TEST-RETEST STUDY OF THE SIX-MINUTE WALK TEST IN PEOPLE WITH BIPOLAR DISORDER

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SUMMARY

Background: *The multidisciplinary care for bipolar disorder is highly fragmented with limited opportunities for prevention and treatment of medical co-morbidities. We examined the reliability of the 6-minute walk test (6MWT). Secondary aims were to assess minimal detectable changes (MDC_{95}), practice effects and the impact of clinical conditions.*

Subjects and methods: *Two 6MWTs were administered within 3 days to 46 (23♂) inpatients with a DSM-V diagnosis of bipolar disorder. Physical complaints before and after the 6MWT were recorded. Patients completed the Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR) and Hypomania Check List-32.*

Results: *Patients walked 594.7±121.3 meters and 600.0±122.9 meters at the first and second test. The intraclass correlation coefficient was 0.98 (95% confidence interval 0.97-0.99). The MDC_{95} was 37.8 meters for men and 52.9 meters for women. No practice effect was detected. Longer illness duration, higher QIDS-SR scores and the presence of feet or ankle static problems or pain were independently related to shorter 6MWT distance accounting for 59.8% of the variance.*

Conclusion: *The 6MWT is a clinically feasible tool for evaluating the functional exercise capacity in patients with bipolar disorder. Health care professionals should consider depression and physical pain when developing rehabilitation programmes.*

Key words: *exercise – walking – pain – depression - bipolar disorder - the 6-minute walk test*

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INTRODUCTION

According to the World Health Organization global burden of disease study, bipolar disorders (BD) rank within the top 20 causes of disability among all medical conditions worldwide and 6th among the mental disorders (Whiteford et al. 2010). This is exemplified by a more than 10 years reduced life expectancy (Chang et al. 2011) due to increased suicide risk (Novick et al. 2010) but, especially, due to an increased risk for medical co-morbidity (Carney et al. 2006) associated with unhealthy life styles (Vancampfort et al. 2013a) and adverse effects of treatments (Vancampfort et al. 2013b). Despite the recognition that BD imposes a tremendous health burden, lifestyle interventions designed to address medical co-morbidities are scarce (Leboyer & Kupfer 2010). Currently, the multidisciplinary care for BD is highly fragmented with less opportunity for screening, prevention and treatment of medical co-morbidities than would be expected in a non-psychiatric population. Only a limited number of screening, monitoring and treatment guidelines refer to the role of physical activity and exercise in people with severe mental illness (De Hert et al. 2011), yet none of these guidelines have an adequate focus on the importance of physical fitness testing within this population. Fitness testing has important clinical implications and

can be used to help guide the intensity of exercise prescriptions whilst providing a clinically useful measure of change in response to an intervention (American College of Sports Medicine 2013). Various forms of fitness testing are available, with the 6-minute walk test (6MWT) being of particular interest in BD. The 6MWT is a safe, easy to administer and inexpensive physical fitness test in mental health care settings (Bernard et al. 2015). It evaluates the global and integrated responses of the cardiovascular, peripheral circulation and neuromuscular systems involved during exercise. Although the 6MWT does not provide specific information about the function of each of the different systems involved in exercise or about the mechanism of exercise limitation as is possible with maximal cardiopulmonary exercise testing, it assesses the sub-maximal level of physical fitness (i.e., the functional exercise capacity) (American Thoracic Society 2011). Because most activities of daily living are performed at sub-maximal levels of exertion, the 6MWT may better reflect the functional exercise level for daily physical activities (American Thoracic Society 2011). Furthermore, among the physically inactive population of people with BD who usually develop symptoms below their theoretical maximal exercise capacity (Vancampfort et al. 2013a), the 6MWT may be particularly relevant. Despite the frequent use of the 6MWT in physical

activity and exercise programmes for patients with schizophrenia (Bernard et al. 2015), its reproducibility has never been assessed among patients with BD.

The primary aim of the present study was to investigate the test-retest reliability of the 6MWT in patients with BD. Secondary aims were: (a) to explore whether there was a practice effect with repeated testing, (b) to determine limits for the smallest difference that indicated a real change, and (c) to assess clinical and demographic characteristics and presence of co-morbid physical conditions and perceived physical symptoms that might interfere with performing the 6MWT.

SUBJECTS AND METHODS

Participants

Over an 8-month period, inpatients with a DSM-V diagnosis (American Psychiatric Association 2013) of BD at the UPC KU Leuven campus Kortenberg in Belgium were invited to participate in this study. Since severe substance abuse might impair walking capacity, participants were excluded if they had a co-morbid DSM-5 diagnosis of substance abuse during the previous 6 months. Somatic exclusion criteria included evidence of significant cardiovascular, neuromuscular and endocrine disorders, which, according to the American College of Sports Medicine (2013), might prevent safe participation in the study. All participants received a physical examination and baseline electrocardiogram by a specialized physician before testing. Participants were also requested to refrain from eating, drinking coffee or smoking during a two-hour period prior to the tests. The study procedure was approved by the Scientific and Ethical Committee of the UPC KU Leuven, campus Kortenberg, Belgium, and conducted in accordance with the principles of the Declaration of Helsinki. All participants gave their informed written consent.

Test-retest 6MWT

A test-retest design was used to test the reproducibility of the 6MWT. The test was performed according to the American Thoracic Society (2002) guidelines in an indoor corridor with lack of external stimuli. Two cones 25m apart indicated the length of the walkway. Participants were instructed to walk back and forth around the cones during 6 minutes, without running or jogging. Resting was allowed if necessary, but walking was to be resumed as soon as the participants were able to do so. The protocol stated that the testing was to be interrupted if threatening symptoms appeared, including (a) chest pain, (b) intolerable dyspnea, (c) leg cramps, (d) staggering, (e) diaphoresis, and (f) pale or ashen appearance. Standardised encouragements were provided at recommended intervals. The total distance walked in six minutes was recorded to the nearest decimetre. The test was repeated within three days at the same time of the day. All supervisions and measurements of the 6MWT were performed by the same mental health physical therapist. Prior to the first 6MWT, participants were asked for conditions that might interfere with their walking capacity. They were asked whether they had known hip problems or pain, foot or ankle static problems or pain. Furthermore, they were asked to state if they suffered at least sometimes from knee or lower back pain. Directly after the first test, patients were also asked to report any physical complaints or discomfort.

Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR16)

The QIDS-SR16 (Rush et al. 2003) consists of 16 items that assess the nine symptom domains used to diagnose a major depressive episode. The responses for each item range from0 to 3, with 0 indicating the absence of that symptom in the past week. The total score ranges from 0 to 27.

Hypomania Check List-32 (HCL-32)

To assess hypomanic mood, the HCL-32 (Angst et al. 2003) was completed. Hypomania is assessed by "yes/no" responses to 32 statements concerning behaviour. Answers are given on a 7-point-rating scale, with possible scores ranging from 0-32.

Anthropometric assessments

Anthropometric measurements included body weight and height in order to calculate the body mass index. Body weight was measured in light clothing to the nearest 0.1kg using a SECA beam balance scale, and height to the nearest 0.1cm using a wall-mounted stadiometer.

Medication use

We recorded the medication use. Antipsychotic dose was recorded and converted into a daily chlorpromazine equivalent dosage according to an international consensus (Gardner et al. 2010). Mean dosages of specific mood stabilisers and antidepressants were reported when they were used by at least 10 participants.

Smoking

Smoking behaviour was determined at the day of the first test performance. Participants were asked whether they smoked or not, and if so, how many cigarettes they smoke per day on average.

Physical co-morbidity

The presence of anICD-10(World Health Organisation 1993) of physical co-morbidity was obtained from patients' medical records.

Statistical analysis

Continuous data were assessed for normality using the Shapiro-Wilk test and found to be normally distributed. Descriptive statistics are therefore presented as mean ± standard deviation (SD) or as percentages when appropriate. The ICC between the two 6MWT using a one-way random single measures intraclass correlation analysis and its associated 95% CI were calculated to objectively assess reliability between two 6MWTs. To assess whether there was a practice effect with repeated testing, the four following methods were used; (a) an ICC of less than 0.75 for 6MWT in two successive tests, (b) a statistically significant improvement in the mean 6MWT between two trials evaluated with a paired t-test, (c) a Pearson correlation of less than 0.75 between 6MWT in successive trials, (d) the Bland-Altman method (Bland & Altman 2007) illustrating the means and the differences in 6MWT for each subject. A P-value for the Spearman rank correlation coefficient between the means and the differences in 6MWT scores of less than 0.05 indicates that the magnitude of the difference in 6MWT scores at baseline varies by level of walking capacity. Because previous studies didnot operationally define practice effects and no single method of evaluation has been identified as superior to the others, the present study considers in parallel with a previous study in schizophrenia (Vancampfort et al. 2011) that a practice effect was to be present only if all four criteria were fulfilled. The minimal detectable change (MDC) was calculated following previous recommendations (Vancampfort et al. 2011). A backward stepwise multivariable regression analysis was performed to evaluate independent variables explaining the variance in the 6MWT performance. To prevent over fitting of the models, only variables significant ($P<0.05$) in univariate analyses were entered into the final model. To test for multicollinearity, a variance inflation factor was computed for each independent variable in the model. Values above 3 were used to indicate a multi-collinearity problem in the model. A priori, a two sided level of significance was set at $P<0.05$. Statistical analysis was performed using the statistical package SPSS version 22.0 (SPSS Inc., Chicago, IL).

Sample size calculation

An a-priori sample size calculation was conducted following the recommendations of Donner & Eliasziw (1987). With a more than acceptable intraclass correlation coefficient (ICC) of 0.80, and alpha of 0.05 and power of 0.8 (β=0.2) it was established that 46 participants were required in the final analysis. It was anticipated that approximately 20% of patients needed to be excluded, 10% would refuse for motivational reasons and 10% would dropout from the testing for both motivational and practical reasons. Therefore, a pre-specified sample size of 65-70 participants was utilized to account for these factors in order to ensure the final analysis was adequately powered.

RESULTS

Participants

Out of 67 patients with BD, 57 met the inclusion criteria of which 11 declined to participate (n=5) or dropped-out (n=6). Reasons for exclusion and drop-out are presented in Figure 1. The final sample consisted of 23 men (age=44.5±10.7 years; illness duration= 17.7±9.8 years; body mass index, BMI=26.7±3.2 kg/m^2) and 23 women (age=41.4±12.4 years; illness duration= 15.0±12.0 years; body mass index, BMI=25.6±4.7kg/m^2). All participants except one were Caucasian and 19 (41.3%) smoked. Men (n=13) smoked 16.1±12.1 cigarettes per day, women (n=6) smoked 23.7±14.2 (p=0.61). Mean daily equivalent dosage of chlorpromazine (n=42) was 441.6±278.3 mg/day, of lithium carbonate (n=15) 870.0±549.9 mg/day and of valproic acid (n=14) 1603.8±597.0 mg/day. An overview of the medication of the entire sample (n=46) is available upon request from the first author. The mean QIDS-SR and HCL-32 score were 8.3±5.5 and 15.8±6.5, respectively. The physical co-morbidity of the included participants is presented in Table 1. Medical records indicated that the metabolic syndrome, diagnosed according to the International Diabetes Federation criteria (20), was the most prevalent physical co-morbidity (15/46, 32.6%).
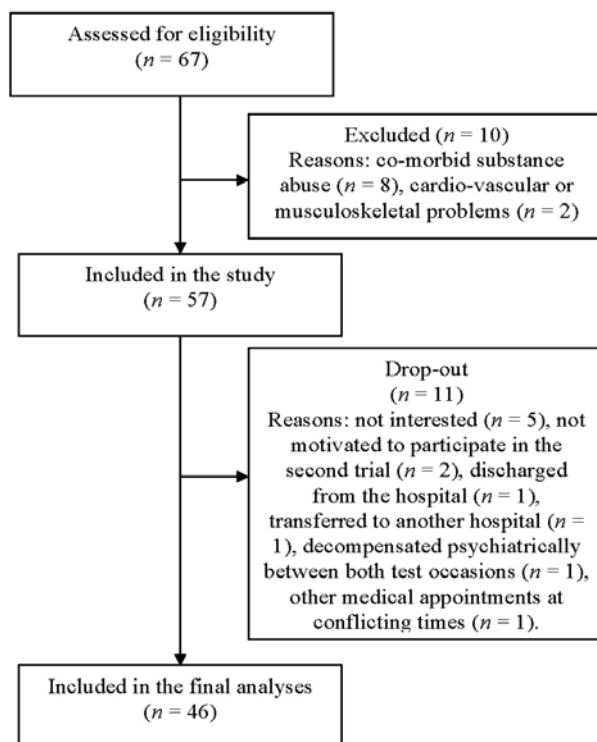

Figure 1. Flowchart of the eligible patients in the current study

Before the 6MWT, 8.9% (n=4) of patients with BD reported suffering from hip pain and 28.3% (n=13) from feet or ankle static problems or pain. More than half of the patients (52.2%, n=24) complained of at least some times having pain in their knees and 67.4% (n=31) reported

experiencing lower back pain at least sometimes. After the 6MWT, patients with BD experienced most often musculoskeletal pain (32.6%, n=15), followed by dyspnea (19.6%, n=9) and muscular fatigue (15.2%, n=7).

Table 1. Physical co-morbidity* in assessed people with bipolar disorder (n=46)

Locomotor disorders	1
Neurological disorders	1
Gastrointestinal disorders	1
Thyroid diseases	1
Cardiovascular disorders	1
Diabetes	3
Metabolic Syndrome	15

*Two patients with a cardiovascular or neuromuscular disorder which was a contra-indication for exercise testing according to the American College of Sports Medicine were already excluded; according to International Diabetes Federation criteria (Alberti et al. 2006).

Reliability and minimal detectable changes of the 6MWT

The mean 6MWT score on the first and second test were 594.7±121.3 meters and 600.0±122.9 meters, respectively, without significant difference between the two trials (P=0.12). Analyses of reproducibility of the 6MWT showed that the ICC was 0.98 with a 95% confidence interval of 0.97 to 0.99. The MDC_{95} in the present study was 37.8 meters for men and 52.9 meters for women.

Determination of a practice effect

The correlation between 6MWT scores at trial 1 and 2 was 0.98 (P<0.001). The r^2 value indicates that the performance on trial 1 explained 96.6% of the variability

in the second trial performances. The Bland-Altman plot in Figure 2 showed no apparent pattern between the mean 6MWT scores and differences in 6MWT scores at the individual level, and this was supported by a Spearman rank correlation coefficient of -0.010 with a P-value of 0.95. The plot revealed only one outlier. As expected, 95% of the differences were within 2 SDs of the mean.

Multivariable analyses of factors affecting the 6MWT

All significant (P<0.05) continuous and dichotomous correlates of the 6MWT in univariable analyses (data available upon request) were included in the multivariable backward stepwise regression analysis. Following exclusion of age, variance inflation factors were all less than 1.6, meaning that there was no indication of multicollinearity. Longer illness duration (P<0.001), higher QIDS-score (P=0.003) and the presence of feet or ankle static problems or pain (P=0.014) remained significant predictors of shorter 6MWT distance (see Table 1). The final model explained 59.8% of the variance in the distance walked.

DISCUSSION

Reliability and minimal detectable changes

Recently a call was made that the clinical rehabilitation of BD should target improvement of functional outcomes (Geddes & Miklowitz 2013). This study adds to the current knowledge suggesting that the 6MWT, which is highly related to functioning in daily life, might be a clinically feasible and relevant outcome measure in multidisciplinary rehabilitation programs for patients with BD. In addition, our findings demonstrate that
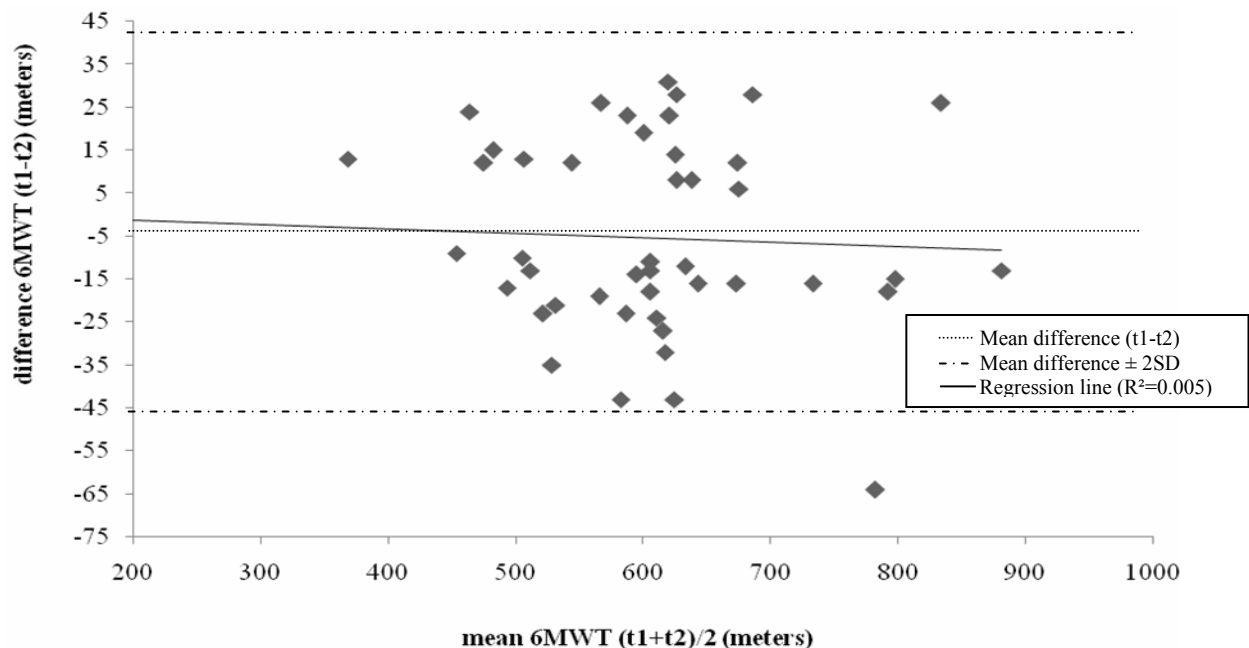

Figure 2. Agreement assessment (Bland-Altman plot) of the six minute walk tests (6MWT) between time 1 (t1) and time 2 (t3) (interval maximum 3 days) in patients with bipolar disorder

Table 2. Backward stepwise regression analysis with the mean 6-minute walk test score as the dependent variable

Variables°	B	SE	β	t	p
(Constant)	757.8	25.7	/	29.5	<0.001
Illness duration (years)	-4.4	1.1	-0.4	-4.0	<0.001
QIDS score	-7.8	2.5	-0.3	-3.1	0.003
Ankle or feet problems†	-80.0	31.2	-0.3	-2.6	0.014

°Only significant correlates were included in the model, †yes=1, no=0, B= unstandardized coefficient, SE= standard error, β= standardized coefficient, VIF= variance inflation factor, QIDS=Quick Inventory of Depressive Symptomatology

the 6MWT is highly reliable (ICC=0.98), indicating that it can be used to quantify the functional exercise capacity of these patients and monitor changes in functional exercise capacity over the course of illness, as well as in response to pharmacological or lifestyle interventions, both as part of clinical care and in treatment studies.

Interpreting change scores and identifying clinically significant changes in performance have become an explicit focus of the clinical rehabilitation profession. Clinicians are encouraged to understand how changes in scores translate into clinical relevance. The present study calculated the MDC_{95}, which provides meaningful criteria for assessing performance changes. A MDC_{95} of 37.8 meters for men (=6.0% of the mean distance) and 52.9 meters (9.4% of the mean distance) for women implies that changes greater than these distances are necessary to be 95% certain that the changes are not due to measurement error or patient variability.

Practice effects

None of the different methods used to detect a practice effect showed indications of such an effect. It can therefore be concluded that no practice walk is required and that one single test provides sufficiently accurate information. Adequacy of one single test has relevant research and clinical consequences since repeated tests are often difficult to implement in clinical trials and are less feasible and cost effective within clinic settings.

Factors affecting the 6MWT

An interesting observation of the current study was that longer illness duration was a stronger correlate for poorer 6MWT performance than higher biological age. It can be hypothesised that a longer lifetime exposure to psychiatric symptoms and/or treatments translates into a poorer functional exercise capacity. Supporting the former assertion, we found a significant association between 6MWT scores and higher levels of depression. A possible reason for these associations might include lower self-efficacy and increased negative outcome expectations that people with depressive feelings often experience when performing exercise tests. It can also be speculated that physical inactivity is a mediator. People who are depressed are less likely to engage in physical activity, which in turn might result in a lower functional exercise capacity (Krämer et al. 2014).

A recent meta-analysis (Stubbs et al. 2015) showed that patients with BD experience a two-fold increased risk for chronic pain. However, based on the available data, the authors were unable to determine to which extent this comorbid pain has an impact on activities of daily life. Our study is the first to show that in particular, musculoskeletal problems in the ankle and foot are associated with a lower functional exercise capacity. Although obesity consistently emerges as a key and potentially modifiable risk factor in the onset and progression of such musculoskeletal conditions (Wearing et al. 2006), a higher BMI was not associated with self-reported physical problems or with poorer performance on the 6MWT in the current study.

Study limitations

A limitation of the present study is that it included only a sample of inpatients. This may affect the ability to generalize present results. However, the sample size was pre-specified and included participants with a wide age range. Nevertheless, future studies should determine whether present results are also applicable to outpatients. Second, the present study did not investigate the potential influence of prior physical activity participation. Third, the internal validity could have been improved by adding an age- and gender matched control group. Future research comparing 6MWT scores in BD with an age- and sex-matched healthy control group and including levels of physical activity participation would provide a valuable point of reference. Finally, future prospective studies should be conducted in order to disentangle the impact of musculoskeletal pain on the functional exercise capacity. Such studies should also explore the extent to which patients with BD are more or less responsive to behavioural, pharmacological, and non-pharmacological treatments for chronic pain. Further, the impact of improving physical fitness on psychiatric symptoms and functional capacity in patients with BD and other disorders requires further examination. Strategies to encourage patients with BD to become more physically active and that do not exacerbate pain are likely to be key in improving the functional outcome and quality of life of these patients.

CONCLUSIONS

Although with limitations, the present study demonstrates that the 6MWT is a reliable and feasible test to assess the functional exercise capacity in inpatients with BD. Because it is easy to perform, safe and inexpensive, the 6MWT could be used in daily psychiatric care. The identification of a minimal detectable change of 37.8 meters for men and 52.9 meters for women supports the use of the 6MWT to identify patient-important changes in research and clinical practice. Finally, the current study found that there is no need for a practice walk. The elimination of such a habituation trial will save time and reduce participant's fatigue.

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