wright et al., 2012).

Prior reviews on this subject have only included a limited number of studies, and not research published in the last few years (Thomson et al., 2015; Vancampfort et al., 2013; Wright et al., 2009). Some reviews did not focus specifically on physical activity, but discuss exercise in context of other lifestyle interventions (Bauer et al., 2015; Kemp, 2014; Lopresti and Jacka, 2015; Nierenberg et al., 2015; Ward et al., 2015). Other reviews reported on the effects of exercise in mental illness as an umbrella diagnosis and did not analyze separately and thoroughly bipolar patients (Barbour et al., 2007; Kucyi et al., 2010; Stanton and Happell, 2014).

Considering the current evidence, the relationship between exercise and mood symptoms in bipolar patients needs to be further clarified. The objective of this study is to perform a systematic review in order to investigate the practice of physical exercise in bipolar patients and its influences in bipolar disorder.

2. Methods

2.1. Search strategies

Two researchers performed an electronic search of PubMed and Cochrane Library. The following keywords were used: 'physical activity' or 'sedentary' or 'physical exercise' and 'bipolar disorder' or 'mania' or 'bipolar depression'. Manual searches were also conducted, using reference lists from identified articles.

We included all articles published since 1995 Jan until 2016 Jan evaluating the relationship between bipolar disorder and physical exercise. Reviews, case reports, conference abstracts, and expert opinions were excluded. Articles that were duplicated or unavailable in English language were eliminated. Studies of patients with mental disorders without analysis according to diagnosis were removed.

2.2. Data analysis

The data was classified according to study design and participants. All articles were displayed on a table with the following data: names of authors, publication year, study design, physical activity assessment, main results and limitations, when available.

3. Results

3.1. Study selection

The initial electronic database search yielded 1671 hits. Five records were found from the reference list of identified studies. Initially, 1676 articles were included. After careful examination, 1542 were excluded: 115 were duplicated; 673 focused on other conditions; 182 referred to animal experiments and 572 were case reports, conference abstracts, and expert's opinions. Thereafter, 94 articles were removed: 8 were unavailable in English language; 1 was not located; 11 were reviews; 47 analyzed bipolar disorder and other mental diseases in the same group and 36 were evaluated physical health and not physical activity or exercise. Thirty-one studies were finally selected and included 15,587 patients with bipolar disorder in total (Fig. 1).

The results were organized considering the relevant topics: (1) physical activity levels in bipolar patients – 15 studies; (2) exercise and biomarkers – 3 studies; (3) comorbidities – 3 studies; (4) beneficial effects of exercise – 7 studies; (5) complications of exercise – 4 studies (Table 1).

3.2. Physical activity levels in bipolar patients

Most studies showed that bipolar patients commonly had sedentary lifestyle, defined as absent or irregular practice of physical activity (Table 1). The majority of investigated psychiatric disorders (including bipolar disorder) were associated with lack of exercise (Chwastiak et al., 2011). The percentage of sedentary lifestyle in bipolar disorder varied from 40% to 64.9% in self-reported questionnaires (Cairney et al., 2009; Chwastiak et al., 2011; Gomes et al., 2013; Sylvia et al., 2013a).

Only one study assessed physical activity through objective measures. Motor activity levels of 60 bipolar patients were assessed using an actigraph. Most of them were classified as sedentary (around 78%). Moreover, 21% practiced light physical activity; and 1%, moderate/vigorous (Janney et al., 2014).

Physical activity in children and adolescents was rarely studied. To the best of our knowledge, two studies focused on adolescents and none in children. Jewell et al. (2015) and Subramaniapillai

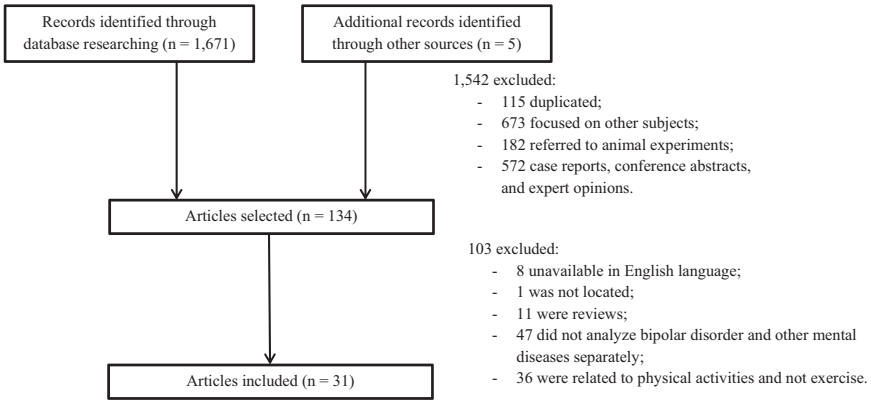

Fig. 1. Flowchart for study selection.

et al. (2016) compared adolescents with bipolar disorder and controls. In the first study, bipolar adolescents tended to practice less physical activities in general ($p=0.10$) and they reported less vigorous physical activity than controls ($p=0.005$) (Jewell et al., 2015). The second study showed that bipolar adolescents and controls experience a bout of exercise largely similar. Nevertheless, healthy adolescents reported a significantly greater tolerance for high intensity exercise than bipolar ones ($p<0.05$) (Subramaniapillai et al., 2016).

Few studies evaluated motor and functional details of physical performance. Bipolar disorder was associated with poorer functional exercise capacity. They walked a shorter distance ($p<0.001$), were less physically active ($p=0.005$) and reported more musculoskeletal pain ($p=0.03$) than controls (Vancampfort et al., 2015b). Patients had reduced speed of limb movement ($p<0.001$), explosive leg strength ($p=0.003$) and abdominal muscular endurance ($p<0.001$) (Vancampfort et al., 2015a). It was also observed that men had higher explosive muscle ($p=0.001$) and handgrip strength ($p<0.001$) than women (Vancampfort et al., 2015a).

Most studies revealed that exercise duration and intensity were reduced in bipolar disorder when compared with controls (Elmslie et al., 2001; Hausdorff et al., 2004; Shah et al., 2007). Only one study found no difference in the total energy expenditure between the groups (Cairney et al., 2009).

Comparisons between bipolar disorder and major depressive disorder showed conflicting evidence. Cairney et al. (2009) demonstrated higher total energy expenditure in bipolar disorder than major depressive disorder ($p=0.02$); however there were no differences compared to control group ($p=0.39$) (Cairney et al., 2009). Hausdorff et al. (2004) showed no differences in walking speed, swing time and stride time between depressive and bipolar patients (Hausdorff et al., 2004). However, compared to the control group, swing time variability was significantly larger in bipolar subjects ($p<0.0001$) and in subjects with major depression ($p<0.0004$). Chuang et al. (2008) concluded that the frequency of vigorous exercise did not differ between depression, bipolar and schizophrenia groups ($p=0.16$). There were also no differences in the frequency of getting as much exercise as is needed in three groups ($p=0.32$) (Chuang et al., 2008).

Two studies compared the physical activity in schizophrenia and bipolar patients. Bly et al. (2014) reported more physical activity in bipolar group ($p=0.004$) (Bly et al., 2014). On the other hand, Chuang et al. (2008) found no difference in frequency of vigorous exercise between these groups ($p=0.16$) (Chuang et al., 2008).

3.3. Exercise and biomarkers

Alterations of biomarkers associated with physical exercise in bipolar patients were rarely investigated (Table 1). El-Mallakh et al. (2010) described an aberrant regulation of ouabain-like factor (OLF), an endogenous cardenolide, in bipolar subjects during exercises. In contrast, salivary cortisol levels were not different in two groups. Patients showed low rates of OLF before ($p=0.019$), during ($p=0.029$) and after exercise ($p=0.020$). Higher levels of OLF and an evident peak activity was found in controls. The physiologic actions of the endogenous cardenolides and the implications of this finding are still unknown (El-Mallakh et al., 2010).

Schuch et al. (2015) demonstrated higher brain-derived neurotrophic factor (BDNF) in bipolar patients before and after exercise testing. Only bipolar women had increased serum BDNF from pre- to post-test ($p=0.004$). No significant changes were observed in bipolar men or healthy people (men and women). These results indicate a gender related difference of exercise on BDNF levels in bipolar patients (Schuch et al., 2015).

Hays et al. (2008) assessed the effect of aerobic exercise on DHEAS levels (a precursor of the adrenal steroid dehydroepiandrosterone) and perceptions of well-being in bipolar patients. It was observed an improvement in perception of global well-being after exercise ($p<0.05$). However, there was no correlation between DHEAS levels and perceptions of well-being ($p=0.38$) (Hays et al., 2008).

3.4. Comorbidities

Studies have suggested an association between sedentary lifestyle and comorbidities in bipolar patients. Strohle et al. (2007) reported decreased prevalence of co-morbid mental disorder in patients who practices physical activity ($p<0.05$) (Strohle et al., 2007). Sedentary lifestyle was associated with sleep disturbance in bipolar patients ($p<0.01$), but not in controls (McGlinchey et al., 2014). The direction of the association is uncertain because these studies are cross-sectional.

Goodrich et al. (2010) assessed determinants of access to weight counseling in bipolar disorder. Atypical antipsychotics and increased BMI were associated with exercise counseling ($p<0.05$). Therefore, the study highlights the importance of advice on weight loss for bipolar patients, especially for those with increased cardiovascular risk (Goodrich et al., 2010).

3.5. Beneficial effects of exercise

Studies indicate that physical activity is associated with less depressive symptoms, better quality of life and increased functioning (Table 1). Sylvia et al. (2013a, 2013b) showed that less self-

Table 1
Summary of selected studies.

Author	Study design	Participants	Physical activity assessments or interventions	Results
Elmslie et al., 2001	Case-control	89 euthymic BD and 445 controls	Life in New Zealand Questionnaire	Patients had fewer episodes of low- to moderate-intensity and high-intensity physical activity
Hausdorff et al., 2004	Case-control	23 BD, 19 MDD and 9 control	Stride time and swing time during walking	Patient groups tended to walk slowly, decreased swing time and increased stride time
Kilbourne et al., 2007	Case-control	2032 BD, 1895 Sz and 3065 control	Self-report	BD patients report poorer exercise habits – infrequent walking or strength exercises
Ng et al., 2007	Retrospective cohort (24 months)	49 BD: 14 in a walking group and 35 without physical activity	Walking program	No differences in clinical global impression (CGI), but participants had lower scores for depression anxiety stress scales (DASS)
Shah et al., 2007	Case-control	14 BD and 10 controls	Time of exercise in treadmill with increase of speed	BD patients had reduced exercise duration. No difference in respiratory and echocardiographic variables.
Strohle et al., 2007	Community cohort (4 years)	2548 people (39 BD)	Self-report	Increased physical activity was associated with high incidence of BD. Co-morbid mental disorder associated with less exercise
Chuang et al., 2008	Cross-sectional	60 BD, 61 Sz, and 61 MDD or anxiety disorders	Leisure-time physical activity questionnaire	24.2% reported daily physical activity. Frequency of vigorous exercise did not differ between groups.
Hays et al., 2008	Intervention	26 BD	Walking on a treadmill for 20 min	Improvement in perception of global well-being after exercise. No association between Dehydroepiandrosterone Sulfate (DHEAS) levels and global well-being
Salvi et al., 2008	Cross-sectional	108 BD	Self-report	No relationship between exercise and metabolic syndrome
Cairney et al., 2009	Cross-sectional	831 BD vs 4713 MDD vs 31,834 control	Total energy expenditure (EE)	EE did not differ between BD and control. EE was higher among BD than in MDD
El-Mallakh et al., 2010	Case-control	14 euthymic BD and 10 controls	Walking on a treadmill with progressively increased speed	Downregulation of a endogenous cardenolide before, during and after exercise in BD patients
Goodrich et al., 2010	Cohort study (2 years)	298 BD	Self-report	Atypical antipsychotics and increased BMI were associated with exercise counseling.
Guan et al., 2010	Cohort study (6 months)	148 BD and 65 control	Self-report	No relationship between exercise and metabolic syndrome
Chwastiak et al., 2011	Cross-sectional	501,161 md (9522 BD)	Self-report	All psychiatric disorders (including BD) had lack of exercise as compared to control
Salvi et al., 2011	Cross-sectional	200 BD	Self-report	BD patients with metabolic syndrome had lower exercise levels
Sylvia et al., 2011	Intervention	10 BD	Therapy with 3 modules: Nutrition, Exercise, and Wellness	BD patients improved quality of life, depressive symptoms and weight
Dakwar et al., 2012	National cross-sectional	23,505 md (851 BD)	International Physical Activity Questionnaire	Vigorous exercise was associated with BD II and alcohol dependence
Proudfoot et al., 2012	Cross-sectional	198 BD	Self-report	Decreased physical exercise was associated with depressive episodes
Wright et al., 2012	Qualitative study	25 BD	Self-report	Almost 50% used exercise to regulate symptoms. Exercise had different effects on mood according to intensity
Gomes et al., 2013	Cross-sectional	159 BD	Self-report	High rates of physical inactivity (64.9%)
Sylvia et al., 2013a	Cross-sectional	482 BD	Self-report	Less exercise was associated with higher BMI, depressive symptoms, lower quality of life and functioning. In contrast, more exercise was associated with mania
Sylvia et al., 2013b	Intervention	5 BD	Therapy with 3 modules: Nutrition, Exercise, and Wellness	Less physical activity was associated with more depressive symptoms, lower quality of life and functioning.
Bly et al., 2014	Cross-sectional	116 BD and 143 Sz	Total Activity Measure 2 (TAM2)	BD patients reported more physical activity than Sz.
Janney et al., 2014	Cross-sectional	60 BD	Actigraphy	BD patients were more inactive (78%). 21% practiced light physical activity; and 1.4% moderate/vigorous
McGlinchey et al., 2014	Case-control	32 euthymic BD and 36 controls	Self-report and actigraphy	BD patients tended to have reduced physical activity. It was a predictor of sleep disorder in BD, but not in controls
Jewell et al., 2015	Case-control	86 BD adolescents and 50 controls	17-item Quick Weight, Activity & Excess Screener (WAVE)	Physical activity tends to be lower in BD. Patients with low physical activity were less likely to have a family history of substance use ($p=0.03$)
Schuch et al., 2015	Case-control	18 BD and 18 controls	Measurement of BDNF before and after exercise	BD patients had higher BDNF levels, both at pre-and post-test
Vancampfort et al., 2015a	Cross-sectional	46 BD	EUROFIT test battery	Men had higher explosive muscle and handgrip strength than women.
Vancampfort et al., 2015a	Case-control	30 BD and 30 controls	EUROFIT test and International Physical Activity Questionnaire	BD patients had reduced speed of limb movement, explosive leg strength and abdominal muscular endurance
Vancampfort et al., 2015b	Case-control	30 BD and 30 controls	International Physical Activity Questionnaire and 6 min walk test	BD patients had poorer functional exercise capacity
Subramaniapillai et al., 2016	Case-control	32 BD adolescents and 31 controls	Exercise-Induced Feeling Inventory (EFI)	There were no differences between groups on any subscales. Controls reported greater tolerance for high intensity exercise than BD.

BD: Bipolar disorder
md: mental disorders
MDD: Major depressive disorder
Sz: Schizophrenia
EE: energy expenditure

reported exercise was associated with higher depressive symptoms ($p < 0.001$), and lower quality of life ($p = 0.032$) and functioning ($p < 0.001$) (Sylvia et al., 2013a). Proudfoot et al. (2012) also identified a relationship between decreased physical exercise and depressive episodes ($p < 0.001$) (Proudfoot et al., 2012).

In a qualitative study, 25 bipolar patients answered a semi-structured interview about their views on the relationship between exercise and bipolar disorder. Almost 50% used exercise to regulate symptoms (Wright et al., 2009).

Some intervention studies support effects of exercise on mood. Ng et al. (2007) invited bipolar inpatients to participate voluntarily in a walking group during admissions. The walking group had lower scores in Depression Anxiety Stress Scales – DASS ($p = 0.005$) and all its subscales (Depression $p = 0.048$, Anxiety $p = 0.002$, Stress $p = 0.01$). Nevertheless, there was no difference in Clinical Global Impression (CGI) between two groups ($p > 0.05$) (Ng et al., 2007). Sylvia et al. (2011,2013b) assessed the effects of nutrition/weight loss, exercise, and wellness treatment. These studies involved a combined of three treatment modules, administered in twelve 60-min group sessions over 14 weeks. The treatment tends to improve quality of life, depressive symptoms, functioning and weight (Sylvia et al., 2011, 2013b).

Most studies revealed a high prevalence of metabolic syndrome in bipolar patients. Nonetheless, the relationship between metabolic syndrome and physical activity in this population is uncertain. Guan et al. (2010) and Salvi et al. (2008) showed higher rates of hyperglycemia, dyslipidemia, hypertension and metabolic syndrome in bipolar patients. However, a relationship between metabolic syndrome and physical activity was not found (Guan et al., 2010 $p = 0.986$; Salvi et al., 2008 $p = 0.232$). Salvi et al. (2011), in a larger sample, demonstrated that bipolar with the metabolic syndrome practiced less exercise ($p = 0.030$) (Salvi et al., 2011).

3.6. Complications of exercise

Two studies estimates higher incidence of bipolar disorder in people that practices more physical activities. Strohle et al. (2007) followed 2548 people over four years in a community, including 959 with mental disorders and 39 with bipolar. At baseline, any mental disorder was associated with irregular physical activity (OR 0.69; CI 0.56–0.84, $p < 0.05$), but not in bipolar patients (OR 1.23, CI 0.58–2.60, $p > 0.05$). Over 4 years, the incidence of mental disorders in general was higher in people with irregular exercise or no exercise (OR 0.71, CI 0.53–0.95, $p > 0.05$). In contrast, those who practices regularly physical activity were associated with bipolar disorder (OR 10.29, CI 1.36–78.08, $p < 0.05$) (Strohle et al., 2007). In a national survey with 23,505 people with mental disorders (851 with bipolar disorder), vigorous exercise was associated with a vulnerability to some mental illness, especially alcohol dependence (OR 1.43, CI 1.12–1.84, $p < 0.05$) and bipolar II disorder (OR 2.29, CI 1.31–4.02, $p < 0.05$) (Dakwar et al., 2012).

Interestingly, some studies associated physical activity with manic episodes. Sylvia et al., 2013a showed that less exercise was associated with depressive symptoms ($p < 0.001$), and frequent exercise with mania ($p = 0.012$) (Sylvia et al., 2013a). However, this study is cross-sectional, which limits its conclusions. The findings possibly can be explained because individuals who are manic tend to exercise more. In a qualitative study, Wright et al. (2009) suggested that physical activity has different effects on bipolar patients, depending upon the severity of the exerciser's mood state (Wright et al., 2009). It could relieve symptoms of hypomania and prevent severe mood swings. However, vigorous exercise may worsen mania or hypomania.

4. Discussion

This review shows that evidence about the effects of physical activity on bipolar disorder is scarce. The majority of studies are cross-sectional evaluations of patients compared, or not, to controls. Only three prospective cohorts were reported in this review. However, neither of them evaluated the effects of physical activity on symptoms, quality of life and functioning. Two intervention studies evaluated the effects of a combined therapy including nutrition, physical activity and lifestyle. They showed benefit in quality of life, depressive symptoms and functioning. However, none assessed the exercise as a single intervention strategy. No prospective randomized controlled trial was identified.

Current evidence shows that bipolar patients lead a sedentary life, which has been associated with more comorbidities, poorer quality of life, worse functioning and more depressive symptoms in bipolar disorder. These findings are in accordance with studies in populations with mental disorders (Carneiro et al., 2016; Ho et al., 2016), indicating worse evolution of sedentary patients. However, studies in children and adolescents are scarce and needy.

The pathways by which exercise acts in bipolar disorder are unclear. The effects of exercise on BDNF levels in bipolar were poorly studied, despite its strong influence on brain functions. Aerobic exercise raises BDNF levels, associated with the chronic stress suppression, frequently found in bipolar patients (Heijnen et al., 2016; De Sá Filho et al., 2015). Some animal experiments showed that exercise independently attenuate mania-like behavior (Kirshenbaum et al., 2014). Besides, exercise contributes to reduce oxidative stress and inflammatory activity (Muneer, 2016; Sallam and Laher, 2016). Available evidence supports the important role of inflammation on bipolar disorder (Goldstein et al., 2009). Studies with BDNF and inflammatory cytokines in bipolar patients are much needed.

The impact of physical activity on sleep has been little studied in bipolar patients. There is a complex and bilateral interaction between exercise and sleep (Chennaoui et al., 2015). Poor sleep quality has been associated with residual mood symptoms, mood episode recurrence in bipolar patients and poor work performance (Boland et al., 2015; Cretu et al., 2016). It is necessary to study the influence of physical activity on sleep in bipolar patients.

Studies about the effects of physical activity on the metabolic syndrome in bipolar patients showed uncertain results. Similarly to other physical and mental conditions (Kahl et al., 2015; Liu et al., 2015; Park and Larson, 2014), physical activity should improve anthropometric measures and impact positively on metabolic syndrome. Possibly, an explanation for the few available studies may be the difficulty in recruiting and the adherence to physical exercise in bipolar population with frequent severe behavioral symptoms. In summary, the relationship between physical exercise and metabolic syndrome also needs further clarification.

Despite the highlighted beneficial effects of exercise, some studies suggest that frequent exercise is associated with mania in bipolar patients. It is unknown if the exacerbation of manic symptoms is cause or consequence of increased physical activity. It is also unclear if the manic state is associated with only vigorous exercise or with any kind of physical activity. Therefore, cohorts are needed to clarify this important subject.

Although there are previous reviews about the topic (Thomson et al., 2015; Vancampfort et al., 2013; Wright et al., 2009), this systematic review includes a larger number of articles. Eight recent publications (including 390 patients) are new to this review compared three prior ones. Furthermore, many gaps remain and it implies that the subject should be studied constantly.

Several limitations should be acknowledged. The small number of studies about same topic, the diversity in physical activity measures, the different types of study design and the

heterogeneous samples prevented us from performing meta-analysis. Most studies were cross-sectional, which limits establishing a cause and effect relationship. Furthermore, the motivation for exercising can be a selection bias in majority of cases. Some intervention simultaneously promoted nutrition, lifestyle changes and physical activity, hampering to infer conclusions about the only physical exercise. Other limitation was the lack of studies comparing exercise across mood states and assessing effects of medications on exercise.

In conclusion, sedentary lifestyle is common in bipolar patients. Physical exercise was associated with better functioning, quality of life and depressive symptoms. Some studies report the relationship between vigorous exercise and mania. However, evidence was insufficient to infer a cause-effect relationship and randomized trials are suggested. Other issues to be considered are the influence of exercise on sleep and its neurochemical changes on bipolar disorder.

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Declaration of interest

The authors report no conflicts of interest. The authors are responsible for the content and writing of the paper.

Contributors

MCAM conceived and designed the study, collected data and analyzed data. EDFD, SGCA and VMSB contributed to the conception and design of the study. All authors contributed to the drafting, and revisions of the manuscript. All authors read and approved the final manuscript.

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