

Reasons for Adherence and Nonadherence: A Pilot Study Comparing First- and Multi-Episode Schizophrenia Patients

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Abstract

Rationale: Most first-episode schizophrenia patients will stop their medication after their acute symptoms improve. Understanding the salient motivations and attitudes that drive adherence—as well as nonadherence—is an important part of developing strategies to prevent or delay nonadherence during the early phases of the illness. **Methods:** Self-reported reasons for adherence and nonadherence among first-episode and multi-episode patients with schizophrenia were obtained from cross-sectional adherence interviews from two prospective adherence studies: one composed of a first-episode sample (n=33) and the other with recently relapsing multi-episode patients (n=16). Both groups received the Rating of Medication Influences (ROMI) Scale at approximately 16 to 20 weeks after an acute psychotic episode. The specific ROMI items were ranked in order of percentage (%) strong, and were compared both within each patient group for rank order of importance, and also compared between groups to determine the differences in specific adherence and nonadherence influences. **Results:** The doctor-patient relationship was more likely to be endorsed as a strong adherence influence in the first-episode sample (74%) than in the multi-episode sample (13%, $X^2=18.07$, $p<.01$). Change in physical appearance attributed to medication was a more commonly endorsed nonadherence influence for the multi-episode sample (25%) relative to the first-episode sample (0%, $X^2=9.2$, $p<.01$). **Conclusions:** The doctor-patient relationship stands out as being the major reason for ongoing adherence for first-episode schizophrenia patients. Our post hoc interpretation is that lack of prior experience with medication and treatment elevates the importance of the relationship with the treating clinician for first-episode patients.

Key Words: Adherence, First-Episode Schizophrenia, Antipsychotics, Subjective Reasons

Introduction

Ongoing maintenance antipsychotic treatment of first-episode schizophrenia is an enormous challenge for patients and clinicians. Usually, the patient enters the mental health system in a crisis and learns of his diagnosis of schizophrenia. Once the acute symptoms resolve, clinicians know

that antipsychotics are still needed for relapse prevention and need to somehow convey this recommendation to patients and their families. The need to continue antipsychotic medication beyond the acute episode is far from obvious to patients who often feel better and wish to put this traumatic experience behind them. Information and education pertaining to the ongoing nature of schizophrenia, especially the individual's vulnerability to future psychotic episodes, is often done in a setting of high turmoil and stress in the patient's social environment. This atmosphere of crisis, fear and uncertainty often is the unspoken backdrop for discussions about medications and future treatment.

From a disease management perspective, a confirmatory diagnosis of schizophrenia after an initial psychotic episode means that antipsychotics should be continued into maintenance, long after the acute psychotic episode is over. While

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Clinical Implications

Our major finding is that the doctor-patient relationship seems to be a particularly important factor for the first-episode patients who stayed with their outpatient treatment and have remained on medication for the time being. Put another way, many of the other salient attitudinal factors—such as perceived benefit of medication—were relatively less influential for first-episode patients than would be expected. Initially we were surprised by this finding, but in retrospect have a post hoc explanation. “First-episode” patients have, at best, limited experience with ongoing maintenance treatment. Initial pharmacologic treatment of the acute psychotic episode occurs during a time of crisis, and treatment occurs with multiple changes and interventions that happened simultaneously during the period of acute treatment, and medication intervention is only one of many events. From the patient’s perspective, there is no inherent reason that antipsychotic medication rather than other interventions was the key factor in reducing symptoms and distress (19). Further, even if improvement in symptoms is attributed to medication, the patient may still conclude that medication is no longer needed, following the logic of antibiotic treatment.

The very limited illness and treatment experience of first-episode patients makes it difficult, if not impossible, for patients to generate their own “cause and effect” experience with medication. However, this finding does not by itself explain why or how certain patients value the doctor-patient relationship more than others. One implication of this finding is that strategies to help strengthen the therapeutic relationship with treating clinicians might be particularly influential for individuals early in the illness course. It is the treating clinician who informs the patient and family that the recent improvements were primarily related to the antipsychotic medication. The clinician is asking the patient to follow treatment recommendations and, given this context, it is understandable that the perceived credibility and relationship are key influences for the patient’s decision to continue with medication.

there is still some debate among clinical experts about the recommended duration of antipsychotic therapy after the first-episode diagnosis, the debate centers on how many years of maintenance therapy should be recommended before attempting a discontinuation, if ever. There is no debate that the majority of stabilized first-episode patients will relapse unless antipsychotic medications are continued (1, 2). Of course, in clinical practice, the theoretical optimal length of recommended antipsychotic therapy is often a moot point. Clinicians may debate how many years of maintenance antipsychotic, but patients are thinking, “How many days or weeks do I need to stay on this medication?” Therefore, translating this evidence-based knowledge into a useful treatment plan is easier said than done (3). Despite the clinicians’ recommendations, the question usually is not “Will the patient stop antipsychotic medications too soon?” A more realistic question is “When will the patient stop medication (4-6)?” More than 40% of the patients with first-episode psychosis discontinue medication during the first nine months of treatment, resulting in increased relapse rates as well as greater likelihood of the emergence of treatment-resistant symptoms (7).

Although the adherence literature tends to focus more on reasons for nonadherence than reasons for adherence, we believe that understanding motives for adherence is at least as important as nonadherence. Data on a patient-centered perspective on adherence provide valuable information because they can help clinicians develop better strategies to improve duration of medication adherence overall. Our belief is that the reasons for adherence may change over time, so

we evaluated self-reported reasons for adherence and non-adherence in recently diagnosed first-episode schizophrenia patients who were enrolled in an adherence treatment study (8). We were particularly interested in understanding motivations for continued adherence in a first-episode patient population. Why would a first-episode patient choose to stay on medication after an initial acute episode? In what way do the influences and motivations for adherence differ between first-episode and more persistently ill patients (9-11)?

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We hypothesize that there may be salient factors promoting medication adherence that go beyond patients’ awareness of direct benefits of maintenance antipsychotic medication. There is a very limited literature assessing the therapeutic relationship and medication adherence. The classic study on the importance of therapeutic alliance on adherence during early stages of schizophrenia comes from the Boston Collaborative Psychotherapy Study, which was a longitudinal study comparing two forms of psychotherapy (in addition to antipsychotic medication). The strength of the therapeutic alliance at the start of the treatment was a better predictor of medication adherence than was the specific type of therapy given (12, 13).

We assessed a broad range of reasons for adherence

and nonadherence to compare factors related to perceived benefits versus factors related to relationships with others, especially family members and mental health clinicians. Specifically, we hypothesized that the doctor-patient relationship is a critical factor in explaining ongoing medication adherence after an initial psychotic episode.

Methods

This was a post hoc data analysis of two data sets of prospectively assessed adherence attitudes in studies of adherence interventions. We hypothesized that the importance of the therapeutic relationship would be reflected in the independent adherence attitude assessments done by masked independent assessors who were not involved in the clinical care of the patients. At the time of formulation of the above hypothesis the investigators did not know the results of the primary adherence attitude outcome for the first-episode sample. The comparison between first-episode and multi-episode patient populations was done with a post hoc comparison of two studies using the same adherence attitude outcome assessments.

Sample

The first-episode schizophrenia sample was obtained from patients entering a prospective maintenance study comparing the effectiveness of long-acting versus oral atypical antipsychotics for first-episode schizophrenia patients. The multi-episode sample was obtained from a cognitive behavioral therapy (CBT) adherence intervention, randomized, pilot study (14). The CBT adherence intervention was a brief, time-limited intervention in addition to standard treatment for schizophrenia, which includes medication and group psychoeducation. Participants were enrolled from December 2004 to March 2007 from Kings County Hospital Center (Brooklyn, New York). Institutional Review Board approval was obtained for both studies. All subjects gave written informed consent for participation in the study after the procedure was fully explained and questions answered.

Subjects

First-Episode Sample

Subjects were between the ages of 16 and 40 who were admitted to the inpatient and outpatient services of the site and who had a Structured Clinical Interview for DSM-IV (SCID) confirmed diagnosis of schizophreniform disorder, schizophrenia or schizoaffective disorder; clinical indication for long-term maintenance antipsychotic treatment; clinical response to oral antipsychotic medication; and, a history of recent willingness to attend outpatient treatment services and had completed at least one dedicated baseline psychoeducation session that included a key family member. These subjects were recruited from a study whose primary aim was to

compare the effectiveness of long-acting versus oral route of medication delivery. Details of the study design have been reported elsewhere (8).

Multi-Episode Sample

We used an earlier study of an adherence intervention in a chronically ill sample to provide a quasi-comparison group for the first-episode cohort. The inclusion criteria were: ages between 18 and 65; clinical diagnosis of schizophrenia or schizoaffective disorder; recent treatment (within past six weeks) for a worsening of acute psychotic symptoms defined by either psychiatric hospitalization or signs of relapse without hospitalization; clinical response to oral antipsychotic medication; and, willingness to participate in an individual psychosocial intervention focusing on medication and health outcomes.

Comparison of Study Design

Because the key variables in the analysis were based on two separate studies, to evaluate any inference of differences in self-reported adherence influences between first-episode and persistently ill patients it is important to consider whether such a contrast is ecologically valid. Key similarities between the two adherence studies include: 1) primary diagnosis of schizophrenia; 2) having a recent acute psychotic episode; 3) the same treatment environment; 4) the same adherence outcome measures; 5) comparable rater training and adherence assessments; and, 6) similar cross-sectional assessment times. Important differences between the studies include the following: 1) when the studies were conducted; 2) primary research goals; 3) research and clinician staffing changes; and, 4) differences in intrinsic characteristics of the two samples that cannot be completely separated from the primary contrast (e.g., differences in age of sample).

Procedures

Most of the assessments for the two studies were identical; therefore, they are presented as a single assessment battery. Research procedures for both samples included Structured Clinical Interview for DSM-IV (SCID) diagnosis, as well as psychopathology assessment using the Positive and Negative Syndrome Scale (PANSS) (15), the Calgary Depression Rating Scale (CDRS) (16), and the Clinical Global Impressions-Severity (CGI) subscale (17). Adherence attitudes were ascertained by an independent blinded assessor using the Rating of Medication Influences (ROMI) Scale (18) at baseline. The ROMI is a reliable and valid scale developed to measure salient attitudes and influences for schizophrenia patients taking antipsychotic medications. The ROMI is divided into two subscales: reasons for adherence (ROMI-A; 9 items) and reasons for nonadherence (ROMI-NA; 10 items). Each item covers a specific aspect known to influence medi-

Table 1 Comparison of Characteristics of the First-Episode and Multi-Episode Samples

Characteristic(s)	First Episode N=33	Multi Episode N=16	Statistical Test & Significance
Age Yrs—mean (SD)	25.8 (6.7)	33.7 (9.3)	t=3.44, (df=47), p=.001
Gender—% male	73	68	$\chi^2=0.084$, (df=1), p=0.77
Living situation—% living with others	79	75	$\chi^2=0.089$, (df=1), p=0.77
Duration of illness Yrs—mean (SD)	0.8 (1.4)	8.9 (6.0)	t=7.43, (df=47), p<0.0001
PANSS total score—mean (SD)	68.5 (16.0)	78.9 (14.2)	t=2.21, (df=47), p=0.03
CGI-S score—mean (SD)	3.6 (1.3)	4.1 (0.7)	t=1.44, (df=47), p=0.16

SD=standard deviation; PANSS=Positive and Negative Syndrome Scale;
CGI-S=Clinical Global Impressions-Severity.

ation adherence. Scaling of individual items ranges from 0 (“no influence”) to 2 (“strong influence”).

Statistical Analysis

The study examined the mean scores of individual items of the ROMI Scale at 16 to 20 weeks after stabilization of the acute episode in the first-episode sample to understand the relative influence of different items on adherence and non-adherence to treatment. Each individual item on the ROMI Scale was dichotomized to either strong (score=2) or not strong (score = 0 or 1). For categorical comparison in each of the two groups, Fisher’s exact test was done. For comparison between the two groups, chi-square analysis was used.

Results

Characteristics of the First-Episode Sample

The mean age of patients was 25.8 years, 73% were male, 97% were single, 79% lived with others and 73% had a high school education. The majority of patients were Caribbean (63.6%) and African American (33.3%). Out of the 33 first-episode patients, 18 (54.5%) patients were on long-acting risperidone injection and 15 (45.5%) were on oral risperidone.

Characteristics of the Multi-Episode Sample

The average age was 33.7 years, 68% were male, 93.8% were single, 75% lived with others, and 75% had a high school education. Most (88%) were African American or Caribbean. Out of the 16 patients in the multi-episode sample, 19% of the patients were prescribed conventional anti-psychotics including haloperidol (12%) and fluphenazine (6%), and 81% of patients were prescribed atypical anti-psychotics including risperidone (44%), ziprasidone (19%), olanzapine (12%), and aripiprazole (6%).

Table 1 shows the comparison of the characteristics of the two groups. There were significant differences for patient age and duration of illness between the two groups.

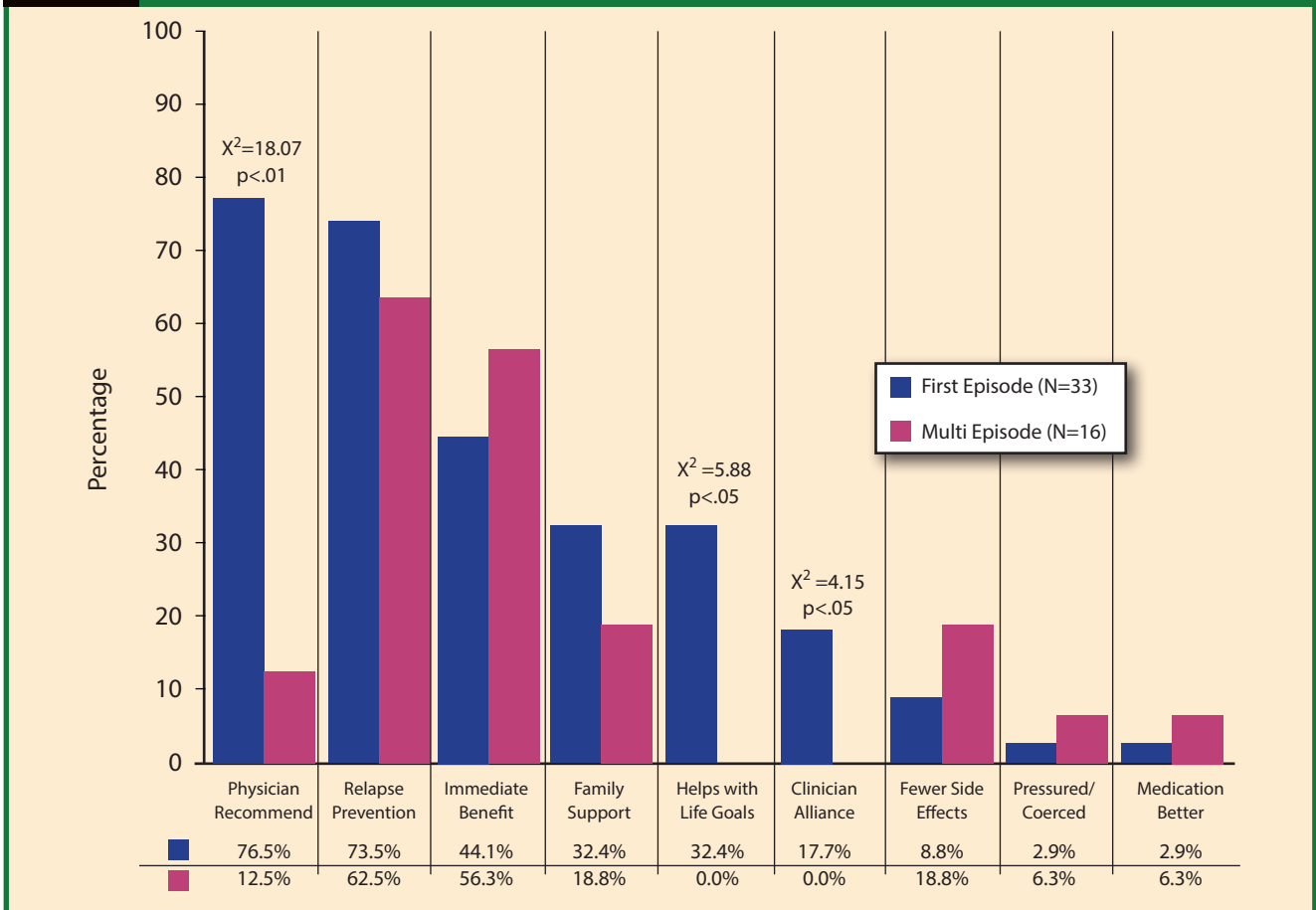
Reasons for Adherence

Figure 1 shows the rank order of self-reported reasons for adherence between first-episode and multi-episode groups. The columns represent the percent of patients endorsing that factor as a strong influence. The top four adherence influences reported by the first-episode sample were: 1) doctor-patient relationship (76.5% strong adherence influence); 2) relapse prevention (73.5%); 3) day-to-day (immediate) benefit from medication (44.1%); and, 4) help with life goals (32%). The top four adherence influences reported by the multi-episode sample were: 1) relapse prevention (62.5% strong adherence influence); 2) day-to-day (immediate) benefit from medication (56.3%); 3) family support (18.8%); and, 4) fewer side effects of current medications (18.8%). Comparing the relative frequency of self-reported reasons for adherence, doctor-patient relationship was much more frequently endorsed by the first-episode sample compared with multi-episode patients (76.5% vs. 12.5%, $X^2=18.07$, $p<.01$). There was a significant difference ($X^2=4.15$, $p<.04$) in clinician alliance (non-prescribing), with 18% of first-episode patients considering it as a strong influence and none of the chronically ill patients considering it of any influence. There was also a significant difference ($X^2=5.9$, $p<.02$) in the endorsement of the ROMI adherence item “help with life goals” between the two groups: 32% of the first-episode sample rated it as strong, whereas none of the multi-episode sample did.

Reasons for Nonadherence

Figure 2 shows the rank order of self-reported reasons for nonadherence between first-episode and multi-episode groups. The columns represent the percent of patients endorsing that factor as a strong influence. The top four subjective

Figure 1 Comparison of Adherence Influences between First-Episode and Multi-Episode Patients (% endorsing 2 vs. 0 or 1)



reasons for nonadherence reported by the first-episode sample were: 1) distress from side effects (32.4% strong nonadherence influence); 2) no benefits from medication (26.5%); 3) denial of illness (26.5%); and, 4) stigma (26.5%). The top four nonadherence influences reported by the multi-episode sample were: 1) distress from side effects (43.8% strong nonadherence influence); 2) medication believed to be unnecessary (31.3%); 3) change in appearance (25%); and, 4) stigma (25%). Comparing the frequency of subjective reasons for nonadherence between the two samples, change in appearance attributed to medication was more frequently endorsed by the multi-episode sample as compared to the first-episode sample (25% vs. 0%, $X^2=9.2$, $p<.01$). Finally, multi-episode patients were more likely to report that medications were unnecessary (31.3% of multi-episode vs. 8.8% of first-episode patients [$X^2=4.1$, $p<.04$]).

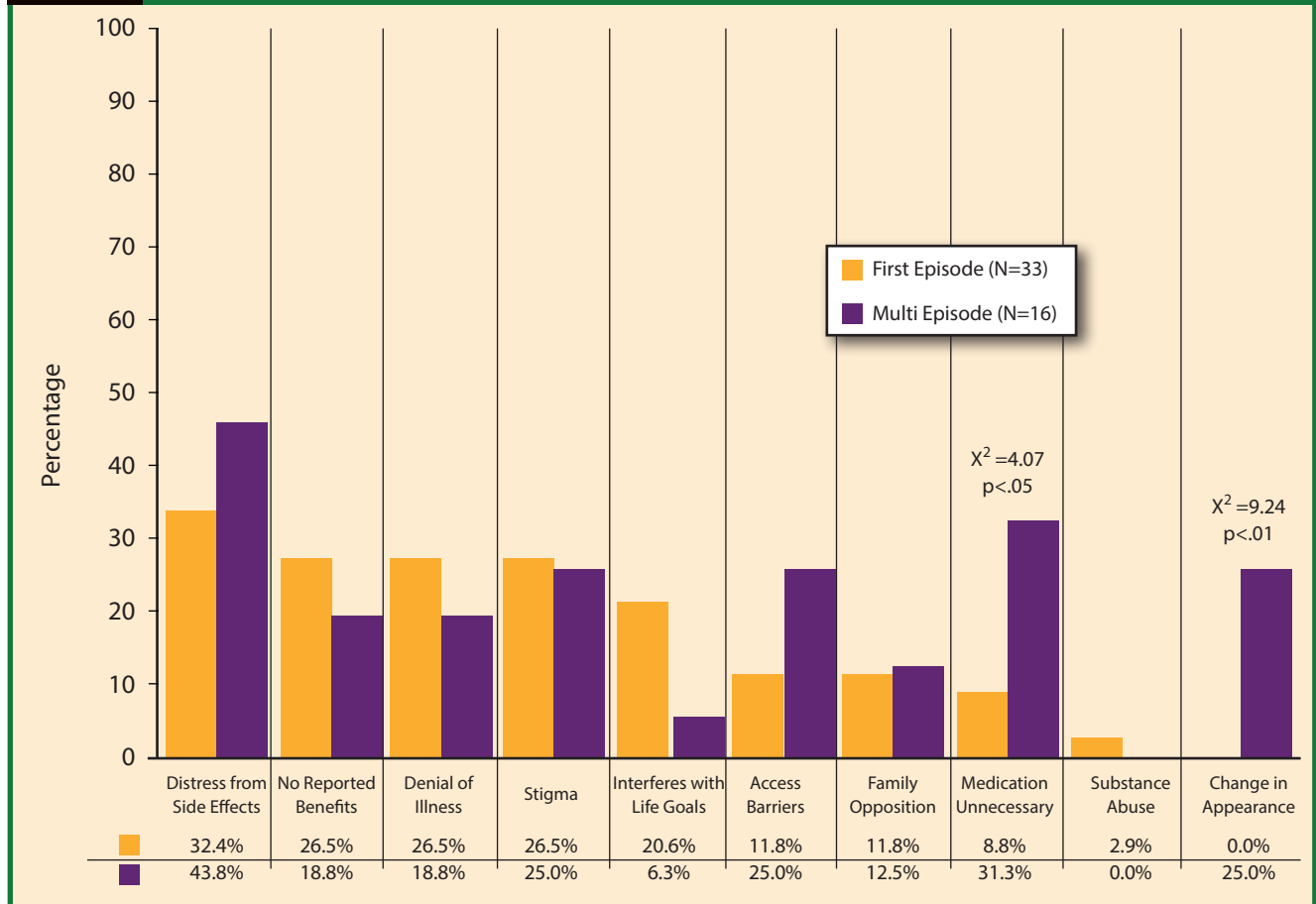
Discussion

Our major finding is that the doctor-patient relationship seems to be a particularly important factor for the first-episode patients who stayed with their outpatient treatment and have remained on medication for the time being. Put

another way, many of the other salient attitudinal factors—such as perceived benefit of medication—were relatively less influential for first-episode patients than would be expected. Initially we were surprised by this finding, but in retrospect have a post hoc explanation. “First-episode” patients have, at best, limited experience with ongoing maintenance treatment. Initial pharmacologic treatment of the acute psychotic episode occurs during a time of crisis, and treatment occurs with multiple changes and interventions that happened simultaneously during the period of acute treatment, and medication intervention is only one of many events. From the patient’s perspective, there is no inherent reason that antipsychotic medication rather than other interventions was the key factor in reducing symptoms and distress (19). Further, even if improvement in symptoms is attributed to medication, the patient may still conclude that medication is no longer needed, following the logic of antibiotic treatment.

The very limited illness and treatment experience of first-episode patients makes it difficult, if not impossible, for patients to generate their own “cause and effect” experience with medication. However, this finding does not by itself explain why or how certain patients value the doctor-patient relation-

Figure 2 Comparison of Nonadherence Influences between First-Episode and Multi-Episode Patients (% endorsing 2 vs. 0 or 1)



ship more than others. One implication of this finding is that strategies to help strengthen the therapeutic relationship with treating clinicians might be particularly influential for individuals early in the illness course. It is the treating clinician who informs the patient and family that the recent improvements were primarily related to the antipsychotic medication. The clinician is asking the patient to follow treatment recommendations and, given this context, it is understandable that the perceived credibility and relationship are key influences for the patient's decision to continue with medication.

The Health Belief Model (HBM) of adherence highlights that a patient's decision to accept the treatment is influenced by his beliefs such as whether he has an illness and whether medications prescribed are beneficial. HBM considers adherence to treatment a dynamic process. There have been some efforts to study interventions to affect this dynamic process to improve actual adherence in first-episode schizophrenia. The preliminary results from a randomized controlled trial pilot of effectiveness of Adherence Coping Education (ACE) therapy in recovering first-episode schizophrenia patients found that ACE was associated with greater decrease in symptoms as well as improved attitudes toward treatment (20). In-

terventions like ACE and Compliance Therapy start with the core therapeutic goal of establishing rapport and maintaining positive therapeutic alliance between clinician and patient. Our study highlights the importance of this alliance from the patient's perspective in its role in adherence behavior. Early beliefs and attitudes of first-episode schizophrenia patients might impact actual adherence behavior. A study of recovering first-episode patients reported medication adherence to be related to beliefs that medication is beneficial and acknowledgment by the patient of having a mental illness (10). The positive therapeutic alliances serve as a building block for developing patients' beliefs/attitudes and establishing insight into illness and treatment.

The study also shows that the role of the family support as influencing adherence was limited, and more so first-episode patients that have fewer social relationships with others outside the immediate family and mental health system (21). This further emphasizes the need for—and importance of—clinicians' efforts to mobilize the patient to cooperate in partnership in treatment and the clinician to share responsibility with the patient for adherence. Techniques in therapeutic engagement may need to be targeted to the appropriate

age group of younger patients (22). Continued contact and positive therapeutic alliance with first-episode patients, even when they have stopped taking their medications, will give opportunities for psychoeducation, help patients identify early relapse and warning signs and possibly prevent rehospitalization.

Given the fact that many of the other factors that influence adherence in multi-episode patients (such as the perception that medication offers day-to-day benefits or helps in relapse prevention) were not as strongly endorsed in our first-episode sample as in the multi-episode sample, it is likely that establishing an alliance with younger first-episode patients at their initial contact with the mental health system has the potential to impact adherence behavior in the long term.

Our findings also suggest that another path to improved adherence may come through helping first-episode patients identify the role of medications and treatment in fulfillment of their life goals, given the relative importance of this factor as endorsed by individuals in the first-episode sample as compared to the multi-episode sample. Assessing educational, social relationship and occupational goals from the beginning and connecting them with treatment and relapse prevention in discussions and psychoeducation sessions with the patient will help initiate and maintain adherence (23).

The differences in responses for reasons for nonadherence were not as pronounced as what was seen in reasons for adherence, especially the doctor-patient relationship. Both groups endorsed more reasons for adherence than nonadherence. This might be due to the samples being representative of individuals who are more stable and willing to participate in research and these patients might have been more likely to be adherent at the time of the ROMI interview than nonadherent. Among findings of nonadherence reasons, the significant difference of stronger influence of change in appearance caused by treatment in multi-episode patients in comparison to first-episode patients probably reflects the long-term side effects of treatment and greater awareness in chronic patients about side effects. Of note is that the multi-episode patients were more likely to endorse “medications not necessary” than first-episode patients, suggesting that—at least in this pilot study sample—many multi-episode patients do not seem to have “learned” from their prior relapse experiences. We speculate that this aspect of not recognizing—or acknowledging—medication benefits may be one of the reasons for becoming a multi-episode patient. Indeed, research from many years ago (24–26) as well as more recently (27, 28) has shown that subjective report of medication benefit is a predictor of better response, and that self-reported opinions of medication efficacy is a valid predictor of outcome.

Limitations

Limitations include the small sample size, the post hoc

nature of the study hypothesis and analysis plan, and that the chronically ill sample was a convenience sample where there may have been other confounds that might have explained the differences in adherence attitude profiles. Adherence represents a complex, multilayered and evolving process. The ROMI was designed to assess patient reported influences for adherence and nonadherence. Its strength is that, for these subjective domains, it is a reliable and valid measure. However, the ROMI does not capture many other important factors that influence adherence, including known predictors such as residual family support, level of medication supervision, and access to treatment services. Because of these limitations, the relative influences of adherence attitudes determined from a subjective measure such as the ROMI on actual adherence behavior cannot be determined in this research.

The first-episode patients that received adherence attitude assessments were probably more likely to have relatively favorable attitudes compared to other subjects who refused the study or who had already dropped out; therefore, our findings on reasons for adherence are more likely to represent the subgroup of first-episode patients who are adherent than do the reasons for nonadherence represent the reasons for medication discontinuation. Pertaining to our main finding of the importance of the doctor-patient relationship, there are no other measures of therapeutic alliance or service engagement aside from the ROMI, which only considers relationship in the context of adherence (29, 30). Finally, the hypothesized relationship between doctor-patient relationship and adherence does not prove that strengthening the doctor-patient relationship would improve adherence since it may be that this is a characteristic of more adherent patients (31).

Some of the strengths of the study include the consistency of measures across patient groups, the similar psychosocial backgrounds and treatment settings of the subjects, and the fact that adherence attitude was ascertained by an independent assessor who was not part of the patient’s treatment team. Although the two studies were not formally designed for comparison, the fact that the patients were drawn from the same hospital and were assessed using the same measure of adherence attitudes makes the comparison plausible for hypothesis generation, although not for a formal test.

These findings should be considered exploratory and hypothesis generating, and need to be replicated. There are important treatment implications that would follow if these findings are replicated, such that the therapeutic engagement and the clinician-patient relationships are of paramount importance to maintaining medication adherence in this stage of the illness.

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