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Impact of symptom resolution on medication adherence in first episode psychosis

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ABSTRACT

Adequate adherence to medication confers benefits on patients with psychotic illness, but is difficult to achieve. Efficacy of medication influences adherence in patients in advanced phases of illness and may have a similar influence on patients with a first episode of psychosis (FEP). We assessed medication adherence and efficacy in 216 FEP patients at program entry and at 3 and 6 months later. "Efficacy" was evaluated as the ability of medication to reduce positive or negative symptoms to below established thresholds for clinical remission at each evaluation. Adherence was defined as adequate (>75%) or not. Resolution of negative symptoms by month 3 of treatment was associated with inadequate adherence at months 3 and 6. In contrast, rapid resolution of positive symptoms showed no relationship to adherence. In a multivariate analysis taking into account other determinants of adherence in FEP, the role of early negative symptom remission was confirmed, and we found that a 3-month sustained remission of positive symptoms was associated with adequate adherence. Medication efficacy may promote adherence if it produces sustained remission of positive symptoms. However, many patients who benefit from medication, particularly those with rapid improvement of negative symptoms, fail to adhere to the treatment.

1. Introduction

Medication adherence improves outcomes in psychotic illness, reducing the risk of relapse and rehospitalization (Valenstein et al., 2002; Ascher-Svanum et al., 2006a, 2006b; Law et al., 2008). For patients with first episode psychosis (FEP), adherence is associated with faster remission of positive symptoms, fewer recurrences and better social/occupational functioning (Robinson et al., 1999; Malla et al., 2006; Lambert et al., 2010). However, many patients with FEP do not adhere to a medication regimen: 26 to 53% of early psychosis patients leave treatment in the first year (Favre et al., 1997; Novak-Grubic and Tavcar, 2002; Robinson et al., 2002) and between 33 and 63% display inadequate levels of adherence (Coldham et al., 2002; Mojtabai et al., 2002; Kamali et al., 2006; Quach et al., 2009). Several studies have found that poor adherence predicts subsequent poor adherence (Verdoux et al., 2000; Lacro et al., 2002; Ascher-Svanum et al., 2006a, 2006b), increasing the importance of understanding this phenomenon in FEP.

Adherence to medication is influenced by numerous factors, including patient-related elements (age and gender; attitudes; symptoms), relationship elements (alliance with caregivers; family support) and health care system elements (cost of care; ease of access; (Velligan et al., 2009)). Many of these factors have been associated with adherence in FEP (see (Miller, 2008; Masand et al., 2009) for review). However, several studies have pointed to a crucial role for attitudes and beliefs about medications. Mutsatsa et al. concluded that attitudes and insight were more important determinants of adherence in FEP than adverse effects or demographics (Mutsatsa et al., 2003). More specifically, Perkins et al. found that positive attitudes towards medications and beliefs that they are beneficial were highly associated with adherence (Perkins et al., 2006).

These results raise questions about how medication attitudes are formed. Studies of multi-episode patients suggest that perceived medication efficacy is an important factor in both attitudes and adherence. In a qualitative study asking patients to list influences on adherence, efficacy was the most often cited factor (Kikkert et al., 2006). Data from a series of antipsychotic clinical trials showed that lack of efficacy, as perceived by the patient, was the most common reason for discontinuation (Liu-Seifert et al., 2005). Although patients and clinicians may have different ways of evaluating efficacy, several studies have found that reduction of symptoms is relevant to patients: Karow et al. found that improvements in both subjective well-being and in symptoms were associated with improvements in adherence (Karow et al., 2007), symptom improvement in the first 2 weeks of a treatment trial predicted completion of a 6-month protocol (Liu-Seifert et al., 2005) and failure of treatment response was associated with non-adherence and study discontinuation in a year-long trial with first episode patients (Perkins et al., 2008).

In the present study, we examined the interaction between medication efficacy and adherence very early in treatment, when patients are learning about medications and attitudes are being formed. Because of the association mentioned above between early symptom

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reduction and remaining in treatment, one might predict that rapid relief of symptoms would be interpreted as proof that medications are useful and would promote adherence. On the contrary, patients who experience rapid elimination of symptoms may be more likely to minimize or dismiss their illness experiences, and see medication as unnecessary (Fenton et al., 1997; Clatworthy et al., 2007). Our aim was to test which of these observations applies to patients being treated for FEP. We hypothesized that rapid improvement of symptoms would be associated with subsequent adherence, especially if improvement was sustained.

2. Methods

2.1. Participants

Subjects were recruited from the Prevention and Early Intervention in Psychosis Program in Montréal, Quebec, Canada (PEPP-Montréal), a specialized assessment, treatment and follow-up program which provides care for FEP to the south-western sector of the greater Montréal area. This program model has been described previously (Malla et al., 2003) and details are also available at our website (Douglas.mcgill.ca/pepp). Upon entry into the program, each patient is asked to sign an informed consent to participate in a longitudinal outcome study of early psychosis, approved by the Institutional Review Board for Human Subjects Research. The data presented here are part of this larger study.

Entry criteria for PEPP-Montréal are age between 14 and 30 years, Diagnostic and Statistical Manual, Fourth Edition, Text Revision (DSM-IV-TR) diagnosis of a psychotic disorder and prior treatment with anti-psychotic medication for not longer than 1 month. Exclusion criteria are IQ of <70, diagnosis of epilepsy or organic brain syndrome or primary diagnosis of substance abuse or dependence. Patients with a primary diagnosis of a psychotic disorder who exhibit concurrent substance abuse are accepted, while those found to have a primary diagnosis of substance-induced psychosis are excluded from research protocols.

2.2. Clinical and demographic evaluations

Diagnoses (primary and secondary) were established for each patient using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-IV) Patient Edition (First et al., 2002). Evaluations were conducted within 3 months of PEPP admission by a trained interviewer and confirmed through consensus with two senior psychiatrists (A.M. and R.J.). Duration of untreated psychosis (DUP) was evaluated using the Circumstances of Onset and Relapse Schedule (Norman et al., 2004) and was calculated as the time from the onset of psychotic symptoms significant enough to reach the threshold for the SCID-IV to the time of adequate treatment with antipsychotics (treatment for 1 month or until significant response was obtained, whichever came first).

Symptom assessments were conducted within 1 month of program entry ("program baseline") and at months 3 and 6. Positive and negative symptoms of psychosis were evaluated using the Scale for Assessment of Positive Symptoms (SAPS; Andreasen, 1984) and the Scale for Assessment of Negative Symptoms (SANS; Andreasen, 1983) respectively. Assessments referred to symptoms over the previous month and were performed by trained raters who had achieved acceptable inter-rater reliability (ICC 0.75 for SAPS total score, 0.75 for SANS total score). Insight was evaluated using item G12 (lack of insight and judgment) from the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), depressive symptoms with the Calgary Depression Scale for Depression in Schizophrenia (Addington et al., 1990) and extrapyramidal symptoms with the Barnes Akathisia Scale (Barnes, 1989) and the Extrapyramidal Symptom Rating Scale (Chouinard et al., 1980).

2.3. Assessment of medication adherence

Medication adherence was assessed using information from clients and case managers, who have, on average, weekly contact with clients during the first 3 months of treatment, and biweekly contact thereafter. Case managers incorporate data from clients and family members whenever possible, and their reports have been found to correlate closely with data obtained by pill count (correlation coefficient 0.93; Cassidy et al., 2010b). They are therefore used as an acceptable single measure of adherence. Case managers assigned adherence to one of the following categories: never adherent (0%), very infrequently adherent (1 to 25%), sometimes adherent (26–50%), quite often adherent (51 to 75%) or always adherent (greater than 75%). Adherence was dichotomized as adequate (greater than 75%) or inadequate (75% or less), as adherence of 75 to 80% has been shown to be effective in preventing re-hospitalization (Valenstein et al., 2002; Karve et al., 2009).

2.4. Evaluation of efficacy and definition of symptom resolution

In order to assess medication efficacy, we evaluated symptom change using the criteria proposed by the Working Group on Remission in Schizophrenia (WGRS; Andreasen et al., 2005) which state that patients are considered "in remission" when their positive and negative symptoms are rated as no more than "mild" using standard rating scales, and their behavior is no longer influenced by symptoms. This level of improvement is likely to be relevant to patients as lack of interference from symptoms is an element in patient-generated definitions of recovery (Corrigan et al., 2004). Furthermore, recent studies have observed that symptomatic remission defined in this way appears to be a pre-requisite for recovery of social and occupational functioning. (San, 2007; Cassidy et al., 2010a).

We employed the Working Group criteria for SAPS and SANS, which require that scores for all "global" items (except attention) are ≤2. For SAPS, the items evaluate hallucinations, delusions, bizarre behavior and positive formal thought disorder. The SANS items are affective flattening, alogia, avolition–apathy and anhedonia-asociality. Although Working Group criteria specify a 6-month duration of remission, we were interested in very early and rapid improvement in symptoms, and therefore chose to employ the definitions cross-sectionally, examining resolution of both positive and negative symptoms at each assessment. We classified patients as having experienced early symptom resolution (by month 3 of treatment), later resolution (by month 6 of treatment) or a 3-month remission (from month 3 to month 6).

2.5. Selection of predictor variables for regression analysis

Predictor variables were selected after review of the literature and examination of the study population. Factors known to be associated with non-adherence in FEP, include younger age (Kampman et al., 2002; Quach et al., 2009), male gender (Kampman et al., 2002), mood disorder (Gearing and Charach, 2009), substance abuse (Kamali et al., 2006; Quach et al., 2009; Lambert et al., 2010), baseline positive symptoms (Novak-Grubic and Tavcar, 2002; Kamali et al., 2006; Lecomte et al., 2008), baseline total symptoms (Kampman et al., 2002) and baseline adherence (Verdoux et al., 2000). Insight at study entry has been shown to predict subsequent adherence in some studies (Novak-Grubic and Tavcar, 2002; Kamali et al., 2006), but in other studies, only concurrent insight is predictive (McEvoy et al., 2006). We selected insight at study baseline as the most appropriate predictor because the PANSS definition of insight includes recognition of the need for treatment and may be conflated with adherence. We did not examine the effect of first vs. second generation antipsychotics (Mojtabai et al., 2002) because all but five of our subjects were treated with second generation agents. For the same reason, extrapyramidal side effects were rare in our sample, and were not included as predictors. We examined our chosen variables for co-linearity, and found no correlation coefficient greater than 0.29.

2.6. Analysis

Statistical analysis was performed using the Statistical Software Package for Social Sciences version 18. Groups of subjects were compared using chi-squared analysis for categorical variables and ANOVA for continuous variables. However, comparison of DUP was performed with the Mann–Whitney *U*-test, as DUP is not normally distributed in our sample. Within groups, change in symptoms or adherence behavior over time was assessed using paired sample T-tests. Regression analysis was performed using binary logistic regression with adequate adherence at month 3 or month 6 as the outcome variable. Statistical significance was set at $P<0.05$, using a two-tailed statistic.

3. Results

3.1. Demographic characteristics

Between January 2003 and April 2010, 301 first episode psychosis patients received at least 3 months of treatment at PEPP-Montreal. Complete symptom and adherence data were available at program baseline (within 1 month of entry) and at month 3 for 216 of these. Seventy patients were excluded from the analysis because of incomplete data (10 patients were not prescribed medications very early in treatment, while 60 failed to complete evaluations). In addition, 15 patients were excluded from the analysis because their positive and/or negative symptoms were below the remission threshold at both program baseline and month 3. Table 1 compares the demographic characteristics of the included subjects with those who were excluded. Patients who were excluded due to missing data were less likely to be adherent at baseline, reflecting the fact that non-adherent patients tend not to present for evaluations. We also observed that patients excluded due to lack of symptoms had a shorter median DUP than included subjects. As expected, these subjects had lower SAPS and SANS total scores at baseline than included subjects. There were no other significant demographic differences among the three groups.

At the 6-month follow-up, adherence data were available for 204 subjects and symptom data for 185. Four subjects were no longer prescribed medication at month 6, and 31 subjects failed to complete the