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D Vancampfort

S Rosenbaum

M Probst

J Connaughton

University of Notre Dame Australia, joanne.connaughton@nd.edu.au

C du Plessis

See next page for additional authors

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Authors

D Vancampfort, S Rosenbaum, M Probst, J Connaughton, C du Plessis, T Yamamoto, and B Stubbs



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JOURNAL OF AFFECTIVE DISORDERS**Top 10 research questions to promote physical activity in bipolar disorders: A consensus statement from the International Organization of Physical Therapists in Mental Health**

Davy Vancampfort^{a,b}, Simon Rosenbaum^c, Michel Probst^a, Joanne Connaughton^d, Christy du Plessis^e, Taisei Yamamoto^f, Brendon Stubbs^{g,h}

^aKU Leuven - University of Leuven, Department of Rehabilitation Sciences, Leuven, Belgium

^bKU Leuven - University of Leuven, University Psychiatric Centre, Leuven, Belgium

^cSchool of Psychiatry, University of New South Wales, Sydney, Australia

^dUniversity of Notre Dame, School of Physiotherapy, Fremantle, Australia

^eUniversity of the Free State, Bloemfontein, South Africa

^fKobe Gakuin University, Department of Medical Rehabilitation, Kobe, Japan

^gPhysiotherapy Department, South London and Maudsley NHS Foundation Trust, London, United Kingdom

^hHealth Service and Population Research Department, Institute of Psychiatry, King's College London, London, United Kingdom

*Corresponding author: Davy Vancampfort. KU Leuven – University of Leuven, University Psychiatric Centre, Leuvensesteenweg 517, 3070 Kortenberg, Belgium; Tel.: +32 2 758 05 11; Fax: +32 2 759 9879. E-mail address: davy.vancampfort@uc-kortenberg.be

Abstract

Background: Research has only recently started to consider the importance and applicability of physical activity (PA) for people with bipolar disorder (BD). The aim of the current study is to highlight 10 pertinent PA research questions in people with BD.

Methods: The International Organization of Physical Therapy in Mental Health executed a consultation with all National organizations (n=13) to identify the most salient questions to guide future research on PA in BD.

Results: We identified the following 10 questions: (1) What are the benefits of PA for people with BD? (2) What are the most prominent safety issues for PA prescription in BD? (3) What is the optimal PA prescription for people with BD? (4) What are the key barriers to PA among people with BD? (5) What are the most effective motivational strategies for ensuring PA adoption and maintenance in BD? (6) How do we translate PA research into community practice? (7) If one treatment goal is increased physical activity, what type of professionals are needed as part of a multidisciplinary team? (8) How do we incorporate PA as a vital sign in clinical practice? (9) How can we prevent sedentary behavior in BD? (10) What is the most appropriate PA assessment method?

Limitations: We did not consult people with BD.

Conclusions: Addressing these questions is critical for developing evidence-based approaches for promoting and sustaining an active lifestyle in BD. Ultimately, achieving this will reduce the burden of cardiovascular disease and improve the quality of life of this population.

Keywords: physical activity; exercise; mood

Introduction

People with bipolar disorder have higher levels of morbidity and mortality than the general population (De Hert et al., 2011). A recent meta-analysis (Walker et al., 2015) demonstrated that mortality rates are approximately two to three times higher than those of the general population. The underlying causes for the increased premature mortality are complex and multi-factorial (Hayes et al., 2015). However, natural causes account for a substantial proportion of this premature mortality and increased comorbid cardio-metabolic disease (Goldstein et al., 2009; Prieto et al., 2015; Vancampfort et al., 2015a) is a significant risk factor. Although genetic factors (Ellingrod et al., 2012) and shared pathophysiological mechanisms (Dargél et al., 2015) contribute significantly to this high risk profile, poor lifestyle habits including higher prevalence of smoking and high rates of substance abuse (Waxmonsky et al., 2005), and sedentary behavior and lower levels of physical activity (Janney et al., 2014) play a prominent role contributing to this risk. The relationship between bipolar disorder and poor physical health is complex, since many people with bipolar disorder are treated with psychotropic medication which often improves psychiatric symptoms, but in turn, can predispose the individual to increased cardiovascular risk (Vancampfort et al., 2013a).

Despite the well-known benefits of physical activity to prevent and treat cardiovascular disease in the general population (Naci and Ioannidis, 2013), research has only recently started to consider its importance and applicability for people with bipolar disorder (Thomson et al., 2015). There is consequently a need to consider how physical activity can be utilized and incorporated into the routine care of people with bipolar disorder.

The International Organization of Physical Therapists in Mental Health (IOPTMH) (Probst, 2012) aims to address this need. The IOPMTH represents physical therapists with considerable experience designing and delivering physical activity interventions for people

experiencing bipolar disorder. The IOPTMH set out to summarize, appraise and strengthen the direction of physical activity endeavors in this vulnerable population. We sought to define the 10 most pertinent questions regarding physical activity and bipolar disorder, to ensure that future research endeavors are on a strong footing whilst providing answers to the most pressing issues for clinicians today.

Methods

All the National organizations (n=13; Belgium, Denmark, Finland, Iceland, Japan, Norway, The Netherlands, Spain, South-Africa, Sweden, Switzerland, Turkey, United Kingdom) of the IOPMTH, an official subgroup of the World Confederation of Physical Therapy and representing more than 1100 physical therapists (Probst, 2012), were invited to provide a list of the 5 leading physical activity research questions. Data were collected in a 5-month period, from January to May 2015. The National Board of the National organizations were requested by e-mail to consult their own members and to ask, based on the members' own clinical and research experience, what are the most pertinent research questions that they believe most researchers and clinicians should consider as critical. In stage 1, each National organization was asked to answer the question "What are the five most important research questions for the next 10 years in the area of physical activity in people with bipolar disorders?" One representative from each National organization put forward five research questions which their organization identified as priorities in the area. They also provided a brief description of each question and reasons why they believed the issue to be a priority. All National organizations received the latest open access systematic review on the topic (Thomson et al., 2015).

In the second stage, 4 different researchers from 4 different continents with at least 10 years of clinical and/or research experience (MP, CP, JC, TY) distilled a list with the 15 most reported research questions. To this end the 4 investigators reviewed all research questions that were provided by each National organization, with common issues combined into a single question.

In a third stage 3 researchers (DV, SR, BS), all with extensive experience and publication history in the areas of physical activity, exercise, and rehabilitation of people with bipolar disorder reviewed and discussed these questions until a consensus was reached on the

top 10 questions. The 3 expert researchers were requested to “review the research questions put forward in stages 1 and 2 and rate how important they believe each issue is for global research in physical activity in bipolar disorders”. The 3 experts rated each research issue independently using a 5-point Likert scale (5 = very important, 4 = important, 3 = moderately important, 2 = of little importance and 1 = unimportant). The three study investigators then short-listed the research questions to 10 according to those with highest mean Likert scale ratings.

Results

All 13 National organizations completed stage 1. Collectively this provided a total of 65 questions. Following qualitative reduction of overlapping issues, 19 questions remained, and the 15 most reported ones were carried forward to stage 3. From stage 3, the mean Likert-scale ratings were used to determine the top 10 research questions. The mean Likert-scale ratings of the top 20 issues ranged from 3.5 to 5.0, with exactly 10 of 19 questions having a median rating of >4.0 (“important”). The mean Likert-scale ratings of the top 10 questions ranged from 4.0 to 5.0.

The top 10 questions are listed in Table 1. Importantly, the numerical number given to each question does not reflect the relative importance of the questions. In accordance with similar research in multiple sclerosis, we have organized the questions by topics such that two reflect consequences of physical activity prescription, six reflect processes for promoting physical activity, and two reflect issues of sedentary behavior and physical activity measurement. In the discussion, we provide a brief background and rationale for the top 10 questions with reference to the latest research evidence.

[Insert Table 1 about here]

Interestingly, many of our top 10 questions run parallel with those developed for other chronic conditions such as cancer (Courneya et al., 2015) and multiple sclerosis (Motl et al., 2015). We provide a brief background and rationale for each of our top 10 selected research questions. Our primary goal is to highlight why these questions are important rather than to provide a comprehensive systematic review of the literature for each question.

Discussion of the top 10 research questions

1. What are the benefits of physical activity for people with bipolar disorder?

Perhaps the most compelling physical activity research question is whether physical activity has the potential to change the course of the disease. Although, there is rigorous evidence for the anti-depressive effects of physical activity (Krogh et al. 2011; Cooney et al, 2014; Rosenbaum et al. 2014; Knapen et al., 2015), the current literature on this important topic in people with bipolar disorder is scarce. Ng et al. (2007) investigated the efficacy of a walking group and found that those who participated experienced lower levels of depression, anxiety and stress. In a another study, Hays et al. (2008) demonstrated that among 26 bipolar disorder patients, those who walked or ran on a treadmill for 20 minutes at 70% of their age-predicted maximal heart rate reported higher levels of self-reported well-being. Sylvia et al. (2013) conducted a pilot study among five overweight patients with bipolar disorder, and showed that weight, cholesterol, triglycerides, the number of daily calories and sugar intake decreased, while weekly exercise duration more than tripled following an 18-session, 20-week cognitive behavioral therapy (CBT) based lifestyle modification program.

Despite the promise of these studies, the available literature has considerable methodological limitations including small sample sizes, heterogeneous treatment groups, no control interventions, no distinction between types of physical activity (structured exercise versus lifestyle physical activity), no clear definitions of the dose (frequency, intensity, time, type) and lack of comparisons between different stages of bipolar disorder (mania, depression, remission), specific symptoms (psychosis, suicidality) or drug treatment (antidepressants, neuroleptics, lithium). The lack of large-scale trials is potentially due to the range of unique challenges that people with bipolar disorder experience in regards to adopting and maintaining an active lifestyle (Vancampfort et al., 2015b). Literature on the mood-state-dependent effects of physical activity in people with bipolar disorder is currently completely

lacking. For example, future research could focus on the following questions: (1) Can physical activity decrease depression severity when patients are depressed? And (2) Can physical activity decrease the risk of future manic episodes?" Future research should also explore the effects of physical activity interventions on established physical comorbidities including cardiovascular diseases, diabetes, inflammation, pain (Stubbs et al. 2014a), osteoporosis and the risk of falls and fractures, which are common in serious mental illnesses (Stubbs et al., 2014b, 2015).

2. *What are the most prominent safety issues for physical activity prescription in people with bipolar disorder?*

Questions about the safety of physical activity participation are critical in any chronic disease populations including people with bipolar disorder who are at risk of somatic co-morbidities (De Hert et al., 2011). Research regarding adverse events is essential to assist clinicians, researchers and policy makers to develop effective and safe interventions, but data is limited in this population. A qualitative internet survey on self-identified yoga practitioners with bipolar disorders (Uebelacker et al., 2014) reported that negative impacts of yoga practice included increased agitation or relapse into mania, increased lethargy or symptoms of depression, injury or increased pain, and opportunities for self-criticism. There is a need for more longitudinal and observational studies that systematically (a) report adverse events in supervised versus unsupervised physical activity in manic versus depressive versus remitted patients with bipolar disorder, and (b) target higher-risk patients with bipolar disorder. Future research should also focus on which precautions patients with mania or hypomania should employ when they exercise and on the fact whether exercise is contra-indicated or not in the acute stages of mania. Next, the most appropriate safety screening and medical clearance approach for physical activity in clinical and community settings in manic versus depressive

versus remitted patients with bipolar disorder remains a topic for future research. Finally, more research is needed to explore the negative consequences of exercise addiction and overtraining (Berczik et al., 2012; Szabo et al., 2013) in manic versus remitted persons with bipolar disorder.

3. What is the optimal physical activity prescription for people with bipolar disorder?

It has been advocated recently that physical activity is not a one-size-fits-all intervention (Vancampfort et al., 2015c) and that the focus in this debate should not be on the most ideal dose-response (i.e., efficacy), but rather on how people with bipolar disorder can include physical activity as part of their daily lives (i.e., effectiveness). On the other hand, our consultation shows that there is a call from clinicians and researchers worldwide to gain a greater understanding as to what is the most ideal physical activity prescription. To determine the optimal physical activity prescription for people with bipolar disorder, studies directly comparing physical activity prescriptions with each other are needed. The main components of physical activity prescription are the frequency, intensity, type and time. Each of these components can be manipulated to determine its effects on a given bipolar disorder outcome.

The intensity of physical activity is one important component that can be manipulated. For example, the safety and efficacy of high-intensity interval training compared to a standard continuous aerobic exercise prescription or comparing different physical activity intensities using a fixed physical activity volume (i.e., time to achieve the same energy expenditure) has, to date, not been reported in bipolar disorder. The efficacy and effectiveness of different physical activity types with similar physical activity volumes should also be investigated. In particular the increased interest in other types of physical activity such as yoga (Uebelacker et al., 2014) warrants additional studies. Time or duration can also be manipulated in intervention based physical activity studies. Additional studies manipulating different

components of the physical activity prescription will assist in determining their effects on specific outcomes and will enable current general physical activity recommendations for people with bipolar disorder to be refined.

4. What are the key barriers for engaging people with bipolar disorder in physical activity?

Only a small percentage of people with bipolar disorder are meeting recommended levels of physical activity (Janney et al., 2014). Behavioral theories such as socio-ecological models are useful in attempting to understand specific barriers to physical activity participation. Socio-ecological models posit that multiple levels of impact including intrapersonal (e.g. demographic, biological, psychological, cognitive, emotional), interpersonal / cultural (e.g. social support), physical environment (e.g. distance to the facilities, low program cost, enjoyable scenery, neighborhood safety and the presence of sidewalks) and policy (e.g. laws, rules, regulations, codes) factors all influence health behavior (Sallis et al., 2006). A previous systematic review (Vancampfort et al., 2013b) demonstrated that among people with bipolar disorder, significant correlates were found in six of the seven categories (excluding the policy level) of the socio-ecological model supporting the hypothesis that physical activity participation is a complex behavior determined by many factors. The correlates associated with lower physical activity participation were a higher body mass index, older age, a lower self-efficacy, presence of medical co-morbidity, lower educational status, social isolation, financial strain and not being connected to a healthcare service. The current evidence is, however, mainly based on cross-sectional studies highlighting the need for longitudinal and interventional designs comparing manic versus depressive patients and first episode versus chronic patients. If the ultimate purpose of physical activity research is to inform and motivate policy changes that will improve the mental and physical health of people with bipolar disorder, merely documenting the relation of intrapersonal, interpersonal / cultural, physical

environment and policy variables to physical activity behavior is insufficient. Environmental and policy change research is needed and should include assessments of broader health outcomes, such as changes in prevalence of chronic comorbidities, service utilization, as well as the economic costs and benefits of proposed policy changes.

5. *What are the most effective motivational interventions for physical activity adoption and maintenance in people with bipolar disorder?*

Technology promoting physical activity in other clinical populations (e.g. pedometers, online interventions) has received minimal attention in people with bipolar disorder and warrants further research (Rosenbaum et al., 2015) since it may assist in increasing uptake and adherence. Next to this, there is a need to construct interventions targeting the underpinning psychological mediators of behavior change that may result in physical activity interventions being more effective (Vancampfort and Faulkner; 2014). Incorporating mediator analyses into future research will help confirm if any action theory links or conceptual theory links exist between theoretical frameworks and desired behavioral goals. The current evidence indicates that behavior change theories used in the general population, such as the self-determination theory (Deci and Ryan, 2000) and the trans-theoretical model of change (Prochaska and DiClemente, 1983) appear to be applicable for individuals with bipolar disorder (Vancampfort et al., 2015d). Recently it was demonstrated in a cross-sectional study (Vancampfort et al., 2015e) that people with bipolar disorders have higher levels of introjected regulations (i.e. self-imposed guilt, shame, or threats to self-worth) than people with other severe mental illnesses (such as schizophrenia). It might be that people with bipolar disorders experience more feelings of guilt or shame when they do not comply with physical activity demands they pose themselves or which are posed to them by significant others. Large-scale effectiveness trials in real-world settings and comparative effectiveness studies of motivational strategies in

manic versus depressive patients and first episode versus chronic patients are however urgently needed. Implementation of evidence-based behavior change interventions is a critical step in achieving the goals of better quality, improved outcomes, and reduced costs of care.

6. How do we translate physical activity research into community practice?

Until recently, community mental health centers have neglected lifestyle promotion as a core service for clients (Chwastiak, 2015). An important step in future research will be to explore the dissemination of information regarding physical activity benefits and physical activity behavior change interventions to clinicians. Recently available pilot community health center programs such as InSHAPE® (Self Health Action Plan for Empowerment) (Van Citters et al., 2010; Lesley & Livingwood, 2015) for people with severe mental illness in the United States and KBIM (Keeping the Body in Mind) (Curtis et al., 2015) for first episode patients, developed in Australia, should be tested on a larger scale in people with bipolar disorder. Also physical activity intervention algorithm might assist clinicians and researchers. However, such algorithms should be validated. Algorithms should also be adapted when new evidence becomes available regarding the optimal physical activity type, dose, timing, and enablers of response. Another approach for maximizing translation likely resides within the interaction between patients and health care providers. Researchers should explore what patients in clinical and community settings want from their care providers regarding physical activity counseling and what resources are therefore required. This kind of qualitative research can inform clinicians and researchers to develop a physical activity counseling model and tool kit for physical activity promotion through patient-health care provider interactions. Such an approach might bridge the transition between rehabilitation and physical activity promotion in the wider community. Once physical activity interventions have demonstrated efficacy through RCTs, their effectiveness should also be tested in real world settings so that their viability and efficaciousness can be determined outside the artificial RCT paradigm. This is

an important step to ensuring that interventions are feasible and translatable into everyday clinical practice.

7. If one treatment goal is increased physical activity, what type of professionals are needed as part of a multidisciplinary team?

Integration of clinicians with expertise in exercise prescription (e.g. physical therapists and exercise physiologists) and training in psychopathology, as members of the multidisciplinary mental health team are important steps towards ensuring people with bipolar disorder have adequate access to physical activity interventions (Stubbs et al., 2014c). One way of ensuring integration is through educating the existing mental health workforce. There is a clear need for the development of education modules and minimal educational standards outlining the role of physical activity in the treatment of bipolar disorder to be delivered across a range of disciplines including psychiatry, psychology, mental health nursing, occupational therapy and social work. Furthermore, it is imperative that students studying physical therapy receive training in psychopathology. While integration of clinicians with expertise in exercise prescription and educating the existing mental health workforce are commonplace in some European countries (e.g., Belgium and Norway), it is often neglected in other parts of the world (Probst, 2012).

8. How do we incorporate physical activity as a vital sign in clinical practice?

Exercise physiologists or physical therapists should educate people with bipolar disorders about becoming more active, provide comprehensive resources to make active lifestyle choices, and record patients' physical activity levels to highlight the importance of regular physical activity. Future research should also explore the content and discriminant validity of "physical activity as a vital sign" (Sallis, 2011) in people with bipolar disorder. For example,

a simple question method for taking a “physical activity vital sign” of patients to reduce their risk for disease and illness which is validated in the general population (Milton et al., 2013) could be tested for its validity in people with bipolar disorders as well. If valid, health care providers could, during every patient visit along with routine vital sign checks, ask the following question: “In the past week, on how many days have you done a total of 30 min or more of physical activity, which was enough to raise your breathing rate? This may include sport, exercise and brisk walking or cycling for recreation or to get to and from places.” The answer to this question can be recorded in each patient’s medical record as a vital sign. This way, recoding physical activity as a vital sign is also relevant for behavioral health providers (psychiatrists, psychologists, and social workers), who may not have been educated in the need to attend to physical activity. Next, using electronic medical records, longitudinal research should explore whether such physical activity data are associated with health care use, cost, and chronic disease burden. Although guidelines for assessing and monitoring metabolic risks are well established (Ng et al., 2009), consensus is needed on procedures for administering and interpreting the “physical activity vital sign” in clinical practice. Research will in particular be needed to identify the most efficient and cost-effective method to achieve successful implementation of a “physical activity as a vital sign” approach within the mental health care system.

9. How can we prevent sedentary behavior in people with bipolar disorder?

People with bipolar disorder are more sedentary than general populations controls (812 ± 168 min/day versus 539 ± 129 min/day ($p < 0001$)). Sedentary behavior refers to activities that do not increase energy expenditure substantially above the resting level and includes activities such as sleeping, sitting, napping, watching television, and other forms of screen-based entertainment (Pate et al., 2008). There is a growing body of evidence that sedentary

behavior may, even independent of physical activity, be a distinct risk factor for multiple adverse health outcomes (Biswas et al., 2015). Next to this, in the general population sedentary behavior is associated with increased risk of depression. The summary relative risk (RR) of depression for the highest versus non-occasional/occasional sedentary behavior is 1.25 (95%CI=1.16-1.35, $I^2=50.7\%$) (Zhai et al., 2014). The pooled RRs of depression for sedentary behavior are 1.31 (95% CI=1.16- 1.48) in cross-sectional studies and 1.14 (95% CI=1.06-1.21) in longitudinal studies. In subgroup analysis by different types of sedentary behavior, the pooled RRs of depression are 1.13 (95% CI=1.06-1.21) for long-time TV viewing and 1.22 (95%CI=1.10-1.34) for prolonged computer or internet use (Zhai et al., 2014). An understanding of how sedentary behavior changes across the disease (e.g. differences between depressive and manic episodes) is currently lacking. It remains unclear what the association is between sedentary time and physical health outcomes, in particular cardio-metabolic diseases, cardiorespiratory fitness, muscular strength, relapse and risk for premature mortality. It is possible that the strong incremental association between sedentary time and cardiovascular disease and mortality seen in the general population (39) may be attenuated in people with bipolar disorder. Determining the unique contribution of sedentary time to these health outcomes is essential in order to define treatment priorities and to refine the current health recommendations and clinical practice guidelines. In the first instance, it may be necessary to encourage very sedentary people with bipolar disorder to make small lifestyle changes and increase their daily walking. In a next stage patients can then be encouraged to take up more vigorous physical activities.

10. What is the most appropriate physical activity assessment method?

There are a lot of concerns that symptoms of bipolar disorder might influence the psychometric properties of common physical activity measures and thereby undermine the

validity of the score interpretation (Soundy et al., 2014). For example, cognitive impairment in memory might be present in bipolar disorder and might influence recall with self-report questionnaires and compliance with wearing accelerometers. Accelerometers provide objective measurement of physical activity and are particularly useful for measuring light intensity physical activities, which may be interspersed throughout the day, and thus more difficult to recall accurately than moderate to vigorous physical activity. In most mental health care settings it is unlikely that clinicians will have access to these devices. Interviews and questionnaires are, in contrast, cheaper and easier to use but often prone to systematic errors because of poor recall (Soundy et al., 2014). Valid physical activity instruments that accurately capture sedentary behaviors and physical activity in people with bipolar disorder have not been developed to date (Soundy et al., 2014). One of the most important challenges in physical activity research in people with bipolar disorder is producing a low cost, easy to use, reliable and valid physical activity questionnaire that captures sedentary behaviors and physical activities. Such a reliable and valid questionnaire is necessary for standardization across studies and clinical practices that occur worldwide and would permit meaningful comparisons of values, for example between disease stages.

Limitations

Our 10 research questions should be considered in the light of some methodological limitations of the survey executed. First of all, we did not use a systematic approach such as the Delphi method (Dalkey & Helmer, 1963). Secondly, patients were not consulted in this study. Increasingly, patients are regarded as stakeholders and partners in the quest to improve the quality of their care. Moreover, patients are increasingly invited to take part in individual clinical decision making. Patients should be involved as well in setting a research agenda.

Therefore, in a next stage, the current top 10 research questions should be discussed with patient organizations.

Conclusions

There is increasing evidence for the benefits of physical activity in people with bipolar disorder, but this population remains largely physically inactive and sedentary. In this article, the IOPTMH proposed the top 10 research questions for the field of physical activity and bipolar disorder. The IOPTMH believes that these questions are critical for informing our understanding of the short-term and long-term benefits of physical activity in people with bipolar disorder and for developing approaches for promoting and sustaining an active lifestyle. Future research that addresses these questions may greatly improve the quality of life and functioning of people living with this chronic disease.

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Table 1. Top 10 research questions for physical activity research in bipolar disorder

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1. What are the benefits of physical activity for people with bipolar disorder?
 2. What are the most prominent safety issues for physical activity prescription in people with bipolar disorder?
 3. What is the optimal physical activity prescription for people with bipolar disorder?
 4. What are the key barriers for engaging people with bipolar disorder in physical activity and how can these be overcome?
 5. What are the most effective motivational interventions for physical activity adoption and maintenance in people with bipolar disorder?
 6. How do we translate physical activity research into community practice?
 7. If one treatment goal is increased physical activity, what type of professionals are needed as part of a multidisciplinary team?
 8. How do we incorporate physical activity as a vital sign in clinical practice?
 9. How can we prevent sedentary behavior in people with bipolar disorder?
 10. What is the most appropriate physical activity assessment method?
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