

Validity and characteristics of patient-evaluated adherence to medication via smartphones in patients with bipolar disorder: exploratory reanalyses on pooled data from the MONARCA I and II trials

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ABSTRACT

Background Non-adherence to medication is associated with increased risk of relapse in patients with bipolar disorder (BD).

Objectives To (1) validate patient-evaluated adherence to medication measured via smartphones against validated adherence questionnaire; and (2) investigate characteristics for adherence to medication measured via smartphones.

Methods Patients with BD (n=117) evaluated adherence to medication daily for 6–9 months via smartphones. The Medication Adherence Rating Scale (MARS) and the Rogers' Empowerment questionnaires were filled out. The 17-item Hamilton Depression Rating Scale, the Young Mania Rating Scale and the Functional Assessment Short Test were clinically rated. Data were collected multiple times per patient. The present study represents exploratory pooled reanalyses of data collected as part of two randomised controlled trials.

Findings During the study 90.50% of the days were evaluated as 'medication taken', 6.91% as 'medication taken with changes' and 2.59% as 'medication not taken'. Adherence to medication measured via smartphones was valid compared with the MARS (B: -0.049, 95% CI -0.095 to -0.003, p=0.033). Younger age and longer illness duration were significant predictors for non-adherence to medication (model concerning age: B: 0.0039, 95% CI 0.00019 to 0.0076, p=0.040). Decreased affective symptoms measured with smartphone-based patient-reported mood and clinical ratings as well as decreased empowerment were associated with non-adherence.

Conclusions Smartphone-based monitoring of adherence to medication was valid compared with validated adherence questionnaire. Younger age and longer illness duration were predictors for non-adherence. Increased empowerment was associated with adherence.

Clinical implications Using smartphones for empowerment of adherence using patient-reported measures may be helpful in everyday clinical settings.

Trial registration number NCT01446406 and NCT02221336.

BACKGROUND

Bipolar disorder (BD) is estimated to be one of the most important causes of disability worldwide.^{1,2} Naturalistic follow-up studies suggest that

the progressive development of BD is not prevented with the present treatment options,^{3,4} due to delayed intervention for prodromal depressive and manic symptoms as well as decreased adherence to mood stabiliser treatment.^{5,6} Non-adherence has been associated with increased risk of relapse, psychiatric hospitalisation and healthcare costs.^{7–12} Previous studies have reported that between 10% and 66% of patients with BD do not take their medication as prescribed, and often adherence changes over time.^{13–15} Variation in non-adherence between studies may be partly attributable to a lack of consensus on the best methodology for assessing adherence, the period of observation and the criteria for defining non-adherence.¹⁶ Factors such as female gender, younger age, low socioeconomic status and poor therapeutic alliance seem to be risk factors for medication non-adherence in BD.^{5,16}

Adherence to medication refers to the extent to which a patient follows the medication prescribed by their physician.¹⁷ Monitoring and assessment of non-adherence to prescribed medication can be done by both objective approaches such as drug plasma levels, pills count, registry-based information on purchased medication and electronic monitoring of medication event monitoring systems, and subjective approaches such as self-reported, relative reported or clinician reported.^{18,19}

Non-adherence is likely to remain a major public health concern despite treatment advances.^{20,21} Increasing knowledge about factors affecting adherence and leveraging novel technologies can enhance its early assessment and adequate management.^{15,22–26} However, more information to assess adherence in patients with BD is needed.

Today, a median of 76% of adults in 18 advanced economies report having a smartphone,²⁷ and many people use a smartphone on a daily basis.²⁸

No prior study has collected data on patient-evaluated daily smartphone-based measures of adherence to medication in patients with BD.

Objective

The present study aimed (1) to compare and validate patient-evaluated adherence to medication measured daily with smartphones against adherence measured using the Medication Adherence Rating Scale (MARS) questionnaire, and (2) to investigate characteristics for adherence to medication



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measured using smartphones including the severity of depressive and manic symptoms and functioning.

We hypothesised that (1) there would be a significant negative association between patient-evaluated daily adherence measured daily using smartphones and the MARS, and (2) that female gender, younger age, longer illness duration, higher severity of depressive and manic symptoms and lower functioning would be associated with higher non-adherence in patients with BD.^{5 16 29} The present study represents exploratory pooled reanalyses of data collected from two randomised controlled trials (RCT).

METHODS

Participants, settings and design

The present study combines and reanalyses data collected as part of two RCTs investigating the effect of smartphone-based monitoring in patients with BD (the MONARCA I trial and the MONARCA II trial).^{30–33}

Patients with BD

The MONARCA I trial: The patients were recruited from the Copenhagen Clinic for Affective Disorders, Copenhagen, Denmark, during a period from September 2011 to March 2013. The trial had a 6-month follow-up period. The inclusion criteria were a BD diagnosis according to International Classification of Diseases 10th Revision (ICD-10) using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview,³⁴ age between 18 and 60 years, a 17-item Hamilton Depression Rating Scale (HDRS-17) score ≤ 17 ³⁵ and a Young Mania Rating Scale (YMRS) score ≤ 17 ³⁶ at the time of inclusion. The exclusion criteria were pregnancy, a lack of Danish language skills, inability to learn the technicalities for using a smartphone, unwilling to use the trial smartphone as the primary cellphone and severely physical illness or schizophrenia, schizotypal or delusional disorders according to the SCAN interview.

The MONARCA II trial: All patients with a diagnosis of BD who had previously been treated at the Copenhagen Clinic for Affective Disorder, Copenhagen, Denmark, in the period from 2004 to January 2016 and who at the time of recruitment were being treated at community psychiatric centres, private psychiatrists and general practitioners were invited to participate in the trial. Patients were included in the study for a 9-month follow-up period if they had a BD diagnosis according to ICD-10 using the Schedules for Clinical Assessments in Neuropsychiatry (SCAN)³⁴ and previously were treated at the Copenhagen Clinic for Affective Disorder. Patients with schizophrenia, schizotypal or delusional disorders, previous use of the MONARCA system, pregnancy and lack of Danish language skills were excluded. Patients with other comorbid psychiatric disorders and substance use were eligible for the trial.

As part of the MONARCA I trial and the MONARCA II trial, patients were randomised to either a group using a smartphone-based monitoring system (the Monsenso system) for daily self-monitoring (the intervention group) or to a group receiving treatment as usual (the control group). Patients included in the intervention group from both trials collected daily smartphone-based self-monitoring data on adherence to medication and were included in the analyses in the present report. Inclusion criteria, exclusion criteria and clinical evaluations were assessed by an experienced clinical researcher (MFJ).

Daily smartphone-based monitoring

On a daily basis during the follow-up, participants in the trials used a smartphone with the Monsenso app installed and were

instructed to use the system for evaluation.³⁰ The app allowed for daily evaluation of adherence to medication (evaluated as not taken, taken, taken with changes (scale: 0, 1, 2)). Further details regarding the Monsenso system are described elsewhere.³⁰

Clinical measurements and patient-reported questionnaires

In the MONARCA I trial outcome measurements were conducted monthly for the entire trial period of 6 months. In the MONARCA II trial outcome measurements were conducted at baseline and after 4 weeks, 3 months, 6 months and 9 months. All clinical assessments were conducted by researchers (MFJ), who were blinded to all smartphone-based data. Thus, data on severity of depressive and manic symptoms were collected rater blinded.

Clinical rater-blinded assessments: The severity of depressive and manic symptoms was clinically assessed using the HDRS³⁵ and the YMRS.³⁶ Functioning was clinically assessed using the Functional Assessment Short Test (FAST).³⁷

In addition, in the MONARCA II trial, the MARS^{38 39} questionnaire and the Roger's Empowerment Scale⁴⁰ were filled in by the patients at all visits with the researcher. The MARS³⁹ is a 10-item self-reported questionnaire resulting from a combination of the Medication Adherence Questionnaire⁴¹ and the Drug Attitude Inventory⁴² and has been validated in patients with psychiatric disorders.^{42 43} The questionnaire reflects self-reported adherence to pharmacological treatment and covers issues concerning medication adherence behaviour, attitudes to taking medication and experiences of negative side effects. Higher scores indicate higher non-adherence. The empowerment scale is a 28-item self-reported questionnaire and has been validated in patients with psychiatric disorders.⁴⁰ The questionnaire reflects self-reported areas concerning self-esteem, the feeling of being in power of one's life, autonomy, optimism and anger. Higher scores indicate higher empowerment.

Statistical methods

The hypotheses and statistical analyses for the present study were defined a priori. Since the MARS questionnaire reflects adherence during the previous week, measures of adherence to medication measured using smartphones for the days the MARS scale was reflecting were used in the present report. Calculated total scores for the MARS were used in the present study.

For each measure of interest, a two-level linear mixed effects model, which accommodates both the variation of the variables of interest within patients (intraindividual variation) and between individuals (interindividual variation), was employed. The models included a fixed effect of visit number (baseline, 4 weeks, 3 months, 6 months and 9 months) and a patient-specific random effect allowing for an individual intercept and a slope for each participant. Level 1 represented repeated measures of symptoms (eg, MARS, HDRS, YMRS, FAST) and level 2 represented interindividual variation. In all models, we first considered an unadjusted model (model 1). Second, we considered a model adjusted for age and gender as possible covariates.

In relation to aim 1: To investigate the associations between patient-evaluated adherence to medication measured daily with smartphones and adherence measures using the MARS a two-level linear mixed effects model was employed (table 1). In relation to aim 2: To investigate predictors for adherence to medication measured using smartphones two-level linear mixed effects model was employed (table 2). In addition, we investigated associations between adherence measured using smartphones and severity of depressive and manic symptoms using

Table 1 Association between patient-reported adherence to medication intake measured daily using smartphones versus questionnaire-based data in patients with bipolar disorder, n=84*

	Model 1†			Model 2†		
	B	95% CI	P value	B	95% CI	P value
MARS	-0.044	-0.088 to 0.00033	0.052	-0.049	-0.095 to 0.003	0.033

*Adherence scored as not taken, taken, taken with changes (0, 1, 2).

†Model 1: unadjusted. Model 2: adjusted for age and gender.

MARS, Medication Adherence Rating Scale.

the HDRS and the YMRS using a two-level linear mixed effects model, as well as associations between scores on the MARS and severity of depressive and manic symptoms using the HDRS and the YMRS using a two-level linear mixed effects model. Analyses on the probability of not providing daily self-reports concerning adherence to medication with increasing scores on the MARS were investigated using a two-level logistic mixed effects model (OR), which accommodates both variations of the variables of interest within patients (intraindividual variation) and between individuals (interindividual variation) were employed.

As few prior studies have investigated the associations between daily patient-reported adherence and MARS as well as predictors for daily smartphone-based adherence in patients with BD, statistical power analyses prior to the study were not performed. Data were collected as part of two RCTs, and thus the sample size for each of these trials was defined according to these. Model assumptions were checked visually by means of residuals and QQ plots for each of the statistical analyses. STATA V.13 (StataCorp, College Station, TX, USA) was used for statistical analyses.

FINDINGS

Background characteristics

In the MONARCA I trial, a total of 123 patients with BD receiving treatment at the Copenhagen Clinic for Affective

Table 3 Background characteristics of patients with bipolar disorder using smartphones for daily self-monitoring, n=117

Age, years	30.9 (9.9)
Female gender, % (n)	62.4 (73)
Full time employed, % (n)	17.1 (20)
Illness duration, years	16.3 (8.8)
Bipolar disorder subtype I, % (n)	63.2 (74)
Number of hospitalisations	2 (1–3)
Number of depressive episodes	4 (2–10)
Number of manic episodes	3 (2–7)
17-Item Hamilton Depression Rating Scale score during follow-up	8.77 (7.13)
Young Mania Rating Scale score during follow-up	3.07 (4.32)

Data are mean (SD), median (IQR) or proportions (n) unless otherwise stated.

Disorder, Denmark, at the time of the study were assessed for eligibility. Among these, 78 patients (63.4%) were included. Of these, a total of 33 patients from the intervention group using smartphones for daily monitoring were included in the present study. In the MONARCA II trial, a total of 735 patients with BD previously receiving treatment at the Copenhagen Clinic for Affective Disorder, Denmark, were assessed for eligibility. Of these, a total of 544 patients were not included because they were unreachable (n=240), declined to participate (main reasons: did not have the time, did not want to participate in a research study or had moved too far away, which made transportation a problem) (n=282 patients) or were excluded due to previous use of the MONARCA system (n=22). A total of 84 patients from the intervention group using smartphones for daily monitoring were included in the present study.

Background characteristics are presented in table 3.

During the study the patients had a median HDRS score of 7 (IQR 3–14) and a median YMRS score of 2 (IQR 0–4). During follow-up, patients provided smartphone-based data on adherence to medication on 66.18% of the days, and of these days 90.50% was registered as ‘medication taken as prescribed’.

Table 2 Predictors of patient-reported adherence to medication measured daily via smartphones in patients with bipolar disorder, n=117*

	Model 1†			Model 2†		
	B	95% CI	P value	B	95% CI	P value
Gender‡	0.037	-0.05 to 0.12	0.41	0.052	-0.036 to 0.14	0.24
Age, years§	0.0022	-0.0021 to 0.0065	0.32	0.0039	0.00019 to 0.0076	0.040
Bipolar disorder subtypes I and II	-0.056	-0.14 to 0.033	0.22	-0.058	-0.15 to 0.30	0.20
Illness duration, years	-0.0011	-0.0055 to 0.0034	0.64	-0.0057	-0.011 to -0.00035	0.037
Years of education after primary school	0.0085	-0.0075 to 0.025	0.30	0.0056	-0.010 to 0.022	0.49
Number of previous affective episodes	0.00085	-0.00053 to 0.0022	0.23	0.00071	-0.00062 to 0.0022	0.27
Number of previous hospitalisations	0.0015	-0.0065 to 0.0094	0.75	0.0014	0.0066 to 0.0094	0.74
Patient-evaluated mood (euthymic to manic) measured daily using smartphones	0.031	0.0073 to 0.056	0.011	0.24	0.091 to 0.30	0.002
Patient-evaluated mood (euthymic to depressive) measured daily using smartphones	0.012	0.005 to 0.019	<0.0001	0.32	0.11 to 0.54	0.003
HDRS	-0.0088	-0.016 to -0.0022	0.009	-0.010	-0.016 to -0.0029	0.005
YMRS	-0.0032	-0.014 to 0.0079	0.57	-0.0032	-0.014 to 0.0077	0.56
FAST	-0.0025	-0.0061 to 0.0011	0.17	-0.0032	0.0068 to 0.00041	0.083
Empowerment¶	0.012	0.0038 to 0.020	0.004	0.011	0.0034 to 0.019	0.005

*Adherence scored as not taken, taken, taken with changes (0, 1, 2).

†Model 1: unadjusted. Model 2: adjusted for age and gender.

‡Adjusted model only adjusted for age (female served as reference).

§Adjusted model only adjusted for gender.

¶Roger's Empowerment Scale.

FAST, Functional Assessment Short Test; HDRS, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale.

6.91% registered as ‘medication taken with changes’ and 2.59% registered as ‘medication not taken’. There were no differences in age, gender, illness duration, BD subtype (I or II), number of previous hospitalisations and educational level between patients evaluating adherence to medication using smartphones or patients not providing data (all $p > 0.05$).

The validity of patient-reported adherence to medication measured using smartphones and questionnaire-based measure of adherence

The results from the unadjusted and adjusted linear mixed effects models regarding the association between smartphone-based patient-reported adherence to medication and questionnaire-based patient-reported adherence to medication, as reflected by the scores on the MARS, are presented in [table 1](#). In the models adjusted for age and gender, there was a significant negative association between smartphone-based patient-reported adherence to medication and scores on the MARS (adjusted model: B: -0.049 , 95% CI -0.095 to -0.003 , $p = 0.033$). There was no increased risk of non-adherence to providing smartphone-based monitoring of adherence (missing data) with increasing scores on the MARS (unadjusted model: Odds: -0.31 , 95% CI -0.73 to 0.099 , $p = 0.14$; model adjusted for age and gender: Odds: -0.32 , 95% CI -0.73 to 0.095 , $p = 0.13$).

Characteristics for patient-reported adherence to medication measured using smartphones

The results from the unadjusted and adjusted linear mixed effects models regarding predictors for smartphone-based patient-reported adherence to medication and predictors are presented in [table 2](#).

In the models adjusted for gender, younger age was a significant predictor for patient-reported non-adherence to medication (model adjusted for gender: B: 0.0039 , 95% CI 0.00019 to 0.0076 , $p = 0.040$). In the models adjusted for age and gender, longer illness duration was a significant predictor for patient-reported non-adherence to medication (adjusted model: B: -0.0057 , 95% CI -0.011 to -0.00035 , $p = 0.037$).

In unadjusted models and models adjusted for age and gender, smartphone-based patient-reported mood between euthymic and manic as well as patient-reported mood between euthymic and depressive were significantly associated with patient-reported adherence to medication (euthymic to manic, adjusted model: B: 0.24 , 95% CI 0.091 to 0.30 , $p = 0.002$; euthymic to depressive, adjusted model: B: 0.32 , 95% CI 0.11 to 0.54 , $p = 0.003$).

In unadjusted models and models adjusted for age and gender clinically rated depressive symptoms measured using the HDRS were significantly associated with adherence to medication measured using smartphones. Clinically rated manic symptoms measured using the YMRS were not significantly associated with adherence to medication measured using smartphones.

In unadjusted models and models adjusted for age and gender, empowerment according to Roger’s Empowerment Scale was significantly associated with adherence to medication measured using smartphones (unadjusted model: B: 0.012 , 95% CI 0.0038 to 0.020 , $p = 0.004$; adjusted model: B: 0.011 , 95% CI 0.0034 to 0.019 , $p = 0.005$).

Additionally, there was a significant negative association between scores on the MARS and scores on the HDRS (unadjusted model: B: -0.033 , 95% CI -0.070 to -0.0046 , $p = 0.086$; adjusted model: B: -0.038 , 95% CI -0.075 to -0.0007 , $p = 0.046$). There were no significant associations between scores on the MARS and scores on the YMRS.

Gender, BD subtype (I or II), years of education, number of previous episodes, number of previous hospitalisations and functioning according to the FAST were not significantly associated with patient-reported adherence to medication ([table 2](#)).

DISCUSSION

This is the first study to investigate associations between patient-evaluated adherence to medication measured in a fine-grained and real-time manner via smartphones and questionnaire-based data on adherence to medication as well as predictors for adherence to medication in patients with BD. Interestingly and as hypothesised, we found that adherence to medication evaluated via smartphones was valid compared with validated questionnaire-based information on adherence. As further hypothesised, younger age and longer illness duration were predictors for non-adherence, and decreased empowerment was associated with non-adherence. In contrast to what we hypothesised a priori, female gender and impaired functioning were not associated with non-adherence. Further, in contrast to what we hypothesised a priori, decreased severity of affective symptoms measured with both patient-reported mood measured on smartphones as well as with clinical ratings was associated with non-adherence, and increased severity of depressive symptoms was associated with increased adherence.

The finding that patient-evaluated adherence to medication measured with smartphones was valid compared with validated questionnaire-based information on adherence to medication in patients with BD was novel. During recent years others have suggested that using technology to track adherence may provide new perspectives and opportunities to provide real-time feedback to patients and clinicians and deliver low-threshold support to patients.^{22–24} Using smartphones for this type of monitoring enables clinicians to track adherence in detail over longer periods and between visits with the clinicians and may provide insights into individual and daily variations in adherence during prolonged time periods outside the clinical settings.

The finding that younger age and longer illness duration were predictors for non-adherence is in line with findings from previous studies.^{5 16 29 44} This implies that assessment of adherence to medication in these patient populations should receive close attention. Regarding the association between the empowerment questionnaire fulfilled several times during the study and adherence it should be stressed that the causality is unknown. It may be that patients who report higher empowerment are also more adherent to medication. Another possibility could be that the daily registration of adherence via smartphones and the possibility to get an overview of the daily medication intake increased the feeling of being in control.⁴⁵ This association stresses the importance for clinicians to discuss and include patients in the process of treatment, which has also been emphasised by others.^{15 46}

The finding that female gender was not a predictor for non-adherence adds to the evidence of contradictory results for a link between gender and adherence in BD.^{15 29 47 48} Other predictors associated with non-adherence in patients with BD in previous studies were not significant in the present study (eg, lower levels of education, BD subtype, number of previous episodes and decreased functioning).^{16 29 48}

The finding that decreased severity of affective symptoms measured with both clinical ratings and patient-reported mood measured on smartphones was associated with non-adherence contrasts with previous findings, suggesting that the severity of BD is associated with non-adherence.^{29 44 48} It cannot be excluded

that the differences in the granularity of data on adherence could influence the differences in findings between studies. A previous study suggested that a proportion of patients with BD find that as long as they are taking medication they do not really know if it is necessary,⁴⁹ which may be in line with the findings from the present study.

Advantages

The smartphone-based system used in the present studies (the Monsenso system) was developed by the authors and has been shown easy to use with a high usability, usefulness, ease of learning to use and interface quality—also when compared with other smartphone-based systems.^{50 51} Along this line, the use of smartphones for real-time fine-grained monitoring may have reduced the risk of potential recall bias on adherence to medication.

Limitations

It is possible that a larger sample with a longer follow-up period could have resulted in other findings. Also, the patients were participating in two RCTs as part of the intervention group and as such the intervention in itself could have influenced the patients' adherence. In addition, the sample size for each of the two RCTs was defined according to the outcome measure for each of the trials. Thus, the outcome of adherence to medication was not the primary outcome in any of the two trials. The findings from the present study are based on exploratory reanalyses that were not defined during the design phase of the two trials. Thus, findings should be interpreted with caution. The patients did not provide data on adherence in a total of 33.82% of the days, and we do not have information on whether these days reflect days with non-adherence or not. Nevertheless, there were no differences in age, gender, illness duration, BD subtype (I or II), number of previous hospitalisations, educational level and scores on the MARS between patients evaluating adherence to medication using smartphones or patients not providing data. Detailed information on medication use covered by scorings using 'medication taken with changes' was not available and thus not investigated. We were not able to investigate the effect of a positive doctor–patient relationship on adherence in the present study, but prior research has highlighted this as an important factor for continuous adherence in patients with BD.^{15 45 46} Also, routine conversations concerning adherence during doctor–patient visit are important and reminders of adherence have been found effective to increase adherence in patients with BD.^{26 48} The included patients may be more favourably oriented towards a smartphone-based monitoring tool and may have differed from patients who were not.

Perspectives

The rapid evolution of smartphone-based technology has fostered increasing growth of tools for remote self-monitoring in general and in BD. Smartphones allow for long-term fine-grained real-time assessments in naturalistic non-experimental settings and between clinical appointments⁵² and provide unique opportunities to a better understanding of the nature, correlates and clinical implications of adherence to medication in patients with BD.

CONCLUSIONS

In a sample of motivated patients with BD, a smartphone-based system used for monitoring of adherence to medication was valid compared with validated questionnaire-based data on adherence.

Younger age and longer illness duration were predictors for non-adherence, whereas female gender was not. Empowerment was associated with higher adherence. Using smartphones for long-term monitoring of adherence using patient-reported measures may be helpful in everyday clinical settings.

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Contributors MFJ and LVK performed the statistical analyses and wrote the first draft of the manuscript. All authors contributed to and have approved the final version of the manuscript.

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Competing interests MFJ has no conflicts of interest. MF and JEB are co-founders and shareholders in Monsenso ApS. EMC has been a consultant for Eli Lilly, AstraZeneca, Servier, Bristol-Myers Squibb, Lundbeck and Medilink. MV has been a consultant for Lundbeck within the last 3 years. LVK has been a consultant for Lundbeck during the recent 3 years.

Patient consent for publication Not required.

Ethics approval The trials were approved by the Regional Ethics Committee of the Capital Region of Denmark (H-2-2011-056, H-2-2014-059 and H-7-2014-007) and the Danish Data Protection Agency (2013-41-1710). The law regarding the handling of personal data was respected. The electronic data collected from the smartphones were stored at a secure server at Concern IT, Capital Region, Denmark (I-suite number RHP-292 2011-03). The trials complied with the Helsinki Declaration of 1975, as revised in 2008.

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