Schizophrenia Research 208 (2019) 167–172

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Relationships between smartphone social behavior and relapse in schizophrenia: A preliminary report

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A R T I C L E I N F O

Article history:
Received 30 November 2018
Received in revised form 5 March 2019
Accepted 18 March 2019
Available online 30 March 2019

Keywords:
Schizophrenia
Mobile health
Technology
Social functioning
Relapse

A B S T R A C T

Social dysfunction is a hallmark of schizophrenia. Social isolation may increase individuals' risk for psychotic symptom exacerbation and relapse. Monitoring and timely detection of shifts in social functioning are hampered by the limitations of traditional clinic-based assessment strategies. Ubiquitous mobile technologies such as smartphones introduce new opportunities to capture objective digital indicators of social behavior. The goal of this study was to evaluate whether smartphone-collected digital measures of social behavior can provide early indication of relapse events among individuals with schizophrenia. Sixty-one individuals with schizophrenia with elevated risk for relapse were given smartphones with the CrossCheck behavioral sensing system for a year of remote monitoring. CrossCheck leveraged the device's microphone, call record, and text messaging log to capture digital socialization data. Relapse events including psychiatric hospitalizations, suicidal ideation, and significant psychiatric symptom exacerbations were recorded by trained assessors. Exploratory mixed effects models examined relationships of social behavior to relapse, finding that reductions in number and duration of outgoing calls, as well as number of text messages were associated with relapses. Number and duration of incoming phone calls and in-person conversations were not. Smartphone enabled social activity may provide an important metric in determining relapse risk in schizophrenia and provide access to sensitive, meaningful and ecologically valid data streams never before available in routine care.

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1. Introduction

Social dysfunction is a hallmark of schizophrenia-spectrum disorders (Green et al., 2018). Individuals with schizophrenia often have limited support networks (Buchanan, 1995; Gayer-Anderson and Morgan, 2012) and diminished motivation for social interaction (Fulford et al., 2018). They experience deficits in social skills and social cognition that impede their ability to form and maintain bonds with others (Fett et al., 2011; Mueser and Bellack, 1998; Penn et al., 2008). These deficits do not suggest that people with schizophrenia prefer disconnection or that they benefit from solitude – many report feeling profoundly lonely (Michalska Da Rocha et al., 2018), in need of companionship (Sundermann et al., 2013), and dissatisfied with their level of social connection (Trémeau et al., 2016). Lacking social support strongly predicts quality of life even after controlling for all psychiatric symptoms (Eack and Newhill, 2007).

Social deficits may emerge as a consequence of one's symptoms (e.g., people keep their distance from an individual who responds verbally to auditory hallucinations) but they may also play a causal role in the development and maintenance of psychosis. When faced with social stressors, individuals with schizophrenia report greater subjective distress (Lataster et al., 2013; Myin-Germeys et al., 2003; Veling et al., 2016), and present with aberrant hypothalamic-pituitary-adrenal axis (Jones and Fernyhough, 2007) and dopaminergic (Mizrahi et al., 2012) activity. To avoid perceived threats or potential rejection (Grant and Beck, 2009), individuals with schizophrenia often isolate from others. These behaviors paradoxically increase dysphoria and prevent disconfirmation of their dysfunctional threat beliefs, which in turn may

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https://doi.org/10.1016/j.schres.2019.03.014
0920-9964/Published by Elsevier B.V.

become even more severe (Freeman, 2016; Freeman et al., 2007). When symptom exacerbation leads to hospitalization, this further disrupts the social and vocational lives of individuals with schizophrenia (Hawthorne et al., 2012; Hor and Taylor, 2010; Koyanagi et al., 2015) and compounds social functioning deficits (Penttilä et al., 2014).

Given the significance of social functioning in the overall health and wellbeing of people with schizophrenia, effective monitoring and detection of shifts in social behavior can play an important role in identification of deterioration in patients' clinical status. Continuous monitoring of social behavior is hampered by the limitations of traditional clinic-based assessment strategies such as interviews, rating scales, and self-report measures. These approaches require direct patient contact, which may be logistically complex and prohibitively time and resource intensive for standard practice. Assessor rated measures are susceptible to interpretative inconsistency across raters (Crippa et al., 2001; Khan et al., 2013) or cultures (Aggarwal et al., 2012; Eack et al., 2012). Retrospective measures are vulnerable to patient recall biases and inaccuracies (Blum et al., 2015) and may be affected by the patient's motivation to under-report (e.g. to avoid treatments, stigma and embarrassment) or hyper-endorse (e.g. to receive benefits, faster care, "white coat" effects) symptoms or behavioral problems (Ben-Zeev et al., 2012; Frueh et al., 2000). Unlike internal mental states that must be inferred using self-report, social activity can be objectively observed and recorded behaviorally.

Mobile technologies such as smartphones are increasingly prevalent among people with schizophrenia (Firth et al., 2016; Torous et al., 2017) and introduce new opportunities to continuously capture digital indicators of social behavior (Bell et al., 2017; Ben-Zeev et al., 2015; Faurholt-Jepsen et al., 2018). Ben-Zeev and colleagues developed CrossCheck, a multimodal data collection system designed to aid clinical monitoring of individuals with schizophrenia using both momentary self-report and "passive" (i.e., not requiring intentional effort by the user) data collection strategies which leverage the sensors and functionalities of standard smartphones (Ben-Zeev et al., 2015; Wang et al., 2017). CrossCheck gathers data continuously as individuals using the smartphone go about their daily lives, allowing for highly acceptable, granular, ecologically-valid remote monitoring (Ben-Zeev et al., 2016b). Previous systems (e.g. MONARCA in bipolar disorder) have been shown to be feasible in other populations and to gather passive data that correlates with in-person assessments (Faurholt-Jepsen et al., 2018, 2014).

The goal of the current study was to evaluate whether smartphone-collected measures of social behavior can serve as early behavioral indicators of relapse among individuals with schizophrenia. We examined whether participants with schizophrenia spectrum disorders who used the CrossCheck system for one year of remote monitoring socialized in an atypical manner (i.e., in-person, via text, and by phone calls) prior to documented relapse events. Digital indicators of social functioning were examined in the 30-day periods that preceded relapse events, as this time period reflects a feasible time interval to engage established interventions that have been demonstrated to reduce risk for imminent relapse (Morriss et al., 2013).

2. Methods

Data were collected as part of a randomized controlled trial in which people with schizophrenia-spectrum disorders participated in a year-long smartphone-assisted relapse prevention initiative (Ben-Zeev et al., 2017; Wang et al., 2017). This trial was approved by the IRBs of Dartmouth College (#24356) and Northwell Health/Long Island Jewish Medical Center (#14-100B) and registered as a clinical trial (#NCT01952041). For the purposes of the current study we report on the digital socialization activity and relapses of individuals who were assigned to the smartphone arm.

2.1. Participants

All participants (n = 61) were receiving care in outpatient treatment programs at a large psychiatric hospital in New York. They were recruited with the use of flyers at the study site and regular research staff review of hospital electronic medical records. Clinicians described the study to potential candidates and referred interested patients to study staff for eligibility screening. Inclusion criteria required that participants (1) were 18 years or older; (2) had a diagnosis of schizophrenia, schizoaffective disorder, or psychosis not otherwise specified; and (3) a significant psychiatric event (i.e. an inpatient psychiatric hospitalization, daytime intensive psychiatric program, outpatient crisis management visit, or short-term psychiatric hospital emergency room visit) within the last 12 months. Exclusion criteria included (1) hearing, vision, or motor impairment that prevented engagement with a mobile device, (2) a reading level lower than the 6th grade (assessed with the reading section of the Wide Range Achievement Test; WRAT, Wilkinson and Robertson, 2006); or (3) being unable to provide informed consent (i.e. failing a competency screen). Study demographics are reported in Table 1.

Of 1376 individuals who were initially assessed for eligibility, 149 enrolled in the study. The most common reasons for failed screening were no longer receiving care at the hospital (n = 682), failing to meet diagnostic criteria (n = 131), not wanting to participate (n = 129), or not meeting severity criteria (n = 108). Of those enrolled, 62 were randomized to the passive sensing condition. Eight participants withdrew after randomization (n = 3 no longer receiving services at the hospital; n = 3 no longer interested, n = 1 felt that the study required too much effort, and n = 1 died unrelated to the study intervention), one of whom providing no passive sensing data. Nine participants were lost to follow up, but many provided days of passively sensed data despite not returning for in-person assessment. The majority (n = 45) of participants fully completed the study; on average, participants registered data for 262.80 days (SD = 97.17).

2.2. Procedures

All participants were given a Samsung Galaxy S5 Android smartphone with an unlimited data/call/text plan for one year. Participants were asked to carry the device with them and charge it each night. Staff explained all monitoring functions of the device to each participant and encouraged participants to follow-up if concerns emerged during the study.

2.3. Measures

2.3.1. Digital social activity

CrossCheck logged the number of incoming and outgoing text messages and phone calls but did not collect or record their content. The software activated the smartphone microphones every 3 min to capture surrounding sound. CrossCheck does not record raw audio on the device, but applies a speech detection algorithm to identify and log when human speech is present. Based on these logged events we calculated speech duration (overall time classified as speech being present, measured in hours) and speech frequency (the number of distinct periods with spoken language separated by 5 min or more of no human speech).

2.3.2. Relapse

Trained clinical assessors met with study participants at baseline and at three month intervals throughout the year-long data collection period to administer the Brief Psychiatric Rating Scale (BPRS; Kay et al., 1987) and to inquire about their symptoms and functioning. Hospital electronic health record data were made available to the research team. The following events, reported during assessments or recorded in the EHR, were designated as relapses: a psychiatric hospitalization,

Table 1
Demographic characteristics of study participants, separated by those that experienced a relapse and those that did not during the study period.

	Relapse (n = 20)	Non-relapse (n = 41)	Total (n = 61)
Age	36.25 (13.96)	37.54 (13.95)	37.11 (13.85)
Gender			
Male	12 (60.0%)	24 (58.5%)	36 (59.02%)
Female	8 (40.0%)	17 (41.5%)	25 (40.98%)
Race			
White/Caucasian	7 (35.00%)	15 (36.59%)	22 (36.07%)
Black/African-American	3 (15.00%)	15 (36.59%)	18 (29.51%)
Pacific Islander	2 (10.00%)	2 (4.88%)	4 (6.56%)
American Indian or Alaskan Native	0 (0.00%)	1 (2.44%)	1 (1.64%)
Asian-American	0 (0.00%)	1 (2.44%)	1 (1.64%)
Multiracial	7 (35.00%)	6 (14.63%)	13 (21.31%)
Missing/declined	1 (5.00%)	1 (2.44%)	2 (3.28%)
Ethnicity			
Hispanic/Latino	5 (25.00%)	12 (29.27%)	17 (27.87%)
Non-Hispanic/Non-Latino	15 (75.00%)	29 (70.73%)	44 (72.13%)
Years of education			
Some high school	2 (10.00%)	4 (9.76%)	6 (9.84%)
High school/GED	6 (30.00%)	13 (31.71%)	19 (31.15%)
Some college	6 (30.00%)	10 (24.40%)	16 (26.23%)
Associates	1 (5.00%)	4 (9.76%)	5 (8.20%)
Bachelor's	4 (20.00%)	8 (19.51%)	12 (19.67%)
Master's or above	1 (5.00%)	2 (4.88%)	3 (4.92%)
Employment status			
Unemployed	15 (75.00%)	29 (70.73%)	44 (72.13%)
Working part-time	3 (15.00%)	3 (7.31%)	6 (9.84%)
Working full-time	2 (10.00%)	7 (17.07%)	9 (14.75%)
Working less than part-time	0 (0.00%)	2 (4.88%)	2 (3.28%)
Living status			
Substance use treatment facility	0 (0.00%)	1 (2.44%)	1 (1.64%)
Assisted/supported housing	2 (10.00%)	2 (4.88%)	4 (6.56%)
Living with family	16 (80.00%)	29 (70.73%)	45 (73.77%)
Independent	2 (10.00%)	9 (21.95%)	11 (18.03%)
Diagnosis			
Schizophrenia	9 (45.00%)	17 (41.46%)	26 (42.62%)
Schizoaffective disorder	9 (45.00%)	17 (41.46%)	26 (42.62%)
Psychosis NOS	2 (10.00%)	7 (17.07%)	9 (14.75%)
Lifetime hospitalizations			
1–5	14 (70.00%)	29 (70.73%)	43 (70.49%)
6–10	2 (10.00%)	8 (19.51%)	10 (16.39%)
11–15	1 (5.00%)	3 (7.32%)	4 (6.56%)
16–20	1 (5.00%)	0 (0.0%)	1 (1.64%)
20+	1 (5.00%)	1 (2.44%)	2 (3.28%)
Missing/declined	1 (5.00%)	0 (0.0%)	1 (1.64%)

Twenty-seven relapse events occurred during the study period. Of those events, they were characterized (non-exclusively) as follows: Psychiatric hospitalization (n = 22, 81.48%), increased frequency of services (n = 7, 25.93%), increased medication and BPRS increase (n = 6, 22.22%), suicidal ideation (n = 4, 14.81%) homicidal ideation (n = 1, 3.70%), self-injury (n = 2, 7.41%), violence (n = 1, 7.41%).

significant increase in the level of psychiatric care (i.e., frequency and intensity of services, dosage increase or additional medicines prescribed) coupled with either an increase of 25% from baseline on BPRS total score, suicidal or homicidal ideation that was clinically significant in the investigators' judgment, deliberate self-injury, or violent behavior resulting in damage to another person or property (Csernansky et al., 2002). When corroborating documentation was not available (e.g., instances of self-reported suicidal ideation that did not lead to hospitalization or suicide attempt) assessors worked with participants to determine the relapse event date.

2.4. Data analytic plan

We created an exploratory data analytic framework examining relationships between digital social functioning indicators and relapse events. Indicators examined included incoming and outgoing call counts and their total duration, incoming and outgoing SMS messages, and frequency and duration of nearby human speech. Each digital social functioning indicator was computed within four six-hour time epochs within a day (6 am to 12 pm, 12 pm to 6 pm, 6 pm to 12 am, 12 am to 6 am) as well for the entire day. Each indicator was then averaged across the 30-day period preceding a relapse event to create a summary of the indicator in a pre-relapse block of time. Thirty-day blocks were chosen in our exploratory analysis to balance selecting a long enough period of time to detect changes against a short enough period that would be clinically actionable. Daily indicators from days that were not in windows preceding relapse events were also averaged across 30-day blocks, creating a summary of the indicator in blocks of time not preceding relapse events. Each indicator summary was modeled as a function of whether or not it preceded a relapse. This allows an estimate of the mean value of the indicator in the days preceding a relapse compared to the mean value of the indicator in the days not preceding a relapse. Generalized estimating equations were used to account for individuals contributing multiple blocks of data to the analysis (i.e. multiple relapse blocks in some cases and multiple non-relapse blocks in all cases).

3. Results

Twenty-seven relapse events occurred for twenty participants during the study period (see Table 1). These events were (non-exclusively) most often coded as involving psychiatric hospitalization (n = 22, 88.0%), but also included increased intensity of services (n = 7, 28.0%), increased medication (n = 6, 24.0%), suicidal ideation (n = 4, 16%), homicidal ideation (n = 1, 4.0%), self-injury (n = 2, 8.0%), or interpersonal violence (n = 1, 4.0%). The number and duration of outgoing calls, as well as the total number of incoming and outgoing text messages, were significantly associated with relapse (see Table 2).

Entire day averages were lower in blocks preceding relapse for three of these indicators: outgoing call duration, incoming text messages, and outgoing text messages. One indicator – number of outgoing calls – did not significantly relate to relapse when collapsed across the entire day, but relapse was related to reductions in three different time periods: between 6 am and 12 pm, 12 pm to 6 pm and 12 am to 6 am. Outgoing call duration had similar relationships with relapse with the exception of the 6 am to 12 pm time block; it was associated with relapse only in the 12 am to 6 pm and 12 am to 6 am time blocks. There were no significant associations with relapse for duration or number of incoming calls. Relationships to relapse of incoming and outgoing SMS were quite similar, with fewer texts sent and received between 6 pm and 12 am as well as between 12 am and 6 am. There were no significant associations with relapse for speech frequency or duration recorded by CrossCheck.

4. Discussion

Our exploratory analysis found that smartphone-collected digital indicators of social functioning of people with schizophrenia spectrum disorders in the 30-day periods that preceded psychiatric relapses differed from their typical patterns. In these blocks, individuals placed fewer and shorter outgoing phone calls, as well as sent and received fewer SMS messages. Extant models of the emergence and maintenance of psychotic symptoms are defined by social stress (Corcoran et al., 2003) and avoidance (Freeman, 2016). The present study suggests that this stress-avoidance cycle may be identified in information passively detected by a mobile device.

The indicators that were significantly related to relapse in the current study were social behaviors that directly involved the use of the smartphone. Generally, decreases in SMS text message behavior in the evening (i.e. after 6 pm) and late at night (after midnight) were most closely related with relapse. There was a less discernible daily pattern in phone call behavior, as a decrease in outgoing calls was associated with relapse at nearly all time windows, and a decrease in outgoing call duration was related to relapse at spaced epochs (i.e. 12 pm to 6 am as well as 12 am to 6 am). The epoch data provides some nuance

Table 2
Model results, regression coefficient given represents the mean difference between indicator mean during 30-day blocks that precede relapse compared to 30-day blocks that do not precede relapse.

	Entire day			6 am–12 pm			12 pm–6 pm			6 pm–12 am			12 am–6 am		
	β	SE(β)	p-Value	β	SE(β)	p-Value	β	SE(β)	p-Value	β	SE(β)	p-Value	β	SE(β)	p-Value
Outgoing call duration (h)	**−0.019**	**0.009**	**0.030**	−0.001	0.001	0.579	**−0.009**	**0.003**	**0.005**	−0.001	0.006	0.885	**−0.010**	**0.004**	**0.014**
Number of outgoing	−0.475	0.311	0.127	**−0.046**	**0.015**	**0.002**	**−0.188**	**0.069**	**0.006**	−0.065	0.218	0.765	**−0.209**	**0.103**	**0.043**
Incoming call duration (h)	−0.013	0.010	0.184	−0.002	0.001	0.143	−0.004	0.002	0.052	−0.007	0.006	0.235	−0.001	0.006	0.941
Number of incoming calls	−0.161	0.132	0.222	−0.014	0.009	0.111	−0.047	0.042	0.263	−0.041	0.068	0.543	−0.056	0.041	0.172
Number of incoming SMS	**−2.228**	**0.906**	**0.014**	−0.041	0.112	0.716	−0.274	0.151	0.070	**−1.080**	**0.452**	**0.017**	**−0.819**	**0.311**	**0.009**
Number of outgoing SMS	**−2.435**	**1.040**	**0.019**	−0.069	0.110	0.535	−0.294	0.173	0.089	**−1.070**	**0.496**	**0.031**	**−0.986**	**0.331**	**0.003**
Speech duration (h)	0.727	0.614	0.237	0.073	0.163	0.655	0.246	0.180	0.172	0.262	0.223	0.240	0.140	0.213	0.510
Speech event frequency	−1.066	4.227	0.801	−0.214	0.901	0.813	−0.698	1.142	0.541	0.316	1.623	0.845	−0.335	0.990	0.736

$p < .05$ in bold text.

in our understanding of behavior changes that might precede relapse. Specifically, while sleep disturbances are thought to be key predictors of symptom exacerbation, our data suggest that individuals who were awake and placing calls and text messages after midnight were actually those that were *less* likely to relapse. This counterintuitive finding requires further investigation and replication.

Counter to expectations, recordings of the number and duration of in-person conversations were not associated with relapse. While this seems to suggest that phone – and not in-person – social behavior might be more closely related to relapse risk, a number of alternate explanations also exist. Specifically, as conversation totals are passive recordings of any nearby conversation, they do not determine specifically whether the CrossCheck user is a participant, observer, or simply a bystander (Ben-Zeev et al., 2017). Totals of phone calls and SMS text messages, on the other hand, are by definition specific and active manifestations of the user's social behavior. For a text message to be sent or a phone call to be placed, it must be sent or placed by the user. Second, individuals with schizophrenia report isolation and loneliness at higher levels regardless of phase of illness (Michalska Da Rocha et al., 2018; Sundermann et al., 2013; Trémeau et al., 2016). If individuals at risk are on average already typically not engaged in conversation with others, speech duration data may lack the variability to result in a significant statistical relationship to relapse.

The study has proximal and distal clinical implications. First, it suggests that in addition to global reports of social functioning, report of phone calls and SMS message activity could be assessed in clinical settings to improve indications of relapse risk. These data suggest it may be useful for providers to assess whether patients' are using their mobile devices to keep in contact with social supports. Second, more distally, if a mobile monitoring system is incorporated into ongoing monitoring and care, this study identifies specific digital social indicators that could trigger additional assessment or outreach and support. Ongoing remote assessments appear feasible and useful in a variety of settings and populations (Goldberg et al., 2018), including psychotic disorders (Ben-Zeev et al., 2016a, 2014; Depp et al., 2010; Niendam et al., 2018; Španiel et al., 2012). While the novelty of these approaches necessitates tempered enthusiasm, the present study results suggest that continued development of storage, modeling and use of passive data is warranted.

This study has several limitations. First, our analyses were exploratory and involved multiple statistical tests. As such, without further replication, results should be interpreted with caution in light of potential Type I error. Second, although all participants received a smartphone and unlimited data plan, some still elected not to use this as their primary mobile phone. Consequently, some variability in these participants' texting and phone call activity may not have been captured during the study period. Phone inactivity might be indicative of social dysfunction or of other behaviors including a choice not to carry the study device. Additionally, project team members reviewed and responded to data-derived composite risk scores in an effort to prevent relapse events (Wang et al., 2017). In these instances, mobile data collection led to active outreach in the form of check-in calls. However, post study analyses found no group differences in number of relapse events or time to relapses in the smartphone and control arms of the study. This suggests the risk scores had little predictive value or that outreach had little impact on relapse. We cannot rule out all additional explanatory variables that might concurrently impact both predictors and outcomes. For example, if individuals' phone use behaviors and relapse risk are both associated with depression, it is possible that an increase in depressive symptoms might account for both. The present study provides no insight into which behaviors might function as primary causal factors, rather just information about which precede relapse. Our models might also be affected by systematic trends in participants choosing not to carry the smartphone device with them during the study period, particularly among those who discontinued the study. Last, it is possible that our intervention is susceptible to observer effects; namely, as participants are aware that their activities are tracked, this might make their behaviors less naturalistic. While this is a concern for validity of data, it is not clear that this observation would bias our data toward significant relationships.

While extant literature demonstrates that social isolation (Michalska Da Rocha et al., 2018) and social stress (Lataster et al., 2013; Myin-Germeys et al., 2003; Veling et al., 2016) have significant impacts on individuals with schizophrenia, widely-used assessment tools are limited in their ability to effectively quantify social dysfunction in a sensitive and timely manner. Mobile devices are a nexus of social channels. They provide information never before accessible in research and clinical care that could perhaps improve prediction of risk (Faurholt-Jepsen et al., 2018). Timely interventions have been demonstrated to prevent relapses when they are administered prophylactically (Morriss et al., 2013). If collaboratively integrated into regular care, indicators of relapse risk detected through passive sensing could trigger intensive preventive action (Ben-Zeev et al., 2017; Španiel et al., 2012). Future studies are needed to replicate quantitative models of relapse prediction using these device-enabled digital social functioning measurement techniques, particularly in light of the low base-rate of relapse events. Future work is also necessary to develop multi-stream combined algorithms as well as to compare the extent to which these tools add predictive value above and beyond existing assessment tools. Implementation-oriented work is needed to develop and test ways in which these models can be translated into routinely accessible and clinically useful dashboards that provide clinical support.

Role of the funding source

This project was funded by the NIMH Exceptional Unconventional Research Enabling Knowledge Acceleration (EUREKA) Program grant number R01MH103148 (PI: Ben-Zeev).

Contributors

Dr. Buck conducted the literature search and wrote the first and subsequent revised drafts of the manuscript. Dr. Scherer conducted the data analysis. Ms. Brian managed study activities and consulted on analytic strategy. Drs. Ben-Zeev, Campbell, Choudhury,

Hauser, and Kane oversaw the study resulting in this publication, including drafting the grant application, designing the study protocol and supervising research staff managing study activities. Drs. Campbell, Choudhury, Wang, and Mr. Wang developed and refined mobile technologies employed. Dr. Ben-Zeev supervised the drafting and revising of the manuscript. All authors contributed to and approved the final version of the manuscript.

Conflicts of interest

Dr. Ben-Zeev has an intervention content licensing and consulting agreement with Pear Therapeutics. Dr. Campbell is a consultant for Verily Life Sciences. Dr. Choudhury is a co-founder and holds equity stake at HealthRhythms Inc. Dr. Kane has been a consultant for or received honoraria from Alkermes, Eli Lilly, EnVivo Pharmaceuticals (Forum), Forest (Allergan), Genentech, H. Lundbeck. Intracellular Therapies, Janssen Pharmaceutica, Johnson and Johnson, LB Pharmaceuticals, Merck, Minerva, Neurocrine, Otsuka, Pierre Fabre, Reviva, Roche, Sunovion, Takeda, LB Pharmaceuticals and Teva. He has received grant support from Otsuka, Lundbeck and Janssen, and participated in Advisory Boards for Alkermes, Intracellular Therapies, Lundbeck, Neurocrine, Otsuka, Pierre Fabre, Takeda, Teva. Dr. Kane is also a shareholder in Vanguard Research Group and LB Pharmaceuticals, Inc. The other authors have no other potential conflicts to disclose.

Acknowledgements

Dr. Buck is currently supported by a VA Academic Affiliations' Advanced Fellowship in Health Services Research and Development (TPH 61-000-24).

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