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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

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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 randomized 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 is tested in a parallel-group single-blind randomized controlled trial so far including 78 patients suffering from bipolar disorder age 18-60 years are allocated to using a Smartphone with the MONARCA application (intervention group) or to using a cell phone without the application (placebo group) during a 6 months study period. The study is carried out from September 2011. The outcomes are 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

Both positive, neutral and negative findings of the study will be publised.

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 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 to previous psychosocial function and the prevalence of cognitive disturbances is prevalent also 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 significant by treatment with lithium or other mood stabilizers (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). 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 organizational shift in paradigm from inpatient to outpatient treatment in health care, and in Bipolar Disorder there is an emerging shift in illness paradigm from focus on mood episodes to focus on the inter-episodic mood instability (16). However, current monitoring of bipolar disorder illness activity is based on identification and analysis of mood episodes at different intervals of time, often at 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 providers can intervene shortly after prodromal symptoms appear (17). However, the used electronic devises have been rather simple not including a bi-directional feedback loop between patients and providers and without electronic data on “objective” measures of the affective psychopathology. It has never been tested in a randomized trial whether 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 testingin a randomized controlled trial (RCT) the software for Android Smartphones to monitor the subjective and objective activities of bipolar disorder alongside with treatment adherence in a bi-directional feedback loop between patients and providers. The

software system includes 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; 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) predict switch to hypomania (19,23,24). Similarly, social activity (25), i.e., engaging in relations to others, as well as physical activity (26,27) represent 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 randomized 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 CONSORT statement (CONsolidated Standards Of Reporting Trials) and SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) (28–30).

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

Trial design and study organization

The trial is a single-blind, placebo-controlled, parallel-group study stratified on age (18-29 years and 30- 60 years) and former hospitalization (yes and no) with balanced randomisation of bipolar disorder patients (1:1) to either 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 to design or methods after trial commencement.

Participants and setting

All patients are 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 out-patient 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 health care when a diagnosis of a single mania or bipolar disorder is made for the first time (31) or if occurrence of treatment resistance, i.e. 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 comprised combined psychopharmacological treatment and supporting therapy for a two year period.

Bipolar patients are referred to the clinic after 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 for 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 18-60 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 none of the exclusion criteria are enrolled in the study .

Study procedure

Following referral to the MONARCA trial potential participants are screened and if they meet the criteria for participating in the trial they are included. Following inclusion in the trial a baseline assessment on all patients are done **(Table 1).** Immediately after this baseline assessment the study nurse get the allocation envelope (see page 10-13) and patients meet with her and are randomized to receive either an intervention MONARCA Smartphone or a placebo MONARCA Smartphone for the six months study period.

Interventions

All patients receives 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 is used and all patients receives a Smartphone free of charge for the six months study period. The placebo group has to use the MONARCA Smartphone for normal communicative purposes and the intervention group has to use the application for self-monitoring once a day, every day, for six months.

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 has been used for four years. Based on an interactive process between four patients suffering from bipolar disorder, 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 of bipolar disorder prior to this RCT (Figure 2-5). During this interactive user-centered design process, the system was developed and the items to monitor and corresponding scoring system selected. Subsequently, the application was tested in a pilot trial with 12 patients for three months to test the usability, 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 hereafter the system was "locked" into a final version to be tested in the present trial.

Subjective items for monitoring in the active intervention group

The patients in the active intervention group enters the following subjective items every evening: mood (scored from depressive to manic: –3, -2, -1, 0, +1, +2, +3), sleep duration (number of hours per night, measured in half-hour intervals), medicine (taken as prescribed: yes, no, if changes the

patient is asked to specify these), activity (scored on a scale of -3, -2, -1, 0, 1, 2, 3), irritability (yes or no), mixed mood (yes or no), cognitive problems (yes or no), alcohol consumption (number of units per day), stress (scored on a scale of 0, 1, 2, 3, 4, 5), menstruation for women (yes or no)and individualized early warning signs (yes or no). Patients are prompted by a reminder in the Smartphone to evaluate these items every evening at a chosen time. After midnight the entered data is "locked" and further changes cannot be made. If the patients forget to evaluate the subjective items it is possible to retrospectively enter data for two days. It is then noted in the system that the data is collected retrospectively. Screenshots from the software can be seen from Figure 2-5. A user's guide for the MONARCA system is developed and handed out to all patients in the intervention group (can be obtained by contact to the author).

Objective parameters monitored in both the intervention and placebo arm

All the Smartphones in the study automatically collects objective data every day for the intervention group as well as the placebo group. The following objective items is chosen: speech duration (minutes of speech per 24 hours 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 hours and physical activity measured by the accelerometer installed in the Smartphones as well as amount of physical movement measured through the accelerometer in the Smartphone (sampled every five minutes). 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 is assigned to the patients allocated to the active intervention arm of the MONARCA study. She monitors on a daily basis all self-reported subjective electronic patient data and when these data suggests upcoming or deterioration of depressive or manic symptoms she contacts the patients by text messages, telephone or e-mail as part of the feedback loop during the entire period of this study (see later).

Patients allocated to the placebo arm are similarly assigned a nurse (other than HSN, but similarly experienced within bipolar disorder) on clinical indication as part of the standard treatment in the

clinic, e.g. when upcoming or deterioration of depressive or manic symptoms, but this nurse does 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 is set up on a server and the patient can connect to the homepage using secure codes. By giving informed consent to participate in the MONARCA trial patients allows 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 the patients is made. For example the patients should be contacted if; the patients registers ≥ -2 or+ 2 in mood for two days, if changes in sleep of one hour more or less for three days, if medication is not taken or changed for more than two days, if the activity level is registered ≥ -2 or+ 2 for two days, if mixed mood is registered for more than three days and if alcohol intake is > 2 units for more than three days (full version of standard scoring thresholds can be obtained from the authors upon request). These thresholds are individualized for every patient within the first four weeks of the trial. The study nurse reviews the monitored data for all of the patients in the intervention group every day and in case of signs of bipolar disorder instability she contacts the patient. The patients can 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 four weeks, the patient and study nurse -in collaboration with the clinicians, and relatives(if accepted by the patient) agrees on a concordance status in 1) his/her most important items for identifying prodromal symptoms of mania (e.g. sleep or alcohol consumption) as well as depression (e.g. social activity) 2) the threshold for future signal warnings of prodromal symptoms (e.g. sleeps one hour less than the average monitored historic sleep time for three consecutive nights, has been drinking alcohol for three consecutive days, does not call anyone on the Smartphone for four consecutive days, does not take medication as prescribed for three consecutive days, etc.) and 3) actions to be taken (e.g. contact the caregiver within three days following the alarm signal and if he does not, the caregiver

contacted the patient for clinical evaluation and intervention, e.g. increase the dose of the mood stabilizer).

Assessments

All assessments are done by two physicians (MFJ or ASJ) whom are not involved in treatment of the patients. The patients are enrolled in the trial for a six months study period and is assessed every month (Table 1). The bipolar diagnosis is confirmed by SCAN interview before inclusion of the patient (32). Every month the affective symptoms are clinically rated using HDRS (33) and YMRS (34). The following questionnaires are full filled every month when visiting the researcher; Psychosocial Functioning (Functioning Assessment Short Test, FAST) (36), Cohens's Percieved 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 patients prescribed medicine (mood stabilizers, antipsychotics, antidepressants) are taken at baseline, after 3 months and 6 months. Cognitive function according to the Screen for Cognitive Impairment in Psychiatry (SCIP-S) (50,51) is assessed at baseline, after 3 months and after 6 months.

Outcomes

Primary outcomes:

Clinically rated affective symptoms based on HDRS- 17 items (33) and respectively YMRS (34) assessed every month for six months (Table 1).

Secondary outcomes:

Psychosocial Functioning (Functioning Assessment Short Test, FAST) (36), Cohens's Percieved 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 are 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 stabilizers, antipsychotics, antidepressants). These are measured at baseline, after 3 months and 6 months (Table 1).

No changes in trial outcomes are made after trial commencement.

Sample size

The statistical power and sample size was calculated using http://stat.ubc.ca/~rollin/stats/ssize/n2.html. The primary outcome is differences in the level of affective symptoms based on HDRS score and YMRS score respectively. The clinical relevant difference is defined as minimum of 3 scores and the standard deviation was set to 4 with a mean score of 10 versus 7 in the two groups. The statistical power to detect a 3 score difference in the areas under the curves between the intervention and the control group on the HDRS score or the YMRS score, respectively, is 80% with alpha = 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%.

Randomization

Sequence generation

A computer-generated list of random allocation numbers was done by an independent researcher (KM) using randomization.com. Since the course of illness and effect of the intervention could be influenced by age and previous hospitalization, stratification is done on age (18-30 versus > 30)

and previous hospitalization (yes or no). Stratification is done to ensure good balance of these patient characteristics in each randomization group, and so that the number of patients receiving intervention MONARCA Smartphone or placebo MONARCA Smartphone is balanced within each stratum. Allocation is 1:1. Within each stratum a fixed block randomization size of 10 is used. The block size is unknown to all the clinicians recruiting patients to the trial and the study nurse allocating participants to their correct randomization arm.

Allocation concealment and implementation

The allocation sequence is concealed form the researcher (MFJ and ASJ) enrolling and assessing patients. Allocation is concealed in numbered, opaque and sealed envelopes stored in a securely locked cabinet by a secretary until the moment of randomization. Allocation is identified by the letter A or B written on the paper in the envelopes and this indicates the type of intervention. The translation of allocation as A or B was made and known only by LVK and the study nurse. A paper with this translation is kept in a securely locked cabinet unknown to others than LVK. The secretary gives the envelope to the study nurse. Corresponding envelopes are opened only after all baseline assessment is done and patients name is written on the envelope. The study nurse assigns patients to their allocation of intervention.

Blinding

Due to the type of intervention in this trial, patients and the study nurse are aware of the allocation arm. The researchers responsible for outcome assessments (MFJ and ASJ) and data analysis (MFJ) are kept blinded to allocation at all times during the trial. The trial is therefore single-blinded. The study nurse does not collect any kind of outcome measures. All patients are 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 patients hands are minimized since all patients receives 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 randomized patients will be collected until dropout or end of study period. The outcome is changes in affective symptoms measured as HDRS and YMRS during the six months study period. We will employ a linear mixed effects model with random intercept for each participant. Differences between outcomes of the interventions during the six months study period will be analyzed, firstly unadjusted and then adjusted for age, previously psychiatric hospitalizations (yes/no) and sex, if these variables presents with a p-value≤ 0.1 in univariate analyses. Analysis will be done with intention-to-treat (ITT). The statistical threshold for significance is $p \leq 0.05$ (2-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. Both positive, neutral and negative findings of the study will be published according to the CONSORT guidelines (28). All electronic monitored data is 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 signsa 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 does not receive any economic compensation for participating in the MONARCA-trial.

Results

Until time at submission a total of 141 patients suffering from Bipolar Disorder has been identified, but 11 of these were over 60 years of age and 7 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 2 were unable to speak Danish. Thus, so far a total of 118 patients has been eligible, but 32 declined to participate, 4 were unwilling to use our Smartphone as their primary Smartphone and we could not get contact to 4 patients. Until time at submission participation rate is 66.1% and the dropout rate during the six months follow up period is 12.8%. Until time at submission a total of 8 patients dropped out at baseline before knowledge of their allocation to intervention and 2 patients dropped out during the 6 months study period.

Discussion

This is the first randomized 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 e.g. the effect of subjective self-monitoring in 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 receives the same Smartphone but without the MONARCA software system, i.e., a placebo Smartphone. Patients in the placebo group does not make any subjective electronic self-monitoring of symptoms or behavior and they are not monitored with the feedback loop, but their illness activity is 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 follows 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 health care 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 six months period. Anyhow, as this is the first trial to investigate electronic monitoring we are 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 for the patients in a future revised MONARCA application.

Generalizability

The study is carried out in a tertiary specialized mood disorder clinic. However, the trial has a pragmatic design with few exclusion criteria and few patients are 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 findings of the trial can be generalized to patients with bipolar disorder in general.

Perspectives

If the Smartphone self-monitoring system is proved effective in preventing mood symptoms and improving psychosocial functioning and quality of life in the present study there will be basis for extending the use of the system to treatment of patients with bipolar disorder in clinical practice in other clinical settings (e.g. community psychiatric centres) and in 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.

Table 1 Investigation overview- MONARCA RCT

	SCAN	Questionnaires*	Rating scales**	Blood analysis***	Urine analysis****	Saliva analysis*****	SCIP
Screening	x		x				
Randomization 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 Stategies (CISS), Quality of life (WHOQOL), Percieved 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**

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Competing interests

Lars Vedel Kessing (LVK) has been a consultant for Bristol-Myers Squibb, Eli Lilly, Lundbeck, AstraZenica, Pfizer, Wyeth and Servier. Maj Vinberg (MV) has been a consultant for Eli Lilly, Lundbeck, AstraZenica and Servier. Ellen Margrethe Christensen has been a consultant for Eli Lilly, AstraZenica, Servier, Bristol-Myers Squibb, Lundbeck and Medilink. Maria Faurholt-Jepsen (MFJ) has been a consultant for Eli Lilly. Mads Frost (MF) and Jakob E. Bardram (JB) has no competing interests.

Authors' contributions

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

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Daily electronic self-monitoring of subjective and objective symptoms in bipolar disorder- The MONARCA trial protocol~~project~~

(MONitoring, treAtment and pRediCtion of bipolAr disorder episodes)-

A randomised controlled single-blind trial

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Wordcount: 4507

Abstract:

Introduction~~Background~~

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 randomized 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 is~~was~~ tested in a parallel-group single-blind randomized controlled trial so far including 78 patients suffering from bipolar disorder age 18-60 years are allocated to using a Smartphone with the MONARCA application (intervention group) or to using a cell phone without the application (placebo group) during a 6 months study period. The study ~~was~~is carried out from September 2011. The outcomes are~~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~~Results~~

Recruitment is ongoing.

Ethics

Ethical permission has been obtained.

Dissemination

Both positive, neutral and negative findings of the study will be publised.

~~*Discussion*~~

~~The trial used a pragmatic naturalistic design. If the Smartphone application is proved effective, it could be a practical and inexpensive way to improve outcome in bipolar disorder.~~

~~Trial r~~Registration details

The trial ~~was~~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~~was~~ registered at ClinicalTrials.gov as NCT01446406.

~~*Trial status and funding*~~

~~The trial is still recruiting patients. The study was funded by The EU, 7-th Frame Program and Mental Health Services, Copenhagen, Denmark.~~

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 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 to previous psychosocial function and the prevalence of cognitive disturbances is prevalent also 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 significant by treatment with lithium or other mood stabilizers (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). 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 organizational shift in paradigm from inpatient to outpatient treatment in health care, and in Bipolar Disorder there is an emerging shift in illness paradigm from focus on mood episodes to focus on the inter-episodic mood instability (16). However, current monitoring of bipolar disorder illness activity is based on identification and analysis of mood episodes at different intervals of time, often at 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 providers can intervene shortly after prodromal symptoms appear (17). However, the used electronic devises have been rather simple not including a bi-directional feedback loop between patients and providers and without

electronic data on “objective” measures of the affective psychopathology. It has never been tested in a randomized trial whether 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 testinged in a randomized controlled trial (RCT) the software for Android Smartphones to monitor the subjective and objective activities of bipolar disorder alongside with treatment adherence in a bi-directional feedback loop between patients and providers. The software system includes 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; 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) predict switch to hypomania (19,23,24). Similarly, social activity (25), i.e., engaging in relations to others, as well as physical activity (26,27) represent 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 randomized 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 CONSORT statement (CONsolidated Standards Of Reporting Trials) and SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) (28–30).

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

Trial design and study organization

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

Participants and setting

All patients are~~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 out-patient 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 health care when a diagnosis of a single mania or bipolar disorder is made for the first

time (31) or if occurrence of treatment resistance, i.e. 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 comprised combined psychopharmacological treatment and supporting therapy for a two year period.

Bipolar patients are~~were~~ referred to the clinic after first, second or third admission and asked to participate after initial assessment by a psychiatrist. Following referral to the clinic the clinicians ma~~d~~ke the diagnosis of bipolar disorder and subsequently introduce~~d~~ the MONARCA study to all patients except for those who are~~were~~ either pregnant, older than 60 years or have~~had~~ 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 18-60 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 none of the exclusion criteria are~~were~~ enrolled in the study ~~(Figure 1)~~.

Study procedure

Following referral to the MONARCA trial potential participants are~~were~~ screened and if they meet the criteria for participating in the trial they are~~were~~ included. Following inclusion in the trial a baseline assessment on all patients are~~were~~ done **(Table 1).** Immediately after this baseline assessment the study nurse g~~o~~et the allocation envelope (see page 10-13) and patients meet with

her and arewere randomized to receive either an intervention MONARCA Smartphone or a placebo MONARCA Smartphone for the six months study period.

Interventions

All patients receivesd 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 iswas used and all patients receivesds a Smartphone free of charge for the six months study period. The placebo group hasds to use the MONARCA Smartphone for normal communicative purposes and the intervention group hasds to use the application for self-monitoring once a day, every day, for six months.

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 has been used for four years. Based on an interactive process between four patients suffering from bipolar disorder, 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 of bipolar disorder prior to this RCT (Figure 2-5). During this interactive user-centered design process, the system was developed and the items to monitor and corresponding scoring system selected. Subsequently, the application was tested in a pilot trial with 12 patients for three months to test the usability, 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 hereafter the system was "locked" into a final version to be tested in the present trial.

Subjective items for monitoring in the active intervention group

The patients in the active intervention group entersed the following subjective items every evening: mood (scored from depressive to manic: –3, -2, -1, 0, +1, +2, +3), sleep duration (number of hours per night, measured in half-hour intervals), medicine (taken as prescribed: yes, no, if changes the patient iswas asked to specify these), activity (scored on a scale of -3, -2, -1, 0, 1, 2, 3), irritability (yes or no), mixed mood (yes or no), cognitive problems (yes or no), alcohol consumption (number of units per day), stress (scored on a scale of 0, 1, 2, 3, 4, 5), menstruation for women (yes or no)and individualized early warning signs (yes or no). Patients arewere prompted by a reminder in the Smartphone to evaluate these items every evening at a chosen time. After midnight the entered data iswas "locked" and further changes could notcannot be made. If the patients forgoet to evaluate the subjective items it iswas possible to retrospectively enter data for two days. It iswas then noted in the system that the data iswas collected retrospectively. Screenshots from the software can be seen from Figure 2-5. A user's guide for the MONARCA system iswas developed and handed out to all patients in the intervention group (can be obtained by contact to the author).

Objective parameters monitored in both the intervention and placebo arm

All the Smartphones in the study automatically collectsed objective data every day for the intervention group as well as the placebo group. The following objective items iswas chosen: speech duration (minutes of speech per 24 hours 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 hours and physical activity measured by the accelerometer installed in the Smartphones as well as amount of physical movement measured through the accelerometer in the Smartphone (sampled every five minutes). 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 iswas assigned to the patients allocated to the active intervention arm of the MONARCA study. She monitorsed on a daily basis all self-reported subjective electronic patient data and when these data suggestsed upcoming or deterioration of depressive or manic symptoms she contactsed the patients by text

messages, telephone or e-mail as part of the feedback loop during the entire period of this study (see later).

Patients allocated to the placebo arm arewere similarly assigned a nurse (other than HSN, but similarly experienced within bipolar disorder) on clinical indication as part of the standard treatment in the clinic, e.g. when upcoming or deterioration of depressive or manic symptoms, but this nurse doesid 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 iswas set up on a server and the patient canould connect to the homepage using secure codes. By giving informed consent to participate in the MONARCA trial patients allowsed clinicians to connect to the homepage. The homepage presentsed all the monitored items graphically.

A standard of scoring thresholds on the subjectively monitored items for when the study nurse should contact the patients iswas made. For example the patients should be contacted if; the patients registersed ≥ -2 or+ 2 in mood for two days, if changes in sleep of one hour more or less for three days, if medication iswas not taken or changed for more than two days, if the activity level iswas registered ≥ -2 or+ 2 for two days, if mixed mood iswas registered for more than three days and if alcohol intake iswas > 2 units for more than three days (full version of standard scoring thresholds can be obtained from the authors upon request). These thresholds arewere individualized for every patient within the first four weeks of the trial. The study nurse reviewsed the monitored data for all of the patients in the intervention group every day and in case of signs of bipolar disorder instability she contactsed the patient. The patients canould 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 four weeks, the patient and study nurse -in collaboration with the clinicians, and relatives(if accepted by the patient) agreesd on a concordance status in 1) his/her most important items for identifying prodromal symptoms of mania (e.g. sleep or alcohol consumption) as well as depression (e.g. social activity) 2) the threshold for future signal warnings of prodromal symptoms (e.g. sleepts one hour less than the

average monitored historic sleep time for three consecutive nights, hads been drinking alcohol for three consecutive days, doesid not call anyone on the Smartphone for four consecutive days, doesid not take medication as prescribed for three consecutive days, etc.) and 3) actions to be taken (e.g. contact the caregiver within three days following the alarm signal and if he doesid not, the caregiver contacted the patient for clinical evaluation and intervention, e.g. increase the dose of the mood stabilizer).

Assessments

All assessments arewere done by two physicians (MFJ or ASJ) whom arewere not involved in treatment of the patients. The patients arewere enrolled in the trial for a six months study period and is assessed every month (Table 1). The bipolar diagnosis iswas confirmed by SCAN interview before inclusion of the patient (32). Every month the affective symptoms arewere clinically rated using HDRS (33) and YMRS (34). The following questionnaires arewere full filled every month when visiting the researcher; Psychosocial Functioning (Functioning Assessment Short Test, FAST) (36), Cohens's Percieved 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 patients prescribed medicine (mood stabilizers, antipsychotics, antidepressants) arewere taken at baseline, after 3 months and 6 months. Cognitive function according to the Screen for Cognitive Impairment in Psychiatry (SCIP-S) (50,51) iswas assessed at baseline, after 3 months and after 6 months.

Outcomes

Primary outcomes:

Clinically rated affective symptoms based on HDRS- 17 items (33) and respectively YMRS (34) assessed every month for six months (Table 1).

Secondary outcomes:

Psychosocial Functioning (Functioning Assessment Short Test, FAST) (36), Cohens's Percieved 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 are~~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 stabilizers, antipsychotics, antidepressants). These are~~were~~ measured at baseline, after 3 months and 6 months (Table 1).

No changes in trial outcomes are~~were~~ made after trial commencement.

Sample size

The statistical power and sample size was calculated using http://stat.ubc.ca/~rollin/stats/ssize/n2.html. The primary outcome is differences in the level of affective symptoms based on HDRS score and YMRS score respectively. The clinical relevant difference is defined as minimum of 3 scores and the standard deviation was set to 4 with a mean score of 10 versus 7 in the two groups. The statistical power to detect a 3 score difference in the areas under the curves between the intervention and the control group on the HDRS score or the YMRS score, respectively, is 80% with alpha = 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~~was~~ estimated to be around 25%.

Randomization

Sequence generation

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

Allocation concealment and implementation

The allocation sequence is~~was~~ concealed form the researcher (MFJ and ASJ) enrolling and assessing patients. Allocation is~~was~~ concealed in numbered, opaque and sealed envelopes stored in a securely locked cabinet by a secretary until the moment of randomization. Allocation is~~was~~ identified by the letter A or B written on the paper in the envelopes and this indicate~~d~~s the type of intervention. The translation of allocation as A or B was made and known only by LVK and the study nurse. A paper with this translation ~~was~~ is kept in a securely locked cabinet unknown to others than LVK. The secretary gi~~a~~ves the envelope to the study nurse. Corresponding envelopes are~~were~~ opened only after all baseline assessment is~~was~~ done and patients name is~~was~~ written on the envelope. The study nurse assigns~~ed~~ patients to their allocation of intervention.

Blinding

Due to the type of intervention in this trial, patients and the study nurse are~~were~~ aware of the allocation arm. The researchers responsible for outcome assessments (MFJ and ASJ) and data analysis (MFJ) are~~were~~ kept blinded to allocation at all times during the trial. The trial is therefore single-blinded. The study nurse doesi~~d~~ not collect any kind of outcome measures. All patients are~~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 patients hands are~~were~~ minimized since all patients receive~~sd~~ 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 randomized patients will be collected until dropout or end of study period. The outcome is changes in affective symptoms measured as HDRS and YMRS during the six months study period. We will employ a linear mixed effects model with random intercept for each participant. Differences between outcomes of the interventions during the six months study period will be analyzed, firstly unadjusted and then adjusted for age, previously psychiatric hospitalizations (yes/no) and sex, if these variables presents with a p-value≤ 0.1 in univariate analyses. Analysis will be done with intention-to-treat (ITT). The statistical threshold for significance is $p \leq 0.05$ (2-tailed).

Ethical considerations

Ethical permission for the MONARCA study has been~~was~~ 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. Both positive, neutral and negative findings of the study will be published according to the CONSORT guidelines (28). All electronic monitored data is stored at a secure server at Concern IT, Capital Region, Copenhagen, Denmark (I-suite number RHP-2011-03).

All potential participants are~~were~~ invited to be informed about the trial and the information is~~was~~ given in a quiet and undisturbed office. All information is~~was~~ presented in both written and verbal form and participants can~~ould~~ bring a friend or relative to the introduction conversation. Participants are~~were~~ informed that participation is~~was~~ voluntary and that consent can~~ould~~ be withdrawn at any time of the study without this giving any consequences for future treatment possibilities. All participating patients sign~~sed~~ a consent form and g~~o~~et a copy of this and their rights as a participant in clinical trials. All Smartphones are~~were~~ provided by the project and

economic costs from data traffic due to the MONARCA project are refunded. Participants doesid not receive any economic compensation for participating in the MONARCA-trial.

Results

~~Figure 1 presents the flow chart for the trial.~~ Until time at submission a total of 141 patients suffering from Bipolar Disorder has beenwere identified, but 11 of these were over 60 years of age and 7 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 2 were unable to speak Danish. Thus, so far a total of 118 patients has beenwere eligible, but 32 declined to participate, 4 were unwilling to use our Smartphone as their primary Smartphone and we could not get contact to 4 patients. Until time at submission participation rate iswas 66.1% and the dropout rate during the six months follow up period iswas 12.8%. Until time at submission a total of 8 patients dropped out at baseline before knowledge of their allocation to intervention and 2 patients dropped out during the 6 months study period.

Discussion

This is the first randomized 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 iswas 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~~was~~ 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 e.g. the effect of subjective self-monitoring in 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 receivesd the same Smartphone but without the MONARCA software system, i.e., a placebo Smartphone. Patients in the placebo group doesid not make any subjective electronic self-monitoring of symptoms or behavior and they arewere not monitored with the feedback loop, but their illness activity is~~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 followsed 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 health care 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 six months period. Anyhow, as this is the first trial to investigate electronic monitoring we arewere 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 for the patients in a future revised MONARCA application.

Generalizability

The study is~~was~~ carried out in a tertiary specialized mood disorder clinic. However, the trial has~~d~~ a pragmatic design with few exclusion criteria and few patients are~~were~~ excluded ~~(see Figure 1, flow chart)~~. The majority of patients entering the trial are~~were~~ 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 findings of the trial can be generalized to patients with bipolar disorder in general.

Perspectives

If the Smartphone self-monitoring system is proved effective in preventing mood symptoms and improving psychosocial functioning and quality of life in the present study there will be basis for extending the use of the system to treatment of patients with bipolar disorder in clinical practice in other clinical settings (e.g. community psychiatric centres) and in 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.

Tabel 12 Investigation overview- MONARCA RCT

	SCAN	Questionnaires*	Rating scales**	Blood analysis***	Urine analysis****	Saliva analysis*****	SCIP
Screening	x		x				
Randomization 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 Stategies (CISS), Quality of life (WHOQOL), Percieved 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**

Acknowledgement

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Competing interests

Lars Vedel Kessing (LVK) has been a consultant for Bristol-Myers Squibb, Eli Lilly, Lundbeck, AstraZenica, Pfizer, Wyeth and Servier. Maj Vinberg (MV) has been a consultant for Eli Lilly, Lundbeck, AstraZenica and Servier. Ellen Margrethe Christensen has been a consultant for Eli Lilly, AstraZenica, Servier, Bristol-Myers Squibb, Lundbeck and Medilink. Maria Faurholt-Jepsen (MFJ) has been a consultant for Eli Lilly. Mads Frost (MF) and Jakob E. Bardram (JB) has no competing interests.

Authors' contributions

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

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry Page 3 and 14
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support Page 3 and 19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors Page 1 and 19
	5b	Name and contact information for the trial sponsor Page 19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities Page 19
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention Page 4
	6b	Explanation for choice of comparators Page 5
Objectives	7	Specific objectives or hypotheses Page 5

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) Page 6
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained Page 6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) Page 7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered Page 8-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) Page 10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial Page 6 and 8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended Page 11-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) Table 1 page 18
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations Page 12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size Page 6-7
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions Page 12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned Page 13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions Page 13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how Page 13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial Page 13
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol Page 7 and 11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol Data entry has not yet begun. Data entry page 13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol Page 13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) Page 14

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial No interim analyses will be carried out.
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval Page 14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) No protocol modifications will be done
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Page 14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable Not relevant
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site Page 19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation Page 14

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions No publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers Not relevant. Writers are the authors of the protocol.
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	12
Sample size	7a	How sample size was determined	12
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	12
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	12
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	13
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	12
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	13

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	13-14
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	13-14
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	15
	13b	For each group, losses and exclusions after randomisation, together with reasons	15
Recruitment	14a	Dates defining the periods of recruitment and follow-up	15
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	15
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	14
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	19

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

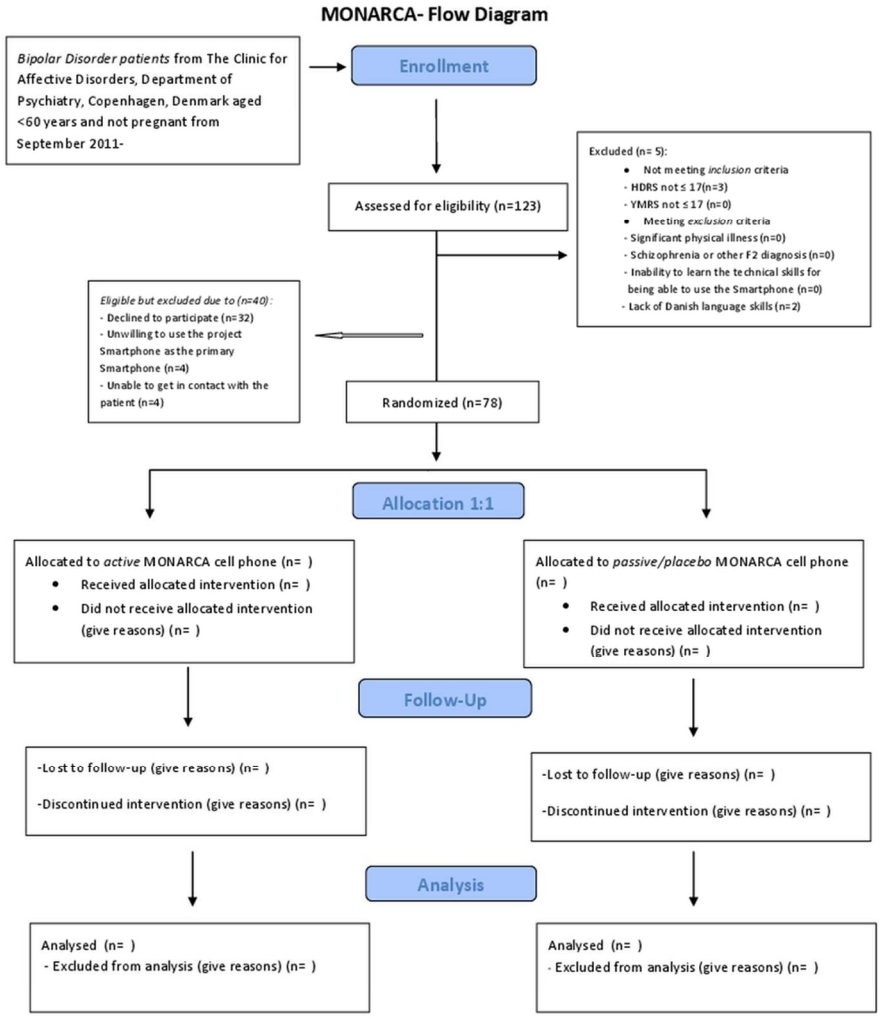

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Figure 2: Frontpage

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Figure 3: Selfassessment

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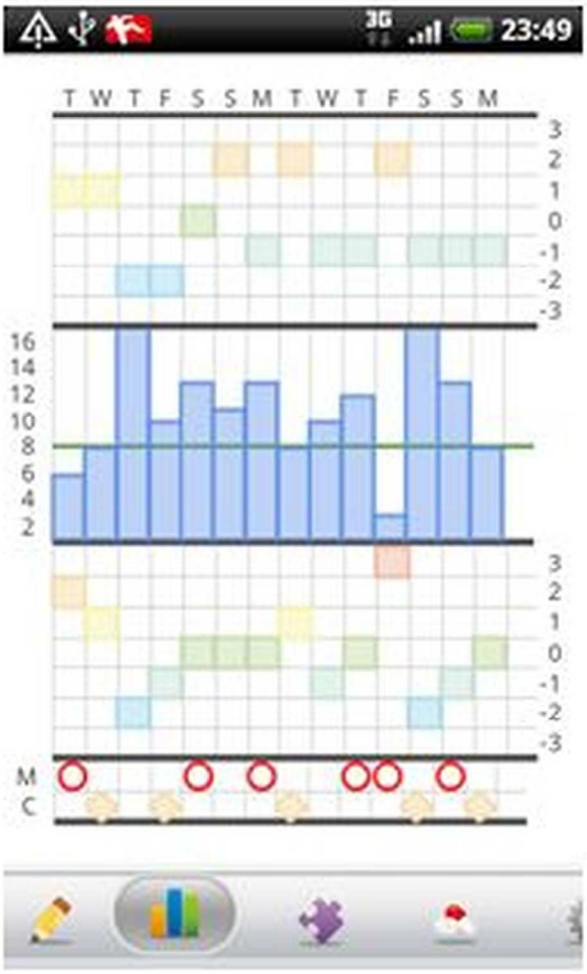

Figure 4: Visualization

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Figure 5: Medication

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