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Daily electronic self-monitoring of subjective and objective symptoms in bipolar disorder—the MONARCA trial protocol (MONitoring, treAtment and pRediCtion of bipolAr disorder episodes): a randomised controlled single-blind trial

Maria Faurholt-Jepsen,[1] Maj Vinberg,[1] Ellen Margrethe Christensen,[1] Mads Frost,[2] Jakob Bardram,[2] Lars Vedel Kessing[1]

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[1]Clinic for Affective Disorders, Psychiatric Center Copenhagen, Rigshospitalet, Copenhagen, Denmark
[2]PIT Lab, IT University of Copenhagen, Copenhagen, Denmark

Correspondence to
Dr Maria Faurholt-Jepsen; maria@faurholt-jepsen.dk

ABSTRACT

Introduction: Electronic self-monitoring of affective symptoms using cell phones is suggested as a practical and inexpensive way to monitor illness activity and identify early signs of affective symptoms. It has never been tested in a randomised clinical trial whether electronic self-monitoring improves outcomes in bipolar disorder. We are conducting a trial testing the effect of using a Smartphone for self-monitoring in bipolar disorder.

Methods: We developed the MONARCA application for Android-based Smartphones, allowing patients suffering from bipolar disorder to do daily self-monitoring—including an interactive feedback loop between patients and clinicians through a web-based interface. The effect of the application was tested in a parallel-group, single-blind randomised controlled trial so far including 78 patients suffering from bipolar disorder in the age group 18–60 years who were given the use of a Smartphone with the MONARCA application (intervention group) or to the use of a cell phone without the application (placebo group) during a 6-month study period. The study was carried out from September 2011. The outcomes were changes in affective symptoms (primary), social functioning, perceived stress, self-rated depressive and manic symptoms, quality of life, adherence to medication, stress and cognitive functioning (secondary and tertiary).

Analysis: Recruitment is ongoing.

Ethics: Ethical permission has been obtained.

Dissemination: Positive, neutral and negative findings of the study will be published.

Registration details: The trial is approved by the Regional Ethics Committee in The Capital Region of Denmark (H-2-2011-056) and The Danish Data Protection Agency (2013-41-1710). The trial is registered at ClinicalTrials.gov as NCT01446406.

INTRODUCTION

Bipolar disorder is a common and complex mental disorder with a prevalence of 1–2%[1 2] and accounts as one of the most important causes of disability at age 15–44 years worldwide.[1] Bipolar disorder is a long-term and persistent illness with need for treatment over many years.[3] The disorder is associated with a high risk of relapse and hospitalisation and the risk of relapse increases along with the number of previous episodes.[4–6] Many patients do not recover from previous psychosocial function and the cognitive disturbances are also prevalent during remitted phases.[7] It is well documented from randomised clinical trials (RCT) that the risk of a new episode in bipolar disorder can be reduced significantly by treatment with lithium or other mood stabilisers.[8] Further, the prophylactic effect of medical treatment may be enhanced by psychoeducation or cognitive behavioural therapy.[9] However, results from naturalistic follow-up studies suggest that the progressive development of the disease is not prevented in clinical practice with the present treatments.[4–6 10] The major reasons for the decreased effect of interventions in clinical practice are delayed intervention for prodromal depressive and manic episodes[11 12] as well as decreased medical adherence.[13–15]

During the last decades, there has been an organisational shift in paradigm from inpatient to outpatient treatment in healthcare, and in bipolar disorder there is an emerging shift in illness paradigm from a

focus on mood episodes to a focus on the interepisodic mood instability.[16] However, current monitoring of bipolar disorder illness activity is based on the identification and analysis of mood episodes at different intervals of time, often on a monthly basis during outpatient facility visits.

Recently, electronic self-monitoring of affective symptoms using cell phones to prompt patients to respond to weekly text messages was proposed as an easy and inexpensive way to monitor and identify early signs of emerging affective episodes so that providers could intervene shortly after prodromal symptoms appeared.[17] However, the used electronic devices have been rather simple, not including a bidirectional feedback loop between patients and providers and without electronic data on 'objective' measures of the affective psychopathology. It has never been tested in a randomised trial whether the continued use of an electronic device, including a feedback loop, improves affective symptoms and other outcomes in bipolar disorder.

In the MONitoring, treAtment and pRediCtion of bipolAr disorder episodes (MONARCA) study, we developed and are currently testing in a randomised controlled trial (RCT) the software for Android Smartphones to monitor the subjective and objective activities of bipolar disorder alongside with treatment adherence in a bidirectional feedback loop between patients and providers. The software system includes the recording of subjective items such as mood/irritability,[17] sleep[18 19] and alcohol[20] that may reflect or correlate with illness activity in bipolar disorder. As the ability of these subjective measures to detect prodromal symptoms of depression and mania may not be sufficient, we have also included objective measures such as speech, social and physical activity in the software system. Decreased activity in speech (paucity of speech) seems to be a sensitive and valid measure of prodromal symptoms of depression[21 22] and conversely increased speech activity (talkativeness) predicts a switch to hypomania.[19 23 24] Similarly, social activity,[25] that is, engaging in relations to others, as well as physical activity[26 27] represents central and sensitive aspects of illness activity in bipolar disorder.

Hypotheses

Daily electronic monitoring using an online interactive Smartphone including a feedback loop between patients and clinicians reduces the severity of depressive and manic symptoms and stress and increases social functioning, quality of life, adherence to medication and cognitive functioning.

Objectives

To investigate in a randomised controlled trial whether the use of an online monitoring system including a feedback loop in patients suffering from bipolar disorder reduces symptoms of affective disorder and stress and increases social functioning, quality of life, adherence to medication and cognitive functioning.

METHODS

This protocol is reported according to the CONsolidated Standards Of Reporting Trials (CONSORT) statement and Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).[28–30]

This protocol describes a randomised controlled trial comparing the effect of using a Smartphone with the MONARCA system including a feedback loop with the use of a placebo Smartphone without an active MONARCA system.

Trial design and study organisation

The trial is a single-blind, placebo-controlled, parallel-group study stratified on age (18–29 and 30–60 years) and former hospitalisation (yes and no) with balanced randomisation of bipolar disorder patients (1:1) to either the active use of MONARCA application on a Smartphone (intervention group) or a placebo MONARCA Smartphone. The study is conducted at The Clinic for Affective Disorders, Psychiatric Center Copenhagen, Rigshospitalet, Copenhagen, Denmark. There are no changes in the design or methods after the start of the trial.

Participants and setting

All patients were recruited from The Clinic for Affective Disorder, Psychiatric Center Copenhagen, Rigshospitalet, Copenhagen, Denmark. Recruitment started in September 2011. The Clinic for Affective Disorders is a specialised outpatient clinic that covers a recruitment area of the Capital Region, Denmark, corresponding to 1.4 million people. The staff consists of full-time specialists in psychiatry with specific clinical experience and knowledge about the diagnosis and treatment of bipolar disorder as well as certified psychologists, nurses and a social worker with experience in bipolar disorder. Patients with bipolar disorder are referred to the clinic from secondary healthcare when a diagnosis of a single mania or bipolar disorder is made for the first time[31] or in the case of occurrence of treatment resistance, that is, persistent affective symptoms or recurrences despite treatment in standard care. The physicians at the clinic follow the patients with evidence-based pharmacological treatment and regular appointments depending on their clinical status and needs. Treatment at the clinic comprises combined psychopharmacological treatment and supporting therapy for a 2-year period.

Bipolar patients are referred to the clinic after the first, second or third admission and asked to participate after initial assessment by a psychiatrist. Following referral to the clinic, the clinicians make the diagnosis of bipolar disorder and subsequently introduce the MONARCA study to all patients except those who are

either pregnant, older than 60 years or have a lack of Danish language skills.

Inclusion criteria: bipolar disorder diagnosis according to ICD-10 using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN),[32] Hamilton Depression Rating scale score (HDRS), 17 items ≤17[33] and Young Mania Rating Scale (YMRS) score ≤17[34] at the time of inclusion and age between 18 and 60 years.

Exclusion criteria: significant physical illness, schizophrenia or other F2 diagnoses according to the SCAN interview, unwillingness to use the project Smartphone as the primary cell phone, inability to learn the necessary technical skills for being able to use the Smartphone, lack of Danish language skills and pregnancy.

Patients meeting the inclusion criteria and having none of the exclusion criteria were enrolled in the study.

Study procedure

Following referral to the MONARCA trial, potential participants were screened and if they met the criteria for participating in the trial, they were included. Following inclusion in the trial, a baseline assessment was performed on all patients (table 1). Immediately after this baseline assessment, the study nurse got the allocation envelope and patients met with her and were randomised to receive either an intervention MONARCA Smartphone or a placebo MONARCA Smartphone for the 6 month study period.

Interventions

All patients received standard treatment at The Clinic for Affective Disorder, Psychiatric Center, Copenhagen, Rigshospitalet, Copenhagen, Denmark as described above.

The Smartphone

In MONARCA, the 'HTC Desire' and 'HTC Desire S' Smartphones running the Android operating system were used and all patients received a Smartphone free of charge for the 6-month study period. The placebo group had to use the MONARCA Smartphone for normal communicative purposes and the intervention group had to use the application for self-monitoring once a day, every day, for 6 months (figure 1).

Pilot study

As part of the clinical assessment at The Clinic for Affective Disorder, a paper version with daily monitoring of subjective items such as mood and medication was used for 4 years. Based on an interactive process between four patients suffering from bipolar disorder, the clinicians, bipolar researchers with clinical and scientific experience of bipolar disorder and IT researchers involved in the study, we developed an android application for monitoring bipolar disorder prior to this RCT (figures 2–5). During this interactive user-centred design process, the system was developed and the items to monitor and the corresponding scoring system were selected. Subsequently, the application was tested in a pilot trial with 12 patients for 3 months to test the usability and relevance of the selected monitoring items and to validate the technical part of the software.[35] Following the pilot study, minor adjustments were made and thereafter the system was 'locked' into a final version to be tested in the present trial.

Subjective items for monitoring in the active intervention group

Patients in the active intervention group entered the following subjective items every evening: mood (scored from depressive to manic: −3, −2, −1, 0, +1, +2 and +3), sleep duration (number of hours per night, measured in half-hour intervals), medicine (taken as prescribed: yes, no, if changed, the patient was asked to specify these), activity (scored on a scale of −3, −2, −1, 0, 1, 2 and 3), irritability (yes or no), mixed mood (yes or no), cognitive problems (yes or no), alcohol consumption (number of

Table 1 Investigation overview—MONARCA RCT

	SCAN	Questionnaires*	Rating scales†	Blood analysis‡	Urine analysis§	Saliva analysis¶	SCIP
Screening	x		x				
Randomisation 1:1 using MONARCA application or not							
Baseline		x	x	x	x	x	x
1 month		x	x				
2 month		x	x				
3 month		x	x	x	x	x	x
4 month		x	x				
5 month		x	x				
6 month		x	x	x	x	x	x

*Questionnaires: Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, Altman Self-rating scale for mania (ASRM), Psychosocial Functioning (FAST), Coping Strategies (CISS), Quality of life (WHOQOL), Perceived Stress and MDI.
†Rating scales: HDRS and YMRS.
‡Blood analysis: BDNF, psychotropic medication and one sample of whole-blood at baseline.
§Urine analysis: oxidative stress.
¶Saliva analysis: cortisol.

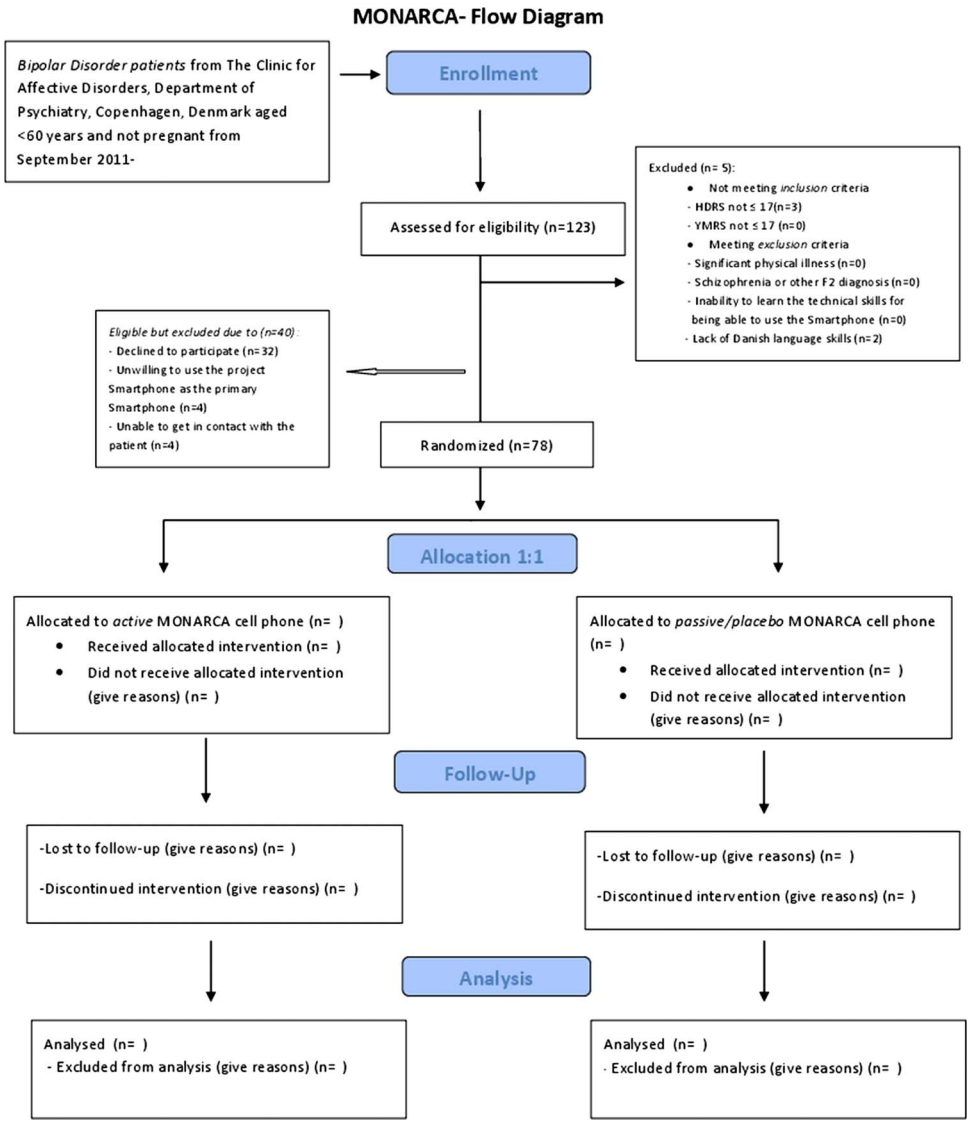

Figure 1 MONARCA—flow diagram chart.

units per day), stress (scored on a scale of 0, 1, 2, 3, 4 and 5), menstruation for women (yes or no) and individualised early warning signs (yes or no). Patients were prompted by a reminder in the Smartphone to evaluate these items every evening at a chosen time. After midnight, the entered data were 'locked' and further changes could be made. If the patients forgot to evaluate the subjective items, it was possible to retrospectively enter data for 2 days. It was then noted in the system that the data were collected retrospectively. Screenshots from the software can be seen in figures 2–5. A user's guide for the MONARCA system was developed and handed out to all patients in the intervention group (can be obtained by contacting author).

Objective parameters monitored in the intervention and placebo arms

All the Smartphones in the study automatically collected objective data every day for the intervention group as well as the placebo group. The following objective items were chosen: speech duration (minutes of speech per 24 h on the Smartphone), social activity measured as numbers of outgoing and incoming calls per day and numbers of outgoing and incoming text messages per 24 h and physical activity measured by the accelerometer installed in the Smartphones as well as the amount of physical movement measured through the accelerometer in the Smartphone (sampled every 5 min). Thus, we can investigate the correlation between the activity on the Smartphone and affective symptoms based on HDRS and YMRS.

A study nurse from the clinic (HSN) with experience with bipolar disorder was assigned to the patients allocated to the active intervention arm of the MONARCA study. She monitored on a daily basis all self-reported subjective electronic patient data and when these data suggested upcoming or deterioration of depressive or manic symptoms, she contacted the patients by text messages, telephone or email as part of the feedback loop during the entire period of this study (see later).

Figure 2 Frontpage.

Figure 3 Self-assessment.

Patients allocated to the placebo arm were similarly assigned a nurse (other than HSN, but similarly experienced with bipolar disorder) on clinical indication as part of the standard treatment in the clinic, for example, when upcoming or deterioration of depressive or manic symptoms, but this nurse did not have access to electronic daily data of the patient.

Identification of the early warning signs and triggers, and the interactive feedback loop in the active intervention group

In the intervention group, a personal homepage for each patient was set up on a server and the patient could connect to the homepage using secure codes. By giving informed consent to participate in the MONARCA trial, patients allowed clinicians to connect to the homepage. The homepage presents all the monitored items graphically.

A standard of scoring thresholds on the subjectively monitored items for when the study nurse should contact patients was made. For example, the patients had to be contacted if they registered ≥−2 or+ 2 in their mood for 2 days, if they registered changes in their sleep patterns of 1 h more or less for 3 days, if medication was not taken or changed for more than 2 days, if the activity level registered was ≥−2 or +2 for 2 days, if mixed mood was registered for more than 3 days and if alcohol intake was >2 units for more than 3 days (full version of standard scoring thresholds can be obtained from the authors on request). These thresholds were individualised for every patient within the first 4 weeks of the trial. The study nurse reviewed the monitored data for all the patients in the intervention group every day and in case of signs of bipolar disorder instability, she contacted the patient. The patients could also contact the study nurse by phone or email in case of subjective signs of bipolar disorder instability.

Following a run in monitoring of approximately 4 weeks, the patient and study nurse, in collaboration with the clinicians, and relatives (if accepted by the patient) agreed on a concordance status in (1) his/her most important items for identifying prodromal symptoms of mania (eg, sleep or alcohol consumption) as well as depression (eg, social activity); (2) the threshold for future signal warnings of prodromal symptoms (eg, slept 1 h less than the average monitored historic sleep time for three consecutive nights, had been drinking

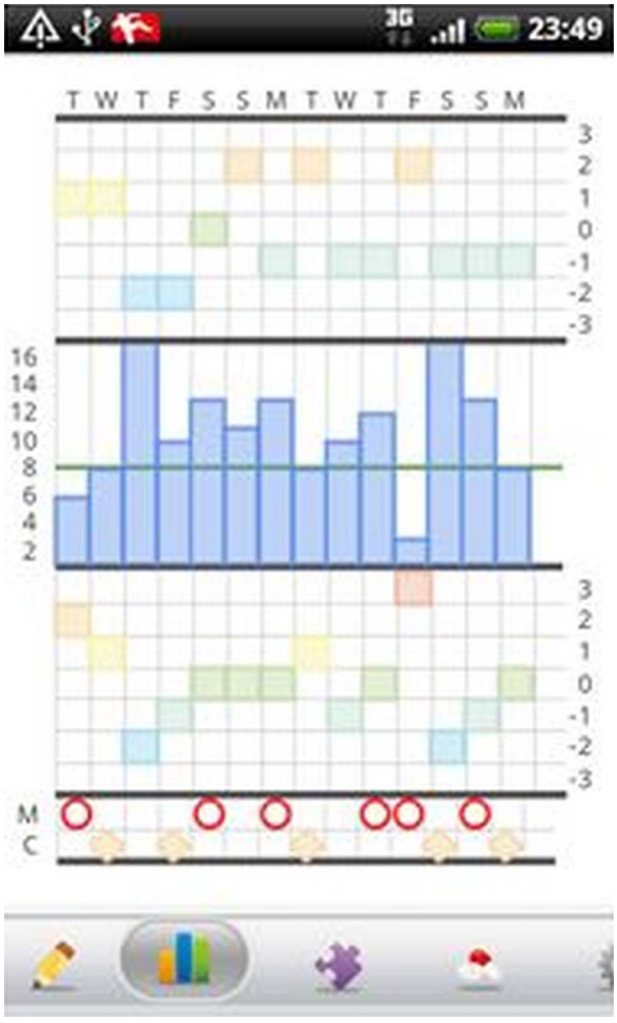

Figure 4 Visualisation.

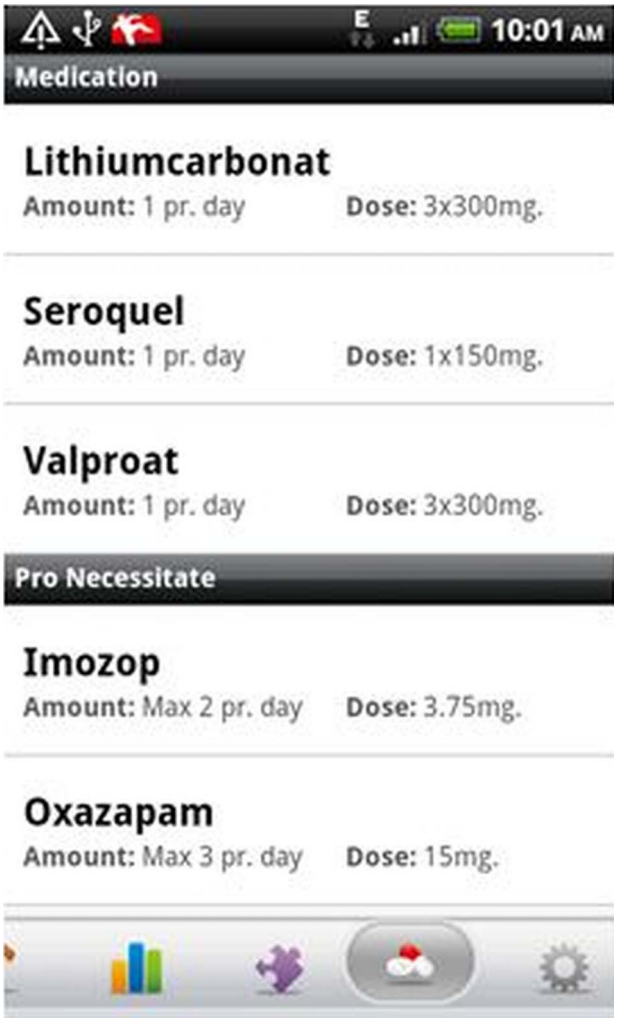

Figure 5 Medication.

alcohol for three consecutive days, did not call anyone on the Smartphone for four consecutive days, did not take medication as prescribed for three consecutive days, etc) and (3) actions to be taken (eg, contact the caregiver within 3 days following the alarm signal and if he did not, the caregiver contacted the patient for clinical evaluation and intervention, for example, increase the dose of the mood stabiliser).

Assessments

All assessments were carried out by two physicians (MFJ and ASJ) who were not involved in the treatment of the patients. The patients were enrolled in the trial for a 6-month study period and assessed every month (table 1). The bipolar diagnosis was confirmed by a SCAN interview before inclusion of the patient.[32] Every month the affective symptoms were clinically rated using HDRS[33] and YMRS.[34] The following questionnaires were fulfilled every month when visiting the researcher; Psychosocial Functioning (Functioning Assessment Short Test, FAST),[36] Cohens' Perceived Stress Scale,[37] quality of life (WHOQOL),[38] coping strategies (CISS),[39] self-rated depressive[40–42] and manic symptoms[43] and cognitive functioning.[44]

Biological samples of awakening salivary cortisol,[45 46] urinary oxidative stress,[47 48] plasma BDNF[49] and adherence to medication as measured by plasma concentration of the patient-prescribed medicine (mood stabilisers, antipsychotics, antidepressants) were taken at baseline, after 3 and 6 months. Cognitive function according to the Screen for Cognitive Impairment in Psychiatry (SCIP-S)[50 51] was assessed at baseline and after 3 and 6 months.

Outcomes

Primary outcomes

Clinically rated affective symptoms based on HDRS 17 items[33] and YMRS.[34] These were assessed every month for 6 months (table 1).

Secondary outcomes

Psychosocial Functioning (Functioning Assessment Short Test, FAST),[36] Cohens' Perceived Stress Scale,[37] quality of life (WHOQOL),[38] coping strategies (CISS),[39] self-rated depressive[40–42] and manic symptoms[43] and

cognitive functioning.[44] These questionnaires were fulfilled at the time of clinical assessments (table 1).

Tertiary outcomes

Awakening salivary cortisol, [45 46] urinary oxidative stress,[47 48] plasma BDNF,[49] cognitive function according to the screen for cognitive impairment in psychiatry (SCIP-S)[50 51] and adherence to medication as measured by plasma concentration of the prescribed medicine (mood stabilisers, antipsychotics, antidepressants). These were measured at baseline and after 3 and 6 months (table 1).

No changes in trial outcomes were made after the start of the trial.

Sample size

The statistical power and sample size were calculated using http://stat.ubc.ca/~rollin/stats/ssize/n2.html. The primary outcome was differences in the level of affective symptoms based on the HDRS score and YMRS score respectively. The clinical relevant difference is defined as the minimum of three scores and the SD was set to four with a mean score of 10 vs 7 in the two groups. The statistical power to detect a three score difference in the areas under the curves between the intervention and the control groups on the HDRS score or the YMRS score, respectively, was 80% with α=0.05 for a two-sample comparison of means including 28 patients in the intervention group and 28 patients in the placebo group. The dropout rate is estimated to be around 25%.

Randomisation

Sequence generation

A computer-generated list of random allocation numbers was carried out by an independent researcher (KM) using randomisation.com. Since the course of illness and effect of the intervention could be influenced by age and previous hospitalisation, stratification is carried out on age (18–30 vs >30) and previous hospitalisation (yes or no). Stratification is carried out to ensure good balance of these patient characteristics in each randomisation group so that the number of patients receiving the intervention MONARCA Smartphone or placebo MONARCA Smartphone was balanced within each stratum. Allocation was 1:1. Within each stratum, a fixed block randomisation size of 10 is used. The block size was unknown to all the clinicians recruiting patients to the trial and the study nurse allocating participants to their correct randomisation arm.

Allocation concealment and implementation

The allocation sequence was concealed from the researcher (MFJ and ASJ) enrolling and assessing patients. Allocation was concealed in numbered, opaque and sealed envelopes stored in a securely locked cabinet by a secretary until the moment of randomisation. Allocation was identified by the letter A or B written on the paper in the envelopes and this indicated the type of intervention. The translation of allocation as A or B was made and known only to LVK and the study nurse. A paper with this translation was kept in a securely locked cabinet unknown to others than LVK. The secretary gave the envelope to the study nurse. Corresponding envelopes were opened only after all baseline assessment was performed and the patient's name was written on the envelope. The study nurse assigned patients to their allocation of intervention.

Blinding

Owing to the type of intervention in this trial, the patients and the study nurse were aware of the allocation arm. The researchers responsible for outcome assessments (MFJ and ASJ) and data analysis (MFJ) were kept blinded to allocation at all times during the trial. The trial was therefore single-blinded. The study nurse did not collect any kind of outcome measures. All patients were thoroughly and repeatedly instructed not to mention anything about allocation to intervention at each visit with the researcher. The risk of unblinding due to simply seeing the type of mobile phone in the patient's hands was minimised since all patients received the same type of mobile phone.

Statistical methods

Data will be managed by MFJ and entered using Epidata. All analyses will be done using *Statistical Package for the Social Sciences* (SPSS). Data from all randomised patients will be collected until dropout or the end of the study period. The outcome is changes in affective symptoms measured as HDRS and YMRS during the 6-month study period. We will employ a linear mixed effects model with random intercept for each participant. Differences between outcomes of the interventions during the 6 months study period will be analysed, first unadjusted and then adjusted for age, previously psychiatric hospitalisations (yes/no) and sex, if these variables present with a $p \leq 0.1$ in univariate analyses. Analysis will be carried out with intention-to-treat (ITT). The statistical threshold for significance is $p \leq 0.05$ (two-tailed).

Ethical considerations

Ethical permission for the MONARCA study has been obtained from the Regional Ethics Committee in The Capital Region of Denmark (H-2-2011-056) and The Danish Data Protection Agency (2013-41-1710). The trial is registered at ClinicalTrials.gov as NCT01446406. All positive, neutral and negative findings of the study will be published according to the CONSORT guidelines.[28] All electronic monitored data are stored at a secure server at Concern IT, Capital Region, Copenhagen, Denmark (I-suite number RHP-2011-03).

All potential participants are invited to be informed about the trial and the information is given in a quiet and undisturbed office. All information is presented in both written and verbal form and participants can bring

a friend or relative to the introduction conversation. Participants are informed that participation is voluntary and that consent can be withdrawn at any time of the study without this giving any consequences for future treatment possibilities. All participating patients sign a consent form and get a copy of this and their rights as a participant in clinical trials. All Smartphones are provided by the project and economic costs from data traffic due to the MONARCA project are refunded. Participants do not receive any economic compensation for participating in the MONARCA trial.

RESULTS

Until the time of submission, a total of 141 patients suffering from bipolar disorder had been identified, but 11 of these were over 60 years of age and seven were pregnant. This left 123 patients to be assessed for eligibility for the trial. Of these, three patients had an HDRS score ≥17 for a prolonged period of time and two were unable to speak Danish. Thus, so far a total of 118 patients have been eligible, but 32 declined to participate, four were unwilling to use our Smartphone as their primary Smartphone and we could not contact four patients. Until the time of submission, the participation rate was 66.1% and the dropout rate during the 6 months follow-up period was 12.8%. Until the time of submission, a total of eight patients dropped out at baseline before knowledge of their allocation to intervention and two patients dropped out during the 6-month study period.

DISCUSSION

This is the first randomised trial to test whether electronic monitoring may improve long-term outcome in mental illness, in this case bipolar disorder. A major advantage in the MONARCA trial is that the system is developed and tested in a pilot study in a close collaboration between patients suffering from bipolar disorder, clinicians (specialists in psychiatry and nurses with specific clinical expertise within bipolar disorder) as well as clinical researchers within bipolar disorder and IT researchers.

Limitations

The intervention

We decided to investigate the effect of a total system combining electronic self-monitoring and a feedback system between patients and clinicians in order to help patients acknowledge illness activity and identify and react more adequately on early warning signs and triggers of affective episodes. The study is designed to investigate the total effect of this intervention versus placebo intervention and, consequently, we will not be able to address more specifically the effect of the individual elements of the intervention, such as for example, the effect of subjective self-monitoring on its own.

Control group

It is a major challenge in any non-medical trial to define a proper control group. We decided to include a control group of patients who received the same Smartphone but without the MONARCA software system, that is, a placebo Smartphone. Patients in the placebo group did not make any subjective electronic self-monitoring of symptoms or behaviour and they were not monitored with the feedback loop, but their illness activity was monitored 'objectively' in the same way as for the intervention group using Smartphone data to monitor speech duration, social activity and physical activity and they followed treatment as usual in the clinic.

Objective measures of illness activity?

Possible electronic objective measures of illness activity have never been studied, as electronic monitoring in healthcare is a new and unstudied area. If successful, this may be a major breakthrough for treatment of bipolar disorder and for research in bipolar disorder. We will be able to validate Smartphone generated data of speech duration, social activity and physical activity against repeated measures of HAM D-17 and YMRS score over a 6-month period. Anyhow, as this is the first trial to investigate electronic monitoring, we were not able to provide feedback to the patients allocated to the active intervention arm on these objective data. We are currently transferring the Smartphone-generated data on these objective items into useful simple information that can be provided to the patients in a future revised MONARCA application.

Generalisability

The study was carried out in a tertiary specialised mood disorder clinic. However, the trial has a pragmatic design with few exclusion criteria and few patients were excluded. The majority of patients entering the trial are in an early course of the illness with a newly diagnosis of single mania or bipolar disorder. Further, as the MONARCA system is easy to use for both patients and clinicians with a high appeal and low dropout rate, we believe that the findings of the trial can be generalised to patients with bipolar disorder in general.

Perspectives

If the Smartphone self-monitoring system proves to be effective in preventing mood symptoms and improving psychosocial functioning and quality of life in the present study, there will be a basis for extending the use of the system to treatment of patients with bipolar disorder in clinical practice in other clinical settings (eg, community psychiatric centres) and on a larger scale. Using electronic self-monitoring may improve patient empowerment in relation to bipolar disorder and treatment. Potentially, electronic self-monitoring may be applied in relation to patients suffering from other psychiatric disorders with development of other software systems. In this way, it is possible that outpatient

treatment can be optimised in general and that the frequency of physician and other clinical visits can be decreased.

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Contributors LVK, MV, EMC and MFJ conceived the trial and authored the first draft of the trial protocols. MF and JB have been revising and optimising the trial protocols and the article. All authors contributed to, and approved, the final manuscript.

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Competing interests LVK has been a consultant for Bristol-Myers Squibb, Eli Lilly, Lundbeck, AstraZenica, Pfizer, Wyeth and Servier. MV has been a consultant for Eli Lilly, Lundbeck, AstraZenica and Servier. EMC has been a consultant for Eli Lilly, AstraZenica, Servier, Bristol-Myers Squibb, Lundbeck and Medilink. MFJ has been a consultant for Eli Lilly. MF and JB has no competing interests.

Ethics approval The trial was approved by the Regional Ethics Committee in The Capital Region of Denmark (H-2-2011-056) and The Danish Data Protection Agency (2013-41-1710).

Provenance and peer review Not commissioned; internally peer reviewed.

Data sharing statement All collected data will be used and handled by the study group consisting of the all authors of this study.

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