Psychiatry Research 285 (2020) 112780

Contents lists available at ScienceDirect

Psychiatry Research

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

Short communication

Brief interventions for improving adherence in schizophrenia: A pilot study using electronic medication event monitoring

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ARTICLE INFO

Keywords:
Schizophrenia
Medication adherence
Non-adherence
Intervention
Electronic monitoring
Medication event monitoring system

ABSTRACT

Poor medication adherence remains frequent in schizophrenia. The present study examined the efficacy of two month-long pilot interventions using the Medication Event Monitoring System (MEMS®). Thirty-three outpatients at high risk for relapse were randomized to receive a smartphone-based intervention, a nurse-based intervention, or treatment as usual. All patients then used the MEMS® to objectively measure medication adherence over six months. No differences were observed in adherence measures or relapse rates across the three groups. When using electronic medication monitoring as an objective measure of adherence, easily-implemented interventions may not significantly improve adherence in patients at high risk for relapse.

1. Introduction

Medication non-adherence is prevalent in patients with schizophrenia, highlighting the need for novel approaches to support patients through frequent contact. In the goal of providing lower cost or easily-implemented interventions, nurse-administered approaches have shown positive results (Gray et al., 2004; Hudson et al., 2008), including investigations using weekly or monthly telephone contact to foster adherence (Montes et al., 2010; 2012). Autonomous smartphone-based strategies have also demonstrated high feasibility and acceptability for patients with schizophrenia, as well as positive effects on adherence rates (Kreyenbuhl et al., 2019; Velligan et al., 2013). However, previous findings have been based almost exclusively on self-reported adherence that may bias evaluations of intervention efficacy (Velligan et al., 2007). In particular, subjective evaluations of behavior and experiences are frequently affected by memory biases, social desirability and psychological states of the individual at the moment of assessment (Baillet et al., 2016; Stone et al., 2003). Although electronic medication event monitoring is regarded as a reliable and accurate measure of adherence, few studies of schizophrenia have used such devices when testing adherence strategies. Some researchers (Velligan et al., 2013) using this approach reported significant improvements for patients receiving active interventions relative to treatment as usual, but also included very frequent clinical monitoring with additional interventions (every three days) if nonadherence continued. Information concerning the objective efficacy of less intensive but perhaps more feasible interventions is currently lacking. The aim of this controlled pilot study is to provide an initial comparison of smartphone-based and nurse-based interventions in a sample of outpatients with schizophrenia who are at high risk for relapse. All patients used the Medication Event Monitoring System (MEMS®) over a six-month period.

2. Methods

2.1. Participants

Thirty-three outpatients were recruited from an ambulatory care clinic in Bordeaux, France, from December 2014, to December 2016. Inclusion criteria were a DSM-IV-TR diagnosis of schizophrenia or schizoaffective disorder, high-risk relapse status (defined by a recent hospitalization within the last two years), being at least 18 years of age,

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https://doi.org/10.1016/j.psychres.2020.112780
Received 3 October 2019; Received in revised form 24 December 2019; Accepted 9 January 2020
Available online 16 January 2020
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capable of understanding the study protocol, and treated with at least one oral antipsychotic. If more than one antipsychotic was prescribed, the principal antipsychotic was identified as the medication to be delivered using MEMS caps. Exclusion criteria were presence of comorbid neurological diseases, mental retardation, or disability due to a serious medical condition.

2.2. Procedures

The study was approved by the regional ethics committee and was in accordance with the Declaration of Helsinki. All participants provided informed written consent prior to inclusion. The interventions were designed to require low to moderate resources, thereby increasing their feasibility in real-world clinical settings. They were administered over a one-month period immediately after hospital discharge in light of previous research using MEMS that demonstrated particularly poor adherence during this period for patients at high relapse risk (Misdrahi et al., 2018). Adherence and clinical outcomes were then examined over a six month period in order to evaluate the potential impact of the interventions beyond their immediate effects in the month following hospital discharge. After baseline evaluations, participants were informed of their computer-generated random assignment to one of three study groups: a smartphone-based intervention (SI) developed for this study that administered daily medication reminders for one month asking whether or not the patient had taken his or her medications, and then provided automated supportive statements to encourage adherence on days of medication non-use (e.g. “taking your medications today is important for your health and well-being”); Data were extracted at the end of the study from smartphones dedicated to this investigation; A manualized nurse-based intervention (NI) that provided weekly telephone contact with patients for one month to discuss potential barriers to medication use and to encourage adherence; or treatment as usual (TAU) that did not provide additional strategies to encourage adherence beyond baseline information. All participants were trained to use MEMS caps that recorded the time and date of each opening and closing of the bottle for a six-month period. MEMS caps were refilled every month by the nurse, do not provide reminders or alarms, and the MEMS data were not used in feedback to patients.

Severity of schizophrenia and psychopathological variables were also assessed using the PANSS (Kay et al., 1987) and the CGI-SCH (Haro et al., 2003). Global functioning was assessed using the GAF scale (DSMIV, 1995), insight regarding their illness with the SUMD (Amador et al., 1991), and antipsychotic side-effects with the UKU (Lingjaerde et al., 1987). Medication adherence using the MEMS® was evaluated by medication taking compliance (TAC), correct dosing (COD) and timing compliance (TIC) (see Misdrahi et al., 2018, for additional information). Relapse was defined as psychiatric re-hospitalization, and such events were recorded over the full six months of follow-up.

2.3. Statistical analysis

Adherence data were analyzed using logistic models for longitudinal binary data (Generalized Estimating Equations models). Due to the small number of participants in each group and the non-normality of data, we used the independent-sample Kruskal-Wallis test to compare the ordinal variables between the 3 groups.

3. Results

The socio-demographic and clinical characteristics of the three groups for baseline and follow-up assessments are summarized in Table 1, as well as primary outcomes for medication adherence using the MEMS caps. Participants differed only relative to age ($p = 0.003$) with patients in the NI group being older. Seven patients did not return the MEMS device or complete the follow-up appointment, and technical problems with two additional devices precluded data extraction on adherence. No differences were observed between these individuals and the rest of the sample.

The average adherence using the MEMS caps was 59.8% over the entire follow-up period. Among adherent patients, implementation was high and consistent over time with 91.53% of patients taking their medication as prescribed on any given day. The persistence measures, which represent the length of time between initiation and treatment discontinuation, decreased significantly over time in all groups and a log-rank test found no significant difference in adherence between groups ($p = 0.295$). In addition, no difference was observed at follow-up concerning relapse rates for the three groups. At six months, two patients were hospitalized in each of the TAU and SI groups and three patients were hospitalized in the NI group.

4. Discussion

This study examined pilot interventions to manage adherence in a sample of outpatients suffering from schizophrenia and at high risk for relapse. The principal findings indicate that: (i) compared to TAU, the two active interventions were not efficacious in significantly improving medication adherence in patients at high risk for relapse; (ii) there was a strong decrease in medication adherence over time in all study groups. Despite the small numbers of participants that may preclude the detection of certain effects, the mean adherence scores in the intervention groups were very similar to patients receiving treatment as usual over the six-month duration of the study and with no difference in relapse rates.

These findings suggest that objective measures of adherence may provide essential information that may differ from other studies showing positive results based only on subjective reports by patients (Misdrahi et al., 2018). Patient self-reports may be inaccurate due to a range of factors including cognitive deficits, social desirability influences, and ecological momentary assessment investigations have observed stark differences when comparing patient reports of the timing of data collection compared to times recorded electronically (Stone et al., 2003). Subjective evaluations of other daily experiences in other populations, such concerning sleep quality and duration, have also been shown to differ from objective measures as a function of the intensity of momentary emotional states (Baillet et al., 2016). For these reasons, populations known to have considerable cognitive and affective difficulties may be particularly prone to biases in personal evaluations of daily behaviors such as medication adherence.

The limitations of this pilot study include the restricted number of participants and the short duration of the interventions. As such, the findings should not be interpreted as providing a sufficient test of specific interventions per se, rather than suggesting methodological issues that should be considered in developing future clinical trials of adherence. To our knowledge only one previous investigation demonstrated positive effects for adherence interventions in this population while using objective measures (Velligan et al., 2013), but it was based on a sample with relatively high baseline adherence levels and that utilized frequent clinical monitoring and additional interventions in case of poor adherence.

Although considered the most reliable method available to measure adherence, electronic monitoring of medication events is still an indirect measure of treatment adherence. It remains possible that a patient could open the pill container, but not take the prescribed dose. However, it is unlikely that somebody would repeat this behavior over the entire course of the study. We did not use additional methods to check for extra openings nor self-report measures for adherence in these patients. However, a staff nurse was charged with filling the MEMS caps each month and recorded the remaining medication to reduce such potential bias.

Interventions that are less intensive and more easily-implemented in

Table 1
Clinical characteristics of the three study groups at inclusion (M0) and follow-up (M6).

	M0							M6						
	TAU $N = 10$		SI $N = 12$		NI $N = 11$			TAU $N = 10$		SI $N = 12$		NI $N = 11$		
	M	SD	M	SD	M	SD	p	M	SD	M	SD	M	SD	p
Socio-demographic characteristics														
Age (years)	**36.30**	**5.50**	**30.67**	**7.66**	**47.55**	**12.41**	**<0.001**			–		–		–
BMI (kg/m^2)	24.82	5.22	25.57	6.32	28.67	6.98	0.329	25.98	7.04	25.52	4.36	28.78	3.30	0.553
Clinical variables														
Illness duration (years)	7.10	6.30	9.41	7.04	16.27	12.23	0.062	–		–		–		–
GAF score	48.75	8.45	58.45	16.64	50.50	13.43	0.260	–		–		–		–
CGI-SCH score	3.25	1.04	2.73	1.35	3.60	0.97	0.232	3.25	1.71	2.00	1.22	3.00	1.00	0.336
PANSS positive score	17.22	4.35	15.73	4.80	18.80	6.05	0.404	14.50	5.32	13.60	4.77	14.20	2.59	0.949
PANSS negative score	17.44	5.46	15.36	6.30	18.30	6.34	0.529	17.25	4.27	17.20	4.66	16.00	3.94	0.880
PANSS general score	38.11	7.83	36.36	9.43	44.10	10.45	0.165	32.50	7.05	36.00	8.00	36.00	10.12	0.794
PANSS total score	72.78	13.89	67.45	16.36	81.20	19.97	0.197	64.25	14.43	66.80	16.38	66.20	15.16	0.968
SUMD score	8.11	4.46	7.55	3.88	7.90	4.07	0.953	–		–		–		–
UKU score	10.44	13.14	6.64	3.35	7.10	4.77	0.529	6.00	4.08	5.20	2.77	6.20	4.32	0.908
4PAS score	35.60	6.77	37.17	5.08	34.64	4.90	0.554	34.75	6.85	33.40	7.70	37.40	5.03	0.635
Adherence variables														
MEMS duration (days)	–		–		–		–	125.50	61.41	119.30	60.74	122.75	47.34	0.511
COD	–		–		–		–	76.74	25.79	80.69	13.42	82.88	20.93	0.750
TAC	–		–		–		–	89.63	14.84	91.28	12.30	93.78	21.18	0.622
TIC	–		–		–		–	65.73	34.33	70.07	21.93	70.89	31.59	0.813

SD: Standard Deviation; BMI: Body Mass Index; GAF: Global Assessment of Functioning; CGI-SCH: Clinical Global Impression-Schizophrenia; PANSS: Positive And Negative Symptoms Scale for Schizophrenia; SUMD: Scale of Unawareness of Mental Disorder; UKU: Udvalg for Kliniske Undersogelser Side Effect Rating Scale; 4PAS: 4-Point ordinal Alliance Scale; COD: Correct adherence; TAC: Taking adherence; TIC: Timing adherence. Significant associations are in bold text.

community-dwelling samples may therefore require further development to achieve efficacy, particularly among patients at high risk for relapse. The promising findings observed for previous adherence interventions should be pursued with a greater emphasis on new tools that improve reporting accuracy.

Disclosures

B.V. and A.C.L. were employees of Aardex/WestRock Healthcare Company during this investigation. No authors received financial compensation for their participation or have agreed to use or promote specific products or technologies. All authors report no conflicts of interest.

Funding source

This work was supported by a grant from the Clinical Research Hospital Program from the French Ministry of Health (PHRC "2009–04–01"). The funding source had no role in the design, analysis, interpretation, or publication of this study.

CRediT authorship contribution statement

Arnaud Tessier: Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Maud Dupuy:** Writing - original draft, Writing - review & editing. **Franck Jean Baylé:** Conceptualization, Methodology, Writing - review & editing. **Corinne Herse:** Data curation, Formal analysis, Writing - review & editing. **Anne-Catherine Lange:** Conceptualization, Methodology, Writing - review & editing. **Bernard Vrijens:** Conceptualization, Methodology, Writing - review & editing. **Pierre Schweitzer:** Conceptualization, Methodology, Writing - review & editing. **Joel Swendsen:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **David Misdrahi:** Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2020.112780.

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