Electronic monitoring in bipolar disorder

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This review has been accepted as a thesis together with twelve previously published papers by University Copenhagen 3th November 2017 and defended on 8th of December 2017.

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Dan Med J 2018;65(3):B5460

THE 12 ORIGINAL PAPERS ARE

1. Faurholt-Jepsen M, Brage S, Vinberg M, Christensen EM, Knorr U, Jensen HM, Kessing LV. Differences in psychomotor activity in patients suffering from unipolar and bipolar affective disorder in the remitted or mild/moderate depressive state. Journal of Affective Disorders 2012 Dec 10;141(2-3):457-63.
2. Faurholt-Jepsen M, Vinberg M, Christensen EM, Frost M, Bardram J, Kessing LV. 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. BMJ Open 2013 Jul 24;3(7).
3. Faurholt-Jepsen M, Frost M, Vinberg M, Christensen EM, Bardram JE, Kessing LV. Smartphone data as objective measures of bipolar disorder symptoms. Psychiatry Research 2014 Jun 30;217(1-2):124-7.
4. Faurholt-Jepsen M, Frost M, Ritz C, Christensen EM, Jacoby AS, Mikkelsen RL, Knorr U, Bardram JE, Vinberg M, Kessing LV. Daily electronic self-monitoring in bipolar disorder using smartphones- the MONARCA I trial: a randomized, placebo-controlled, single-blind, parallel group trial. Psychological Medicine 2015 Jul 29: 1-14.
5. Faurholt-Jepsen M, Ritz C, Frost M, Mikkelsen RL, Christensen EM, Bardram J, Vinberg M, Kessing LV. Mood instability in bipolar disorder type I versus type II- continuous daily electronic self-monitoring of illness activity using smartphones. Journal of Affective Disorders 2015, Nov. 1; 186:342-9.
6. Faurholt-Jepsen M, Vinberg M, Frost M, Christensen EM, Bardram JE, Kessing LV. Smartphone data as an electronic biomarker of illness activity in bipolar disorder. Bipolar Disorders 2015 Nov;17(7):715-28.
7. Faurholt-Jepsen M, Munkholm K, Frost M, Bardram JE, Kessing LV. Electronic self-monitoring of mood using IT platforms in adult patients with bipolar disorder: A systematic review of the validity and evidence. BMC Psychiatry 2016 Jan 15;16:7.*
8. Faurholt-Jepsen M, Brage S, Vinberg M, Kessing LV. State related differences in the level of psychomotor activity in patients with bipolar disorder- Continuous heart rate and movement monitoring. Psychiatry Research 2016 Mar 30;237:166-74.
9. Faurholt-Jepsen M, Vinberg M, Frost M, Debel S, Christensen EM, Bardram JE, Kessing LV. Behavioral activities collected through smartphones and the association with illness activity in bipolar disorder. International Journal of Methods in Psychiatric Research 2016 Apr 1. doi: 10.1002/mpr.1502.
10. Faurholt-Jepsen M, Busk J, Frost M, Vinberg M, Christensen EM, Winther O, Bardram JE, Kessing LV. Voice analysis as an objective marker in bipolar disorder. Translational Psychiatry (2016) 6, e856; doi:10.1038/tp.2016.123.
11. Faurholt-Jepsen M, Brage S, Kessing LV, Munkholm K. State-related differences in heart rate variability in bipolar disorder. Journal of Psychiatric Research 2017 Jan, 84, 169-173 *
12. Faurholt-Jepsen M, Kessing LV, Munkholm K. Heart rate variability in bipolar disorder- a systematic review and meta-analysis. Neuroscience and Biobehavioral Reviews, In press, Accepted manuscript; doi: 10.1016/j.neubiorev.2016.12.007.

* Supplementary information for the article can be retrived from the publisher's website.

READER'S GUIDE

As smartphone-based and heart rate-based electronic monitoring are rather new areas of research in bipolar disorder, few data have been published prior to the studies performed by the author. Consequently, this dissertation is predominantly based on studies conducted by the author.

The dissertation is based on a review of the literature, including 12 articles on data from four original studies and two systematic reviews (one including meta-analyses) conducted by the author concerning electronic monitoring in bipolar disorder.

The Background section describes the overall background and aims of the dissertation and is divided into two sections according to monitoring method: i.e. smartphone-based electronic monitoring and heart rate-based electronic monitoring. The background section is followed by a brief presentation of the author's work. A discussion and review of the literature follows each of the two sections concerning electronic monitoring in bipolar disorder.

Lastly, an overall discussion and conclusion followed by a section on clinical implications and future perspectives are presented.

The dissertation is divided into two main sections, as follows:

1: Smartphone-based electronic monitoring in bipolar disorder
Author's contribution described in articles II-VII, IX and X (1–8).

2: Electronic monitoring of psychomotor activity and heart rate in bipolar disorder
Author's contribution described in articles I, VIII, XI and XII (9–12).

Further details regarding the methodologies used, the results and a discussion of the findings from the individual studies by the author can be found in the articles included in the dissertation.

TERMINOLOGY
Electronic mental health: Mental health services provided through an electronic medium (E-mental health).
Telepsychiatry: Mental health services delivered over distances via videoconferencing (virtual face-to-face).
Mobile mental health: Mental health services delivered via electronic mobile devices (mHealth).
Ecological momentary assessments: Methods used to collect assessments of an individual's real-time states, sampled repeatedly over time and in naturalistic settings.
Psychomotor activity: Consists of multiple domains, such as gross motor activity, body movements, speech and motor response time.
Heart rate variability: Reflects the oscillation in the time intervals between consecutive heartbeats.
Application: A software program designed to run on mobile devices such as smartphones and tablet computers.
The MONARCA system: A smartphone-based electronic monitoring system for patients with bipolar disorder that includes a bidirectional feedback loop between patients and mental health care providers.
Smartphone-based electronic self-monitored data: Self-assessed electronic data regarding depressive and manic symptoms collected using the MONARCA system for smartphones.
Smartphone-based electronic automatically generated data: Electronic data on different activities and behavioral aspects collected automatically by smartphones.

ABBREVIATIONS
RCT: Randomized controlled trial
AEE: Activity energy expenditure (J/min/day)
ACC: Acceleration (m/s2)
BMI: Body mass index (kg/m2)
HRV: Heart rate variability
BPM: Beats per minute
PDA: Personal digital assistant

BACKGROUND
Bipolar disorder is characterized by changes in mood with episodes of depression, (hypo)mania and mixed episodes with intervening periods of euthymia (13). It is differentiated by the duration and severity of mood elevations into bipolar disorder type I and bipolar disorder type II (14). The changes in mood that characterize bipolar disorder are accompanied by observable shifts in energy, activity, sleep and other behavioral aspects that may be quantified (14,15).

Bipolar disorder is a common and complex illness with an estimated prevalence of 1-2%, and it is one of the most important causes of disability worldwide (16,17). Bipolar disorder is associated with an elevated risk of mortality due to suicide and medical comorbidities such as cardiovascular disease and diabetes (18–20), and among people with bipolar disorder, life expectancy is decreased 8 to 12 years (21,22). The disorder is associated with a high risk of relapse and hospitalization, and on average, the risk of relapse increases with the number of previous affective episodes (23–25). Despite the separation of bipolar disorder into type I and II, the clinical presentation and course of illness in bipolar disorder are complex and heterogeneous both cross-sectionally and longitudinally (26). Patients with bipolar disorder type II are thought to spend more time depressed and less time euthymic than patients with bipolar disorder type I (27–34).

In clinical practice, there are major challenges in diagnosing and treating bipolar disorder (35). Regarding clinical diagnosis, patients with bipolar disorder are often misdiagnosed, and the correct diagnosed can be delayed for several years after illness onset (36–38). Currently, due to the lack of objective tests, the diagnostic process and the clinical assessment of the severity of depressive and manic symptoms relies on subjective information, clinical evaluation and rating scales (13). This subjective evaluation involves a risk of patient recall bias, other recall distortions, decreased illness insight (mainly during affective episodes) and individual observer bias (39–43). Furthermore, when patients present in a remitted or depressive state, it may be difficult for clinicians to determine whether the patients suffer from unipolar disorder or from bipolar disorder. Patients may not recall prior (hypo)manic episodes, and clinicians may not be sufficiently observant of the prior course of illness (44). In this way, a bipolar disorder diagnosis could be overlooked. Furthermore, study findings may be unreliable when rating scales are used as outcome measures because of methodological issues such as the nonblinding of raters and patients, differences in rater experiences, missed visits for outcome assessments, baseline score inflation and recall bias (45,46). Thus, these issues call for less biased and more objective markers of bipolar disorder.

Regarding treatment, it is well known from randomized controlled trials (RCT) that the risk of new affective episodes can be reduced by psychopharmacological treatment with lithium or other mood stabilizers (47,48). Furthermore, the prophylactic effect of psychopharmacological treatment may be enhanced by psychological interventions, including psychoeducation (49–52). However, naturalistic follow-up studies suggest that the progressive development of bipolar disorder is not prevented with the present treatment options (24,25,53,54). Major reasons for the insufficient effect of treatment options in clinical practice include decreased adherence to psychopharmacological treatment (55,56) and delayed intervention for prodromal depressive and manic symptoms (57–59).

CLINICAL FEATURES OF BIPOLAR DISORDER THAT CAN BE MEASURED ELECTRONICALLY
Core clinical features of bipolar disorder that have been addressed in the literature include changes in psychomotor activity and behavioral activities (15,60–64). Psychomotor activity consists of multiple domains, such as gross motor activity, body movements, speech and motor response time (64). Psychomotor retardation during depression and increased motor activity during mania were described in an eighteen-century monograph by Andrés Piquer-Arrufat (65,66) and in more recent scientific articles (15,60,61,63,64,67–72). However, in most of the previous studies, psychomotor activity was assessed using clinical assessments or questionnaires, and the studies showed inconclusive results (63,67–69,73,74). Accelerometers were first used to quan-

tify human movement in the early 1950s (75) and have been used to assess psychomotor activity in small case-control studies within bipolar disorder research with divergent findings (61,76–80).

Studies have shown that changes in the level of engagement in social and communicative activities (60,81–83) and in speech activity (84–87) represent central aspects of illness activity in bipolar disorder. Studies analyzing spoken language in affective disorders date back as early as 1938 (88). Alterations in psychomotor and speech activity are central features in the clinical presentation of bipolar disorder and are included in standardized clinical rating scales measuring the severity of depressive and manic symptoms.

Over the last decade, there has been a gradual paradigm shift from a focus on affective episodes to an increasing focus on interepisodic mood instability (26,89–91). A large proportion of patients with bipolar disorder experience subsyndromal mood swings on a daily basis (28,57,90,92,92,93), and mood instability at a subclinical level is associated with impaired global functioning and a high risk of relapse (89,92,94,95). Consequently, mood instability has been suggested as a treatment target in its own right and as a more sensitive measure of outcome in RCTs than, for example, the relapse or recurrence of depressive or manic episodes (26,32,90,96). However, despite the increasing focus on mood instability, the longitudinal patterns of mood instability and possible differences in mood instability between bipolar disorder type I and II are poorly understood as mood instability is difficult to assess validly because it is influenced by factors such as decreased illness insight and recall distortions (89,90,94,97–99). The continuous long-term monitoring and assessment of mood instability and other features that reflect illness activity may be clinically advantageous because they would allow continuous detailed characterization of the course of illness and early treatment intervention for subsyndromal depressive and manic symptoms. Combining fine-grained data with advanced mathematical models would further allow for the characterization of the non-linear course of illness.

The central autonomic network (100,101) and the brain-heart axis (102) reflect the link between the central nervous system and the cardiovascular system (101,103) via the autonomic nervous system. Both a decreased risk of sudden cardiac death and healthy life expectancy have been suggested to depend on intact autonomic functioning (104). In bipolar disorder, several lines of evidence indicate the presence of autonomic dysfunction and central autonomic disturbances (105–107). Heart rate variability (HRV) describes the oscillation in the time intervals between consecutive heartbeats and is a validated measure of balance in the activity of the autonomic nervous system (108–110). In recent years, HRV has been described as reduced in individuals with bipolar disorder compared with healthy control individuals (111–121). In addition, an increased risk of cardiovascular disease is found in bipolar disorder (122), and it is possible that a reduced HRV in bipolar disorder could predict sudden cardiac death in this population.

Biological markers, or biomarkers, refer to "characteristics that are objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic response to a therapeutic intervention" (123). Electronic monitoring of features of bipolar disorder may represent a type of electronic marker for bipolar disorder.

The present dissertation concerns the use of electronic monitoring in bipolar disorder as a marker of state and trait and treatment intervention.

ELECTRONIC MONITORING IN BIPOLAR DISORDER

Electronic devices for collecting self-assessed features, such as mood, activity and medicine intake (32,124–128), and automatically generated features, such as heart rate, movement and other behavioral aspects (15,61,79,83,114,129), have been used in bipolar disorder research. However, most previous studies collected data within laboratory or hospital settings, included small sample sizes of patients who were followed for short periods, or did not monitor both self-assessed features and automatically generated features.

With electronic devices, detailed data regarding complex psychopathological aspects of bipolar disorder that otherwise would be difficult to collect can be evaluated over prolonged time-periods, in naturalistic settings and in a relatively unobtrusive manner. Moreover, data collected using electronic devices could represent candidate markers of diagnosis and illness activity in bipolar disorder and further could allow early intervention for prodromal symptoms outside clinical settings.

Prior to the work by the author, no studies had investigated whether the severity of smartphone-based electronically self-monitored symptoms or electronic automatically generated features correlate with scores on the standardized clinical rating scales that are currently used as the gold standards to assess the severity of depressive and manic symptoms. Furthermore, no studies had investigated whether these electronic automatically generated features could represent diagnostic markers in bipolar disorder. Lastly, the extent to which the use of smartphone-based electronic self-monitoring affects clinically relevant outcomes, and importantly, whether it may in fact have harmful effects, had not been investigated.

SMARTPHONE-BASED ELECTRONIC MONITORING IN BIPOLAR DISORDER

E-health reflects the process of providing health services and health-related communication through an electronic medium, such as the internet or a telephone, and mobile health (mHealth) refers to health services delivered by mobile devices, such as mobile phones, mobile monitoring devices, personal digital assistants (PDAs), and other wireless electronic devices (130). mHealth is a relatively new area within health care, and the use of sensors embedded within mobile monitoring devices could provide enormous opportunities for new areas of research, development and treatment. A report by the World Health Organization in 2011 stated that "the use of mobile and wireless technologies to support the achievement of health objectives (mHealth) has the potential to transform the face of health service delivery across the globe" (130). Furthermore, it has been suggested that mHealth interventions have the potential to minimize the traditional barriers of distance, time and costs (131,132).

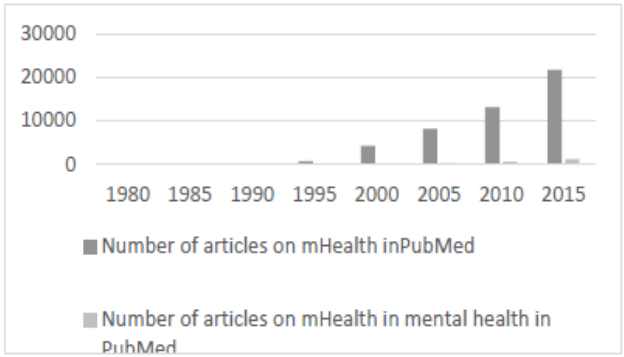
Currently, approximately 1/3 of the world's adult population owns and uses a smartphone, and it has been estimated that by the year 2018, this proportion will increase to 50% (133,134). Data suggest that more than half of smartphone users seek health-related information from their phone, and more recently, the use of sensors embedded within mobile devices to monitor behavioral aspects has provided new areas of research (134,135).

In recent years, the use of mHealth solutions for the management of various medical conditions, such as diabetes, cardiovascular disease, hypertension, asthma, chronic obstructive lung disease, HIV and headache, has been addressed in a large number of studies with varying findings (132,136–146). The potential for

mHealth solutions to transform access to health care and to provide opportunities for early intervention has been emphasized in most of these studies. However, a number of limitations and ethical complications arising from rapid technological developments, including a lack of scientific studies and publications within the area of mHealth, have recently been emphasized (131,147–151).

In parallel with the use of mHealth for medical conditions, electronic mental health (e-mental health) services, mHealth (152,153), and telepsychiatry, referring to mental health services delivered over distances via videoconferencing (virtual face-to-face services) (154) have been used within the mental health field. mHealth aims to improve access to mental health services, and in recent years, there has been a large increase in the interest in and use of mHealth services (130,155–162). The increasing number of articles published on the topic reflects the increase in mHealth services in recent years (163).

Figure 1



Number of mHealth-related articles published per year.

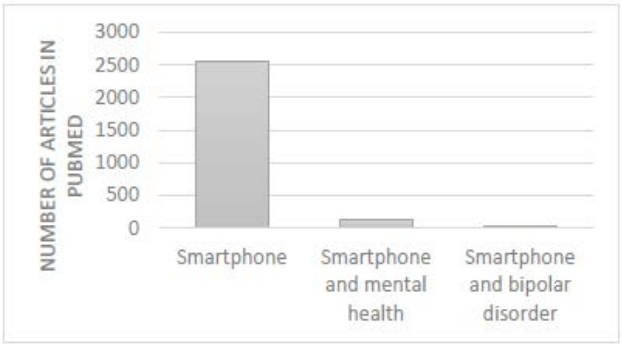
Ecological momentary assessments (EMA) reflect the methods used to collect assessments of individuals' real-time states repeatedly over time and in naturalistic settings (164–166). EMA may minimize recall bias, may be sensitive to daily mood fluctuations, can be performed using smartphones and provides the potential to collect both self-monitored and automatically generated data in an unobtrusive way outside laboratory settings using frequently repeated, fine-grained data collection methods (156,166,167). EMA may be used to reveal dynamic processes, can be integrated with physiological data, can identify context-specific symptoms and allows for interactive feedback loop options. The use of smartphones extends the use of EMA beyond its classical use for self-reports (156,168).

Within bipolar disorder, various paper-based daily mood charting instruments, such as the National Institute of Mental Health LifeChart Method (NIMH-LCM) (169), the Systematic Treatment Enhancement Program (170) and the ChronoSheet (171), have been developed. These types of charting instruments enable the collection of detailed longitudinal information regarding daily mood swings and other symptoms relevant to bipolar disorder when patients are outside the clinical setting, and they are often used in the treatment of bipolar disorder. Paper-based mood charting instruments can be viewed as a facilitating tool to help patients to gain illness insight, facilitate patient empowerment, and teach patients to recognize early warning signs of the recurrence of mania, depression and mixed states. However, several problems regarding paper-based mood charting instruments have been addressed, such as an error-prone entry process, low compliance and potential recall bias when filling in data retrospectively, i.e. when patients complete batches of daily ratings at a single time (124,172). Recently, different types of electronic self-monitoring instruments using computers (124,127,173,174), personal digital assistants (PDAs) (126,175–177), text messages (32,155), and smartphone applications (3,128,178) have been developed and described in the literature, and a large number of commercial smartphone applications are available in the App Store and Google Play (179,180). Smartphones are readily available and unobtrusive devices that enable the continuous collection of various types of self-monitored and automatically generated data reflecting illness activity that would not be measured otherwise. Furthermore, smartphones can deliver treatment interventions outside clinical settings.

Strikingly, few smartphone applications have been evaluated in scientific studies (150,156). Reviews of smartphone applications for bipolar disorder reported that only 22% addressed privacy issues, only 15% used best practice guidelines regarding treatment advice and only 31% cited their information source (181,182). Prior to the work by the author, no studies combining the use of smartphone-based electronic self-monitoring and smartphone-based electronic automatically generated data in bipolar disorder had been published. In addition, no studies investigating the possible harmful effects of smartphone-based electronic monitoring had been published.

Thus, questions regarding the associations between smartphone data and clinically rated depressive and manic symptoms, the safety of smartphone use and evidence supporting the use of smartphones as treatment interventions were unanswered.

Figure 2



Number of smartphone-related articles published per year.

ELECTRONIC MONITORING OF PSYCHOMOTOR ACTIVITY AND HEART RATE IN BIPOLAR DISORDER

Central to the diagnosis and assessment of affective state in mood disorders are alterations in psychomotor activity (14,183,184). The ability to discriminate between bipolar disorder and unipolar disorder is crucial as the two disorders have different psychopharmacological treatments, courses of illness and outcomes (23,25,185). Differences in psychomotor activity during depression and mania have been described (14,15,72,77), and unbiased automatically generated assessments of changes in affective states and severity could be useful in the diagnosis and monitoring of the course of illness in bipolar disorder. Prior studies investigating psychomotor activity are based on clinical assessments or questionnaires and have yielded inconclusive results

(63,67–69). Furthermore, the studies included small samples of hospitalized patients in cross-sectional designs and used worn accelerometers that did not collect heart rate data (61,76–78,80). Thus, it was not possible to estimate differences in energy expenditure and other physiological constructs, such as heart rate, between disorders and affective states.

The gold standard method for measuring energy expenditure during free-living circumstances is the doubly labelled water technique (186,187). However, this method cannot quantify subcomponents of activity patterns, such as activity energy expenditure, hourly variation of movement, intensity etc. Prior to the work by the author, no study of bipolar disorder had combined accelerometry and heart rate measurement, a method that has been suggested to offer greater measurement precision (188). Psychomotor activity may be correlated with other mood symptoms (64), but studies comparing psychomotor activity in unipolar disorder and bipolar disorder have not adjusted their analyses for differences in the severity of mood symptoms. More specifically, results from some studies suggest that bipolar depression is more likely than unipolar depression to manifest with psychomotor retardation and other atypical symptoms (15,60,62,189). Additionally, psychomotor inhibition in unipolar disorder has been associated with an increased risk of a later bipolar course of illness (190). Concordantly, although the evidence is poor, reviews suggest that psychomotor retardation is more prevalent in bipolar disorder and may be a signature symptom (14,62,129).

The heart rate is continuously modulated through complex interactions between both branches of the autonomic nervous system: the sympathetic nervous system and vagal systems (191,192). Since the heart rate and autonomic nervous system activity are nonlinearly related, changes in sympathetic activity or vagal tone alone have the potential to alter the dynamic heart rate response to stimulation from either branch of the system (191). HRV reflects the oscillation in the time intervals between consecutive heartbeats and is a validated measure of the balance of the autonomic nervous system activity (108–110). The ability of the nervous system and heart rate to adapt to environmental changes is crucial. Healthy individuals exhibit a high degree of HRV, and both a decreased risk of sudden cardiac death and healthy life expectancy have been suggested to depend on intact autonomic functioning (104). Further, reduced HRV has been found to be a strong and independent predictor of mortality after an acute myocardial infarction and to predict an adverse prognosis in the general population and (193–195). In bipolar disorder, several lines of evidence implicate autonomous dysfunction in bipolar disorder (105,107). HRV can be assessed using readily available non-invasive methods. In bipolar disorder research, individual studies have found reduced HRV during different affective states in patients with bipolar disorder compared with healthy control individuals (112–119,121,196,197). Thus, HRV may represent a potential objective candidate marker for differentiating between patients with bipolar disorder and healthy control individuals. Previous review articles on HRV have investigated differences in HRV in a variety of psychiatric disorders without separate analyses for bipolar disorder and have not addressed factors responsible for between-study heterogeneity (198–201). Furthermore, confounding issues and the quality of included studies have not been evaluated systematically, and meta-analyses of patients with bipolar disorder in different affective states have not been performed. Extended case series have suggested intra-individual changes in HRV between affective states (202–206); however, no previous study has investigated differences in HRV between affective states using a longitudinal design with repeated measurements and compared the data between groups of patients. Thus, whether HRV could serve as an objective state marker discriminating between affective states in bipolar disorder has only been sparingly investigated.

Measuring psychomotor activity and HRV with electronic devices that can collect data automatically over the long term and in naturalistic settings may be useful for diagnosing and assessing state in bipolar disorder, but no studies of such measurements had been conducted prior to the work by the author.

SUMMARY

Continuous electronic monitoring of clinical features that are central to bipolar disorder could represent markers of diagnosis and affective state and further allow for early diagnosis, monitoring and treatment. With the use of electronic devices for monitoring, detailed fine-grained data can be collected unobtrusively over the long term in naturalistic settings. Prior to the work by the author, no investigations had examined whether the severity of smartphone-based electronic self-monitored symptoms and electronic automatically generated features correlate with scores on the standardized clinical rating scales that are currently the gold standards for assessing the severity of depressive and manic symptoms in bipolar disorder. Furthermore, few published studies had examined whether electronic automatically generated features could potentially represent markers of bipolar disorder. Lastly, the extent to which the use of smartphone-based electronic self-monitoring affects clinically relevant outcomes and, importantly, whether such monitoring may in fact have harmful effects was unaddressed. RCTs are the methodological standard of excellence in medical research. Prior to the work by the author, no RCTs investigating the effect of electronic self-monitoring had been published.

AIMS OF THE DISSERTATION

The overall aim of the dissertation was to review the literature related to electronic monitoring in bipolar disorder, including the work by the author.

More specifically, the aims were the following:

- To review the literature on **electronic self-monitoring** in bipolar disorder overall and with respect to 1) its correlation with clinically rated depressive and manic symptoms; 2) mood instability in bipolar disorder type I versus bipolar disorder type II; 3) its effect on depressive and manic symptoms; and 4) the advantages and limitations of the studies.

- To review the literature on **smartphone-based electronic automatically generated data**, e.g. behavioral data and voice data, in bipolar disorder with respect to its correlation with clinically rated depressive and manic symptoms and identify the advantages and limitations of the studies.

- To review the literature on **electronic monitoring of psychomotor activity** in bipolar disorder and identify the advantages and limitations of the studies.

- To review the literature on **heart rate variability** in bipolar disorder and identify the advantages and limitations of the studies.

The present dissertation includes data from 1) four original studies conducted by the author, including more than 170 patients with affective disorder and healthy control individuals and more than 700 clinical assessments of depressive and manic symptoms using standardized clinical rating scales, and 2) two systematic reviews (one including meta-analyses).

The results of the individual studies are presented and discussed in relation to prior research within the area. The dissertation is divided in two main sections: 1) smartphone-based electronic monitoring in bipolar disorder; and 2) electronic monitoring of psychomotor activity and heart rate in bipolar disorder. Each section is followed by a discussion section and conclusion. At the end of the dissertation, an overall discussion and conclusion, potential implications and suggestions for future research are presented.

SMARTPHONE-BASED ELECTRONIC MONITORING IN BIPOLAR DISORDER

THE AUTHOR'S WORK

Ethics

All studies were approved by the Regional Ethics Committee of The Capital Region of Denmark (H-2-2011-056) and The Danish Data Protection Agency (2013-41-1710). The studies complied with the Declaration of Helsinki.

The MONARCA studies

In 2010, as part of a European Union 7th Framework Program-funded consortium consisting of partners from five different European countries, a smartphone-based electronic self-monitoring system (the MONitoring, treAtment and pRediCtion of bipolAr disorder episodes system (the MONARCA system)) for patients with bipolar disorder was developed (207). The MONARCA system includes a feedback loop between the patient and mental health care providers and was developed in close collaboration among clinicians, researchers in psychiatry (including the author), IT researchers and patients with bipolar disorder. The adherence, usability and usefulness of the MONARCA system was tested in patients with bipolar disorder in pilot studies by our group (207–209). Overall, the patients reported that the MONARCA system was easy to use and was very helpful and the adherence to self-monitoring was higher with the MONARCA system than with paper-based charts (208).

The MONARCA system includes a smartphone-based electronic self-monitoring part and a clinical feedback loop part. The self-monitoring part of the MONARCA system allows daily electronic self-monitoring of features such as mood, sleep length, medicine intake and activity level to be registered on a smartphone (**Figure 3**). The clinical feedback loop part of the MONARCA system is two-tiered; it includes: 1) a feedback loop in which the electronic self-monitored data are sent to the mental health care providers, allowing a nurse or clinician to contact the patients in case signs of deterioration appear, and 2) a feedback loop in which the self-monitored data are presented graphically to the patients themselves, providing possibilities for increased illness insight, empowerment and understanding. In addition, the MONARCA system allows the collection of smartphone-based electronic automatically generated data using sensors embedded within the smartphone.

We hypothesized that these smartphone-based electronic automatically generated data would reflect changes in social activities, physical activities, speech and other behavioral activities that correlate with illness activity in bipolar disorder.

The initial pilot studies by our group showed high acceptance and usability of the MONARCA system, and adherence to the smartphone-based electronic self-monitoring was higher than adherence to self-monitoring using paper-based charts (207,208). Prior to the work by the author, the associations between smartphone-based electronic self-monitoring and smartphone-based electronic automatically generated data and clinically rated depressive and manic symptoms in bipolar disorder and the effect of smartphone-based electronic self-monitoring in bipolar disorder were unaddressed.

Figure 3

Screenshots from the self-monitoring part of the MONARCA-system.

STUDY I: THE MONARCA I RANDOMIZED CONTROLLED TRIAL

Articles II, IV, V and VI by the author present data collected as part of the MONARCA I trial (1,3–5).

To investigate the effect of smartphone-based daily electronic self-monitoring using a monitoring system that included a clinical feedback loop (the MONARCA system) on the severity of depressive and manic symptoms in patients with bipolar disorder, an RCT (the MONARCA I trial) was conducted (1,3).

A total of 78 patients with bipolar disorder diagnosed according to ICD-10 criteria, aged 18-60 years, with a Hamilton Depression Rating Scale 17-item (HDRS-17) score ≤17 (210) and a Young Mania Rating Scale (YMRS) score ≤17 (211) were randomized to the use of the MONARCA system (the intervention group) or the use of a smartphone for normal communicative purposes (a placebo smartphone; the control group) for a 6-month trial period. Outcomes were assessed monthly.

In the overall intention-to-treat analyses, there were no significant effects of smartphone-based daily electronic self-monitoring with a clinical feedback loop on depressive or manic symptoms. Regarding the HDRS-17, the overall analyses showed a trend towards higher HDRS-17 scores in the intervention group compared with the control group (B=2.02, 95% CI: -0.13; 4.7, p=0.066). In exploratory analyses excluding mixed depressive symptoms and mixed manic symptoms, the intervention group had higher HDRS-17 scores than the control group (model adjusted for baseline HDRS-17 scores, previous hospitalization (yes/no), age (≥ or < 29 years) and gender: B= 2.57, 95% CI: 0.40; 4.74, p=0.020). Similarly, in analyses that included patients with an HDRS-17 score >7 at baseline, the intervention group had higher HDRS-17 scores than the control group (model adjusted for baseline HDRS-17 scores, previous hospitalization (yes/no), age (≥ or < 29 years) and gender: B=2.69, 95% CI: 0.001; 5.37, p=0.049). In analyses that included patients who presented with manic symptoms during the trial, the intervention group had lower YMRS scores than the control group (model adjusted for baseline YMRS scores, previous hospitalization (yes/no), age (≥ or < 29 years) and gender: B= -0.98, 95% CI: -1.80; -0.16, p=0.019). Similarly, when

patients presenting with manic symptoms at baseline were included, the intervention group had lower YMRS scores than the control group (model adjusted for baseline YMRS scores, previous hospitalization (yes/no), age (≥ or < 29 years) and gender: B=-6.32, 95% CI: -9.21; -3.34, p<0.001) (3).

As part of the MONARCA I trial, we aimed to investigate whether smartphone-based electronic self-monitored data and smartphone-based electronic automatically generated data reflected the levels of clinically rated depressive and manic symptoms measured using the HDRS-17 and the YMRS, respectively (5). Furthermore, we aimed to characterize differences in illness activity between bipolar disorder type I and bipolar disorder type II using these smartphone-based electronic self-monitoring data (4).

During the MONARCA I trial, the patients randomized to the intervention group provided daily smartphone-based electronic self-monitored data. Analyses showed that self-monitored mood and activity level correlated negatively with the severity of clinically rated depressive symptoms measured using the HDRS-17 (self-assessed mood: B=-0.058, 95% CI: -0.071; -0.045, p<0.001) and correlated positively with the severity of clinically rated manic symptoms measured using the YMRS (self-assessed mood: B=0.039, 95% CI: 0.24; 0.53, p<0.001) in both unadjusted analyses and analyses adjusted for age and gender. Furthermore, there was a negative correlation between the number of hours slept and the severity of manic symptoms measured using the YMRS (adjusted analysis: B=-0.047, 95% CI: -0.088; -0.006, p=0.026) and a positive correlation between stress level and the severity of depressive symptoms measured using the HDRS-17 (adjusted analysis: B=0.046, 95% CI: 0.027; 0.064, p<0.001). No significant correlations between the number of hours slept and the HDRS-17 (p=0.21) or between stress level and the YMRS (p=0.35) were found (5).

Based on the daily smartphone-based electronic self-monitored data, unadjusted analyses and analyses adjusted for age, gender and illness duration showed that patients with bipolar disorder type II, compared with patients with bipolar disorder type I, experienced lower mean levels of mood on a scale from -3 to +3 (-0.54 (95% CI: -0.74; -0.35) versus -0.19 (95% CI: -0.35; -0.02), p=0.02), spent less time euthymic (51% (95%CI: 36.4; 65.7) versus 74.5% (95% CI. 62.4; 86.7), p=0.03) and spent a higher proportion of time experiencing depressive symptoms (45.1% (95% CI: 30.6; 59.5) versus 18.8% (95% CI: 6.9; 30.7), p=0.01). Using a number of calculated indexes reflecting aspects of illness activity, analyses showed that patients with bipolar disorder type II had higher indexes than patients with bipolar disorder type I (4).

Based on smartphone-based electronic automatically generated data collected from patients in the intervention group and the control group in the MONARCA I trial, adjusted analyses showed that the duration of incoming and outgoing calls/day (sec/day) correlated positively with scores on the HDRS-17 (duration of outgoing calls/day: B=26.33, 95% CI: 7.68; 44.98, p=0.006) and the duration of incoming calls/day correlated positively with the YMRS (duration of incoming calls/day: B=30.38, 95% CI: 7.04; 53.17, p=0.011; duration of outgoing calls/day: p=0.071). The number of incoming and outgoing calls/day and the number of outgoing text messages/day correlated positively with the YMRS (number of outgoing calls/day: B=0.15, 95% CI: 0.043; 0.25, p=0.006) but not with the HDRS-17. The number of outgoing text messages/day correlated positively with the YMRS (B=0.24, 95% CI: 0.019; 0.47, p=0.034). Finally, the electronic automatically generated data were able to discriminate between affective states in many cases (5).

STUDY II: THE MONARCA II STUDY

Article III by the author presents data from the MONARCA II study (2).

Using an updated version of the MONARCA system (209), the MONARCA II study aimed to investigate whether smartphone-based electronic self-monitored data and smartphone-based electronic automatically generated data correlate with clinically rated depressive and manic symptoms measured using the HDRS-17 and YMRS, respectively, in bipolar disorder.

A total of 17 patients with bipolar disorder diagnosed according to ICD-10 criteria and aged 18 to 60 years were included for a three-month follow-up study and were invited to visit the researcher every second week for assessment of the severity of depressive and manic symptoms using the HDRS-17 and the YMRS, respectively.

Analyses showed that self-monitored mood correlated negatively with HDRS-17 (B=-0.051, 95% CI: -0.062; -0.039, p<0.001) but did not correlate with the YMRS (B=0.008, 95% CI: -0.044; 0.027, p=0.41). Furthermore, the number of changes in cell tower IDs/day correlated borderline negatively with the HDRS-17 (B=-0.43, 95% CI: -0.88; 0.064, p=0.064) (2).

STUDY III: THE MONARCA III STUDY

Articles IX and X by the author present data from the MONARCA III study (7,8).

In response to the findings of the MONARCA I trial and the MONARCA II study and the increasing technological possibilities of the MONARCA system (**Figure 4**), the aims of the MONARCA III study were as follows: 1) to investigate whether smartphone-based electronic self-monitored data correlate with clinically rated depressive and manic symptoms measured using the HDRS-17 and YMRS, respectively; 2) to investigate whether detailed smartphone-based electronic automatically generated data correlate with clinically rated depressive and manic symptoms measured using the HDRS-17 and YMRS, respectively; and 3) to investigate whether detailed smartphone-based electronic automatically generated data discriminate between affective states in bipolar disorder.

A total of 29 patients with bipolar disorder diagnosed according to ICD-10 criteria were followed for 12 weeks during the early phase of their course of treatment and thus presented with more severe depressive and manic symptoms than had been previously investigated. The patients were invited to visit the researcher every second week for assessments of the severity of depressive and manic symptoms using the HDRS-17 and the YMRS, respectively.

Figure 4

The self-monitoring part of an updated version of the MONARCA system

Analyses showed that self-monitored mood and activity level correlated negatively with the HDRS-17 (self-assessed mood: B=-0.049, 95% CI. -0.063; -0.034, p<0.001) and positively with the YMRS (self-assessed mood: B=0.045, 95%CI. 0.030; 0.060, p<0.001). Regarding depressive symptoms, self-assessed stress level and anxiety level correlated positively with the clinically rated depressive symptoms measured using the HDRS-17. Self-assessed sleep length did not correlate with the HDRS-17. Regarding manic symptoms, self-assessed sleep length correlated negatively with the clinically rated manic symptoms measured using the YMRS, and self-assessed activity level and stress level correlated positively with the YMRS. Self-assessed stress level did not correlate with the YMRS.

Regarding depressive symptoms, the number of changes in cell tower IDs/day and the number of outgoing calls/day correlated negatively with the HDRS-17, whereas the number of incoming text messages/day, the number of incoming calls/day, the number of missed calls/day and the duration the screen was 'on'/day (sec/day) correlated positively with the HDRS-17.

Regarding manic symptoms, the number of outgoing text messages/day, the duration of calls/day (sec/day), and the number of changes in cell tower IDs/day correlated positively with the YMRS, whereas the number of characters in incoming text messages/day and the duration of outgoing calls/day correlated negatively with the YMRS. In addition, the models showed that most of the smartphone-based electronic automatically generated data discriminated between a euthymic state and a depressive or (hypo)manic state.

The number of outgoing text messages/day, the number of changes in cell tower IDs/day, and the number of characters in incoming text messages/day discriminated between a depressive state and a (hypo)manic state (7).

During the MONARCA III study, voice features were extracted during the patients' phone calls using the open-source Media Interpretation by Large Feature-Space Extraction (OpenSMILE) toolkit (212). Analyses of the classification of affective states using voice features in user-dependent and user-independent models were conducted. In the user-independent models, the mean accuracy of the classification of a depressive state versus a euthymic state based on voice data was 0.68 (SD: 0.006), with a sensitivity of 0.81 (SD: 0.008); for a manic state or mixed state versus a euthymic state, the accuracy was 0.74 (SD: 0.005) with a sensitivity of 0.97 (SD: 0.002). For the user-independent models, the corresponding AUC for the classification of a depressive state versus a euthymic state was 0.78; for a manic state versus a euthymic state, the AUC was 0.89. The accuracy, sensitivity and specificity did not increase when voice features were combined with smartphone-based electronic automatically generated data compared with when voice features alone were used, but they did increase when voice features were combined with smartphone-based electronic self-monitored data (8).

As part of the MONARCA III study, in addition to using the MONARCA system, the patients were invited to wear a combined heart rate and movement sensor (Actiheart, Cambridge Neurotechnology Ltd, Papworth, UK) for a minimum of three consecutive days during different affective states. The results are presented as part of the heart rate-based electronic monitoring part of the dissertation (section 9.1) (11,12).

STUDY IV: ELECTRONIC SELF-MONITORING OF MOOD IN BIPOLAR DISORDER: A SYSTEMATIC REVIEW

Article VII by the author presents data from the systematic review on electronic self-monitoring of mood in bipolar disorder (6).

To evaluate the validity of electronic self-monitoring of mood compared with clinically rated depressive and manic symptoms and to evaluate the effect of electronic mood self-monitoring interventions on clinically relevant outcome measures in bipolar disorder, a systematic review reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (213) was conducted.

The review included original studies that involved IT platforms for the electronic self-monitoring of mood in patients with bipolar disorder aged ≥18 years and reported on either a) correlations between electronically self-monitored mood and validated clinical rating scales for depression and mania or b) RCTs investigating the effects of IT platform-based electronic self-monitoring tools.

Studies were identified by searching the electronic databases MEDLINE (January 1950 to July 2015), PsychINFO (1806 to July 2015), Embase (1974 to July 2015) and the Cochrane Library (issue 6, 2015) and by hand-searching the reference lists of retrieved articles. A total of 13 studies were included for review; of these, seven were RCTs, and six had a non-RCT longitudinal design. The follow-up periods ranged between 2 weeks and 24 months, and the sample sizes ranged between 10 and 233 patients with bipolar disorder. Of the included studies, eight (representing six different electronic systems) used computers as the IT platform for electronic self-monitoring, two used personal digital assistants (PDAs), and five (representing four different electronic systems) used smartphones.

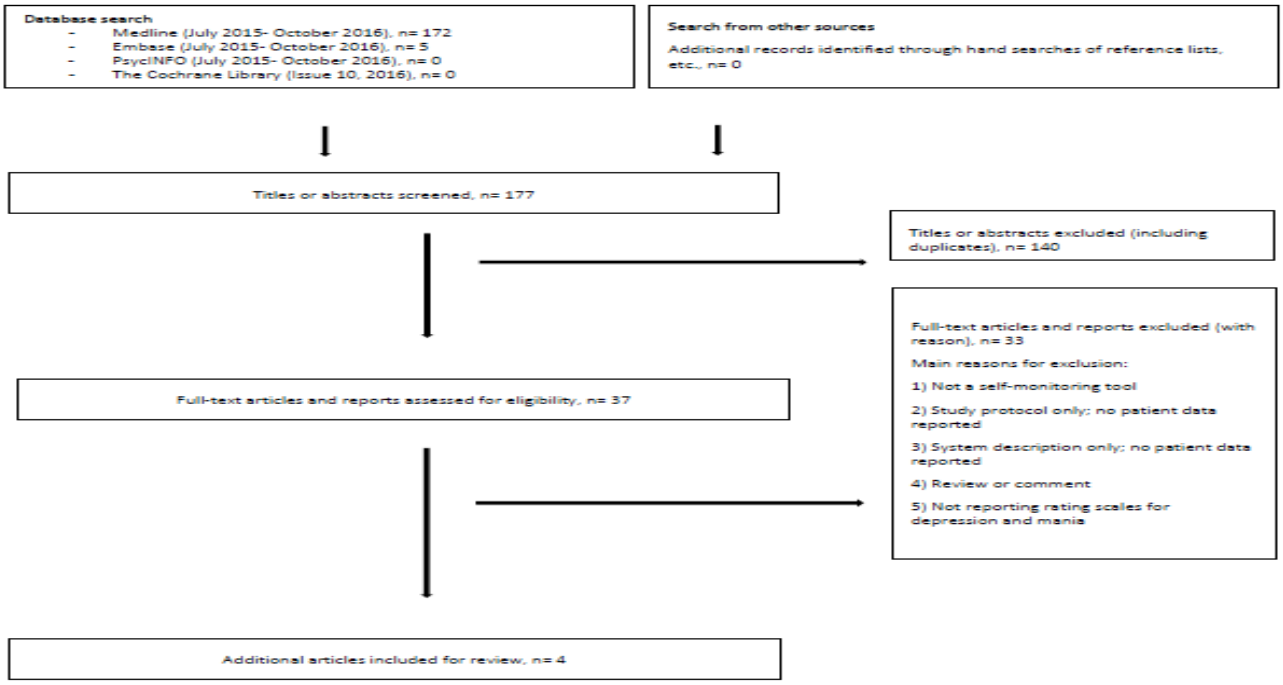
Electronic self-monitoring of mood was considered valid in six out of six studies that compared it with validated clinical rating scales for depression and in only two out of seven studies that compared it with validated clinical rating scales for mania. The seven RCTs included a total of 759 patients with bipolar disorder and primarily investigated the effect of heterogeneous electronically delivered intervention programs in studies with follow-up periods ranging between 12 weeks and 12 months. None of the seven RCTs investigated the sole effect of electronic mood self-monitoring tools; they primarily used web-based intervention programs. Methodological issues related to the risk of bias at different levels limited the evidence in the majority of the studies. Given the nature of the intervention programs, none of the RCTs included were double-blinded and therefore carried the risk of performance bias. Self-assessed outcome measures with no researcher-blinded outcome measures were reported in five of the seven RCTs. Except in two RCTs, no differences in primary outcomes between the intervention group and the control group were reported at the end of the trials (6).

In addition, an updated literature search covering the period from July 2015 to October 2016 using the same electronic databases and search terms/key words that were used in the original literature search for the systematic review was conducted. A total of 177 additional titles were identified, and of these, four studies fulfilled the inclusion criteria (5,7,214,215) (**Figure 5**). Of the four studies, two were by the author (5,7) and thus are presented as part of the dissertation, and one study was a RCT (215). Electronic self-monitoring of mood was considered valid in three out of three studies that compared it with validated clinical rating scales for depression (5,7,214) and in two out of three studies that compared it with rating scales for mania (5,7). The additional identified RCT, which used a web-based electronic intervention program, did not investigate the sole effect of the electronic self-monitoring tool and reported no differences in self-assessed

outcomes between the intervention group and the control group at the end of the trial (215).

Figure 5. Flow diagram of the updated literature search on electronic self-monitoring in bipolar disorder

Updated literature search and the selection of studies identified with updated literature searches of the electronic databases MEDLINE, PsychINFO, Embase, and the Cochrane Library conducted in October 2016 according to the PRISMA statement.



SUMMARY OF STUDIES I-IV

In summary, three original studies and one systematic review concerning smartphone-based electronic monitoring in bipolar disorder were conducted by the author. We aimed to investigate the use of smartphone-based electronic monitoring in bipolar disorder as marker of state and trait and treatment intervention.

Regarding the smartphone-based electronic self-monitored data, patients were able to monitor their depressive and manic symptoms in a manner comparable with validated clinical rating scales for depression and mania (HDRS and YMRS, respectively). Regarding the use of smartphone-based electronic data as markers of illness in bipolar disorder, analyses of daily smartphone-based electronic self-monitored data demonstrated that despite ongoing treatment, patients with bipolar disorder type II experienced more symptoms than patients with bipolar disorder type I based on different calculated indexes.

Notably, the author showed for the first time that smartphone-based automatically generated electronic data on different behavioral aspects, including voice features, reflected the severity of clinically rated depressive and manic symptoms and discriminated between affective states.

Regarding the effect of smartphone-based electronic monitoring, no significant effect on the severity of clinically rated depressive and manic symptoms was found when investigating the effect of the MONARCA system in an RCT. However, sub-group analyses indicated that using the MONARCA system maintained depressive symptoms and resulted in fewer manic symptoms compared with not using the MONARCA system.

In a systematic review (including an updated literature search) of studies on electronic self-monitoring in bipolar disorder, electronic self-monitoring of depressive symptoms was generally found to be valid compared with clinically rated depressive symptoms; however, the findings regarding electronic self-monitoring of manic symptoms were more diverse. The quality of evidence of electronic self-monitoring was low, limited by methodological issues and a lack of RCTs.

Prior to the work by the author, the use of smartphone-based automatically generated electronic data as potential markers in bipolar disorder was unaddressed. Furthermore, no RCTs investigating both the positive effects and the possible harmful effects of smartphone-based electronic self-monitoring as a treatment intervention in bipolar disorder had been published.

DISCUSSION

Strengths of the author's work

Smartphone data for monitoring illness activity

The author was the first to investigate the use of self-monitored and automatically generated smartphone data as markers of illness activity in bipolar disorder. Correlations between smartphone-based electronic self-monitored data and smartphone-based electronically generated smartphone data (including voice features) and clinically rated depressive and manic symptoms in bipolar disorder were investigated for the first time.

Apart from the studies by the author (2,5,7,8), few other recent studies on the use of smartphone-based electronic automatically generated data (214,216–220), including voice features (85,216,221–223) in bipolar disorder have been published (**Figure 6**).

However, in contrast to the studies by the author, most of the other published studies did not report on clinically rated depressive and manic symptoms, included patients with a low severity of depressive and manic symptoms, did not address confounding issues in the statistical analyses, and did not compare smartphone-based electronic automatically generated data between affective states; furthermore, some of the studies were single-case studies (85,216), and only one study included more than ten patients (13 patients) (214).

Apart from the studies by the author, only one study addressed the blinding of outcome assessors to smartphone-based data during follow-up (214). In addition, patients willing to participate in studies using electronic monitoring may represent a more motivated and technically oriented group, but apart from the studies by the author, few studies reported the data for non-participants and excluded patients, including the reasons for exclusion/non-participation. Thus, the evaluation of some aspects of selection bias was hindered.

When smartphone-based electronic automatically generated data are used, detailed data reflecting bipolar disorder are collected even though patients do not conduct self-evaluations. In line with the findings by the author (2,5,7,8), three of the studies that measure the severity of depressive and manic symptoms using clinical ratings found that the smartphone-based electronic automatically generated data reflected illness activity in bipolar disorder (214,218,222).

Figure 6. mHealth solutions in bipolar disorder

mHealth treatment solutions and smartphone-based electronic automatically generated data in adult patients with bipolar disorder used in scientific studies, listed according to study type.

Table 1a: Randomized controlled trials; Table 1b: Observational and pilot studies; Table 1c: Other types of studies and articles.

Table 1a. *Randomized controlled trials on mHealth treatment solutions and smartphone-based electronic automatically generated data in adult patients with bipolar disorder.*

System	Author, year	IT platform	Study design	Content of system	Mood monitoring	Smartphone-based electronic automatically generated data	Clinician- or patient-assessed outcomes	Comparison group
Bipolar Education Program (BEP)	(Proudfoot et al. 2007, 2012; Nicholas et al. 2010)	Web-based + E-mail	RCT, Pilot	Psychoeducation+ Peer support+ Mood monitoring	Yes	-	Patient-assessed symptom severity	Waiting list+ Mood monitoring
Recovery Road (RR)	(Barnes et al. 2011, 2015)	Web-based	RCT, Development of system	Psychoeducation+ CBT+ Mood monitoring	Yes	-	Patient-assessed relapse and hospitalization	TAU, Healthy lifestyle
Living with Bipolar (LWB)	(Todd et al. 2012a, 2012b, 2013, 2014)	Web-based	Feasibility RCT, Pilot, Development of system, Study protocol of RCT	CBT+ Discussion forum+ Mood monitoring	Yes	-	Patient-assessed symptom severity	Waiting list
Life-Chart Method (LCM)	(Lieberman et al. 2010, 2011)	Web-based	RCT	Social rhythm stabilization+ Mood monitoring	Yes	-	Patient-assessed social rhythm+ Adherence to mood monitoring	Paper-based mood monitoring
Beating Bipolar (BB)	(Smith et al. 2011; Poole et al. 2012, 2015)	Web-based	Exploratory RCT, Feasibility	Psychoeducation+ Discussion forum	-	-	Clinician-assessed symptom severity	TAU
MoodSwings (MS)	(Lauder et al. 2013, 2015; Gliddon et al. 2015)	Web-based	RCT, Development of system, Study protocol for observational study	Psychoeducation+ CBT+ Mood monitoring+ Discussion forum	Yes	-	Patient-assessed symptom severity	Psychoeducation+ Mood monitoring+ Discussion forum
MONitoring, treAtment and pRediCtion of bipolAr disorder episodes (MONARCA)	(Bardram et al. 2012, 2013, Faurholt-Jepsen et al. 2013, 2014a, 2014b, 2015a, 2015b, 2015c, 2016b, 2016e; Frost et al. 2013)	Smartphone	RCT, Observational, Pilot, Development of system, Study protocols of RCTs	Mood monitoring+ Feedback loop	Yes	Smartphone usage, Cell towers, Acceleration, GPS traces, Speech	Clinician-assessed symptom severity	Placebo smartphone

Abbreviations: RCT: Randomized Controlled Trial; CBT: Cognitive Behavioral Therapy; TAU: Treatment-As-Usual; PDA: Personal Digital Assistant; HC: Healthy Control Individuals.

Table 1a continued *Randomized controlled trials* on mHealth treatment solutions and smartphone-based electronic automatically generated data in adult patients with bipolar disorder.

System	Author, year	IT platform	Study design	Content of system	Mood monitoring	Smartphone-based electronic automatically generated data	Clinician- or patient-assessed outcomes	Comparison group
Personalized Real-time Intervention for Bipolar Disorder (PRISM)	(Depp et al. 2010, 2012, 2015, 2016a; Kaufmann et al. 2016)	PDA, Web-based, Smartphone	RCT, Observational	Psychoeducation+ Personalized management strategies+ Mood monitoring	Yes	-	Clinician-assessed symptom severity	Paper-based mood monitoring
Positive Parenting Programme (Triple-P); Integrated Bipolar Parenting Intervention (IBPI)	(Jones et al. 2014, 2015)	Web-based	Pilot RCT	Improving perceived parenting skills	-	-	Patient-assessed parenting skills	Waiting list+ TAU
Transdiagnostic Internet-Based Maintenance Treatment (TIMT)	(Ebert et al. 2013)	Web-based	RCT	Self-management, Asynchronous patient-coach communication+ Online patient support group+ Symptom monitoring	Yes	-	Patient-assessed symptom severity	TAU
Facilitated Integrated Mood Management (FIMM)	(Bilderbeck et al. 2016a)	Smartphone	RCT	Psychoeducation+ Therapist-facilitated integrated mood management	Yes	-	Patient-assessed symptom severity	Self-administered Manualized Integrated Mood Management (MIMM)

Abbreviations: RCT: Randomized Controlled Trial; CBT: Cognitive Behavioral Therapy; TAU: Treatment-As-Usual; PDA: Personal Digital Assistant; HC: Healthy Control individuals.

Table 1b. *Observational and pilot studies* on mHealth treatment solutions and smartphone-based electronic automatically generated data in adult patients with bipolar disorder.

System	Author, year	IT platform	Study design	Content of system	Mood monitoring	Smartphone-based electronic automatically generated data	Clinician- or patient-assessed outcomes	Comparison group
Social Information Monitoring for Patients with Bipolar Affective Disorder (SIMBA)	(Beiwinkel et al. 2016)	Smartphone	Pilot	Mood monitoring	Yes	Smartphone usage, Smartphone-based acceleration and GPS traces	Clinician-assessed symptom severity	-
ChronoRecord	(Whybrow et al. 2003; Bauer et al. 2004a, 2005a, 2005b, 2006a, 2006b, 2006c, 2007, 2008b, 2008c, 2009)	Web-based	Observational	Mood monitoring	Yes	-	Clinician-assessed symptom severity	-
-	(Schwartz et al. 2016)	Smartphone	Observational	Symptom monitoring	Yes	-	Patient-assessed symptoms and completion rates	HC
MoodRhythm	(Abdullah et al. 2016; Matthews et al. 2016)	Smartphone	Observational, Development of system	Social rhythm	Yes	Smartphone usage, Smartphone-based acceleration and GPS traces, Speech	-	-
-	(Novak et al. 2014)	Text-messages	Observational	Mood monitoring	Yes	-	Patient-assessed symptom severity	-
-	(Bopp et al. 2010; Bonsall et al. 2012; Moore et al. 2012, 2014a, 2014b; Holmes et al. 2016)	Text-messages	Observational	Mood monitoring	Yes	-	Patient-assessed symptom severity	-
True Colours (TC); MoodZoom; Facilitated Integrated Mood Management (FIMM)	(Miklowitz et al. 2012; Saunders et al. 2016; Tsanas et al. 2016)	Smartphones+ E-mail+ Text messages	Observational, Pilot, Development of system, Study protocol of RCT	Mood monitoring	Yes	-	Patient-assessed symptoms and variability	Patients with borderline personality disorders; HC
Bipolar Interactive Psychoeducation (BIPED)	(Simpson et al. 2009; Poole et al. 2015)	Web-based	Pilot (feasibility), Study protocol of RCT	Psychoeducation+ Discussion forum	-	-	Clinician- and patient-assessed symptom severity	TAU
Online, Recovery-Focused, Bipolar Individual Therapy (ORBIT)	(Murray et al. 2015)	Web-based	Pilot	Mindfulness	-	-	Patient-assessed symptom severity	-
Personal Life Chart (PLC)	(Scharer et al. 2002; Schärer et al. 2015)	PDA, Computer-based, Smartphone	Observational	Mood monitoring	Yes	-	Clinician-assessed symptom severity	-
In Flow	(Johnson et al. 2015)	Smartphone	Observational	Symptom monitoring	Yes	-	Patient-assessed symptom severity	HC
MyiMonitor	(Mallaris Y. 2010)	PDA	Pilot	Ambulatory symptom monitoring	-	-	-	-

Abbreviations: RCT: Randomized Controlled Trial; CBT: Cognitive Behavioral Therapy; TAU: Treatment-As-Usual; PDA: Personal Digital Assistant; HC: Healthy Control individuals; -: Information not available or not collected.

Table 1c. *Other types of studies and articles on mHealth treatment solutions and smartphone-based electronic automatically generated data in adult patients with bipolar disorder.*

System	Author, year	IT platform	Study design	Content of system	Mood monitoring	Smartphone-based electronic automatically generated data	Clinician- or patient-assessed outcomes	Comparison group
-	(Prasko et al. 2013)	Web-based	Development of system	Psychoeducation	-	-	-	-
Enhanced Relapse Prevention (ERPonline)	(Lobban et al. 2015)	Web-based	Study protocol of RCT and feasibility	Relapse prevention	-	-	Clinician-assessed symptom severity	Waiting list
BipoLife	(Ritter et al. 2016)	Smartphone	Study protocol of RCT, observational study and cross-over trial	Relapse prevention	Yes	Smartphone-based acceleration, GPS traces and communication patterns	Clinician-assessed relapse and symptom severity	Smartphone-based self-monitoring without clinical feedback

Abbreviations: RCT: Randomized Controlled Trial; CBT: Cognitive Behavioral Therapy; TAU: Treatment-As-Usual; PDA: Personal Digital Assistant; HC: Healthy Control Individuals.

Smartphone data as treatment interventions in bipolar disorder

RCTs are the methodological standard of excellence in medical research (224). The MONARCA I trial by the author was the first RCT to investigate the effects of smartphone-based electronic self-monitoring in bipolar disorder. In contrast to the MONARCA I trial, other studies investigating the effect of different web-based electronic self-monitoring treatment interventions reported on self-assessed outcomes such as self-assessed quality of life and symptom severity (127,128,215,225–227) (Appendix 2). The results of such studies may be influenced by information bias as outcome measures were self-reported by patients who were unblinded to their intervention status. The MONARCA I trial was smartphone-based and reported blinded, clinician-evaluated outcomes regarding the severity of depressive and manic symptoms. Furthermore, the MONARCA I trial included a two-tiered feedback loop between the patients and the clinicians, allowing for early intervention, and the patients allocated to the control group were provided with a placebo smartphone. One other study investigated the effect of smartphone-based self-management strategies but included tools for self-monitoring mood in both intervention groups (228) and thus did not investigate the effect of self-monitoring.

A study protocol including predefined primary and secondary outcome measures, power calculations, sample size and statistical analyses of the MONARCA I trial was published according to the CONSORT statement (229) before the end of the study (1). Furthermore, the study protocol included details on the allocation ratio, the methods used to generate the randomization sequence, who enrolled the patients, and who allocated the patients to interventions. The MONARCA I trial had a pragmatic design with few exclusion criteria, and thus it is likely that the findings of the trial can be generalized to all patients with bipolar disorder.

Limitations of the author's work

Smartphone data for monitoring illness activity

The studies investigating the use of smartphone data as marker of illness in bipolar disorder included rather small sample sizes. The follow-up periods could have been longer, thereby allowing more depressive and manic episodes and more severe depressive and manic symptoms to occur. However, each patient was assessed several times using a longitudinal study design, and the employed statistical models allowed for both within-individual and between-individual variations over time, which added to the statistical power. Nevertheless, it is possible that the limited statistical power of the individual studies may have led to type II errors. Multiple comparisons were not taken into consideration in the statistical analyses as the studies were the first of their kind and therefore were hypothesis-generating.

The patients' affective states were defined according to an ICD-10 diagnosis of bipolar disorder combined with a cut-off score on the HDRS-17 and YMRS. Although the cut-off scores on the HDRS and YMRS were in accordance with prior clinical studies, they were arbitrary; consequently, choosing a different cut-off could have influenced the results. The patients were recruited from a highly specialized clinic, and they received rather intensive treatment and presented with a relatively low severity of depressive and manic symptoms. Including patients from other treatment facilities, such as inpatient units, may have resulted in greater differences in smartphone-based data between affective states and different correlations between smartphone-based data and clinically rated depressive and manic symptoms. However, the participation rate, completeness of the studies and adherence to the researcher's assessments of depressive and manic symptoms may have been lower, and it may have been difficult and complicated to conduct the studies if they had included inpatients.

Regarding the validity of smartphone-based electronic self-monitoring, the external validity of smartphone-based electronic self-monitoring may have been overestimated or underestimated due to the difficulty of self-monitoring the severity of manic and depressive symptoms in more severe cases. Hospitalized patients with severe manic and depressive symptoms were not included in the studies; thus, the validity in those cases was not investigated. Possible confounding factors were considered in the statistical analyses, which increased the internal validity. The long-term stability of the validity of smartphone-based electronic self-

monitoring and the long-term impact of self-monitoring fatigue were not investigated. Furthermore, calculating the sensitivity, specificity, positive predictive value and negative predictive value could provide important information.

For smartphone-based electronic monitoring to reflect surrogates of clinical meaningful endpoints and outcome measures in efficacy trials, further investigation is needed.

The patients received different types, doses and combinations of psychopharmacological treatments during the studies, and this may have influenced the results. However, most of the patients did not alter their medication during the studies, and thus the effect of medication alteration likely did not have a major impact on the study findings.

Some patients declined to participate because the MONARCA system was not available for iPhones or Windows phones. It is possible that patients using operating systems other than Android represent a different sub-group of patients. The MONARCA system currently used is available for both Android smartphones and iPhones. Thus, future results will represent a broader range of smartphone users. Data collection and continuous monitoring using smartphones require high data security and a high degree of trust between patients and mental health care providers so that the patients do not have the feeling of "being watched". However, none of the patients participating in the studies complained that they felt "watched" in their everyday life; rather, they viewed the monitoring system as a safety net.

A control group of healthy control individuals was not included, nor was a group of first-degree healthy individuals at risk of bipolar disorder. Thus, the specificity of smartphone-based electronic automatically generated data as a diagnostic and predictive marker was not investigated.

Consequently, the author is currently conducting a long-term observational study (the Bipolar Illness Onset study (the BIO study)) (registered on clinicaltrials.gov with the identifier NCT02888262) investigating the use of smartphone-based automatically generated data as markers in patients newly diagnosed with bipolar disorder, healthy first-degree relatives at risk of bipolar disorder and healthy control individuals during a five- to ten-year follow-up period.

Smartphone data as treatment interventions in bipolar disorder

Although the MONARCA system investigated in the MONARCA I trial was not found to be effective for reducing depressive and manic symptoms, there were indications that such an electronic system may sustain depressive symptoms and decrease manic symptoms. Our finding are in line with reviews discussing the differential effects of treatment interventions on depressive and manic symptoms in bipolar disorder (230–232). Thus, manic prodromes may be easier to detect and treat than depressive episodes, whereas depressive symptoms are more difficult to differentiate from normal day-to-day hassles and may have a more gradual onset and prolonged duration (233,234). Additionally, it is possible that daily electronic self-monitoring may maintain depressive symptoms due to a negative processing bias induced by daily confrontation and an induced fear of not recovering (58,233).

The MONARCA I trial could have included more patients, but because the findings suggested that such a system may sustain depressive symptoms, including a larger sample would likely not have resulted in positive trial results. Due to the type of intervention used in the MONARCA I trial, it was not possible to blind the patients, the clinicians or the study nurse to the allocation group. However, the researchers performing the outcome assessments were blinded to allocation status, and thus the study was single-blinded. The MONARCA system consisted of multiple elements, and the MONARCA I trial investigated the effect of 'a total monitoring system'. It was not possible from the MONARCA I trial results to distinguish between the effects of the individual elements of the intervention.

In any non-pharmacological trial, it is always difficult to define a proper control group. In the MONARCA I trial (and in the MONARCA II trial), a placebo smartphone for normal communicative purposes was provided to the control group. A placebo smartphone was used to eliminate any effect of receiving a cost-free smartphone on depressive and manic symptoms. Furthermore, by giving the control group a placebo smartphone, it was possible to collect smartphone-based electronic automatically generated data on all the patients included in the trial.

The patients were recruited from a highly specialized clinic, and they presented with a relatively low severity of symptoms. Including patients from other treatment facilities, such as inpatient units, may have resulted in different results regarding the effect of electronic self-monitoring.

The MONARCA I trial showed that the electronical self-monitoring of illness activity combined with a feedback loop system to communicate with clinicians had no effect on depressive and manic symptoms. Compared with smartphone-based electronic automatically generated data, electronic self-monitoring may not be sufficient to detect prodromal depressive and manic symptoms, and the MONARCA I trial did not include feedback to patients and clinicians on smartphone-based automatically generated data. Consequently, the author is currently conducting a MONARCA II trial (235), which is the first RCT to investigate the effect of electronic self-monitoring that includes a feedback loop integrating subjective and smartphone-based electronic automatically generated data on clinically rated depressive and manic symptoms.

An RCT is a study design with high internal validity but with a possible cost of lower external validity and thereby lower generalizability of the study findings. In contrast to the MONARCA I trial, the MONARCA II trial has fewer exclusion criteria; it includes patients with bipolar disorder during more stages of illness and with greater variation in illness duration. Furthermore, a larger sample size will be included, with a follow-up period of nine months, compared with six months in the MONARCA I trial. Thus, the results from the MONARCA II trial are likely to be more generalizable to patients with bipolar disorder in general.

It is difficult to describe enough details of the MONARCA system in the published study protocol to allow exact replication of the intervention by other researchers while keeping the system unknown/blinded so that patients randomized to the control group do not have access to and information regarding the intervention.

As part of the systematic review of electronic self-monitoring in bipolar disorder conducted by the author, it should be mentioned that the author did not have access to the IT platforms of the included studies since the use of most of these systems was restricted to research. Thus, details on the individual intervention programs and IT systems were only available to the extent that they were described in the articles, and thus, elements of the self-monitoring part of the interventions may have been overlooked.

Mobile and wireless technologies (mHealth) in bipolar disorder

A report by the World Health Organization in 2011 stated that "the use of mobile and wireless technologies to support the achievement of health objectives (mHealth) has the potential to

transform the face of health service delivery across the globe" (130). mHealth interventions, particularly in the form of smartphone applications (161), have the potential to minimize the treatment barriers of distance, time and costs (131,132). Furthermore, the use of sensors embedded within these technologies as a monitoring tool could potentially provide opportunities for new areas of research, the development of markers of illness and the delivery of treatment interventions. Using sensor technology opens up the possibility of more individualized context-aware treatment interventions.

During the last decade, various mHealth solutions have been increasingly used worldwide to monitor and treat medical conditions such as diabetes (132,138,145,146), cardiovascular disease and hypertension (132,137,146), asthma (141,146), chronic obstructive lung disease (132,146), HIV (142), headache (143), cancer (236) and other chronic medical conditions (139,140,144). It has been suggested that mHealth solutions may empower patients to play a more active role in their treatment (237), and the effectiveness of mHealth solutions for medication adherence (238), chronic obstructive lung disease exacerbation management (136), weight loss (239,240), physical activity (241), blood pressure reduction (242), diabetes management (243) and smoking cessation (244) has been reported in multiple studies.

Within mental health mHealth, solutions for disorders such as depression, anxiety, substance abuse, eating disorders and schizophrenia have been developed and used, and in general, studies report high acceptability and usefulness (130,155–162,245–250). Recent papers suggest that patients with bipolar disorder use the internet to seek information for coping with a chronic illness (251,252), and mHealth solutions have been used and described in scientific studies of bipolar disorder (Appendix 2).

Although studies have examined the effects of different mHealth interventions within mental health, much of the research has focused on pilot studies examining feasibility (253), and there is a lack of RCTs with large samples sizes, rigorous study methodology and long follow-up periods. Furthermore, most study findings have not been replicated, and the founders or owners of the mHealth solutions rather than independent researchers have conducted many of the studies.
mHealth solutions allow for unique and unparalleled opportunities for unobtrusive, continuous long-term monitoring in naturalistic settings and could provide detailed data on illness activity that otherwise would be difficult to collect (156). Using mHealth solutions, especially smartphones, to develop a detailed and fine-grained characterization of the complex phasic and chronic nature of bipolar disorder could provide opportunities for early intervention for subsyndromal symptoms between outpatient visits, and electronic self-monitoring may increase patients' self-awareness and empowerment and support their interaction with clinicians (92,96,254).

Many smartphone applications for bipolar disorder and other mental health disorders are available for download (148,179,180). However, despite the opportunity for mHealth to improve access to treatment services, improve treatment outcomes and reduce costs, strikingly few RCTs investigating the effects of mHealth interventions within bipolar disorder have been conducted (Appendix 2) (3,127,128,215,225–228,255). The interventions used in these studies were heterogeneous, used different technologies (e.g. web-based, PDA-based, smartphones) and had different levels of clinician involvement. Some of the studies did not include clinician involvement during follow-up (127,215,225–227), whereas others included multiple visits with researchers (3,228). Furthermore, the treatment interventions were complex and consisted of multiple treatment elements. Despite the opportunities for smartphones to increase access to mHealth solutions, only three groups used smartphones as the electronic platform (3,128,215,228), and of these, only one investigated the effect of electronic self-monitoring (3). Regarding studies using web-based platforms as interventions, most reported on self-reported outcomes and did not find any differences between the intervention group and the control group (127,215,226,255). One study using a web-based intervention found an increased self-assessed quality of life, recovery and social functioning and lower self-reported symptom severity in the intervention group compared with the control group (225). A second study found a lower severity of self-reported manic symptoms but no difference in the self-reported severity of depressive symptoms in the intervention group compared with the control group (227). Regarding studies using smartphone-based platforms as interventions, one found higher self-assessed mood variability in the intervention group compared with the control group (128), and two (one of which is by the author) did not find any differences in the clinician-assessed severity of symptoms measured using standardized clinical rating scales between the intervention group and the control group (3,228). Thus, most studies reported on unblinded patient self-reports and were therefore at risk of performance bias and detection bias.

Technological development moves faster than science, and due to rapid development and competitive commercialization, many mHealth solutions are not evidence-based, which undermines the quality and safety of these solutions in treatment settings (131,148,150,182,256,257). Commercial applications are frequently not updated, may be suddenly removed from app stores or malfunction (258). Such grave limitations are important to consider if patients are supposed to rely on commercial applications for everyday use. Recently, the limitations and complications arising from rapid development and the lack of scientific studies and publications within the area of mHealth have been addressed in numerous papers (131,147–151,259–261). Due to the rapid development of mHealth solutions and scant evidence supporting the effectiveness of mHealth solutions, it was even suggested that it may be time for methodological changes, such as the abandonment of RCTs as the primary method of scientific evaluation and an increased use of iterative participatory research and single-case design (262,263). However, as argued by others, given the unique potential of mHealth solutions, these solutions should not be examined with less rigorous scientific approaches than would be used to investigate new pharmacological treatments (147,148,182,264). Findings from the MONARCA I trial (3) emphasize that mHealth solutions should not be implemented as a standard clinical tool before possible positive and negative effects are carefully investigated using well-designed, appropriate RCTs. It is hoped that an increased awareness of the acute need to investigate the effectiveness and safety of mHealth treatment interventions with methodologically rigorous, well-designed RCTs will attract interest and funding for future studies. Most of the studies published to date on mHealth solutions in bipolar disorder were designed as feasibility studies or pilot studies and did not include a comparison group (177,253,255,265–275); thus, a 'digital placebo effect' may explain some of the positive outcomes reported (162). Several authors (148,162,248,276–278) have suggested guidelines for defining, detecting and reporting harms related to these types of interventions to facilitate this process and increase quality and evidence of future mHealth studies and interventions. mHealth solutions often consist of multiple domains, and standardized reporting

guidelines for mHealth interventions could provide tools to clearly define the content and context of the interventions and interpret how the interventions were implemented in the trials. In addition, the use of standardized guidelines could facilitate the replication of study findings within the area of mHealth.

Along this line, important issues concerning patients' online security, privacy, data storage, legal and cultural differences between nations, economic evaluations and potential conflicts of interest need to be clearly addressed and reported for the evaluation and comparison of mHealth solutions (165,254,277,279–283). Establishing an unbiased certification process that is sustainable and free of conflict of interest may help patients, clinicians and administrators during the evaluation process (261,284,285).

Smartphones are ubiquitous; many people own and use a smartphone and carry it with them during large parts of the day (286), and recent reports suggest that almost ¾ of patients with a psychiatric disorder would like to use an application as part of their mental health care (287). The use of smartphones to monitor bipolar disorder provides unique opportunities to collect large amounts of fine-grained data on bipolar disorder in a unobtrusive, passive and continuous way outside of clinical settings and could lead to the identification of new markers for bipolar disorder (282,283,288,289). Studies by the author (2,5,7,8) and others (32,203,214,218–220,270) suggest that automatically generated electronic smartphone data may provide such potential markers. The use of smartphones to capture data could ultimately identify underlying psychopathological processes in bipolar disorder (26). Future studies should identify which smartphone-based automatically generated electronic data or combinations of these are most specific and sensitive in bipolar disorder. By collecting both self-monitored and automatically generated data using smartphones as a monitoring tool, large amounts of data that are generated quickly, show great variety and are very complex ('big data' (290)) are collected, providing opportunities for exploration, observation, hypothesis generation and personalized early intervention treatment strategies (282,291,292). In analyses of 'big data', the explanatory variables included in large datasets may not be independent, noise accumulation may occur, there is an increased risk of false findings, and time-varying confounding and exposure may need to be considered (282,293–296). At the same time, collecting large amounts of complex data requires collaboration among scientists with diverse areas of expertise and requires careful statistical consideration during all phases of planning, implementation and analysis.

However, despite many unaddressed issues and a lack of scientific data, the area of mHealth holds great promise for improving access to and the effects of mental health care services. mHealth solutions may be able to provide personalized early treatment interventions; measure detailed, complex, real-time data that was previously difficult to detect; and may lead to the detection of new markers in bipolar disorder that could be used as outcome measures in efficacy trials (26,156,159,285,288,289,297–299). Nevertheless, the lack of RCTs highlights the fact that interventions should not be used or implemented in clinical practice without critical assessment and that important aspects need further clarification before mHealth is implemented as a standard tool.

CONCLUSIONS

Methodological issues and a lack of RCTs limit the evidence supporting the use of electronic monitoring interventions in bipolar disorder, and thus it seems premature to present any estimation of their potential effects. The MONARCA I trial by the author suggests that electronic monitoring may have harmful effects, and future studies should carefully investigate this possibility further and report results accordingly. Furthermore, studies should report results according to standardized guidelines and address issues related to online privacy, security, legal and cultural differences between nations, and economic aspects.

Interestingly, smartphone-based electronic self-monitoring and smartphone-based electronic automatically generated data seem to reflect illness activity in bipolar disorder. Smartphone-based electronic automatically generated data may represent an electronic marker of illness in bipolar disorder and may be used as objective outcome measures in future efficacy trials.
Taken together, these findings suggest that smartphone-based electronic monitoring could assist with diagnosis, monitoring illness activity, and treatment by providing innovative and novel interventions on-demand with a potentially global reach, filling the gap between the availability of and the demand for treatment interventions.

Electronic monitoring of psychomotor activity and heart rate in bipolar disorder

The author's work

Ethics

All studies were approved by the Regional Ethics Committee of The Capital Region of Denmark (H-B-2007-024; H-2-2011-056) and The Danish Data Protection Agency (KF 01 272130; 2013-41-1710). The studies complied with the Declaration of Helsinki.

Heart rate and movement monitoring studies

Differences in psychomotor activity among individuals with bipolar disorder, individuals with unipolar disorder and healthy controls and state-related differences within bipolar disorder were investigated by the author in the following studies. Furthermore, state-related differences in heart rate variability within bipolar disorder were investigated by the author.

Study V: Heart rate and movement monitoring in bipolar disorder

Article I by the author presents data from the heart rate and movement study (10).

Using an electronic heart rate and a movement sensor, the aim of the study was to investigate differences in the level of psychomotor activity among individuals with bipolar disorder, individuals with unipolar disorder and healthy control individuals.

A total of 38 patients with a diagnosis of bipolar disorder type I (n=18) or unipolar disorder (n=20) diagnosed using the Structured Clinical Interview for DSM-IX Axis I Disorders (SCID) (300), age between 18 to 60 years, and an HDRS-17 score <25 were included. A gender-matched control group of healthy control individuals (n=31) without psychiatric disorders in first-degree relatives was recruited. A combined heart rate and movement sensor (Actiheart, Cambridge Neurotechnology, Ltd., Papworth, UK) attached to the chest using two standard ECG electrodes was used to assess heart rate and movement in naturalistic settings.

The patients had a higher sleeping heart rate (bpm; unipolar disorder: 63.3 (SD 7.0); bipolar disorder: 62.8 (SD 9.0); healthy control individuals: 54.9 (SD 8.0), p<0.001), lower fitness (ml/O2/kg/min; unipolar disorder: 34.0 (SD 7.04); bipolar disorder: 39.2 (SD 6.9); healthy control individuals: 42.4 (SD 8.9), p=0.02), lower acceleration (m/s2; unipolar disorder: 0.085 [0.051-0.13); bipolar disorder: 0.059 [0.051-0.079]; healthy control individuals: 0.11 [0.082-0.14], p=0.004), and lower activity

energy expenditure (kJ/day/kg; unipolar disorder: 35.2 [23.5-53-0]; bipolar disorder: 43.2 [28.8-58.9]; healthy control individuals: 51.9 [41.1-69.6], p=0.004) compared with healthy control individuals. During a remitted or mild/moderate depressive state, the patients with bipolar disorder had lower acceleration (p=0.01) and activity energy expenditure (p=0.02) than the patients with unipolar disorder in an analysis adjusted for HDRS-17 scores (10).

In addition to collecting smartphone data, as part of the MONARCA III study (section 7.1, p 26), the included patients were invited to wear the same combined heart rate and movement sensor that was used in the abovementioned study (study V).

Articles VIII and XI by the author present data from the heart rate and movement part of the MONARCA III study (11,12).

The aims were to investigate state-related differences in psychomotor activity and HRV in bipolar disorder.

A total of 19 patients with bipolar disorder diagnosed according to ICD-10 criteria were followed for 12 weeks during the early phase of their course of treatment, and they were invited to visit the researcher every second week for an assessment of the severity of their depressive and manic symptoms using the HDRS-17 and the YMRS, respectively. A combined heart rate and movement sensor (Actiheart, Cambridge Neurotechnology, Ltd., Papworth, UK) attached to the chest using two standard ECG electrodes was used to assess heart rate and movement in naturalistic settings during different affective states.

Compared with patients in a euthymic state, patients in a manic state had a higher activity energy expenditure (B=14.79, 95% CI: 0.90; 28.68, p=0.037). Compared with patients in a manic state, patients in a depressive state had lower acceleration (B=-0.064, 95% CI: -0.005; -0.12, p=0.030) and activity energy expenditure (B=-16.57, 95% CI: -30.80; -2.35, p=0.020). Furthermore, there was a positive correlation between the severity of manic symptoms and acceleration (p=0.015) and activity energy expenditure (p=0.038) (11).

In unadjusted analyses and analyses adjusted for age, gender and heart rate, HRV was increased by 18% during a manic state compared with a depressed state (adjusted analysis: eB=1.18, 95% CI: 1.16; 1.20, p<0.001) and was increased by 17% in a manic state compared with a euthymic state (adjusted analysis: eB=1.17, 95% CI: 1.15; 1.19, p<0.001), whereas there was no difference between a depressive state and a euthymic state (p=0.12). Lastly, in both the unadjusted analyses and the analyses adjusted for age, gender and heart rate, there was a negative correlation between HRV and the severity of depressive symptoms measured using the HDRS-17 (adjusted analyses: eB=0.99, 95% CI: 0.99; 0.99, p<0.001) and a positive correlation between HRV and the severity of manic symptoms measured using the YMRS (adjusted analyses: eB=1.02, 95% CI: 1.02; 1.02, p<0.001). Including BMI as a covariate in any of the analyses of HRV did not alter any of the associations; therefore, BMI was omitted from the final analyses (12).

STUDY VI: HEART RATE VARIABILITY IN BIPOLAR DISORDER: A SYSTEMATIC REVIEW AND META-ANALYSIS

Article XII by the author presents data from the systematic review and meta-analysis (9).

To investigate the evidence of HRV alterations in bipolar disorder, a systematic review and meta-analysis reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (213) was conducted.

The review included original studies reporting on HRV in 1) adult patients with bipolar disorder above 18 years of age; and 2) cross-sectional or longitudinal studies comparing HRV in adult patients with bipolar disorder a) with healthy control individuals or with patients with major depressive disorder or schizophrenia, b) between different affective states, c) longitudinal studies comparing changes in HRV from mania or depression to euthymia or d) treatment intervention studies for an acute affective episode. Studies were identified through searches of the electronic databases MEDLINE (January 1950 to October 2016), PsychINFO (1806 to October 2016), Embase (1974 to October 2016), The Cochrane Library (issue 10, 2016), and Scopus (1995 to October 2016) supplemented by hand-searches of the reference lists of retrieved articles. A total of 15 articles including 2534 individuals (572 patients with bipolar disorder (I, II, both or not specified), 1183 healthy control individuals, 683 patients with major depressive disorder, and 96 patients with schizophrenia) were included for review. Of the 15 studies included in the meta-analysis, 13 investigated differences in HRV between patients with bipolar disorder and healthy control individuals, four studies investigated differences in HRV between patients with bipolar disorder and patients with unipolar disorder, and three studies investigated differences in HRV between patients with bipolar disorder and patients with schizophrenia. One of the included studies investigated differences in HRV between affective states or changes in HRV during affective states. Information regarding matching between patients with bipolar disorder and healthy control individuals on parameters such as age, gender and BMI was provided in four out of 13 studies. Only three of the included studies reported statistical analyses adjusted for confounding factors, nine studies reported estimates based on unadjusted analyses, and five studies did not provide information regarding this matter.

Overall, when different affective states were not considered, HRV was reduced in individuals with bipolar disorder compared with healthy control individuals (g=-1.77, 95% CI: -2.46; -1.09, P<0.001, 10 comparisons, n=1581). A large proportion of heterogeneity due to between-study variation was found (p<0.001). More recent publication year, larger study size and higher study quality were associated with a smaller difference in HRV between individuals with bipolar disorder and healthy control individuals. Large between-study heterogeneity, low study quality, and a lack of consideration of confounding factors were observed in individual studies.

The analyses did not show any differences in HRV between patients with bipolar disorder and those with unipolar disorder (p=0.30) or schizophrenia (p=0.29) (9).

Summary of studies V-VI

In summary, two original studies and one systematic review and meta-analysis concerning electronic monitoring of psychomotor activity and heart rate in bipolar disorder were conducted by the author. We aimed to investigate the use of electronic monitoring of psychomotor activity and heart rate in bipolar disorder as markers of state and trait.

Regarding psychomotor activity, patients with bipolar disorder and unipolar disorder had lower psychomotor activity measured using a combined heart rate and movement sensor compared with healthy control individuals. Furthermore, patients with bipolar disorder had lower psychomotor activity compared with patients with unipolar disorder. Within bipolar disorder, patients in a manic state had increased psychomotor activity compared with patients in a depressive or euthymic state.

Regarding HRV alterations in bipolar disorder, HRV was increased during manic states compared with depressive and euthymic states. A systematic review and meta-analysis of HRV alterations in bipolar disorder found that HRV was reduced in

individuals with bipolar disorder overall compared with healthy control individuals, but methodological issues in individual studies limited the findings.

Prior to the work by the author, no studies investigating psychomotor activity and HRV in bipolar disorder using a combined heart rate and movement sensor had been published. Furthermore, the evidence of HRV alterations in individuals with bipolar disorder compared with healthy control individuals was unaddressed.

DISCUSSION

Strengths of the author's work

In contrast to prior studies using wrist- or ankle-worn accelerometers to measure movement of the extremities and ECGs, the studies by the author investigated differences in psychomotor activity and HRV using a combined heart rate and movement sensor worn on the truncus, which reflected 'whole body' movement, and collected data on heart rate and movement at the same time. The reference method for measuring energy expenditure under free-living circumstances is the doubly labeled water technique (186). However, unlike a combined heart rate and movement sensor, this method cannot quantify subcomponents of activity patterns, such as activity energy expenditure, hourly variations and intensity, or provide information on heart rate.

Unlike most previous studies, the studies by the author investigated differences in psychomotor activity and HRV between patients with bipolar disorder, patients with unipolar disorder and healthy control individuals and investigated state-related differences in bipolar disorder using a longitudinal study design; additionally, they compared psychomotor activity with clinically rated depressive and manic symptoms measured using standardized rating scales and addressed confounding issues known to influence activity and heart rate (e.g. age, gender and BMI) in the statistical analyses. Furthermore, the studies by the author included outpatients and collected data during everyday life and in naturalistic settings. Prior studies primarily investigated differences in psychomotor activity and HRV using a cross-sectional case-control study design and did not investigate differences in psychomotor activity and HRV between affective states within bipolar disorder.

The author was the first to conduct a focused systematic review and meta-analysis of HRV in bipolar disorder. Prior systematic reviews and meta-analyses did not employ separate analyses for bipolar disorder, and thus the use of HRV as a marker of bipolar disorder was not investigated (198). Furthermore, the systematic review and meta-analysis of HRV in bipolar disorder by the author was the first focused meta-analysis of HRV in bipolar disorder to include analyses of publication bias, quality assessment and moderator analyses.

Limitations of the author's work

The original studies by the author included rather small samples of patients with bipolar disorder, patients with unipolar disorder and healthy control individuals. First-degree relatives at risk of bipolar disorder were not included, and thus the use of heart rate-based electronic monitoring as an early diagnostic marker was not investigated. The original study investigating state-related differences in psychomotor activity and HRV did not include healthy control individuals, and thus trait-related alterations in HRV were not investigated.

As with the smartphone-based electronic monitoring studies, the follow-up periods could have been longer, thereby allowing more depressive and manic episodes and more severe depressive and manic symptoms to present. Furthermore, the patients' affective states were defined according to clinical ICD-10 diagnoses of bipolar disorder current episode manic/mixed, depression or euthymia combined with pre-defined cut-off scores on the HDRS-17 and the YMRS. The cut-off scores were chosen to achieve high specificity of a current depressive and manic state, and consequently a euthymic state included patients in full and partial remission.

Due to the small sample size, some of the non-significant findings may be the result of type II errors, and the findings are based on small numbers and should be interpreted with caution. However, each patient was assessed several times using a longitudinal study design, and the statistical models allowed for both within-and between-individual variations over time, which increased the statistical power.

Furthermore, the patients received different types, doses and combinations of psychopharmacological treatments during the studies, which may have influenced the results. However, most of the patients did not alter their medication during the studies, and thus medication alteration likely did not have a major impact on the study findings. The studies were not designed or powered to investigate possible differences in psychomotor activity and HRV between bipolar disorder type I and bipolar disorder type II.

The HRV data were collected over prolonged periods sampled in 30-seconds epochs and thus not did not represent beat-by-beat data. However, sensor data were collected consecutively over a minimum of three days, and more than 100,000 data points were included in the analyses. Furthermore, the HRV proxy measure was calculated as the mean difference between the second-shortest and the second-longest interbeat interval collected during the epochs and thus was potentially prone to movement artefacts. However, only resting data collected at night (between midnight to 6 am) when acceleration was zero were included in the analyses.

Even though meta-analyses have the potential to overcome issues related to low power by combining studies, they carry a risk of producing spurious results due to bias issues in individual studies. In the systematic review and meta-analysis of HRV in bipolar disorder, several concerns regarding the individual studies and outcomes limit the overall findings. Because only two randomized controlled intervention trials were available, the meta-analyses were solely based on case-control studies, which have inherent risks of selection bias, performance bias and confounding. Since large degrees of unexplained heterogeneity were observed, the mere effect sizes included in the present meta-analyses should be interpreted with caution. Due to the rather small number of studies available for analyses, meta-regression analyses were conducted as univariate analyses that did not account for multiple comparisons. Furthermore, few studies investigating differences in HRV among psychiatric disorders were identified; thus analyses of differences in HRV across diagnoses should be interpreted with caution, and the lack of statistically significant findings on differences in HRV among psychiatric disorders could represent type II errors. The inclusion of patients with bipolar disorder regardless of illness stage, subtype of bipolar disorder, affective state or medication status may have made our results more generalizable but at a cost of heterogeneity among studies. Finally, the quality of the included studies was assessed using a non-validated quality assessment tool (198), and the results from these assessments may be considered arbitrary; however, using this assessment tool allowed standardized grading

of study quality, which is an important aspect in critical appraisal of the evidence.

Electronic monitoring of psychomotor activity and heart rate in bipolar disorder

Alterations in psychomotor activity represent central aspects of bipolar disorder. Psychomotor activity consists of several aspects concerning movement and behavior, and psychomotor retardation during bipolar depression and increased psychomotor activity during mania have been described in the literature (14,15,60,61,64,70–72). HRV is a validated measure of balance in the autonomic nervous system, and studies have suggested that HRV is reduced in individuals with bipolar disorder compared with healthy control individuals (105,111–117,119,121,197). Thus, alterations in psychomotor activity and HRV could possibly be used as objective markers of trait and state in bipolar disorder.

Previous studies investigating alterations in psychomotor activity in bipolar disorder have used clinical assessments and self-reports (63,67–69,301), and self-reports have been found unreliable, with a tendency to overestimate physical activity levels and underestimate levels of sedentary behavior in bipolar disorder (302–304). The use of clinical assessments and self-reports is based on evaluations and subjective information, often collected retrospectively, which introduces a risk of decreased validity and recall bias. Other studies using various types of objective wrist- or ankle-worn accelerometers to investigate psychomotor activity have been published (15,61,76,77,79,80,305–309), and some studies using these wrist- or ankle-worn accelerometers have investigated various types of sleep rhythm disruptions in bipolar disorder (306,310–320). The use of accelerometers allows for a more objective estimation of psychomotor activity compared with self-reports and eliminates the risk of recall bias. The results of studies using accelerometers to investigate levels of psychomotor activity in bipolar disorder have been divergent, and most such studies monitored the level of psychomotor activity during hospitalization, thus not reflecting the level of movement during everyday life and in naturalistic settings (15,61,76,77,79,80). Furthermore, measuring the psychomotor activity levels of patients with bipolar disorder during hospitalization complicates comparisons with healthy control individuals measured during everyday life. In addition, the estimation of other physiological constructs, such as heart rate, has not been possible with studies using accelerometers. Furthermore, the placement of a movement monitor is important, and the monitor needs to be placed on the part of the body relevant to the movement that is being studied (321). Prior studies have measured psychomotor activity at a single time-point in cross-sectional design that did not include the longitudinal study of patients with bipolar disorder during different affective states, and thus intra-individual alterations have not been investigated (10,15,61,76,77,79,80,306). Furthermore, prior studies have not addressed confounding issues known to influence activity level and heart rate (e.g. age, gender and BMI) in the statistical analyses (61,76,77,306), and thus it is difficult to estimate whether alterations in psychomotor activity were due to bipolar disorder or simply due to differences in other confounding factors that might affect the level of psychomotor activity. Along this line, prior studies have suggested that bipolar depression is more likely to manifest as psychomotor retardation and other atypical symptoms compared with unipolar depression (10,14,15,60,62,189), and patients suffering from unipolar disorder presenting with psychomotor retardation have been reported to be at risk of a later bipolar course (14,190). However, studies comparing psychomotor activity between bipolar disorder and unipolar disorder have not adjusted their statistical analyses for differences in mood symptoms, e.g. HDRS-17 scores.

As with prior studies concerning psychomotor activity, most prior studies investigating HRV alterations in bipolar disorder have used cross-sectional case-control study designs (105,111–117,119,121,197), and in individual studies, patients were compared with healthy control individuals during different affective states. Thus, two studies investigated differences between individuals in a bipolar manic state and healthy control individuals (112,116), another study investigated differences between individuals in a bipolar depressive state and healthy control individuals (113), while other studies used different and heterogeneous state definitions (118). Differences in HRV between affective states in bipolar disorder have only been reported in one study (12) and described in recent extended case-series (202–205). Thus, the potential use of HRV as a state marker is unknown.

Confounding factors (e.g. age, gender, BMI, respiratory frequency, psychopharmacological medication use) that are known to affect HRV were addressed in the statistical analyses of only one study (121), and it thus it is possible that the identified differences in HRV between individuals with bipolar disorder and healthy control individuals were due to differences in some of these factors. Limited information was provided on whether the cases were reliably assessed according to international criteria, whether the control individuals were recruited from the same background population as the cases, and whether the HRV assessors were blinded to disease status during HRV assessments, and there was a lack of clear inclusion and exclusion criteria. Overall, several methodological issues were identified in the individual studies, limiting the quality of evidence.

CONCLUSIONS

Electronic monitoring of psychomotor activity, heart rate and HRV seems to reflect illness activity in bipolar disorder and differentiate between individuals with bipolar disorder and healthy control individuals. However, methodological issues in individual studies and a lack of studies using rigorous methodology limit the evidence. Although the studies need to be replicated, electronic monitoring of psychomotor activity, heart rate and HRV in bipolar disorder may be able to assist the diagnosis and monitoring of illness activity in bipolar disorder in naturalistic settings.

OVERALL DISCUSSION AND CONCLUSIONS

There is a need to identify objective markers relevant to diagnosis, illness activity monitoring and early treatment intervention in bipolar disorder. Electronic monitoring enables the collection of fine-grained data over the long term in naturalistic settings that may identify underlying pathophysiological processes in bipolar disorder and provide markers and outright treatment interventions. Ultimately, such markers could be used as outcome measures in future efficacy trials in bipolar disorder.

mHealth interventions, particularly in the form of smartphone applications, have the potential to minimize the treatment barriers of distance, time and costs. Furthermore, the use of sensors embedded within these technologies as a monitoring tool could potentially provide opportunities for new areas of research and for developing markers of illness, and it opens up the possibility of more individualized treatment options. However, there are methodological issues in individual studies and a severe lack of RCTs, limiting the evidence regarding electronic monitoring in bipolar disorder, and thus it seems premature to draw conclusions regarding these effects.

Few observational studies have investigated whether smartphone-based electronic self-monitoring and smartphone-based electronic automatically generated data reflect illness activity in bipolar disorder, but the results seem promising despite several methodological issues in individual studies. Smartphone-based electronic automatically generated data such as the number of text messages sent/day, the number of incoming and outgoing calls/day, the number of changes in cell tower IDs/day, and voice features may represent electronic markers of illness in bipolar disorder. Smartphone-based electronic monitoring may be able to assist in the diagnosis, monitoring, and treatment of bipolar disorder, providing innovative and novel interventions on-demand with a potentially global reach and filling the gap between the availability of and demand for treatment interventions.

Electronic heart rate-based monitoring of psychomotor activity and HRV seem to reflect illness activity in bipolar disorder and to differentiate between individuals with bipolar disorder and healthy control individuals. However, methodological issues, such as the inclusion of small sample sizes, reliance on a case-control study design, bias issues at different levels and a lack of control for confounding factors in statistical analyses in individual studies, limit the evidence. Strikingly, although bipolar disorder is characterized by recurrent affective episodes of different polarity, state-related differences in electronically monitored activity and HRV have been sparingly investigated. Although the studies need to be replicated, heart rate-based electronic monitoring of psychomotor activity and HRV in bipolar disorder may be able to assist in the diagnosis and monitoring of illness activity in bipolar disorder.
10. methodological considerations and clinical implications
The present dissertation has several implications regarding the use of electronic monitoring as a marker and treatment intervention in bipolar disorder.

METHODOLOGICAL CONSIDERATIONS AND CLINICAL IMPLICATIONS

The present dissertation has several implications regarding the use of electronic monitoring as a marker and treatment intervention in bipolar disorder.

Methodological considerations

The dissertation showed that the results regarding electronic monitoring in bipolar disorder are based on individual studies with methodological challenges at different levels. Few of the studies addressed confounding issues in the statistical analyses, and most of the study findings were based on case-control designs that have an inherent risk of confounding. Longitudinal studies investigating within-individual alterations in electronically monitored parameters during the course of bipolar disorder were rare, and in studies investigating state-related differences in electronic data, information on definitions of depressive, manic and euthymic states was limited.

Few RCTs were available, and most of these reported unblinded self-reported outcome measures.

Clinical implications

Despite the seeming appeal and ease of use of electronic monitoring in the clinical care of bipolar disorder, the present dissertation illustrates the need for careful consideration and precautions before electronic monitoring is implemented as a standard clinical tool. Thus, the dissertation indicates that there is currently a lack of evidence due to few RCTs and that possible harmful effects have not been addressed and reported appropriately in individual studies. Furthermore, economical evaluations are currently not available; therefore, the cost-effectiveness of electronic monitoring is unknown.

FUTURE PERSPECTIVES

Based on the data presented in the dissertation, some suggestions for future research regarding electronic monitoring in bipolar disorder may be considered.

Methodological considerations

Study design

Randomized controlled trials

Well-designed and well-conducted RCTs set the methodological standard of excellence in medical research (224). To evaluate the evidence regarding electronic monitoring, rigorously designed and pre-registered RCTs with critical evaluations of the beneficial and harmful effects of electronic interventions on both depressive and manic symptoms/episodes should be conducted, and positive, negative and neutral findings should be reported accordingly. Journals should be encouraged to publish reports from RCTs regardless of the results, thus limiting bias on all levels. These studies could provide a more nuanced picture of the use of electronic monitoring as a treatment intervention and marker in bipolar disorder, and future meta-analyses combining data from individual studies should be able to include positive, neutral and negative findings from individual studies. In this way, estimates of effect sizes would be based on more variable study findings. Furthermore, future RCTs should report according to the CONSORT statement (229); systematic reviews and meta-analyses should report according to the PRISMA statement, providing enough details on search strategy to allow for replication (213); and observational studies should be reported and designed according to the STROBE statement (322).

Individual studies of complex electronic treatment interventions using standardized reporting guidelines could provide tools to clearly identify the content and context of the interventions, interpret how the interventions were implemented in the specific trial settings and facilitate the replication of study findings (147). Furthermore, when investigating complex treatment interventions, considerations on measuring the study participants' fidelity to the investigated intervention should be considered.
Future RCTs investigating the possible effect of interventions consisting of prediction analyses and forecasts of upcoming deteriorations based on models from the collected smartphone-based automatically generated data without self-monitoring in bipolar disorder should consider the challenges involved in delivering probabilistic warnings to patients who may not be able to interpret the information or react appropriately (323).

The complex episodic nature of bipolar disorder requires long-term studies to demonstrate the effects on depressive symptoms, manic symptoms and affective episodes. Thus, to provide more valid and robust findings, RCTs with larger sample sizes are needed. One way to meet this need could be by conducting multicenter studies that include larger samples of patients representing a broad range of patients with bipolar disorder, thereby also increasing the external validity of study results. Including clinically assessed, register-based (e.g. readmission) or other more objective, unbiased outcome measures (e.g. smartphone-based electronic automatically generated data) could minimize the potential detection bias in outcome measures. Designing studies with longer follow-up periods could provide detailed information on the long-term course of illness and the effects of interventions over the long term. Furthermore, longitudinal studies provide opportunities to investigate within-individual changes in electron-

ic measures over time, thus evaluating the potential for such measures to function as individual markers of affective states and prognosis.

To allow the evaluation of the possible selection bias in studies, detailed information regarding excluded patients and non-participants and the reasons patients declined to participate should be provided.

Case-control studies

Investigating the correlations between smartphone-based electronic self-monitoring and HDRS-17 and YMRS scores in patients with bipolar disorder with other courses of illness, age groups, cultural backgrounds, etc. could provide further knowledge regarding the validity of such monitoring. Likewise, investigating the correlations between smartphone-based electronic automatically generated data and HDRS-17 and YMRS scores in these populations would add to the validity of these measures.

Case-control studies carry an inherent risk of bias at different levels, such as selection bias, information bias and confounding, necessitating strict methodological requirements and thorough considerations of the study design and analyses. Defining and recruiting a proper control group in case-control studies is always difficult. Including healthy control individuals representative of the same background population as the patients and only differing from the patients with regard to the bipolar disorder diagnosis should be a priority. Furthermore, including statements on the physical health status of mentally healthy control individuals, including information regarding whether the controls represent 'super-healthy' individuals should be provided (324). Establishing and reporting clear eligibility criteria for both cases and controls is necessary.

To compare findings regarding state-related differences in electronic data across studies, clear definitions of affective states should be provided. Considerations regarding how to address confounding in both the design phase and the analysis phase should be a priority, and blinding outcome assessors to group allocation (case or control) could minimize detection bias.

Including healthy first-degree relatives at risk of bipolar disorder and healthy control individuals, as the author are currently doing (in the BIO study; clinicaltrials.gov identifier: NCT02888262), could provide further information on the use of electronic monitoring as an early predictive or diagnostic marker and could provide important knowledge regarding the causality of changes in electronically monitored markers in bipolar disorder (299).

Statistical analyses

Considering, planning and documenting the statistical analyses in advance and predefining possible confounding factors to include in the statistical analyses should be a priority in RCTs, case-control studies, longitudinal follow-up studies, systematic reviews and meta-analyses. To allow evaluations of the impact of individual confounding factors, both unadjusted and adjusted analyses should be reported. The advance publication of study protocols specifying all phases of the study regardless of the design could assist in this process.

Blinding researchers to data during as many phases of the study process as possible could minimize possible sources of bias. Such blinding could occur by blinding the researchers collecting the data to the participants' status during the data collection phase, blinding the researchers to the electronic data, and blinding the researchers conducting the statistical analyses.

In RCTs, combining electronic data to produce composite outcome measures requires thorough planning of which variables to combine and how to combine them; consequently, it should be based on predefined hypotheses and discussed in advance. The CONSORT statement recommends that the primary predefined outcome measures be as relevant to the patients as possible; however, combining outcome measures may not provide the information needed for patient care because each patient may have a different risk profile for each of the components being combined (229). In a complex disorder such as bipolar disorder that is characterized by different polarities of (hypo)mania, depression, euthymia and mixed states, it may be difficult to interpret the net effect of any given treatment intervention on a combined outcome measure, and decisions regarding patient management may be complicated (231,232). Furthermore, if the direction of an effect of a given treatment intervention is equal on all of the combined measures, the net effect may be overestimated or even diluted (325–327).

Estimates using the receiver operating curves (ROC), sensitivity, specificity, positive predictive values and negative predictive values of potential electronic markers could allow for clinically relevant evaluations that compare performance between tests and appear to be a necessary step in future evaluations of electronic markers.

'Big data' refers to a large amount of data that are generated fast, have great variety and are complex. Furthermore, big data provides opportunities for exploration, observation and hypothesis generation, and analyses may lead to the detection of new markers in bipolar disorder. Statistical analyses of large data sets that include large numbers of variables introduce the risk of false findings, and some of the explanatory variables may not be independent. In addition, future analyses should address and consider issues regarding time-varying confounding and exposure. Statistical analyses using machine-learning techniques based on adjustable user-dependent models learning as more data from each individual become available over time may increase the accuracy of electronic automatically generated smartphone-based data as markers in bipolar disorder and may provide forecasts of upcoming deteriorations. A forecasting analytic approach to future events derived from user-dependent models based on the patient's own historical data could provide opportunities for truly personalized early treatment intervention. However, at the same time, predictive information on possible upcoming deteriorations could be delivered to patients who may or may not be capable of interpreting and acting on these forecasts. Consequently, access to clinicians who know how to interpret and act on the information provided by these forecasts needs to be a priority when using such a system.

Electronic data considerations

Strikingly, none of identified studies on electronic monitoring in bipolar disorder, including those by the author, provided information regarding the economical aspect of the development, use and maintenance of the IT platforms, but this is a relevant factor for future efforts and clinical implementations. Evaluations of the cost-effectiveness of using electronic monitoring compared with other treatment interventions will be important in evaluating future treatment options.

Ethical considerations

Electronic monitoring offers new directions in the treatment and monitoring in bipolar disorder. However, the use of electronic monitoring in bipolar disorder also raises some ethical aspects

that should be considered. The regulation of mHealth is opaque, and it is currently unclear whether and when mHealth solutions should be considered medical devices and regulated accordingly. The use of unvalidated applications with potentially poor quality information or maybe even misinformation may lead to harmful effects. It may not in all cases be clearly stated whether or not a monitoring tool is for commercial or medical purposes. One of the main concerns to consider and address continuously when using electronic monitoring in bipolar disorder should be patient safety and personal privacy. When using electronic monitoring as part of the treatment, clear criteria and consensus between patients and mental health care providers regarding when clinicians should react and contact patients based on the collected data should be established before an electronic monitoring method is used and should be addressed and reevaluated continuously. The safety of data storage and encryption requires continuous consideration. Clear agreements for whom the data is shared with should be made before electronic monitoring begins, and the patients should always have the possibility to withdraw their consent for data sharing and have their data deleted. Furthermore, data collection and detailed, continuous monitoring using electronic data requires a high degree of trust between patients and mental health care providers. During the studies performed by the author, none of the patients reported that they felt 'watched'; nonetheless, several ethical considerations need to be a priority and should be reevaluated and addressed continuously. Further issues that need to be addressed continuously include confidentiality and privacy, data security, the possible harmful effects of using mHealth interventions, individual wishes and requirements, individual technical skills, and cultural and legal differences between nations. Methodologically rigorous, large and long-term studies, including RCTs, should be a priority, and some kind of international certification and re-certification process should be considered.

Another issue relates to whether to allow relatives to have access to the electronically monitored data. Views on this matter will surely differ according to many factors, such as culture, nation, age, gender, etc. In some settings, including relatives may be viewed as an extra support element, while in others, it may not.

If patients are using an electronic monitoring system, clear standard operation procedures regarding the actions that both mental health care providers and IT personnel should take if the system fails should be prepared and ready to deploy.

Whether future electronic monitoring systems should include a self-monitoring part, a passive monitoring part or both requires careful and thorough considerations. Self-monitoring provides opportunities for increased illness insight and empowerment and for continuous medication adherence monitoring.

Electronic monitoring: specific considerations

Despite several limitations in individual studies, the evidence presented in this dissertation supports electronic monitoring in bipolar disorder as a viable and useful way to monitor illness activity and to deliver personalized early treatment interventions in bipolar disorder. However, study findings need to be replicated to further investigate the use of electronic smartphone-based monitoring as markers of illness and treatment intervention. Study methodologies regarding the electronic monitoring of psychomotor activity, heart rate and HRV must improve.

Considering the complex and heterogeneous nature of bipolar disorder, combining individual electronic measures in composite measures based on user-dependent models could potentially contribute to the sensitivity and specificity of an electronically-based trait and state marker.

Including healthy control individuals, first-degree relatives at risk of bipolar disorder and people with other psychiatric disorders could contribute to the investigation of electronically-based markers of trait. Longitudinal studies with long follow-up periods are recommended to investigate the use of electronic monitoring for prediction, staging, treatment response and prognosis in bipolar disorder.

Including evaluations of adherence to interventions and fidelity could contribute to the understanding of the limitations, barriers and benefits of electronically delivered treatment interventions. Considering combined composite measure as outcome measures in RCTs may help to improve statistical precision. However, limitations include the possibility that the different measures composing the combined outcome measure will not be modified in the same direction. The selection of the measures combined in composite end-points requires notable methodological attention to ensure that the most reliable estimates are retrieved. When applied as outcome measures, however, composite outcomes should be used with caution.

Summary of important aspects to consider

- Investigation of the positive, neutral and negative effects of electronic monitoring in carefully designed large RCTs
- Reporting electronic interventions according to standardized guidelines to enable the identification of all components of the interventions
- Designing methodologically rigorous case-control studies that include patients with bipolar disorder, first-degree relatives at risk of bipolar disorder and healthy control individuals
- Carefully considering multiple levels of the statistical analyses, including predefining which outcomes to consider and confounding factors to include
- Carefully considering ethical and legal aspects
- Conducting cost-effectiveness evaluations
- Considering combining electronic monitoring data into composite measures

OVERALL SUMMARY IN ENGLISH

Major reasons for the insufficient effects of current treatment options in bipolar disorder include delayed intervention for prodromal depressive and manic symptoms and decreased adherence to psychopharmacological treatment. The reliance on subjective information and clinical evaluations when diagnosing and assessing the severity of depressive and manic symptoms calls for less biased and more objective markers. By using electronic devices, fine-grained data on complex psychopathological aspects of bipolar disorder can be evaluated unobtrusively over the long term. Moreover, electronic data could possibly represent candidate markers of diagnosis and illness activity in bipolar disorder and allow for early and individualized intervention for prodromal symptoms outside clinical settings.

The present dissertation concerns the use of electronic monitoring as a marker and treatment intervention in bipolar disorder and investigated the scientific literature and body of evidence within the area, which includes ten original study reports and two systematic reviews, one of which included a meta-analysis, conducted by the author of the dissertation.

Taken together, the literature presented in this dissertation illustrates that 1) smartphone-based electronic self-monitoring of mood seems to reflect clinically assessed depressive and manic symptoms and enables the long-term characterization of mood

instability in bipolar disorder; 2) preliminary results suggest that smartphone-based automatically generated data (e.g. the number of text messages sent/day; the number of incoming and outgoing calls/day; the number of changes in cell tower IDs/day; and voice features) seem to reflect clinically assessed depressive and manic symptoms in bipolar disorder; 3) smartphone-based electronic self-monitoring had no effects on the severity of depressive and manic symptoms in bipolar disorder, according to a randomized controlled trial; and 4) electronic monitoring of psychomotor activity and heart rate variability seems to reflect illness activity in bipolar disorder and differentiate between patients with bipolar disorder and healthy control individuals.

These findings point toward the usefulness of electronic monitoring as a marker of illness in bipolar disorder. Using electronic monitoring as a treatment intervention could provide innovative and novel interventions on-demand with a potential global reach, filling the gap between availability and the need for treatment. However, future studies using rigorous methodology and more randomized controlled trials that carefully investigate the positive effects and possible harmful effects of electronic monitoring in bipolar disorder are needed. In addition, patient safety, privacy issues, data security and legal aspects are major concerns that must be considered and addressed when using electronic monitoring.

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