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Evaluation of adherence patterns in schizophrenia using electronic monitoring (MEMS®): A six-month post-discharge prospective study

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ABSTRACT

Background: Medication Event Monitoring System (MEMS®) is considered the gold standard for the evaluation of medication adherence, yet few studies have applied this method, especially over long periods of time.
Objective: To investigate medication adherence patterns in a sample of post-discharge patients with schizophrenia monitored with MEMS caps during a six-month period.
Method: Adherence to antipsychotics was prospectively investigated using MEMS among 68 patients with schizophrenia. Treatment initiation, implementation or whether or not the patient takes his dosing regimen as prescribed, persistence or the length of time between initiation and discontinuation, and treatment discontinuation were used to describe adherence. Persistence over time was described using Kaplan-Meier curves.
Results: After discharge 16% of the patients never initiated treatment. On average 37.3% of patients adhered to treatment in the first 6 months. However, a strong decrease in adherence was observed over time ($p < 0.0001$), primarily due by treatment non-persistence. Only half of the patients were persistent at 6 weeks, persistence further dropped to 19.0% after 6 months. Among persistent patients, implementation was consistent over time with 87.8% of patients taking their medication as prescribed on any given day.
Conclusions: Dosing profile analysis provides further evidence for the magnitude of non-adherence with antipsychotic prescriptions among post-discharge patients with schizophrenia. Using the high precision of MEMS®, dosing profiles may provide a better understanding of non-adherence patterns and help clinicians determine optimal individualized strategies.

1. Introduction

Rates of antipsychotic medication non-adherence in schizophrenia are estimated to range from 24% to 90% (Dolder et al., 2002; Nose et al., 2003). While factors associated with medication non-adherence are known, the identification of patients with poor adherence remains an important challenge in clinical practice (Misdrahi et al., 2016). Most prior studies investigating medication adherence, however, have relied on subjective or indirect methods such as self-reports, provider-reports, or chart reviews to assess adherence (Nakonezny et al., 2008; Osterberg and Blaschke, 2005; Velligan et al., 2006).

Electronic medication event monitoring is regarded as the most reliable measure of adherence (Chesney, 2006; Velligan et al., 2009). Studies have shown that such techniques are more accurate than pill counts or self-reports, techniques that tend to overestimate adherence (Byerly et al., 2005; Velligan et al., 2007). Furthermore, Medication Event Monitoring System (MEMS®) allows for the precise time of container opening to be recorded, thus providing the ability to identify any disruption or discontinuation of treatment (Diaz et al., 2001; George et al., 2000). Several studies have explored therapeutic adherence using MEMS caps in schizophrenia (Acosta et al., 2009; Brain et al., 2013; Diaz et al., 2001; Remington et al., 2007; Yang et al., 2012). However, the great majority of these studies have relied on a dichotomous definition of adherence, with the exception of one study (Acosta et al., 2013), which used the high potential of electronic dose monitoring to characterize patterns of medication use over time, with greater nuance and

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precision. For instance, the study showed that dose-omission gaps occurred in 18.7% of monitoring days and almost one-third of prescribed doses were taken out of prescribed time. The latter study, however, focused on a limited period of time (3 months) and concerned stabilized outpatients.

The aim of the present study is to characterize adherence patterns in a sample of post-discharge patients with schizophrenia monitored with MEMS® caps over period of a six-month.

2. Method

2.1. Participants

Patients hospitalized in one of the three psychiatric hospitals located in Bordeaux (N = 45), Clermont-Ferrand (N = 10) and Paris (N = 17) between September 2010 and September 2011 were enrolled. To be eligible for the study, patients had to have been diagnosed with schizophrenia or schizoaffective disorders according to DSM-IV-TR criteria (DSMIV, 1995), were at least 18 years old, were capable of understanding the protocol, and were prescribed at least one oral antipsychotic. If more than one antipsychotic was prescribed, the principal antipsychotic was identified as the drug to be delivered with the MEMS®. Exclusion criteria included the presence of comorbid neurological diseases, mental retardation, disability due to a serious medical condition, or treatment with only one long-acting injectable antipsychotic. All patients were informed that their participation would not affect their treatment or discharge plans. The study was approved by an ethical committee (CPP-Ile de France III, N° ID RCB: 2008-A00504-51), and all participants provided written informed consent to participate.

Of the initial 72 patients, two did not return the MEMS device, and there were technical problems preventing data extraction in two other cases. The final sample included 68 patients monitored with MEMS® during a six-month period.

2.2. Procedure

At each participating site, a psychiatrist carried out patient enrollment during hospitalization. Patients were approached less than one week prior to their scheduled discharge, after the remission of acute symptomatology, when patients were considered to be clinically stable. Once discharged, patients received post-discharge care as usual consisting of a monthly appointment with their psychiatrist. During a six-month period, adherence to antipsychotic was monitored using MEMS caps (MEMS®; WestRock Switzerland). Each patient received from a study nurse a pill bottle with a cap that recorded the time and date of each opening and closing of the bottle. MEMS caps do not provide any reminder, timer or alarm for the patient. The study nurse fully informed each patient of the study protocol and monitoring procedures. Patients were informed that the purpose of the study was to use these electronic monitors to estimate adherence with their medication regimen and that MEMS caps recorded dosing history. Patients were instructed to take their antipsychotics as prescribed by their psychiatrist. If patients had multiple prescriptions, they were asked to take their other medication as prescribed. No compensation was offered to the patients for participation. The treating psychiatrists were blind to the nature of the investigation and to the data of adherence patterns provided by the MEMS device. Each month, MEMS caps were filled by the study nurse with the amount of antipsychotic medication prescribed. The baseline evaluation documented socio-demographic variables, clinical variables including the duration of the disorder, number of prior hospitalizations, present and past substance use or abuse, treatment-related variables (antipsychotic dosage regimen, other psychotropic drug use, number of psychotropic pills per day), and psychopathological variables using the PANSS scale (Kay et al., 1987).

2.3. Medication adherence variables

Adherence is a blanket term describing the process by which patients take their medications as prescribed. Treatment initiation, implementation, persistence or the length of time between initiation and discontinuation, and treatment discontinuation can be used to describe temporal events related to medication adherence (Blaschke et al., 2012; Vrijens et al., 2012) (Appendix 1). Treatment initiation is when the patient takes the first dose of the prescribed medication. Treatment implementation describes whether or not the patient takes his dosing regimen as prescribed, from initiation to discontinuation. Daily implementation was operationalized as the percentage of patients that have taken the prescribed dose on any given day. Furthermore, within the implementation phase, three indicators were calculated. These include the following:

- taking compliance (TAC): percentage of number of prescribed doses taken ((number of openings / number of prescribed doses) × 100)
- correct dosing (COD): percentage of days with correct number of doses taken ((number of days with number of openings as prescribed / number of monitored days) × 100)
- timing compliance (TIC): percentage of doses taken within prescribed interval ((number of openings within ± of 3 h around the prescribed interval / number of prescribed doses) × 100).

Discontinuation marks the end of medication intake: the day of discontinuation is defined as the last day with dose intake during which the patient had taken at least 50% of prescribed doses over the last 14 days. Finally, persistence is the length of time between treatment initiation and discontinuation. If 7 days of treatment were missed consecutively, participants would be deemed non-persistent.

2.4. Statistical analysis

Adherence was summarized over time as a sequence of binary data Z_{ij} indicating whether (1) or not (0), at least the prescribed number of doses were taken on day j by patient i. When patient i prematurely discontinued treatment, we defined $Z_{ij} = 0$ for $j >$ premature discontinuation date. This coding retains much of the temporal structure in the individual drug intake patterns and considers that a patient who prematurely discontinued treatment was non-adherent from that time on. For each day of the follow-up period, adherence is summarized as the percentage of patients who have taken the prescribed number of doses on that day. There can be two reasons the medication was not taken on a given day: the patient had previously discontinued treatment (non-persistence) or the patient was still persistent with the dosing regimen but neglected to take a dose on that particular day (non-implementation). Persistence was described over time using Kaplan-Meier curves. Persistence was censored if there was no evidence of discontinuation in treatment at the end of the observation period.

Similarly, implementation was summarized over time as a sequence of binary data Z_{ij} indicating whether (1) or not (0), at least the prescribed number of doses were taken on day j by patient i. The difference with adherence is that when patient i prematurely discontinued treatment, the binary sequence Z_{ij} was censored. Each day, implementation was thus summarized as the percentage of patients who had taken the prescribed number of doses among the patients who were still persistent on that day.

Adherence and implementation were analyzed using logistic models for longitudinal binary data (Generalized Estimating Equations models). The Wilcoxon test was used to compare the implementation measures (TAC, COD, and TIC) between patients taking one daily antipsychotic dose (QD) and those taking two antipsychotic doses daily (BID). Since only two patients had a prescription for more than two daily antipsychotic doses, these two patients were excluded from the analyses. p-

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