Use of automated medication adherence monitoring in bipolar disorder research: pitfalls, pragmatics, and possibilities

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Abstract

Objectives: Medication nonadherence occurs in 20–60% of persons with bipolar disorder (BD) and is associated with serious negative outcomes, including relapse, hospitalization, incarceration, suicide and high healthcare costs. Various strategies have been developed to measure adherence in BD. This descriptive paper summarizes challenges and workable strategies using electronic medication monitoring in a randomized clinical trial (RCT) in patients with BD.

Methods: Descriptive data from 57 nonadherent individuals with BD enrolled in a prospective RCT evaluating a novel customized adherence intervention *versus* control were analyzed. Analyses focused on whole group data and did not assess intervention effects. Adherence was assessed with the self-reported Tablets Routine Questionnaire and the Medication Event Monitoring System (MEMS).

Results: The majority of participants were women (74%), African American (69%), with type I BD (77%). Practical limitations of MEMS included misuse in conjunction with pill minders, polypharmacy, cost, failure to bring to research visits, losing the device, and the device impacting baseline measurement. The advantages were more precise measurement, less biased recall, and collecting data from past time periods for missed interim visits.

Conclusions: Automated devices such as MEMS can assist investigators in evaluating adherence in patients with BD. Knowing the anticipated pitfalls allows study teams to implement preemptive procedures for successful implementation in BD adherence studies and can help pave the way for future refinements as automated adherence assessment technologies become more sophisticated and readily available.

Keywords: bipolar disorder, medication adherence, randomized controlled trial

Introduction

Adherence is defined by the World Health Organization as ‘the extent to which a person’s behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider’ [World Health Organization, 2003] and nonadherence to psychotropic medication continues to be a significant problem in the treatment of bipolar disorder (BD) [Perlick *et al.* 2004; Osterberg and Blaschke, 2005; Velligan *et al.* 2006; Pomykacz *et al.* 2007]. Medication nonadherence estimates for BD range between 20% and 60% [Lingam and Scott,

2002; Perlick *et al.* 2004; Colom *et al.* 2005] and nonadherence is associated with a variety of negative outcomes, including increased rates of relapse, poor treatment response, hospitalization, incarceration, suicidal behavior, as well as high elevated healthcare costs [Svarstad *et al.* 2001; Scott and Pope, 2002; Colom *et al.* 2005]. Given the enormity of the nonadherence problem in this population, multiple strategies and tools have been developed to measure adherence, including pill counts, pharmacy records, biological assays, self-report and interviewer-rated scales, as well as electronic monitoring devices [Sajatovic *et al.* 2010].

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There is agreement among clinicians and researchers alike that each method for measuring adherence comes with both benefits and drawbacks which vary depending on the patient population [Velligan *et al.* 2009]. In this paper we will focus on the Medication Event Monitoring System (MEMS; AARDEX Corporation, Zug, Switzerland), which has been recently acquired by MWV Healthcare, as a prototype for automated medication adherence monitoring devices more broadly. MEMS uses a microprocessor which is embedded in a pill bottle cap and records the time and date each time the cap is opened [Samet *et al.* 2001]. This method has the potential for very detailed and reliable adherence data, particularly when adhering to a specific time is essential. Although electronic monitoring such as MEMS caps, Med-eMonitor (InforMedix, Rockville, MD, USA), eCaps (Information Mediary Corporation, Ottawa, ON, Canada) and Medsignals (MedSignals Corporation, Lexington, KY) is often considered the 'gold standard' for adherence measurement in nonpsychiatric populations and has clear benefits, these devices also have drawbacks.

The use of automated medication monitoring devices such as MEMS caps have been utilized with various patient populations, including individuals with human immunodeficiency virus (HIV) infection [Pearson *et al.* 2007], schizophrenia [Byerly *et al.* 2005], tuberculosis [Hersberger and Arnet, 2012], hypertension [Zeller *et al.* 2007], and stroke [O'Carroll *et al.* 2013]. These studies point out both benefits and challenges of using such automated technologies, which are often population dependent.

In reviewing the literature, there is minimal information regarding the use of MEMS in BD and no known published studies using other automated adherence monitoring systems. Badiie and colleagues compared adherence data using MEMS caps *versus* self-report measures of adherence in individuals infected with HIV with and without comorbid BD [Badiie *et al.* 2012]. This study noted that MEMS may be less reliable in populations with comorbid BD given the cumbersome size, the complexity of using the MEMS in conjunction with adherence assistive methods such as a pill organizer or blister pack, and the tendency of people with BD to have their medications stored in multiple locations due to the unstable nature of their routines. These researchers also brought up the unreasonable cost of the MEMS,

making them ill-suited for clinical use, and noted that while MEMS may be the most reliable measure in the HIV + BD group, the clinical use of MEMS is largely impractical [Badiie *et al.* 2012].

Aim of the study

The aim of the current study was to describe the pitfalls, pragmatics and possibilities of using automated adherence medication monitoring in BD clinical trials. This report used MEMS as a prototype for electronic medication monitoring in a randomized clinical trial (RCT) aimed to improve BD medication adherence.

Materials and methods

This report used data from a larger, National Institute of Mental Health funded RCT testing a novel customized adherence enhancement (CAE) intervention intended to promote BD medication adherence *versus* an educational control (EDU) in poorly adherent individuals with BD. Participants were randomized at baseline on a 1:1 basis to receive either CAE or EDU. All study participants were followed for a 6-month period. Study inclusion criteria included having either type I or type II BD as confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders [First *et al.* 2002], BD for at least 2 years' duration, treatment with at least one evidence-based medication to stabilize mood for at least 6 months (lithium, anticonvulsant, or antipsychotic mood stabilizer) and less than 80% adherent with current BD medication treatment (i.e. lithium, anticonvulsant, or antipsychotic mood stabilizer) as measured by self-report on the Tablets Routine Questionnaire (TRQ) [Harvey, 1991; Harvey and Peet, 1991] for either the past week or the past month. Study inclusion criteria are purposely broad in order to be generalizable to real-world patients with BD and only individuals who were unable to participate in study procedures, unable/unwilling to provide informed consent, and those at immediate risk of harm to self or others were excluded.

A primary outcome of interest in the study is self-reported treatment adherence as measured by the TRQ. The TRQ results are supplemented with automated adherence monitoring using MEMS and qualitative interviews conducted with a subset of the sample intended to provide additional explanatory detail on factors that may shape adherence attitudes and adherence behavior.

Qualitative assessment

Qualitative interviews that included perceived barriers and facilitators to adherence with BD medications were conducted at baseline and at 6-month follow up. We employed a concurrent nested sequential explanatory design, in which the qualitative method is embedded, or nested, within the quantitative method and seeks information from different levels [Creswell *et al.* 2003]. A semi-structured interview guide was used. We analyzed baseline and follow-up interviews of eight patients (16 interviews), another three for which only baseline interview data were available, and one for which only follow-up interview data were available, a number within the recommended number of 5–25 individuals who have all experienced the same phenomenon [Polkinghorne, 1989]. Participation in the qualitative assessment was voluntary and the patients were able to participate in the main study, whether or not they agreed to participate in the qualitative assessment. Qualitative interviews were audio recorded and transcribed. Participants received modest compensation for their participation. In the baseline interview, there were no specific questions/prompts asking about the use of MEMS caps. In the follow-up interview, there was a prompt under the more general question, ‘What did you find helpful about the program?’ For the purposes of this paper, all interviews were screened for the mention of MEMS cap either spontaneously or in response to a prompt and those specific responses were utilized to illustrate various points in the ‘Challenges and pitfalls’ section of the paper.

Adherence assessment

Tablets Routine Questionnaire. TRQ is a self-report measure which identifies partial and full adherence in the past 7 and 30 days [Peet and Harvey, 1991; Scott and Pope, 2002]. TRQ has demonstrated a statistically significant association with past nonadherence, nonadherence in the past month, and nonadherence in the past week, and has been shown to correlate highly with lithium levels [Scott and Pope, 2002]. The TRQ was assessed for each evidence-based oral BD maintenance medication (lithium, anticonvulsant, antipsychotic) prescribed for at least 3 months. For individuals who were on more than one medication, an average TRQ was calculated. In addition, the number of medications to which each subject was less than 80% adherent was calculated. To minimize rater bias, the TRQ was scored by a rater blinded to intervention assignment based upon a video recording of the TRQ interview.

Medication Event Monitoring System. Study participants were given MEMS caps for their pill bottles, which record time/date of bottle opening. Participants were given the MEMS cap at the screening visit if they appeared to fit inclusion/exclusion criteria and asked to use the MEMS cap for the medication that the patient takes the most frequently. In the case of multiple BD medications taken at the same frequency, the medication that was started most recently was selected. MEMS was assessed at the baseline visit, prior to any intervention, based upon pill-taking behavior during the 1–2-week interval between screening and baseline visit. In addition to the report of percentage of doses taken on the MEMS, for comparison purposes, scores were also calculated according to the algorithm used by the TRQ. In the TRQ, the number of days that at least one prescribed dose was missed is tracked for a given period (past week or past month). The number of days a dose was missed is then divided by the total number of days in the period being assessed in order to compute the TRQ score. For example, if over a 7-day period a patient missed doses on four of those days, then four would be divided by seven for a past week TRQ score of 57% nonadherence. For the purposes of this study, we computed the inverse of the TRQ’s nonadherence scores (in our example, 43% adherence) in order to compare the results with the MEMS. In order to make comparisons between MEMS and TRQ, an additional MEMS calculation was computed such that days in which at least one dose was missed was treated as a completely nonadherent day.

The study was approved by the local Institutional Review Board and all study participants provided written informed consent at screening. Data on the first 57 participants provided the basis of this descriptive report.

Results

Sample description

Participants had a mean age of 45 (SD = 10.4), 42 were women (74%), 39 were African American (69%), 16 were white (28%) and 44 had type I BD (77%). Of the available data in our sample, 63% reported being prescribed one foundational drug treatment for BD at baseline while 30% reported being prescribed two drugs. The remaining 7% were prescribed three or more foundational drugs for BD. At baseline, the mean number of BD medications per patient was 1.45

(SD = 0.81) and the mean number of BD medications for which patients were less than 80% adherent was 1.20 (SD = 0.86). Given that the MEMS cap is issued at screening, the first MEMS measurement was at baseline (1–2 weeks following screening). When calculated according to the percentage of prescribed number of doses taken, MEMS was 41.0% doses taken (SD = 28.4) at baseline. Of the 20 qualitative interviews reviewed, a total of 5 (25%) mentioned MEMS. Of these, two were spontaneous and three were in response to a prompt.

Challenges and pitfalls in adherence assessment

During the course of the trial we encountered numerous issues with the implementation of MEMS caps, some of which have been reported in other patient populations and others which are unique to the treatment and research of individuals with BD. In the RCT, we are testing the efficacy of CAE to improve medication adherence compared with a psychoeducation control. As part of the treatment module addressing medication routines, the CAE intervention uses active problem solving to address the commonly reported problem of forgetting to take medication [Sajatovic *et al.* 2011] by integrating medication taking routines into the individual's daily schedule. As part of this process, it is recommended that participants use assistive devices, including weekly pill minders or smaller pill cases to be placed in alternate locations, such as at work or in the car. The use of such devices aims to reduce unintentional nonadherence due to forgetting, a common problem in this population stemming from the absence of daily structure [Sajatovic *et al.* 2009], but may influence the MEMS data as participants need to both have the MEMS cap with them at all times and remember to open the MEMS cap each time they take their medication, even if they are not storing the medication in the cap.

Another significant challenge in using MEMS caps for individuals with BD stems from the issue of polypharmacy [Post *et al.* 2010]. As demonstrated in our sample, patients with BD are often on more than one psychotropic medication to stabilize their condition, with 30% of the current sample on exactly two BD medications and a total of 37% on more than one BD medication. A study by Post and colleagues found that patients with BD who are sustained treatment responders take

an average of three different medications [Post *et al.* 2010]. In our trial, consistent with BD treatment guidelines [American Psychiatric Association, 2006], we counted lithium, anticonvulsants and antipsychotic medications as 'foundational' BD drugs. MEMS is better suited for maintenance or 'foundational' BD treatments, which are likely to be fewer as the bulkiness and cost of MEMS cap bottles limit their use with multiple medications [Bova *et al.* 2005]. This point is particularly salient when looking at the large number of medications prescribed for comorbid psychiatric and non-psychiatric conditions. In our sample, patients reported an average of 2.41 (SD = 2.11) chronic medical conditions and were prescribed an average of 1.97 (SD = 2.21) nonpsychotropic medications. If adherence to both psychotropic and nonpsychotropic medications were being measured in this population, utilizing four or more MEMS caps would not be reasonable, and thus the MEMS would not be a feasible measuring device.

A related challenge with MEMS caps is cost, with a single cap running in the order of US\$130. Additional items that need to be budgeted for when using MEMS technology include a 'reader' that plugs into the USB to download data (US\$122), software (US\$473), and bottles for the caps to ensure that the caps fit uniformly (US\$5.00 for each piece). In our study, shipping and duty charges from Switzerland to the US were approximately \$1200. Finally, since starting our study, the company has moved to utilizing an online database (previously this was optional) which adds an additional cost (quotes are determined on a case-by-case basis).

The size of the monitoring system may also limit portability and may be a contributing factor to subjects failing to bring in the MEMS to assessments. In our sample, none of the participants brought the MEMS cap to all assessments, 16% did not bring in the MEMS to the baseline, 37% of assessment visits occurred without the MEMS, and 9% of participants lost their MEMS caps entirely. In one instance, the MEMS cap was lost by the participant (and ultimately retrieved by the study staff) in the clinic parking lot before the study participant had even returned home with the system from his screening assessment. Of the five participants that permanently lost their caps, one threw the cap away, two lost them while moving, and two misplaced them under unknown circumstances.

Table 1. MEMS and TRQ calculations for percent adherent in 57 nonadherent patients with bipolar disorder.

	Screen	Baseline
MEMS calculated with TRQ algorithm*	–	31.4% (SD = 28.8)
MEMS calculated with % of doses taken	–	41.0% (SD = 28.4)
TRQ in past week with MEMS-monitored medication only	35.6% (SD = 28.5)	45.9% (SD = 33.8)
TRQ in past month with MEMS-monitored medication only	39.6% (SD = 31.1)	44.0% (SD = 31.4)
Mean TRQ in past week with all BD meds	38.1% (SD = 27.6)	49.9% (SD = 30.7)
Mean TRQ in past month with all BD meds	43.2% (SD = 29.3)	48.1% (SD = 28.3)
*TRQ algorithm = the number of days a dose was missed divided by the total number of days in that period [e.g. 4 days with at least one missed dose for the past week = 57% missed or 43% adherent].		
BD, bipolar disorder; MEMS, Medication Event Monitoring System; TRQ, Tablets Routine Questionnaire.		

Another factor that may limit the accuracy of the MEMS cap in research settings is the difficulty in determining a genuine adherence baseline that is not affected by the device. The first adherence measurement can only be taken once the MEMS device is introduced (following informed consent) and research participants are taught how to use it. Following the initial 1–2 week period of using MEMS, a measurement is taken. However, adherence may improve just by virtue of the novelty of the measuring device as well as knowing that one is participating in a study, particularly one whose aim is to improve adherence. This variant of the Hawthorne effect is likely to level off at some point during the study, but the inflated baseline data may potentially impact the outcome of the adherence data. In order to assess the impact of this measurement issue, we compared various calculations of the MEMS data at baseline with the self-reported TRQ data from both screening and baseline. When calculating MEMS baseline according to the algorithm used by the TRQ such that any dose missed in a given day is 0% adherence for that day, there was 31.4% adherence (SD = 28.8). When calculated according to the percentage of prescribed number of doses taken, a more precise measurement, MEMS baseline was somewhat higher, with 41.0% adherence (SD = 28.4). Specific to the MEMS-monitored medication, mean past week TRQ indicated 35.6% adherence (SD = 28.5) at screen and 45.9% adherence (SD = 33.8) at baseline. Mean adherence as measured by the TRQ at screen for all BD medications was slightly higher than the MEMS monitored medication alone, with 38.1% adherence (SD = 27.6) for the past week and mean adherence as measured by the TRQ at baseline for all BD medications was even higher, with 49.9% adherence (SD = 30.7) for the past week. When comparing TRQ and MEMS

at baseline (see Table 1), it is evident that using the TRQ itself leads to higher reported rates of adherence than the MEMS and using the TRQ algorithm for the MEMS calculates lower rates of adherence than the more specific measurement of percentage doses taken that the MEMS provides. There was no significant correlation between the mean past week TRQ and the number of days between screening and baseline ($r = 0.20$, $p = 0.14$). There was also no significant correlation between past week TRQ screening and baseline difference scores and the number of days between the respective visits ($r = 0.08$, $p = 0.57$).

Based on qualitative interviews, the use of the MEMS device does have at least some impact on adherence behavior. A few patients noted that seeing the bottle every day made them more likely to take their medication. However, one of these same individuals also noted that he/she did not always store the pills in the MEMS bottle and could not always remember to open it when taking the pills out from another bottle, a phenomenon referred to as ‘pocket dosing’. Similarly, another person noted that when he/she gets a refill every 30 days, he/she needs to remember to put it in the bottle ‘cause if I don’t put it in there, I’ll just take it out of the bottle that it comes in’. One patient indicated that he/she does not like the bottle ‘cause it’s too big’. Another patient said that he/she ‘kept losing it’ and that because he/she was using a pill minder, he/she would forget to open and close the MEMS bottle. That patient stated, ‘And then you have to make sure it was open for a specific amount of time, and then you have to close it. I mean, I’m already using my pill box, so it’s like – it wasn’t really necessary to me’. The comment regarding the amount of time the bottle stays open is relevant in that if the bottle is left open for more than 30 seconds, an additional ‘medication event’ is recorded.

Another obstacle that we encountered is the need for manual data corrections to address misuse of the MEMS cap for the following situations: forgetting to open the MEMS when a dose was taken or openings that appear unrelated to medication taking (i.e. opening to fill the container, multiple openings over a brief period). In our sample, 13/57 (23%) patients logged self-reported errors. The most common error was taking a medication without opening the MEMS cap. This was typically due to such situations as removing doses from the bottle in advance of taking them or for reasons unknown. Other self-reported errors included opening the bottle, but not taking a dose due to illness or side effects. It should be noted that in our study, some patients completed the exception log in an ambiguous way and thus the entries were difficult to interpret. For example, one patient indicated that doses were taken without opening the MEMS cap, while the electronic event log indicated that the cap was actually opened. In another case, the patient indicated opening the MEMS cap but not taking the doses, while simultaneously reporting that the requisite doses were taken.

Pragmatic solutions to the use of MEMS in a BD research trial

To address the above challenges, we implemented a number of strategies which are summarized in Table 2. To address the challenge of collecting MEMS cap data when utilizing a medication assistive device, participants were instructed to open the MEMS cap each time they took their dose of the measured medication from the assistive device. This strategy appears to be at least partially effective. Based on complete data pairs available ($N = 49$), a baseline comparison was conducted between the MEMS computed according to the algorithm used for the TRQ (31.4% adherence, $SD = 28.8$) and the TRQ in the past week for the MEMS monitored medication (49.0% adherence, $SD = 33.2$). The comparison demonstrated a significant correlation ($r = 0.485$, $p = 0.000$). Moreover, the results of a t -test of paired differences between MEMS and TRQ values were not significant ($p = 0.20$). According to qualitative data as well as exception logs, however, patients did not always remember to open the MEMS cap when they used an assistive device.

To address the issue of polypharmacy in our RCT trial protocol, the BD medication taken most

frequently was chosen to be used with the MEMS cap. Using the most frequently prescribed medication is a conservative method for identifying nonadherence given that adherence tends to be lower with more frequent dosing [Medic *et al.* 2013]. In the case of multiple BD medications taken at the same frequency, the medication started most recently was selected. This method was chosen over monitoring all medications to limit burden to participants as well as research cost.

Measuring only one medication with MEMS, however, does not provide for the analysis of differences in adherence that might occur between BD medications. Supplemental self-report adherence assessments, such as the TRQ, can be administered for each BD medication separately and then an average taken, in order to increase the richness of the adherence data. Supplemental information can also be useful in cases when research participants lose the MEMS cap entirely, as this provides at least some indication of adherence patterns (in our sample 9% lost the MEMS outright). As noted above, there is a difference in TRQ data when using just the MEMS-monitored medication; past week TRQ at screen indicated 35.6% adherence ($SD = 28.5$) and 45.9% adherence ($SD = 33.8$) at baseline. In contrast, mean TRQ at screen for all BD medications indicated 38.1% adherence ($SD = 27.6$) for the past week and 43.2% adherence ($SD = 29.3$) for the past month. Further, mean TRQ at baseline for all BD medications indicated 49.9% adherence ($SD = 30.7$) for the past week and 48.1% adherence ($SD = 28.3$) for the past month.

Also, the problem of not bringing in the MEMS cap device to assessment visits was addressed by collecting the data which remained stored in the cap and 'back filling it' when the MEMS was brought to the following visit. The fact that previous data can be accurately retrieved is an asset of this technology. Given the limitations of the BD population in general and the nonadherent BD population in particular, forgetting to bring in the MEMS cap is a likely problem, and reminders to bring the MEMS cap should be incorporated into the appointment reminder call.

While the MEMS software offers a high degree of customization, it can also be complex. Various customization options are available to the investigator. For example, day/date cutoffs can be specified (e.g. 11:59 p.m.) and multiple openings that

Table 2. Challenges in using MEMS to measure adherence in patients with bipolar disorder and practices to overcome pitfalls.

Pitfall	Data	Practice	Evaluation
Polypharmacy	37% of the sample prescribed two or more fundamental BD drugs at baseline	Monitor medication taken most frequently. If more than one BD medication is at the same prescribed frequency, monitor the medication started most recently rather than monitor all medications to limit burden and cost	Significant correlation between the MEMS computed according to the algorithm used for the TRQ and the TRQ in the past week at baseline for the MEMS monitored medication ($r = 0.485, p = 0.000$). A t -test of paired differences between MEMS and TRQ values was not significant ($p = 0.20$). According to qualitative data as well as exception logs, however, patients did not always remember to open the MEMS cap when they used an assistive device
Use of pill boxes	Unknown frequency	Instructed individuals to open MEMS at the same time that the pill box is opened	
Errors in use of the MEMS cap	23% of patients self-reported errors [e.g. removing doses from bottle in advance of taking them or for unknown reasons]	Patient completes an exception log	
Differences in adherence between two or more BD medications	With MEMS measuring only one BD medication, there is no capacity to identify differences in adherence between BD medications	Administer supplemental adherence assessments including the self-reported TRQ.	For patients on two BD medications at screening, the mean adherence as indicated by the TRQ for the MEMS drug in the past week and the other BD medication was exactly the same (23.29% adherence), with SDs of 28.7 and 31.1, respectively. The correlation of TRQs between the MEMS drug and other BD medication was $r = 0.46, p = 0.13$.
Lost MEMS cap	5/57; 9%	Administer supplemental adherence assessments including the self-reported TRQ	MEMS at baseline when calculated according to the TRQ algorithm was higher than the TRQ screen in the past week, suggesting that using the MEMS in and of itself did not improve adherence
Research participant failed to bring in MEMS cap to assessments	9/57; 16% failed to bring device to baseline and 37% of visits occurred without the MEMS cap	Retroactive data automatically uploads onto the database when the device is scanned	
Hawthorne effect (being in a study to improve adherence and using a special monitoring device increases adherence)	Both past week and past month TRQ increased from screen to baseline, indicating improved adherence, presumably as a function of being in a study to improve adherence	Monitor for a longer period (1–2 weeks)	

BD, bipolar disorder; MEMS, Medication Event Monitoring System; TRQ, Tablets Routine Questionnaire.

are not dose related (e.g. checking to see how many pills are left) can be corrected for manually. Finally, dates during which a patient has been hospitalized should typically be excluded.

Data cleaning procedures need to be included in any report using electronic monitors. In our trial, we had each participant take home a paper log in order to fill in any MEMS errors as close to real time as

possible, including taking a dose from an assistive device and forgetting to open the MEMS, adding a refill, or losing the cap. In our sample, of the 13 (23%) patients who logged errors, six (46%) reported at least one instance of taking a medication without opening the MEMS cap. Among these six patients, this behavior occurred 12.61% of the time. Each reported instance was compared with the automated MEMS event log. The MEMS event log records each time a bottle is opened. Each reported instance for which a match was not found in the event log was counted as confirmed. All confirmed instances were added into the originally calculated prescribed doses taken, and the percentage of prescribed doses taken was adjusted accordingly. Resulting adjustments ranged from 4% to 31% increases in prescribed doses taken per patient, with a mean increase of 14%. Data for the percentage of units of correct number of doses taken automatically adjusts for regimen deviations that are directly traceable by the MEMS device. For example, if a patient is prescribed two doses a day (one in the morning and one in the evening), but opens the cap twice within an hour to take both doses, then MEMS will count this as a dosing error and calculate the percentage of units of correct number of doses taken accordingly. Among the six patients who reported taking their doses without opening the caps, their self-report exception logs indicated that the doses in question were taken in accordance with their regimens. Therefore, adjustments to this variable yielded the same outcomes with adjustments ranging from 4% to 31% increases in the percentage of units of correct number of doses taken.

Missed research visits are to be expected in BD adherence studies that enroll people who are non-adherent or at risk for poor adherence. In cases when a patient misses a visit, a practical solution is to create a time point that uses the scheduled visit date. For instance, if a patient attended a scheduled visit, but missed the next one, the time point for the first visit would be the date it occurred, while the time point for the missed visit would be the date it was scheduled to occur. The aforementioned practices will be helpful in facilitating a consistent analysis of variables across time points. Specifically, if visit dates are being used to evaluate variables across time, then using target dates for missed visits will help maintain uniformity of the intervals between time points.

As MEMS is used to evaluate patient adherence with medications, the cutoffs for time points require careful consideration in terms of study

design. Specifically, investigators need to determine what cutoffs are practical for time points, given the unique features of a study. For example, it needs to be decided whether a cutoff for an interval is just prior to the day of a scheduled visit (e.g. 11:59 p.m. the night before), or at a specific time during the day of the scheduled visit (e.g. just prior to the scheduled time of the visit). While this matter may be arbitrary for some studies, it may be crucial in others. In our study we used a cutoff of 11:59 p.m. So, a given 24 h period covered from 12:00 a.m. (midnight) to 11:59 p.m.

Another advantage of MEMS is that it offers the needed flexibility to change the drug being monitored mid study in the event that a participant was taken off the monitored drug. However, this feature also introduces potential complications. If a drug change occurs between time points, the calculation of adherence is more challenging. One possible way of handling this situation is to create a subject-specific time point which represents the introduction of the new drug. This new time interval would extend from the new time point to the next visit. Then, adherence to the new drug in the new time interval will be accurate for that period and can be factored in when conducting analyses. If a drug change coincides with a pre-existing time point (visit date in accordance with the protocol), then no adjustments will be necessary when analyzing the data. In addition to the fact that MEMS allows for the measurement of patient-unique drugs, it also allows for a unique dosing regimen individualized for each patient. This can be done by setting the regimen in the patient record and making certain that the assigned monitor number (cap) is selected from a drop-down menu. This way, when a desired dosing regimen is set, it will only be applicable to the patient's record it was intended for and adherence will be calculated accordingly.

Discussion

This descriptive paper describes challenges and practical solutions for using MEMS caps in BD research studies. The only other study that we encountered addressing methodological issues related to the use of MEMS in BD was that of Badiie and colleagues who compared patients with HIV with and without BD and found the technology to be largely impractical in the BD population [Badiie *et al.* 2012]. Some of the specific benefits of the technology, including its ability to measure adherence at specific and precise time intervals, is

of particular importance for HIV medication ingestion, but is not as critical a variable when it comes to adherence to BD medication.

While the use of MEMS in BD is sparse, there have been studies with other psychiatric populations. Diaz and colleagues describe the use of MEMS in schizophrenia. These authors point out that the use of MEMS artificially increases adherence in certain individuals and decreases adherence in others. Also, similar to what our qualitative interviews indicated, participants in that study reported that the size and bulk of the MEMS cap prevented them from carrying it in their pockets [Diaz *et al.* 2001]. Diaz and colleagues discuss some of the unique challenges of using MEMS in severe psychiatric illness and suggest solutions to the problems, including more frequent follow ups (increasing the follow up from monthly to weekly), particularly in the initial period following discharge, paying a retrieval fee for MEMS cap return, and having clinicians remind participants to utilize the MEMS cap [Diaz *et al.* 2001]. However, these interventions may not only improve adherence to the MEMS cap technology but also may have the unintended result of artificially increasing adherence itself, thus interfering with the ability to determine the efficacy of the intervention being tested in the study.

While the use of MEMS in psychiatric populations is somewhat limited, the MEMS technology has been examined more closely in nonpsychiatric populations. Samet and colleagues assessed the use of MEMS in people with HIV and noted limitations of this technology given the complex medication regimens and uncontrollable lifestyle factors common in this population [Samet *et al.* 2001]. Similar issues also exist in BD and thus lessons learned are likely to be applicable. Samet and colleagues noted that the MEMS is ideal for individuals who have their medication stored in one place and do not take their medication with them. However, in the HIV-infected sample, to improve the complex and frequent regimens necessary, assistive devices are often incorporated to improve adherence. As was true for our experience with the BD population, Samet and colleagues reported that such devices may complicate the use of MEMS caps and require that the cap is opened each time a pill is taken, even if it is stored in an alternate device. Other practical considerations of using MEMS for medications to treat HIV were reported by Bova and colleagues and suggest that use of MEMS may underestimate

adherence for the following reasons: inconsistency of MEMS use, taking out more than one dose at a time, and opening the cap but not taking out medication [Bova *et al.* 2005]. The main reasons for not using the MEMS cap as instructed in that study were the continued use of a pillbox and forgetting to open the MEMS cap when medication was taken. In another study, Liu and colleagues found that 20% of missed MEMS data could be accounted for by pillbox use [Liu *et al.* 2001]. These findings, coupled with our experience with the use of MEMS in the RCT trial with BD, underline the need for improved technology as well as secondary adherence measures.

Possibilities

While the MEMS cap offers the potential for both accurate and rich data collection in BD research, the drawbacks limit its usefulness somewhat. The question remains as to how the technology can be improved so that it is more convenient, not only for research purposes, but potentially for clinical purposes.

One significant improvement would be a technology whereby the adherence report could be accessed regularly from home rather than having to bring in the cap physically. Furthermore, the cost would need to be brought down significantly, and it would need to be compatible with adherence assistant devices which are constantly evolving. Additionally, for the BD population, the ideal technology would measure multiple medications simultaneously in order to measure intramedication adherence differences due to side-effect profiles or acute effects. For example, antipsychotic mood stabilizers which are more sedating might be taken by patients to manage insomnia on some occasions and then not taken if the individual has a task that requires attention and alertness, such as driving or working. Furthermore, individuals who have relatively rapid mood changes, which can occur in some types of BD, may have different reasons for poor adherence depending on mood state. For example, individuals who are hypomanic may get caught up in activities and forget to take medications, while those with depression may spend more time sleeping or in bed and lack the motivation to get up and take medications. An ideal adherence tool would be able to track mood states in concert with adherence behavior, communicate information to clinicians remotely, possibly prompt patients in pill-taking behavior depending on the individual's circumstances, and measure differential adherence to multiple medications.

Given the ever changing technological advances in the field of adherence, the focus on the MEMS cap serves to exemplify the process of evaluating the strengths and pitfalls in using electronic monitoring in BD rather than as a static review of the measuring device itself. While a complete review of such technologies is beyond the scope of this paper, some notable technologies which have yet to be tested in BD but have been used in other populations include the WisePill (WisePill Technologies, Somerset West, South Africa), the ingestible sensor by Proteus Digital Health (Redwood City, CA, USA), and the Polymedication Electronic Monitoring System (POEMS) (Pharmaceutical Care Research Group, Department of Pharmaceutical Sciences, University of Basel Basel, Switzerland). In reviewing these technologies, some of the benefits and limitations for use in patients with BD are described.

While the WisePill [Haberer *et al.* 2010] has the benefit of utilizing a cellular network to record real-time openings, it does not have the ability to measure differential medication adherence and it does not simultaneously measure mood variability or provide reminders. Finally, it does not complement the use of other tools to improve routines, such as a pillminder. The ingestible sensor by Proteus Digital Health is ingested with medications, giving real-time feedback to researchers/providers which can be linked to a digital health feedback system. At this point, the system sends information from the patient to the provider but the patient does not receive feedback/reminders and the problem of differential adherence is not addressed. Furthermore, the feasibility of enlisting the cooperation of patients with BD to swallow a sensor in the form of yet another pill is unclear and may be considered as invasive. Finally, the POEMS appears to have a number of benefits for BD [Hersberger and Arnet, 2012; Arnet *et al.* 2013]. Namely, it utilizes electronic films affixed to polymedication blister packs and thus does address the issue of differential adherence. Furthermore, it is noninvasive and relatively unobtrusive. As such, as a measurement device alone, it seems to meet the criteria that we have identified for BD. As a tool to improve adherence, however, it does not provide feedback or reminders to the patient. In conclusion, despite the disadvantages and difficulties of the MEMS cap as an electronic monitoring device, it has been widely used with many different populations to obtain extensive data on adherence behavior and has the potential for the collection of very accurate adherence

measurement for clinical research in individuals with BD. The potential benefits are limited by some of its disadvantages for this population given the extent of polypharmacy for symptom stabilization coupled with medications for comorbid medical conditions, which would require prohibitive expense and burden on patients. Furthermore, the potential richness of data available from electronic monitors tends to be translated back into percentage of doses or days adherent per week or month, similar to the data which are obtained via self-report, an easier and less expensive method for collecting adherence data. If the pattern of missed doses or adherence to particular time dosing is hypothesized to have significant outcome implications, then the statistical procedures available to analyze dosing patterns captured by the MEMS technology can be employed. Overall, MEMS offers flexibility and customization that can be of significant value. However, as in any study, careful planning is necessary in order to take full advantage of the software's capabilities. In addition, to get the most out of the technology, it has been recommended that it be combined with at least one other methodology to be chosen from self-report, pill counts, pharmacy records, biological assays or interviewer-rated scales.

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