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The effect of providing patient-specific electronically monitored antipsychotic medication adherence results on the treatment planning of prescribers of outpatients with schizophrenia ☆

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ABSTRACT

Adherence to antipsychotic medication was assessed monthly over a 6-month study period using patient-specific electronic monitoring (EM) of medication bottle opening in 23 outpatients with schizophrenia or schizoaffective disorder. Patient-specific EM adherence results were then shared with the seven participating prescribers, who were surveyed concerning the treatment changes, if any, that they would recommend based on the EM adherence results. Prescribers indicated that they would recommend adherence-related treatment plan changes in 61% of patients, all of whom were $\leq$80% adherent. The strength of this effect was significantly stronger for psychosocial intervention treatment plan change recommendations than for medication treatment plan change recommendations. Of the psychosocial intervention recommendations, an increase in case management intensity was most often recommended. Of the medication treatment plan recommendations, initiation of a long-acting injectable medication and an increase in dosage of current oral antipsychotic medication were each recommended in only one case. Prescriber recommendations of adherence interventions in this study were not necessarily consistent with major guideline recommendations. Findings suggest the need for further study and dissemination of findings regarding evidence-based adherence assessment and interventions.

1. Introduction

Nonadherence to antipsychotic medication is a common problem in persons with schizophrenia and schizoaffective disorder (Byerly et al., 2007a). Compounding this problem is the challenge that nonadherence is difficult to detect by clinicians. In the only study to date, to our knowledge, that compared adherence ratings of patients' actual prescribers to that of a validated objective adherence measure (electronic monitoring (EM)), Byerly et al. (2007b) found that prescribers detected nonadherence in only 7% of schizophrenia outpatient cases. A few other previous studies (Remington et al., 2007; Yang et al., 2012), which compared EM adherence to various subjective-based adherence ratings, found that subjective clinician ratings also tend to over-estimate adherence (or under-estimate nonadherence) in outpatients with schizophrenia.

It is generally and empirically recognized that treating prescribers' (clinicians') ability to detect medication nonadherence is inadequate in schizophrenia populations (Byerly et al., 2005, 2007b; Velligan et al., 2009). What is not known is whether objective adherence assessment methods such as EM can advance the detection of nonadherence, if incorporated into routine care of outpatients with schizophrenia. To our knowledge, no prior studies have evaluated the potential role of objective adherence assessment measures such as EM in real-life settings. Would, for example, informing treating prescribers of objectively determined, previously undetected nonadherence of their own patients affect their decisions regarding treatment and adherence-related intervention planning? If so, what would be the degree of impact, and what specific treatment and intervention plan changes would prescribers recommend? We chose to address these questions in the current study by providing EM adherence results of patients with schizophrenia to their treating prescribers. Although EM adherence has its own shortcomings (Osterberg and Blaschke, 2005), it has become increasingly used as a reasonable "objective reference standard" to assess medication adherence in general medical and schizophrenia outpatient populations (Diaz et al.,

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2004; Osterberg and Blaschke, 2005; Remington et al., 2007; Byerly et al., 2007b; Nakonezny et al., 2008, 2010; Acosta et al., 2009; Yang et al., 2012). Based on patient-specific EM adherence results, the current study examined what treatment plan changes, if any, practicing prescribers (treating psychiatrists) would recommend (albeit hypothetical) for improving antipsychotic medication adherence in their individual outpatients with schizophrenia.

2. Methods

2.1. Participants

The 23 adult outpatients included in the current study were diagnosed with schizophrenia ($n=9$) or schizoaffective disorder ($n=14$), as established by the Structured Clinical Interview for DSM-IV, and were recruited from three Dallas County public mental health outpatient clinics. Most participants were self-referred from flyers (a few being referred by their treating clinician). Participants were recruited and studied at their usual outpatient clinics. Participants were included if they were taking a single oral antipsychotic, and if they were at least 18 years of age. Participants receiving a depot antipsychotic within one treatment cycle or using a pillbox were excluded. There were no restrictions placed on the use of psychotropic or other medications other than those mentioned above for antipsychotics. The study protocol was approved by the Institutional Review Board of The University of Texas Southwestern Medical Center at Dallas, and written informed consent was obtained from all participants. Participants were paid $15 per hour of study participation.

The 23 participants of the current study were a sub-sample of outpatients from our larger parent study of 61 adult outpatients diagnosed with schizophrenia or schizoaffective disorder, which evaluated the effect of antipsychotic medication adherence (using EM) over a 6 month period on prospectively assessed symptom severity/clinical outcomes (Nakonezny and Byerly, 2006). Because a limited number of prescribers ($N=7$) chose to participate in the current study, this circumscribed our sample to the 23 outpatients who were treated by these seven participating prescribers (treating psychiatrists).

2.2. Procedures and measures

2.2.1. Antipsychotic medication

The 23 participants of the current study took either a first- ($n=5$) or second-generation ($n=18$) oral antipsychotic that was prescribed as part of routine care at study entry. No participants switched antipsychotic class during the course of the trial. Regarding dosing schedule, of the 23 participants, 16 (69.6%) received dosing once per day, six (26.1%) received dosing twice per day, and one (4.3%) received dosing three times per day.

2.2.2. Electronic monitoring and adherence

Medication adherence was assessed with the Medication Event Monitoring System (MEMS®), which is a medication vial cap that electronically recorded the date and time of bottle opening. The MEMS® caps used in our studies had no cueing mechanisms and their appearance was similar to any other medication bottle, although the cap was slightly larger than a regular pill bottle cap. The company that makes the MEMS® caps provided no support for the parent study or the current study.

The study period of the parent trial (March, 2003–April, 2004) included a screening, baseline, and up to six consecutive monthly adherence evaluations. The content of study visits was limited to adherence and clinical assessments. No medication or adherence-related education or reminders were provided. Participants were aware of the purpose and function of the MEMS® cap, but did not have access to adherence results.

For a given patient, EM adherence was operationally defined as the proportion of medication vial caps openings in a given month relative to the prescribed doses for that month. If patients with multiple-dosing regimens opened the MEMS® cap at least the number of times prescribed each day, they received full credit for adherence for that particular day. Excessive bottle openings (i.e., openings that exceeded the number of prescribed doses for that month), however, did not count toward overall adherence. Most participants in the current study (19/23, 82.6%) completed the full 6 months of monthly adherence evaluations; one participant (1/23, 4.3%) completed five of the six monthly adherence evaluations (missed month 5), one participant (1/23, 4.3%) completed four of the six monthly adherence evaluations (missed months 5–6), and two participants (2/23, 8.7%) completed three of the six monthly adherence evaluations (missed months 4–6).

To further understand whether a given EM adherence level influenced prescribers' hypothetical treatment plan change recommendations, we also *a priori* operationalized EM adherence as a binary variable using three separate cutoffs: as the proportion of patients who were less than ($<$) and greater than or equal to ($\geq$) the 6-month mean EM adherence of 70%, 80%, and 90%, respectively. The 70% EM adherence cutoff was selected because it was both conservative in detecting nonadherence in schizophrenia and consistent with definitions from prior published research (Byerly et al., 2005, 2007b). The 80% EM adherence cutoff was selected for examination because it was endorsed by an expert consensus panel (Velligan et al., 2009) as an appropriate cutoff for adherence in schizophrenia. The 90% EM adherence cutoff, however, was selected simply for exploratory purposes in this study.

2.2.3. Prescriber evaluation and recommendation

At the completion of the parent study, both monthly average and the 6-month average patient-specific EM adherence results were shared with the seven prescribers who participated in the current study. The seven prescribers, treating psychiatrists, for the current study were then surveyed (via a self-administered questionnaire) concerning the treatment plan changes, if any, that they would recommend (albeit hypothetical) – based solely on the average EM adherence results – for improving antipsychotic medication adherence in their individual outpatients with schizophrenia.

Hypothetical treatment plan changes (from which to select on the structured questionnaire) comprised a general recommendation, "I would not recommend any treatment changes at this time," and seven specific recommendations that encompassed *Medication Treatments* and eight specific recommendations that encompassed *Psychosocial Treatments*. Sample recommendations of the *Medication Treatments* include "increase dose of current antipsychotic", "if patient is on a newer [second-generation] antipsychotic, switch to a different newer oral antipsychotic agent," and "initiate second-generation long-acting injectable". Sample recommendations of the *Psychosocial Treatments* include "increase case management intensity", "initiate use of pill box", and "initiate psychoeducational program". The prescriber responses to the general and specific recommendations were operationalized as binary variables coded as "yes" (dummy-coded as 1) or "no" (dummy-coded as 0). Prescribers were permitted to select all treatment plan changes from among the hypothetical response choices on the structured questionnaire that were applicable, in their clinical judgment, to a given patient. Prescribers were also permitted to write in "other" treatment plan changes for a given patient that were not part of the response choices on the structured questionnaire.

Although there were seven treating psychiatrists for the current study, prescriber 1 rated 10 of the 23 patients (43.48%), prescriber 2 rated four of the 23 patients (17.39%), prescribers 3 and 4 each rated three of the 23 patients (13.04% each), and prescribers 5 through 7 each rated one of the 23 patients (4.35% each). We note that a Likelihood Ratio Chi-Square test of independence found no statistical association (contingency) between the prescriber and the general treatment plan change recommendation ($\chi^2=5.19$, $p=0.52$). This means that any general treatment plan change recommendation was not associated with the prescriber (which, in general, mitigates a rater or prescriber effect).

2.3. Statistical analysis

Demographic and clinical characteristics for the sample of 23 patients were described using the sample mean and standard deviation for continuous variables and the frequency and percentage for categorical variables. A descriptive frequency analysis was carried out to examine the frequency of general and specific medication-based and psychosocial-based treatment plan change recommendations. For analytic purposes, we used (operationalized) adherence as an aggregate based on the 6-month mean EM adherence. Next, the Pearson point-biserial correlation coefficient (r_{pb}) was used to examine the relationship between the continuously measured 6-month mean EM adherence and the prescriber responses to the general and specific medication-based and psychosocial-based treatment plan change recommendations. Finally, Fisher's exact test was used to test for an association (contingency) between the proportion of prescribers who recommended a treatment plan change (general, psychosocial, and medication, respectively) and the proportion of patients who had 6-month mean EM adherences of at least 70%, 80%, and 90%, respectively. We also reported the Phi correlation coefficient (φ) here.

We performed all of the statistical analyses using SAS software, version 9.2 SAS Institute, Inc., 2002-2008). The level of significance for all tests was set at $\alpha=0.05$ (two-tailed) and p-values were left unadjusted for multiple testing.

3. Results

3.1. Participant characteristics

The study sample included 12 females (52.2%) and 11 males (47.8%), with an average age of 46.0 years, S.D.=6.9 (age range=34–59 years). The average age at illness onset was 21.2 years (S.D.=8.7). Participants included 12 (52.2%) Caucasians and 11 (47.8%) African Americans. Four (17.4%) participants had less than a high school education, while 19 (82.6%) had at least a high