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The effects of physical activity on physical and mental health among individuals with bipolar disorder: A systematic review

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ABSTRACT

Problem: Despite calls for physical activity (PA) to be prescribed to individuals with Bipolar Disorder (BD) as a means of improving physical and mental health there has been no systematic review of the potential health risks and benefits of increased PA for individuals with BD. This paper presents the first such review.
Method: Systematic searches of six databases were conducted from database inception until January 2009, using a range of search terms to reflect both PA and BD. Studies were subsequently considered eligible if they reported on quantitative studies investigating the effect of PA upon some aspect of physical or mental health in individuals with BD.
Results: Of the 484 articles retrieved, six studies met the inclusion criteria.
Discussion: Few studies have considered how PA may impact on the physical and mental health of people with BD. Nevertheless existing studies do suggest that physical activity interventions may be feasible and have a role in promoting mental health in this population. We discuss methodological, practical and ethical challenges to research in this area, and outline three research questions that future work should seek to address.
Conclusions: Research into the efficacy and safety of PA as an intervention in BD is required to support the development of detailed, population-specific guidelines.

Bipolar Disorder (BD) has a lifetime prevalence rate of around 2–6% in Europe and North America (Judd & Akiskal, 2003; Merikangas et al., 2007; Regeer et al., 2004; Szadoczky, Papp, Vitrai, Rihmer, & Furedi, 1998). In many cases BD involves repeated episodes of illness spanning many years (Daly, 1997). Significant levels of affective symptoms during inter-episodic periods are common (Judd et al., 2003), whilst episodes of both mania and depression frequently cause great disruption and distress. In addition to the emotional, interpersonal, social and economic burden imposed by the condition itself, there is evidence to suggest that BD is associated with an increased risk of physical health problems such as obesity, circulatory disorders, cancer, and diabetes mellitus (e.g. BarChana et al., 2008; Carney & Jones, 2006; Elmslie, Silverstone, Mann, Williams, & Romans, 2000; Fagiolini, Frank, Scott, Turkin, & Kupfer, 2005; Lin, Tsai, & Lee, 2007; Regenold, Thapar, Marano, Gavireni, & Kondapavuluru, 2002). This increased comorbidity has been ascribed to multiple factors including, but not limited to, the psychological and physiological sequelae of childhood adversity, poor health behaviours associated with the depressive and manic phases of BD, the effects of pharmacological treatment of BD, and disturbances in the hypothalamic-pituitary-adrenal axis (McIntyre et al., 2007). In addition to having a direct impact upon mortality and quality of life, in some cases the presence of a comorbid physical disorder may be associated with a worse course of BD (Fagiolini, Kupfer, Houck, Novick, & Frank, 2003).

There are at least four epidemiological studies that have examined physical activity prevalence among individuals with bipolar disorder. Two epidemiological studies have found reduced levels of physical activity (PA) in individuals with BD. Elmslie, Mann, Silverstone, Williams, and Romans (2001) examined self-reported physical activity provided by 89 individuals with a diagnosis of BD according to DSM-IV criteria, recruited from psychiatric clinics in New Zealand. Participants were required to be currently euthymic with no current major physical illness. Data were compared with a reference group of 445 individuals, matched for sex and age group, and selected randomly from a national database of members of the community. Rates of high and low-to-moderate activity were significantly lower in individuals with BD compared with the reference group. Kilbourne, Rofey, and McCarthy (2007)

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analysed data collected in 1999 from veterans diagnosed with BD ($n = 2032$) or schizophrenia, or from a randomly-selected group of individuals with no serious mental illness who had received care as part of the United States Veterans Affairs health care system in 1999, and had completed a health survey. Consistent with the findings of Elmslie and colleagues, individuals with BD were significantly less likely to report engaging in regular exercise, defined as walking three or more times per week for at least 20 min, or engaging in strength exercises three or more times a week for at least 20 min. The authors suggest that poor exercise habits in individuals with BD may be exacerbated by the disruptive effects of different phases of the disorder, namely increased likelihood of a sedentary lifestyle during depression, and non-adherence to treatment programmes, which may include exercise programmes, during manic phases. In addition they noted that compared with individuals with no serious mental illness, individuals with BD were less likely to report being provided with the opportunity to discuss diet and exercise with their clinician, which may reflect time constraints during appointments and a lack of knowledge amongst clinicians of medical risks in this population.

The findings of a cross-sectional and prospective study, conducted in Germany, suggest that decreased levels of PA may postdate the onset of BD. Strohle et al. (2007) examined PA in 2548 individuals recruited from the community and aged between 14 and 24. Higher rates of psychiatric disorder, specifically anxiety disorders, somatoform disorders or dysthymia, were found amongst individuals reporting low rates of PA. However at four year follow-up, risk of onset of BD ($n = 18$) was increased in those who reported engaging in exercise at baseline, relative to those who reported no exercise. The findings of this aspect of the study are limited by the small number of participants who went on to develop BD, however the authors suggest that this association may reflect shared vulnerability to onset of BD and the propensity to engage in increased exercise in late adolescence or early adulthood.

Finally, Cairney, Veldhuizen, Faulkner, Schaffer, and Rodriguez (2009; see this issue) examined data pertaining to diagnosis and levels of PA gathered as part of a Canadian national survey. They found no differences in the proportion of individuals characterized as active, moderately active or inactive among individuals with BD ($n = 831$), major depressive disorder or the general population. Overall, findings from epidemiological studies appear inconsistent as to whether individuals with bipolar disorder are as active, less active, or even more active than individuals with no psychiatric diagnosis. This may be due to distinct sampling variations in the existing research.

Regular PA confers multiple benefits in terms of physical health, including reduced risk of coronary heart disease, stroke, hypertension, diabetes and some forms of cancer. It can also improve mood and performance on daily tasks (Department of Health, 2004; U.S. Department of Health and Human Services, 1999) and may also reduce depressive symptomatology (Larun, Nordheim, Ekeland, Hagen, & Heian, 2006; Lawlor & Hopker, 2001; Mead et al., 2009). Guidelines have been produced for the treatment of depression using PA as an adjunctive therapy, for example the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom have recommended PA as an intervention for individuals with mild unipolar depression, and individuals with BD who are currently experiencing depressive symptoms (NICE, 2006, 2007). Both the American Psychiatric Association (2004) and NICE (2006) recommend PA to mitigate against weight gain in individuals with severe mental illness or BD, in keeping with calls made by a number of researchers in the field (Basu et al., 2004; Keck & McElroy, 2003; McElroy et al., 2002; Morriss & Mohammed, 2005; Wildes, Marcus, & Fagiolini, 2006). However, it has been recognised that the evidence base underpinning the recommendation of PA to individuals with BD or serious mental illness for mental health benefits is lacking (Barbour, Edenfield, & Blumenthal, 2007; Richardson, Faulkner, et al., 2005). As acknowledged by NICE (2006), the assertion that PA represents a potential means of reducing bipolar depression is based upon studies that investigate unipolar depression primarily. Such studies tend to exclude individuals with BD, or make no distinction between diagnostic groups beyond identifying current depression. Likewise, many studies that yield information about the use of PA by individuals with serious mental illness test samples that are heterogeneous in terms of diagnosis (e.g. Archie et al., 2007; Ball, Coons, & Buchanan, 2001; Littrell, Hilligloss, Kirshner, Petty, & Johnson, 2003; Vreeland et al., 2003).

In summary, there is reason to believe both that PA has the potential to impact favourably upon both physical and mental health in individuals with BD, and that levels of PA may be reduced in at least some subpopulations of individuals with BD. However studies that can inform about potential advantages and disadvantages of PA in BD are limited in number and often investigate serious mental illness rather than BD specifically. Systematic reviews of the evidence constitute a clear first step towards developing interventions to promote mental health through physical activity (Faulkner & Taylor, 2009). Here we report the results of the first systematic review that aims to address the following research question: what are the effects of PA on the physical and mental health of individuals with BD? Our secondary aim was to identify key questions to be addressed by future research studies in this area, and to articulate the methodological and practical challenges these studies face.

1. Method

1.1. Literature search

Searches were conducted across a number of electronic databases for the period from database inception until January 2009. The databases searched were: The Cochrane Library, PUBMED, CINAHL, EMBASE, PSYCHINFO and SPORTDISCUS. Secondary sources and review articles were scanned, and the National Research Register of controlled trials was also searched for information on current or recently completed trials.

The search strategy was developed to maximise the sensitivity of article identification. It used both controlled vocabulary (e.g. Medical Subject Headings [MeSH]) and key words ($ denotes a truncated search term): "exercise or physical activity or physical fitness or strength training or tai chi or isometric or yoga or resistance training or endurance training or walk$ or callisthenic$ or calisthenic$ or weight training or weight lifting or jog$ or run$ or swim$ or sedentary or anti-sedentary or motion sensor or accelerometer or pedometer" and "bipolar disorder or bipolar illness or bipolar depression or bipolar affective disorder or bipolar I or bipolar II or mania or manic or hypomania or hypomanic or cyclothymia or cyclothymic or hyperthymia or hyperthymic or affective psychosis or bipolar manic disorder or psychotic mania". Selection of key words was informed by examination of search terms listed in prior, published, systematic reviews carried out in the areas of BD or PA.

1.2. Study selection

Studies were considered eligible if they were quantitative studies investigating the effect of physical activity upon some aspect of physical or mental health in individuals with BD. BD was defined as including Bipolar I Disorder, Bipolar II Disorder, cyclothymia and Bipolar Disorder not otherwise specified. In order to ensure that the findings of the studies were relevant to BD in

particular, studies that included individuals with non-Bipolar diagnoses and did not report findings in relation to separate diagnostic categories were excluded. No language restrictions were applied in the selection of studies.

Two reviewers (KAW and ESEH) independently carried out study selection based upon study abstract, or upon study title where it was not possible to obtain the abstract, using the above criteria. Selections were compared, and where there was a discrepancy between the two reviewers the abstract in question was examined by the third reviewer (AHT) and consensus reached.

2. Results

A total of 484 titles, abstracts or full papers were retrieved. Of these, six were found to report quantitative studies examining the effect of physical activity upon some aspect of physical or mental health in individuals with BD: two were studies of chronic PA as a therapeutic intervention in BD, two investigated the effects of acute PA upon serum lithium levels in individuals with BD, and two investigated physical responses to an acute session of PA. None were adequately powered randomised controlled trials. Key features of the six studies identified are summarised in Table 1.

2.1. Studies of chronic physical activity

Two studies reported on PA as a therapeutic intervention in BD. The first, an unpublished doctoral dissertation (Edenfield, 2007, as cited in Barbour et al., 2007), tested eight individuals with Bipolar I or II Disorder, recruited opportunistically from a North American community. Regular exercisers, defined as those who carried out three sessions of at least 30 min of structured exercise per week, were excluded, as were individuals with thought disorder, psychotic disorder, or alcohol or substance dependence. The intervention tested was Exercise Prescription (EP), which was compared to Standard Behavioural Activation (SBA) within a randomised cross-over design. EP involved eight walking sessions lasting 30 min each, spaced over a two week period. In the SBA condition 30 min sessions of chosen sedentary activity were prescribed in the place of the walking sessions. Outcomes were: physiological and subjective reactivity to a laboratory stressor, indexed by post-stressor change in skin conductance and rating on the Profile of Mood States (POMS: McNair, Lorr, & Droppleman, 1971); self-reported daily mood and stress level; symptoms of depression and mania, measured using the Beck Depression Inventory – II (BDI-II: Beck, Steer, & Brown, 1996) and the Altman Scale for Rating Mania (ASRM: Altman, Hedeker, Peterson, & Davis, 1997), coping reactions, measured using the brief COPE (Carver, 1997), and level of daily hassles reported, measured using the Survey of Recent Life Events (Kohn & Macdonald, 1992). Interpretation of findings was complicated by 'over-compliance' with the PA intervention, such that exercise behaviour increased even in those participants initially assigned to the SBA condition. Nevertheless descriptive statistics indicated that regular PA, whether prescribed by the researcher or self-initiated, was associated with an overall decrease in depression symptoms and decrease or no change in mania symptoms post intervention.

The second study (Ng, Dodd, & Berk, 2007) examined 98 admissions to an Australian psychiatric inpatient unit, representing 49 individuals with a diagnosis of Bipolar Disorder, irrespective of subtype or index episode. The intervention was a ward-based walking group in which some of the individuals studied had elected to participate. Walking took place for approximately 40 min up to five times per week, and participants determined their own exercise intensity. Comparisons were made between 24 admissions in which the patient attended the walking group and 74 in which the patient chose not to. Outcomes were: clinician ratings of severity and improvement, measured using the Clinical Global Impression Severity (CGI-S) and Improvement (CGI-I) scales (Guy, 1976); patient ratings of depression, anxiety and stress, measured using the Depression Anxiety Stress Scales (DASS, Lovibond & Lovibond, 1995). Whilst the two groups did not differ in clinician ratings at discharge, attendance of the walking group was associated with significantly lower scores on all three subscales of the DASS.

2.2. Studies of acute physical activity

Two studies investigated the possibility that PA may have deleterious effects upon mental state in some individuals with BD due to its potential to affect blood serum levels of lithium. Lithium, in the form of lithium carbonate or lithium citrate, is commonly prescribed to individuals with BD as both an acute and a prophylactic treatment. Norman, Mathews, and Yohe (1987) tested a physically healthy, regularly exercising male with a diagnosis of Bipolar I Disorder and who was prescribed lithium carbonate on an ongoing basis. The intervention was a 5 mile run. Outcomes were: serum lithium level post run and the following morning, and sweat lithium ratio during the run. Serum lithium level was found to decrease by 0.2–0.3 mEq/1 post run and remained lowered the following morning. Analysis of sweat collected during the run revealed a serum to sweat lithium ratio of 1:3. Carroll, Pinnick, and Whitaker (1998) tested two males aged 61 and 31 who were in moderately good physical condition, had been diagnosed with BD, and had both been using lithium for more than five years. The intervention was treadmill exercise at 4–4.5 miles an hour for 90–120 min which, for one participant, was repeated five months later. Outcomes were serum lithium levels and lithium excretion in urine and sweat after exercise. The amount of lithium lost was found to be equivalent to one 100 mg capsule, less than 10% of the daily ingested dose. The authors concluded that decreased urinary secretion and decreased total amount of lithium secreted in urine may compensate for lithium lost in sweat.

Hays et al. (2008; Hays, 2007) tested 26 individuals with Bipolar I or II Disorder according to DSM-IV (American Psychiatric Association, 2000) recruited from a North American outpatient population. The intervention was 20 min of treadmill-based exercise at 70% age-predicted maximal heart rate. Outcomes were: self-reported wellbeing and level of the hormone Dehydroepiandrosterone Sulfate (DHEAS) post exercise. DHEAS is a precursor of the adrenal steroid Dehydroepiandrosterone (DHEA), which is released in response to stress. It has been hypothesised that enhancing DHEA levels may lead to increased feelings of wellbeing, although few studies have tested the proposed causal relationship. It has also been hypothesised that increases in DHEA and DHEAS mediate the relationship between acute PA and increases in wellbeing. Hays and colleagues found significant increases in both DHEAS level and self-reported wellbeing post exercise, but no significant correlation between the degree of change in the two variables.

Shah et al. (2007) tested 14 individuals with euthymic Bipolar I Disorder and 10 individuals with no self-reported history of mood disorder or psychosis. The intervention was treadmill-based exercise at 70% maximum predicted oxygen consumption, continued until exhaustion. Outcomes were: cardiac response to exercise, indexed by diastolic and systolic volume and left ventricular ejection fraction, and duration of exercise before exhaustion. No measure was taken of mood response to exercise. Whilst the two groups did not differ in terms of cardiac response to exercise, duration of exercise before exhaustion was reduced in the BD group.

Table 1
Details of 2 chronic and 4 acute exercise studies meeting inclusion criteria.

Author	Methods	Participants	Intervention	Dependent variables	Results	Limitations
Studies of Chronic PA						
Edenfield (2007).	Combined series cross-over (ABACA, ACABA) and interaction (ABABA, ACACA) single-participant.	$N = 8$ adults with DSM-IV Bipolar I or II Disorder. Ages 26–55, 1 male.	1.Exercise = 8 sessions of 30 min walking over 2 weeks. Control = Standard Behavioural Activation (SBA): 8 sessions of 30 min sedentary activity over 2 weeks.	1. Physiological and subjective reactivity to stressor. 2. Perceived daily mood and stress levels. 3. Depressive symptoms (BDI-II). 4. Manic symptoms (ASRM). 5. Coping strategy use. 6. Perceived daily hassles.	Results confounded by increased physical activity in all conditions. However descriptive statistics indicated decrease in depression symptoms and decrease/no change in manic exercise post intervention across the sample as a whole.	Small number of participants limits generalisability of findings. Contamination of SBA condition by EP condition.
Ng et al. (2007).	Retrospective cohort study with A-B design.	Admissions to inpatient unit with primary diagnosis of ICD-10 Bipolar Disorder. N= 98 admissions (across 49 patients). Mean age = 44 years, 15 males.	Intervention = participation in walking group: 40 min walking, intensity determined by participant, up to five times weekly. Comparison = non-participation.	1. Clinical global impression severity (CGI-S). 2. Clinical global impression – improvement (CSI-I). 3. Scores on subscales of the Depression Anxiety Stress Scales (DASS).	CSI-S: no between-groups difference at time 2. CSI-I: no between-groups difference at time 2. DASS – Sig between-groups difference at time 2 on total (Cohen's $d = 0.82$) and on all three subscales (Depression: $d = 0.57$; Anxiety: $d = 0.92$; Stress: $d = 0.76$).	Self-selection of participants into study conditions. Analysis was not intention-to-treat: excluded those who chose to attend walking group but did not attend regularly.
Studies of acute exercise						
Norman et al. (1987).	Single uncontrolled case-study.	$N = 1$ male aged early 20s, healthy experienced runner, diagnosis of Bipolar I Disorder, currently prescribed lithium carbonate.	Single 5 mile run outdoors, temperature 9 °C.	1. Serum lithium level after intervention. 2. Concentration of lithium in sweat collected during run.	Serum lithium level decreased by 0.2–0.3 mEq/1 post run and remained lowered the following morning. Serum to sweat lithium ratio calculated as 1:3.	
Carroll et al. (1998).	Uncontrolled case-study.	$N = 2$ males aged 61 and 31 in moderately good physical condition. Diagnosed with BD by clinical judgment, using lithium for more than 5 years.	Treadmill exercise at 4–4.5 mph for 1.5–2 h. Case 1: two sessions five months apart. Case 2: one session only.	1. Mg Li2CO3 lost in sweat. 2. Serum lithium after exercise. 3. mEqLi+ in urine after exercise.	Amount of Li lost equivalent to one 100 mg capsule (less than 10% dose). Decrease in serum lithium level of 0.04–0.07 mEq/1 during exercise. Decreased urinary secretion and decreased total amount of lithium secreted in urine may compensate for lithium lost in sweat.	
Shah et al. (2007).	Between-groups AB.	$N = 24$ (14 individuals with Bipolar I Disorder clinically assessed as euthymic, 10 controls reporting no mood disorders or psychosis), mean age = 41.3 and 37.7, 14 males.	Treadmill exercise at 10% gradient, at 70% maximum predicted oxygen consumption. Duration until exhaustion.	1. Duration of exercise. 2. Diastolic volume post exercise. 3. Systolic volume post exercise. 4. Left ventricular ejection fraction.	Exercise duration significantly shorter in BD group ($d = 0.47$). No significant between-group differences in electrocardiographical variables.	
Hays et al. (2008).	Within-participants AB.	$N = 26$ individuals with DSM-IV Bipolar I or II Disorder, mean age 42 years, 13 males.	Treadmill exercise for 20 min at 70% age-predicted maximal heart rate.	1. Dehydroepiandrosterone Sulfate (DHEAS) level post exercise. 2. Self-reported wellbeing post exercise.	Significant increase in DHEAS level post exercise. Significant increase in wellbeing post exercise.	

3. Discussion

Of the six studies identified by our review, only two investigated the potential of PA as a therapeutic intervention in BD. Whilst the results of these two studies were consistent with a beneficial effect of PA in terms of decreasing symptoms of depression, anxiety and stress, methodological limitations constrain the generalisability of their findings. The larger study (Ng et al., 2007) explored the outcomes of a walking group delivered as part of inpatient care, and is the first and only published investigation of the effects of a PA intervention versus inactivity in BD. As the authors note, the study did not use a randomised design, and had a small sample size. Furthermore, due to the naturalistic nature of the study, the phase of the illness during which walking took place was not controlled, and there was no objective or subjective measure of total PA other than recorded attendance at walking sessions.

In the following sections we discuss the methodological, practical and ethical *challenges in conducting research* into the effects of PA on BD. We then offer some *recommendations for future research*, followed by *recommendations for clinical practice*.

3.1. Challenges in research into physical activity and bipolar disorder

We divide challenges faced by research into the impact of PA upon BD into three overlapping categories: issues related to the population being studied; issues related to the intervention being studied; and determination of appropriate and meaningful outcomes.

3.1.1. With whom should research be conducted?

In terms of psychiatric diagnosis, three main dimensions are of particular relevance to the design of PA intervention studies: the subtype of BD; the phase of BD; and the presence of comorbid difficulties. DSM-IV (American Psychiatric Association, 2000) recognises four subtypes of BD: Bipolar I Disorder, Bipolar II Disorder, Cyclothymia and Bipolar Disorder not otherwise specified. The boundaries of these subtypes are an issue of debate in terms of their validity both between individuals and within individuals across time. Nonetheless amongst those individuals who receive a diagnosis of BD, there exist substantial differences in terms of symptom pattern and course, and these differences will have implications for the likely targets of PA as an intervention. For example, subsyndromal symptoms, typically depressive, are more common in individuals with Bipolar I Disorder relative to individuals with Bipolar II Disorder (Joffe, MacQueen, Marriott, & Young, 2004), and therefore psychosocial or PA interventions for Bipolar I Disorder may need to include techniques aimed at improving levels of mood, motivation and energy between major affective episodes.

The design and conduct of PA research must accommodate the multiplicity of affective states that individuals with BD can experience, including mania, hypomania, mixed affective states, depression, and euthymia. First, if a PA intervention aims to reduce symptoms, the intervention must be informed by an understanding of the processes by which these symptoms are maintained, and this is likely to differ between phases. Therefore separate lines of research are needed to investigate PA as an intervention for bipolar depression, versus, for example, PA as an intervention to attenuate the onset of hypomania. These should be complimented and informed by basic research into key maintenance processes that may be influenced by PA. Second, trials of chronic PA as an intervention must anticipate that participants will move between phases of BD, often with little warning, and must account for this in their design. For example, researchers and participants could discuss in advance the possibility of fluctuations in motivation and energy level leading to under (or over) compliance with the intervention, and agree the extent to which PA frequency, intensity and duration may be adjusted to accommodate phase changes without compromising the integrity of the trial.

Third, the heterogeneity of BD raises ethical issues for both cross-sectional and longitudinal research. Little is known about the risks associated with PA in individuals who are experiencing hypomania or mania. Excessive goal-directed activity is symptomatic of mania, as is risk-taking (American Psychiatric Association, 2000), raising the possibility that during a hypomanic or manic phase some individuals may be at risk of engaging in excessive, prolonged and potentially harmful PA. Studies of chronic PA must also accommodate the possibility that participants may temporarily lose capacity to give informed consent to research participation during an episode of mania or severe depression. Finally, medications prescribed for treatment and prevention of BD episodes may impact on the safety and efficacy of PA. The possibility of harmful interactions between lithium and PA has been discussed in the previous section. An additional consideration includes the sedating effects of certain antidepressant, anti-manic and antipsychotic medications, which may impact upon motivation to engage in PA as well as ability to exercise safely.

Psychiatric comorbidity in BD has been estimated at over 50% (Kessler et al., 1994) with anxiety disorders, personality disorders and substance use disorders commonly being reported. The presence of multiple difficulties may increase the complexities inherent in designing and delivering a PA-based intervention, yet there is a need to pursue such interventions. The presence of comorbidity in individuals with Bipolar I Disorder is a risk factor for poor outcome of BD (McElroy et al., 2001). Therefore this group of individuals may have much to gain from developments in and refinements of psychosocial interventions, including those that involve PA. As discussed previously BD is associated with increased risk of a number of serious physical health problems including obesity, circulatory disorders, cancer, and diabetes mellitus (e.g. BarChana et al., 2008; Carney & Jones, 2006; Elmslie et al., 2000; Fagiolini et al., 2005; Lin et al., 2007; Regenold et al., 2002). Again, the high rate of physical comorbidity in BD is a challenge to the design and testing of PA interventions: exercising in accordance with national guidelines may not be possible or appropriate for individuals with severe physical health difficulties, and careful physical screening, in accordance with American College of Sports Medicine guidelines, for example (ACSM, 2009), should be considered in both research and clinical practice before exercise is prescribed.

In summary, it is vital that studies of the effect of PA in BD specify the particular population of interest. If the target of the PA intervention, or its mechanism of action, is likely to be specific to a subgroup of individuals, tightly defined inclusion and exclusion criteria should be employed to allow a valid assessment of the efficacy of the intervention within a circumscribed population. Otherwise, the composition of the sample of individuals studied should be described in detail in terms of diagnosis, current affective state, medication use and comorbid physical and psychiatric difficulties, and heterogeneity within the sample should be taken into account in the analyses or the interpretation of the results. Study design should also account for the relapsing course of BD both in practical terms and in terms of maintaining informed consent, and protocols should be in place that address risk to participants from interactions between PA and medication or existing physical health issues.

3.1.2. What form should the intervention take?

Physical activity is construed as varying along the dimensions of frequency, intensity, duration, timing and type (ACSM, 2009). On

what basis should researchers set these dimensions when selecting PA interventions for BD? One source of guidance is provided by national recommendations concerning optimal exercise levels in the general population. The United States Department of Health and Human Services (2008) recommend 30–60 min per day of moderate to vigorous intensity physical activity on five or more days of the week, whilst in the United Kingdom the Department of Health make a similar recommendation that individuals undertake at least 30 min of moderate intensity activity on five days of the week (or more) (Department of Health, 2004). Richardson, Avripas, Neal, and Marcus (2005) note that whilst structured programmes may be helpful for people with serious mental illness, disadvantages may include their relatively high cost and need for specialised equipment and professional input. Constraints imposed by physical health difficulties, initial fitness levels and medication may also preclude the stringent application of generic guidelines to all individuals with BD.

Particularly when the aim is to enhance mental health benefits, an alternative approach to determining the parameters of a PA intervention is to consider the mediating processes in the relationship between PA and BD. Many candidate explanations exist for the beneficial effects of PA that have been observed in individuals experiencing depression and anxiety, including impact upon neurotransmitter systems, stabilisation of circadian rhythms, modification of patterns of avoidance and approach behaviour, reduction of negative repetitive thoughts or rumination and enhancement of positive self-schema. It is outside the scope of this review to describe these accounts in detail. For a consideration of the mechanisms by which PA may impact upon depression, psychological wellbeing and mental health more generally readers are directed to reviews by Stathopoulou, Powers, Berry, Smits, and Otto (2006), Salmon (2001) and Ekkekakis (2003). In general however, the nature of the supposed mechanism of action of PA should determine the form of PA selected for investigation. For example, the possibility that PA may act to stabilise circadian rhythms is of particular theoretical interest with respect to BD. In the general population, PA has been considered as a means of mitigating against circadian desychronisation (Klein & Wegmann, 1974) because it may facilitate circadian stabilisation following disruptive events. There is evidence to suggest that markers of circadian rhythms are disrupted within episodes of BD and during euthymia (e.g. Jones, Hare, & Evershed, 2005; Kennedy, Kutcher, Ralevski, & Brown, 1996; Linkowski et al., 1994; Meyer & Maier, 2006; Sachar, 1975; Tsujimoto, Yamada, Shimoda, Hanada, & Takahashi, 1990), and critically, events that would be expected to cause acute disturbances to circadian rhythms have been found to be associated with the development of mania (Jauhar & Weller, 1982; Malkoff-Schwartz et al., 1998; Young, 1995). The speculation that regular PA might help individuals with BD adjust to schedule-disrupting events, and thus reduce risk of relapse, is a tentative one. Nevertheless in order to capitalise on this possibility, research into the potential of regular PA to reduce risk of relapse in BD could prescribe exercise frequency and timing in a way that may take advantage of its potential stabilising effects, for example by advising minimal variation in the time of day and regularity with which exercise is performed.

Selection of the intervention will also involve consideration of its purity. With respect to designing PA-based interventions for BD, this will require decisions to be made as to whether PA is delivered in combination with pharmacological "treatment-as-usual", as are most psychosocial treatments for BD within clinical trial settings (Lam, Burbeck, Wright, & Pilling, 2009). This will also involve specifying the extent to which the intervention includes input from exercise or health professionals, and the extent to which it includes techniques used in psychological therapies, such as application of cognitive or behavioural principles, or determination of early signs of relapse and associated coping strategies. Even a relatively "pure" PA intervention may contain a number of potentially active components such as distraction, exposure to sunlight and increased social contact. Determining the relative importance of these is of practical as well as theoretical interest, as this information will allow refinement of PA-based interventions to maximise effectiveness.

3.1.3. What should be the outcomes of interest?

Outcomes targeted by previous psychosocial and pharmacological intervention trials for BD include reduction of affective symptoms within and between episodes, reduced risk of relapse, and enhancements in wellbeing, social functioning and quality of life. Whilst these would appear to be legitimate outcomes for studies of PA-based interventions in BD, the outcomes valued by researchers may not always coincide with those most valued by service users, and collaboration between researchers and individuals with lived experience of BD should begin at an early stage in the construction of the research agenda. Physical health outcomes particularly relevant to known physical health risks in the population of individuals with BD include body mass index, waist-to-hip ratio, type 2 diabetes status, cholesterol level, blood pressure, maximal oxygen consumption, as well as improvement in comorbid physical health conditions.

Trials of PA as an intervention in BD provide an important opportunity to test hypotheses about mechanisms of change. Therefore additional measures (applied at multiple points throughout treatment) might reflect key processes hypothesised to mediate the effects of PA upon mood. These may include self-efficacy to engage in physical activity (or perceived competence), perceived control over symptoms and behaviour, and opportunities for social interaction, routine stability, level of behavioural avoidance, and ability to tolerate stress, using different theoretical frameworks (Michie, Johnston, Francis, Hardemann, & Eccles, 2008). Such research can be preceded or complimented by single-session experimental studies investigating the immediate impact of PA on affective and cognitive variables.

Recent research suggests that mediation of the effects of PA on acute BD at a neurochemical level may involve factors that affect cell growth and cell and DNA resilience. Drawing on data from both human and animal studies it has been hypothesised that irregularities in some neurotransmitter systems in BD may reflect disturbances in brain chemicals that regulate cell plasticity and resilience (Bezchlibnyk & Young, 2002; Chen & Manji, 2006; Manji & Lenox, 2000). Increases in the potentially neurotoxic brain chemical pro-inflammatory cytokine have been found in mania and bipolar depression (Kim, Jung, Myint, Kim, & Park, 2007; O'Brien, Scully, Scott, & Dinan, 2006) whilst emerging evidence suggests that acute BD episodes are associated with reduced levels of antioxidant enzymes and elevated levels of antioxidant stress (Frey et al., 2007; Ranjekar et al., 2003). A number of studies in animals and humans have found a neuroprotective effect of PA (Cotman, Berchtold, & Christie, 2007; Dishman & O'Connor, 2009). Currently issues of measurement constrain comprehensive investigation of neuroprotective processes as mediators between PA and symptoms of BD in humans. Nevertheless this area of research represents a promising avenue for advancing understanding of the mechanisms by which PA which may influence symptoms of BD.

3.2. Recommendations for future research

From amongst the numerous questions that research in this area could seek to address, we select three that address particularly pressing issues associated with different phases of BD, and outline potential approaches to tackling each.

3.2.1. How effective is physical activity in reducing the symptoms of bipolar depression?

There is evidence to suggest that regular PA may reduce depressive symptoms in individuals experiencing an episode of Unipolar Depression, although the magnitude of this effect is smaller in well-designed and conducted trials (Mead et al., 2009). Based on the findings of research with individuals with Unipolar Depression, U.K. guidelines recommend PA for individuals with symptoms of Bipolar Depression. However randomised controlled trials that use intention-to-treat analysis and robust assessor blinding procedures are needed to establish whether PA is effective in reducing symptoms of Bipolar Depression specifically. Our review identified very little research that directly investigates risks associated with PA in BD, and no qualitative research into the views of individuals with BD and their clinicians on this matter. Therefore intervention trials should be preceded by qualitative and pilot work to inform the design of the main intervention, including identifying potential risks of PA that are specific to individuals with Bipolar Depression.

3.2.2. What are the features of an optimal programme of physical activity during hypomania?

Individuals with BD who engage in regular structured exercise face the question of whether, and how, to adapt their programme during periods of hypomania. Furthermore, for those with low levels of PA, there is little guidance as to whether increasing PA represents a helpful means of responding to the increases in energy and activation that accompany early-stage hypomania. Exploratory and basic research to characterise and quantify potential risks and benefits of PA during hypomania is a necessary precursor to intervention trials. Potential risks and benefits could be explored within qualitative work that draws upon the experiences of both individuals with BD and clinicians who work with this group. Basic experimental research might include studies of the impact of single sessions of exercise on mood, energy and cognition, when exercise is carried out during a period of high mood and energy. These could be conducted in non-clinical samples currently experiencing elevated, activated mood states that have been induced by means of mood induction paradigms used in studies of mood-dependent cognition in BD (Johnson, Ruggero, & Carver, 2005; Wright, Lam, & Newsom-Davis, 2005), prior to conducting this research with clinical populations experiencing early-stage hypomania. The findings of these studies will inform the content of PA-based interventions that can be evaluated within phase 2 and 3 clinical trials (Medical Research Council, 2000).

3.2.3. What benefits can be conferred by regular physical activity during euthymia in individuals with bipolar disorder?

Individuals with BD may find themselves advised to exercise by clinicians on the basis of the potential benefits to physical health. Does this intervention bring additional benefits in the form of improvements in psychological health? Studies should investigate whether regular moderate PA, as recommended by national guidelines, leads to reductions in residual depressive symptoms (self and clinician rated), greater mood stability (measured prospectively via daily self-report), and increases in wellbeing and social functioning. Long-term follow up should be incorporated to investigate the duration of any effects, in addition to determining whether regular PA reduces risk of entering an affective episode, or the duration of affective episodes. Such trials may also include measures of key physical health outcomes of particular relevance to the population of individuals with BD as outlined previously.

3.3. Recommendations for clinical practice

In the absence of more detailed empirical data to inform us of the relationship between PA and the course of BD, clinicians should take into account the individual client's past experiences of exercise and a range of other physical characteristics (ACSM, 2009) when recommending future exercise, particularly with regard to his or her sense of the interaction between PA and mood state. In psychosocial therapeutic work this may lead to the inclusion of PA or exercise behaviour within the broad treatment formulation.

The current review raises a number of points relevant to health professionals. High rates of comorbid physical health problems in the population of individuals with BD means that a physical health check is necessary before exercise is recommended. Possible interactions with medications should also be taken into account. For example Norman et al. (1987) and Carroll et al. (1998) recommend monitoring lithium levels in individuals who exercise regularly, whilst NICE (2006) recommend that patients taking lithium should be advised to maintain their fluid intake if they are likely to be sweating due to exercise or to other factors. On the other hand, PA may represent a means of mitigating against possible cardiometabolic side-effects associated with antipsychotic and mood stabilising medications, including weight gain and diabetes. Excessive goal-directed activity is recognised as a symptom of hypomania and mania, and it may be that this could manifest as prolonged or excessive PA in some individuals during hypomania or mania. Such individuals and their clinicians should therefore be alert to the possibility of increased risk of dehydration and injury during these times in clients who exercise. Depressive phases of BD may also bring disruption to normal patterns of regular physical activity necessary to maintain positive physical wellbeing. It may therefore be important to provide therapeutic support targeted at maintaining PA during depression and overcoming relapses in planned exercise programmes. In the absence of research on adapting PA programmes to fluctuations in motivation and energy in individuals with BD, there is useful evidence and guidance from the field of exercise in the treatment of chronic fatigue syndrome which may have relevance here (Edmonds, McGuire, & Price, 2004). In particular, it is recommended that individuals avoid a pattern of exercise cycling, caused by daily fluctuations of fatigue/energy which lead to varying levels of drive or motivation: feeling energetic may lead to a temporary increase in PA, followed by symptoms of fatigue and inactivity. Instead, consistent levels and small daily increments of exercise may help to minimise cycles of low and high levels of PA.

An added consideration is the acceptability of any exercise or PA programme. This includes not only what is practical and convenient for the individual, but also the meaning to him or her of engaging in a particular regime of activity. Choices about PA will be influenced by many factors including past experiences of exercise, beliefs about exercise and one's physical abilities, the attitudes of significant others towards exercise, cost and accessibility of the activity and the fact that many forms of exercise are social activities or take place in public. Those seeking to recommend PA regimes to individuals with BD can be sensitive to this by recognising that some individuals may be experiencing, for example, low self-confidence, social isolation and financial constraints. As with any new exerciser, such factors are likely to influence what is acceptable in terms of deciding when, how, where and with whom to exercise, and importantly future adherence to the programme.

4. Conclusion

The current review, which addressed the question of the effects of physical activity upon physical and mental health in BD, represents the first published systematic review of this issue and leads us to conclude that further research in this area is urgently needed. Findings from studies in other populations suggest that individuals with BD may stand to benefit from regular physical activity in terms

of both physical and mental health, yet our review returned no rigorous clinical studies investigating physical activity as a intervention in BD, and only a small number of pre-clinical and early phase clinical studies. In addition, if recommendations from the research literature and national clinical guidelines are heeded (Elmslie et al., 2001; Fagiolini et al., 2003; Keck & McElroy, 2003; McElroy et al., 2002; Morriss & Mohammed, 2005; NICE, 2006), individuals with Bipolar Disorder may find their clinicians suggesting exercise as a means of addressing both physical and mental health difficulties. Research into the safety and efficacy of PA as an intervention in BD is necessary prior to producing detailed, population-specific guidance concerning the prescription of PA in this population.

References

Altman, E. G., Hedeker, D., Peterson, J. L., & Davis, J. M. (1997). The Altman self-rating mania scale. *Biological Psychiatry, 42*, 948–955.

American College of Sports Medicine. (2009). *ACSM's guidelines for exercise testing and prescription* (8th ed.). Baltimore, MD: Lippincott Williams and Wilkins.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders*. text revision (4th ed.). Washington, DC: American Psychiatric Association.

American Psychiatric Association. (2004). *Treatment of patients with schizophrenia* (2nd ed.). Arlington, VA: American Psychiatric Association.

Archie, S. M., Goldberg, J. O., Akhtar-Danesh, N., Landeen, J., McColl, L., & McNiven, J. (2007). Psychotic disorders, eating habits, and physical activity: who is ready for lifestyle changes? *Psychiatric Services, 58*, 233–239.

Ball, M. P., Coons, V. B., & Buchanan, R. W. (2001). A program for treating olanzapine-related weight gain. *Psychiatric Services, 52*, 967–969.

Barbour, K. A., Edenfield, T. M., & Blumenthal, J. A. (2007). Exercise as a treatment for depression and other psychiatric disorders: a review. *Journal of Cardiopulmonary Rehabilitation and Prevention, 27*, 359–367.

BarChana, M., Levav, I., Lipshitz, I., Pugachova, I., Kohn, R., Weizman, A., et al. (2008). Enhanced cancer risk among patients with bipolar disorder. *Journal of Affective Disorders, 108*, 43–48.

Basu, R., Brar, J. S., Chengappa, K. N. R., John, V., Parepally, H., Gershon, S., et al. (2004). The prevalence of the metabolic syndrome in patients with schizoaffective disorder – bipolar subtype. *Bipolar Disorders, 6*, 314–318.

Beck, A. T., Steer, R. A., & Brown. (1996). *Beck depression inventory* (2nd ed.). San Antonio, TX: The Psychological Corporation.

Bezchlibnyk, Y., & Young, L. T. (2002). The neurobiology of bipolar disorder: focus on signal transduction pathways and the regulation of gene expression. *Canadian Journal of Psychiatry, 47*, 135–148.

Cairney, J., Veldhuizen, S., Faulkner, G., Happitots, A., & Rodriguez, C. (2009). Bipolar disorder and physical activity: results from a national survey of Canadians. *Mental Health and Physical Activity, 2*.

Carney, C. P., & Jones, L. S. (2006). Medical comorbidity in women and men with bipolar disorders: a population-based controlled study. *Psychosomatic Medicine, 68*, 684–691.

Carroll, W. E., Pinnick, H. A., & Whitaker, W. L. (1998). Lithium, exercise and sweat. *Research Communications in Biological Psychology and Psychiatry, 23*, 103–111.

Carver, C. S. (1997). You want to measure coping but your protocol's too long: consider the brief COPE. *International Journal of Behavioral Medicine, 4*, 92–100.

Chen, G., & Manji, H. K. (2006). The extracellular signal-regulated kinase pathway: an emerging promising target for mood stabilizers. *Current Opinion in Psychiatry, 19*, 313–323.

Cotman, C. W., Berchtold, N. C., & Christie, L. (2007). Exercise builds brain health: key roles of growth factor cascades and inflammation. *Trends in Neurosciences, 30*, 464–472.

Daly, I. (1997). Mania. *The Lancet, 349*, 1157–1160.

Department of Health. (2004). *At least five a week: Evidence on the impact of physical activity and its relationship to health*. London: Department of Health.

Dishman, R. K., & O'Connor, P. J. (2009). Lessons in exercise neurobiology: the case of endorphins. *Mental Health and Physical Activity, 2*, 4–9.

Edenfield, T. M. (2007). Exercise and mood: Exploring the role of exercise in regulating stress reactivity in bipolar disorder. Unpublished doctoral dissertation, University of Maine.

Edmonds, M., McGuire, H., & Price, J. (2004). Exercise therapy for chronic fatigue syndrome. *Cochrane Database of Systematic Reviews*, (Issue 3). Art. No.: CD003200.

Ekkekakis, P. (2003). Pleasure and displeasure from the body: perspectives from exercise. *Cognition and Emotion, 17*, 213–239.

Elmslie, J. L., Mann, J. I., Silverstone, J. T., Williams, S. M., & Romans, S. E. (2001). Determinants of overweight and obesity in patients with bipolar disorder. *Journal of Clinical Psychiatry, 62*, 486–491.

Elmslie, J. L., Silverstone, J. T., Mann, J. I., Williams, S. M., & Romans, S. E. (2000). Prevalence of overweight and obesity in bipolar patients. *Journal of Clinical Psychiatry, 61*, 179–184.

Fagiolini, A., Frank, E., Scott, J. A., Turkin, S., & Kupfer, D. J. (2005). Metabolic syndrome in bipolar disorder: findings from the centre for Pennsylvanians. *Bipolar Disorders, 7*, 424–430.

Fagiolini, A., Kupfer, D. J., Houck, P. R., Novick, D. M., & Frank, E. (2003). Obesity as a correlate of outcome in patients with bipolar I disorder. *American Journal of Psychiatry, 160*, 112–117.

Faulkner, G., & Taylor, A. (2009). Editorial: promoting physical activity for mental health: a complex intervention? *Mental Health and Physical Activity, 2*, 1–3.

Frey, B. N., Andreazza, A. C., Kunz, M., Gomes, F. A., Quevedo, J., & Salvador, M. (2007). Increased oxidative stress and DNA damage in bipolar disorder: a twin-case report. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 30*, 283–285.

Guy, W. (1976). *ECDEU assessment for psychopharmacology – Revised*. Rockville, MD: U.S. Department of Health, Education and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs.

Hays, A. E. (2007). Effect of an acute bout of aerobic exercise on dehydroepiandrosterone sulphate (DHEAS) in clinically diagnosed Bipolar subjects. Unpublished doctoral dissertation, University of Pittsburgh.

Hays, A. E., Goss, F., Aaron, D., Abt, K., Friedman, E., Gallagher, M., et al. (2008). Hormonal and perceptual changes in bipolar subjects after acute aerobic exercise. *Medicine & Science in Sports & Exercise, 40*, 17.

Jauhar, P., & Weller, M. P. I. (1982). Psychiatric morbidity and time zone changes: a study of patients from Heathrow airport. *British Journal of Psychiatry, 140*, 231–235.

Joffe, R. T., MacQueen, G. M., Marriott, M., & Young, L. T. (2004). A prospective, longitudinal study of percentage of time spent ill in patients with bipolar I or bipolar II disorder. *Bipolar Disorders, 6*, 62–66.

Johnson, S. L., Ruggero, C. J., & Carver, C. S. (2005). Cognitive, behavioral and affective responses to reward: links with hypomanic symptoms. *Journal of Social and Clinical Psychology, 24*, 894–906.

Jones, S. H., Hare, D. J., & Evershed, K. (2005). Actigraphic assessment of circadian activity and sleep patterns in bipolar disorder. *Bipolar Disorders, 7*, 176–186.

Judd, L. L., & Akiskal, H. S. (2003). The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. *Journal of Affective Disorders, 73*, 123–131.

Judd, L. L., Schettler, P. J., Akiskal, H. S., Maser, J., Coryell, W., Solomon, D., et al. (2003). Long-term symptomatic status of bipolar I vs. bipolar II disorders. *International Journal of Neuropsychopharmacology, 6*, 127–137.

Keck, P. E., & McElroy, S. L. (2003). Bipolar disorder, obesity, and pharmacotherapy-associated weight gain. *Journal of Clinical Psychiatry, 64*, 1426–1435.

Kennedy, S. H., Kutcher, S. P., Ralevski, E., & Brown, G. M. (1996). Nocturnal melatonin and 24-hour 6-sulphatoxymelatonin levels in various phases of bipolar affective disorder. *Psychiatry Research, 63*, 219–222.

Kessler, R. C., McGonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., & Eshleman, S. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. *Archives of General Psychiatry, 51*, 8–19.

Kilbourne, A. M., Rofey, D. L., & McCarthy, J. F. (2007). Nutrition and exercise behaviour among patients with bipolar disorder. *Bipolar Disorders, 9*, 443–452.

Kim, Y. K., Jung, H. G., Myint, A. M., Kim, H., & Park, S. H. (2007). Imbalance between pro-inflammatory and anti-inflammatory cytokines in bipolar disorder. *Journal of Affective Disorders, 104*, 91–95.

Klein, K. E., & Wegmann, H. M. (1974). The resynchronization of human circadian rhythms after transmeridian flights as a result of flight direction and mode of activity. In L. E. Scheving, F. Halberg, & J. E. Pauly (Eds.), *Chronobiology* (pp. 564–570). Tokyo: Igaku Shoin Ltd.

Kohn, P. M., & Macdonald, J. E. (1992). The survey of recent life experiences: a decontaminated hassles scale for adults. *Journal of Behavioral Medicine, 15*, 221–236.

Lam, D. H., Burbeck, R., Wright, K., & Pilling, S. (2009). Psychological therapies in bipolar disorder: the effect of illness history on relapse prevention – a systematic review. *Bipolar Disorders, 11*, 474–482.

Larun, L., Nordheim, L. V., Ekeland, E., Hagen, K. B., & Heian, F. (2006). Exercise in prevention and treatment of anxiety and depression among children and young people. *Cochrane Database of Systematic Reviews, 3*. CD004691.

Lawlor, D. A., & Hopker, S. W. (2001). The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression analysis of randomised controlled trials. *British Medical Journal, 322*, 1–8.

Lin, H. C., Tsai, S. Y., & Lee, H. C. (2007). Increased risk of developing stroke among patients with bipolar disorder after an acute mood episode: a six-year follow-up study. *Journal of Affective Disorders, 100*, 49–54.

Linkowski, P., Kerkhofs, M., Van Onderbergen, A., Hubain, P., Copinschi, G., et al. (1994). The 24-hour profiles of cortisol, prolactin, and growth hormone secretion in mania. *Archives of General Psychiatry, 51*, 616–624.

Littrell, K. H., Hilligloss, N. M., Kirshner, C. D., Petty, R. G., & Johnson, C. G. (2003). The effects of an educational intervention on antipsychotic-induced weight gain. *Journal of Nursing Scholarship, 35*, 237–241.

Lovibond, S. H., & Lovibond, P. F. (1995). *Manual for the depression anxiety stress scales*. Sydney: Psychology Foundation.

McElroy, S. L., Altshuler, L. L., Suppes, T., Keck, P. E., Frye, M. A., Denicoff, K. D., et al. (2001). Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. *American Journal of Psychiatry, 158*, 420–426.

McElroy, S. L., Frye, M. A., Suppes, T., dhavale, D., Keck, P. E., Leverich, G. S., et al. (2002). Correlates of overweight and obesity in 644 patients with bipolar disorder. *Journal of Clinical Psychiatry, 63*, 207–213.

McIntyre, R. S., Soczynska, J. K., Beyer, J. L., Woldeyohannes, H. O., Law, C. W. Y., Miranda, A., et al. (2007). Medical comorbidity in bipolar disorder: reprioritizing unmet needs. *Current Opinion in Psychiatry, 20*, 406–416.

McNair, D. M., Lorr, M., & Droppleman, L. F. (1971). *EITS manual for the profile of mood states*. San Diego: Educational and Industrial Testing Service.

Malkoff-Schwartz, S., Frank, E., Anderson, B., Sherrill, J., Siegel, L., Patterson, D., et al. (1998). Stressful life events and social rhythm disruption in the onset of manic and depressive bipolar episodes. *Archives of General Psychiatry, 55*, 702–707.

Manji, H. K., & Lenox, R. H. (2000). The nature of bipolar disorder. *Journal of Clinical Psychiatry, 61*, 42–57.

Mead, G. E., Morley, W., Campbell, P., Greig, C. A., McMurdo, M., & Lawlor, D. A. (2009). Exercise for depression. *Cochrane Database of Systematic Reviews*(4). CD004366.

Medical Research Council. (2000). *A framework for the development and evaluation of RCTs for complex interventions to improve health*. London: Medical Research Council.

Merikangas, K. R., Akiskal, H. S., Angst, J., Greenberg, P. E., Hirschfeld, R. M. A., & Petakhova, M. (2007). Lifetime and 12 month prevalence of bipolar spectrum disorders in the national comorbidity survey replication. *Archives of General Psychiatry, 64*, 543–552.

Meyer, T., & Maier, S. (2006). Is there evidence for social rhythm instability in people at risk of affective disorders? *Psychiatry Research, 141*, 103–114.

Michie, S., Johnston, M., Francis, J., Hardemann, W., & Eccles, M. (2008). From theory to intervention: mapping theoretically derived behavioural determinants to behaviour change techniques. *Applied Psychology: An International Review, 57*, 660–680.

Morriss, R., & Mohammed, F. A. (2005). Metabolism, lifestyle and bipolar affective disorder. *Journal of Psychopharmacology, 19*, 94–101.

Ng, F., Dodd, S., & Berk, M. (2007). The effects of physical activity in the acute treatment of bipolar disorder: a pilot study. *Journal of Affective Disorders, 101*, 259–262.

National Institute for Health and Clinical Excellence. (2006). *Bipolar disorder clinical guideline*. London: NICE.

National Institute for Health and Clinical Excellence. (2007). *Depression (amended): Management of depression in primary and secondary care*. London: NICE.

Norman, T. C., Mathews, W., & Yohe, C. D. (1987). A case study on the effects of strenuous exercise on serum lithium levels. *The Nebraska Medical Journal, 72*, 224–225.

O'Brien, S. M., Scully, P., Scott, L. V., & Dinan, T. G. (2006). Cytokine profiles in bipolar affective disorder: focus on acutely ill patients. *Journal of Affective Disorders, 90*, 263–267.

Ranjekar, P. K., Hinge, A., Hedge, M. V., Ghate, M., Kale, A., & Sitasawad, S. (2003). Decreased antioxidant enzymes and membrane essential polyunsaturated fatty acids in schizophrenic and bipolar mood disorder patients. *Psychiatry Research, 121*, 109–122.

Regeer, E. J., ten Have, M., Rosso, M. L., Roijen, H., Volleberg, W., & Nolen, W. A. (2004). Prevalence of bipolar disorder in the general population: a reappraisal study of the Netherlands mental health survey and incidence study. *Acta Psychiatrica Scandinavica, 110*, 374–382.

Regenold, W. T., Thapar, R. K., Marano, C., Gavireni, S., & Kondapavuluru, P. V. (2002). Increased prevalence of type 2 diabetes mellitus among psychiatric patients with bipolar I affective and schizoaffective disorders independent of psychotropic drug use. *Journal of Affective Disorders, 70*, 19–26.

Richardson, C. R., Avripas, S. A., Neal, D. L., & Marcus, S. (2005). Increasing lifestyle physical activity in patients with depression or other serious mental illness. *Journal of Psychiatric Practice, 11*, 379–388.

Richardson, C. R., Faulkner, G., McDevitt, J., Skrinar, G. S., Hutchison, D. S., & Piette, J. D. (2005). Integrating physical activity into mental health services for persons with serious mental illness. *Psychiatric Services, 56*, 324–331.

Sachar, E. J. (1975). Twenty-four-hour cortisol secretory patterns in depressed and manic patients. *Progress in Brain Research, 42*, 81–91.

Salmon, P. (2001). Effects of physical exercise on anxiety, depression, and sensitivity to stress: a unifying theory. *Clinical Psychology Review, 21*, 33–61.

Shah, A., Alshaher, M., Dawn, B., Siddiqui, T., Longaker, R. A., Stoddard, M. F., et al. (2007). Exercise tolerance is reduced in bipolar illness. *Journal of Affective Disorders, 104*, 191–195.

Stathopoulou, G., Powers, M. B., Berry, A. C., Smits, J. A. J., & Otto, M. W. (2006). Exercise interventions for mental health: a quantitative and qualitative review. *Clinical Psychology: Science and Practice, 13*, 179–193.

Strohle, A., Hofler, M., Pfister, H., Muller, A., Hoyer, J., Wittchen, H., et al. (2007). Physical activity and prevalence and incidence of mental disorders in adolescents and young adults. *Psychological Medicine, 37*, 1657–1666.

Szadoczky, E., Papp, Z.s., Vitrai, J., Rihmer, Z., & Furedi, J. (1998). The prevalence of major depressive and bipolar disorders in Hungary: results from a national epidemiologic survey. *Journal of Affective Disorders, 50*, 153–162.

Tsujimoto, T., Yamada, N., Shimoda, K., Hanada, K., & Takahashi, S. (1990). Circadian rhythms in depression. Part II: circadian rhythms in inpatients with various mental disorders. *Journal of Affective Disorders, 18*, 199–210.

U.S. Department of Health and Human Services. (1999). *Physical activity and health: A report of the Surgeon General*. Washington, DC: U.S. Department of Health and Human Services.

U.S. Department of health and human services. (2008). *Physical activity guidelines advisory committee report, 2008*. Washington, DC: U.S. Department of Health and Human Services.

Vreeland, B., Minsky, S., Menza, M., Radler, D. R., Roemheld-Hamm, B., & Stern, R. (2003). A program for managing weight gain associated with atypical antipsychotics. *Psychiatric Services, 54*, 1155–1157.

Wildes, J. E., Marcus, M. D., & Fagiolini, A. (2006). Obesity in patients with bipolar disorder: a biopsychosocial-behavioural model. *Journal of Clinical Psychiatry, 67*, 904–915.

Wright, K., Lam, D., & Newsom-Davis, I. (2005). Induced mood change and dysfunctional attitudes in remitted bipolar I affective disorder. *Journal of Abnormal Psychology, 114*, 689–696.

Young, D. M. (1995). Psychiatric morbidity in travelers to Honolulu, Hawaii. *Comprehensive Psychiatry, 36*, 224–228.