Medication Adherence in a Transdiagnostic First-Episode Psychosis Sample

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Abstract

Objective: Medication adherence is an important component of treatment and has the potential to influence illness trajectory in individuals with first-episode psychosis (FEP). We sought to examine time to medication non-adherence as well as factors related to non-adherence in a real-world FEP clinic.

Methods: We conducted a survival analysis to examine time to medication non-adherence using data extracted from medical records of patients admitted to a FEP clinic at an academic psychiatric hospital between May 2012 and October 2017 (n = 219). The risk pool included patients who were adherent during the first 6 months in the clinic (n = 122). Data were extracted for the entire length of participants' time in the clinic, up to 66 months. Pre-selected clinical and demographic variables of interest were extracted and entered into a Cox proportional hazards model.

Results: Of the risk pool of 122 patients, 37 (30%) had documented non-adherence events. The risk of non-adherence was 0.35 (95% CI, 0.25–0.46) and 0.49 (95% CI, 0.37–0.63) at the 24- and 36-month time points, respectively, and plateaued after 36 months. Non-White race (adjusted HR = 3.69; *P* = .003; 95% CI, 1.57–8.70), lack of insight in the prior 6 months (adjusted HR = 3.24; *P* = .005; 95% CI, 1.43–7.35), and substance use in the prior 6 months (adjusted HR = 2.58; *P* = .022; 95% CI, 1.15–5.81) were significant predictors of non-adherence.

Conclusions: Clinicians should consider efforts to strengthen therapeutic alliance with non-White patients, improve insight, and help patients reduce or cease substance use when supporting medication adherence in the FEP population.

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Psychotic illnesses, such as schizophrenia and bipolar disorder with psychotic features, have a lifetime prevalence of about 2%–3% in the United States.[1] Usually chronic, these disorders often lead to significant distress, family burden,[2,3] and economic and health care strain.[4] The mainstay of treatment for psychotic disorders is medications, such as antipsychotics and mood stabilizers. However, patients often struggle with adherence to these medications, and such obstacles to adherence can result in poorer clinical outcomes, including symptom relapse,[5–7] hospital admissions,[8–10] and reduced treatment response.[11,12]

Patients experiencing first-episode psychosis (FEP), usually defined as onset of a psychotic illness within the last 2 to 5 years,[13] are a group of particular interest due to a hope that early intervention could change overall illness course. An important goal in this regard is to reduce the duration of untreated psychosis (DUP), which has been found to contribute to higher symptom burden and lower functioning.[14–16] Critically, any gains made through DUP reduction must be sustained with ongoing treatment. Despite this focus on the importance of adequate treatment in FEP, estimates of medication adherence among FEP patients are low, ranging from 41% to 68% after 1 year.[17–19]

Understanding what may contribute to non-adherence is essential for optimal clinical care. Though multiple studies have explored factors associated with non-adherence in FEP patients, they have generated mixed findings. For example, some studies have found non-adherence to be associated with younger age,[17,20,21] while others have found no association with age.[18,22,23] Similarly, substance use has been associated with non-adherence in multiple investigations,[9,17,21,24] though not universally.[25,26] Poor insight and judgment[17,18,20,24,26] and higher symptom burden[9,19,23,26] are other factors commonly found to be associated with non-adherence. Of note, these studies varied in their definitions of FEP (eg, inclusion or exclusion of affective psychosis) and medication adherence (eg, subjective versus objective measures, length of time of non-adherence).[27] Moreover, while some studies have

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Clinical Points

- Medication adherence can impact illness trajectory in people with first episode psychosis (FEP), and the clinical and demographic factors that affect adherence in FEP are therefore important to understand.
- Contrary to expectation, in our FEP sample, medication-related factors such as antipsychotic generation, dose, or frequency were not significantly associated with adherence.
- Addressing race and culture-related disparities, reducing substance use, and helping patients improve insight may be ways that clinicians can support medication adherence in young people with FEP.

examined medication tolerability and side effect burden in relation to adherence,[17,23,26,27] few have examined medication-related factors, such as medication dosing frequency and the total number of medications, which constitute information of practical significance to treaters.

Our study aims to examine factors associated with medication non-adherence naturalistically in a FEP clinic. Unlike some studies that include only patients with schizophrenia spectrum disorders, our analysis captures a broader range of pathology by including patients with first-episode affective psychosis (FEAP) in addition to those with first-episode primary psychotic disorders (FEPP). Moreover, we hope to better understand the progression of medication non-adherence in FEP over time by conducting a survival analysis, an approach that few studies have applied to the investigation of medication non-adherence in FEP.[23] Given the dearth of literature exploring medication-related variables and non-adherence, we chose to focus especially on clinically modifiable medication-related factors.

METHODS

Study Design and Medical Records

We conducted a longitudinal observational study of medication non-adherence in patients who received treatment in the OnTrack program (abbreviated "OnTrack") at McLean Hospital, an academic psychiatric hospital located in Belmont, Massachusetts. OnTrack is an outpatient early intervention program that uses a comprehensive and multidisciplinary approach to treating individuals aged 18–30 years who have experienced new onset of psychosis (affective or non-affective) within the prior 12 months.[28] Patients did not need to be medication accepting to be treated in the clinic.

We reviewed the health records of all 219 patients admitted to the program between May 2012 and October 2017 and followed them until April 2018 (6 months after the cutoff date for study inclusion). This study was approved by the Mass General Brigham (MGB, formerly Partners Healthcare) Institutional Review Board, which granted a waiver of consent given that this research involved only health record review and no direct contact with patients. Data were extracted for up to 66 months for each patient. While many FEP programs offer treatment for only 2 years, during the study period OnTrack did not require patients to disengage from the clinic when 2 years was reached. Time in the clinic from initial intake ranged from less than 6 months to over 66 months (median = 18.2, mean = 22.4, SD = 17.7 months for n = 219).

Over the study period, records at McLean transitioned from paper to electronic health records (Meditech in 2014, then Epic in 2017). We used all sources of medical records. Baseline characteristics were obtained by reviewing each patient's intake note. Medication adherence and clinical variables were extracted from pharmacology follow-up notes at 6-month intervals. The data were extracted in 6-month intervals for a prior study that was unrelated to adherence.[29] We felt that the 6-month time frame was sufficiently frequent to capture clinically significant changes. Data were entered and reviewed using the Research Electronic Data Capture (REDCap)[30] hosted at MGB. These data have been described previously.[29]

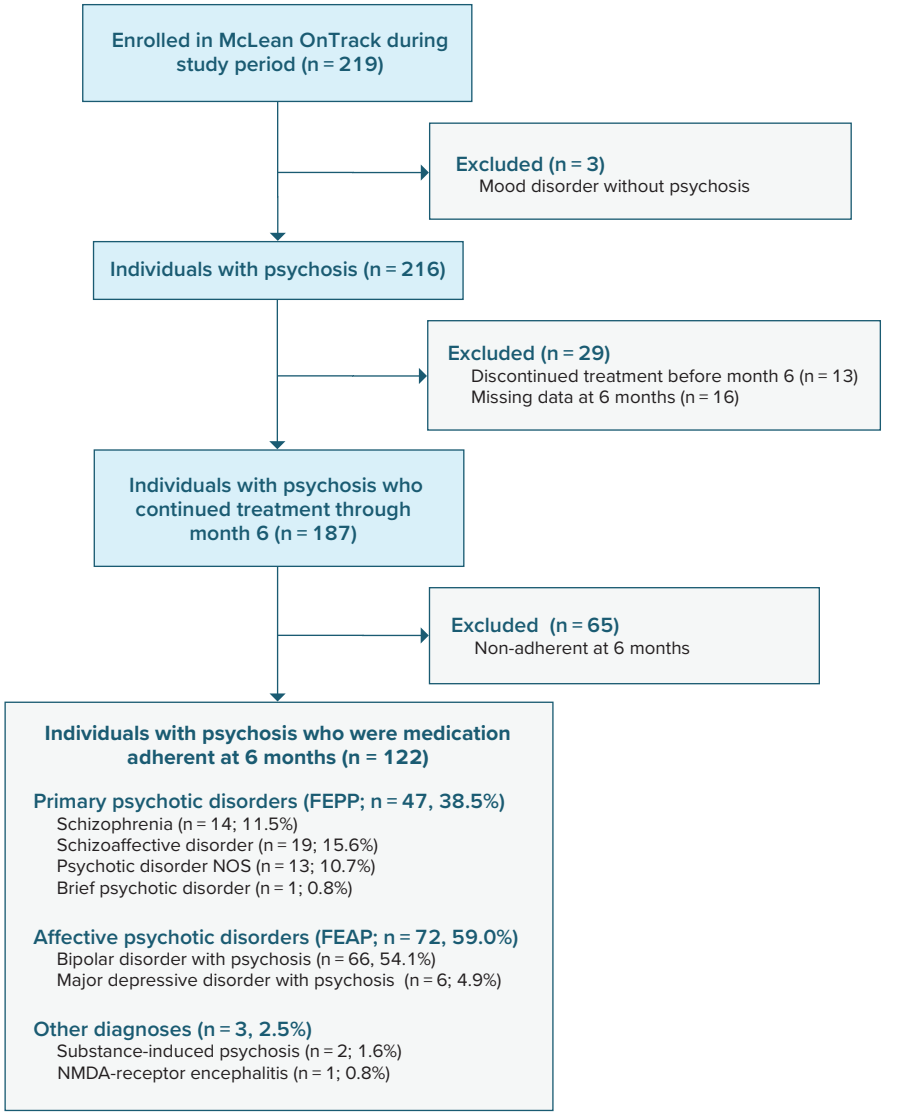
For the current analysis, which sought to assess factors associated with conversion from medication adherence to non-adherence, we included in the risk set only patients with psychosis who started the study period adherent to medications (ie, were adherent during the first 6 months of treatment in the clinic). This yielded a total of 122 patients who composed our risk pool (Figure 1).

Data Analysis

All analyses were performed with Stata version 15.1. First, we compared baseline characteristics of the 122 FEP patients who were adherent at month 6 to those of the 65 patients who were non-adherent at month 6 to assess for any differences at baseline. We used *t* tests for continuous variables and χ^2 tests for categorical variables, both with a significance threshold of $P < .05$.

For our primary analysis, we used a Cox proportional hazards model to conduct survival analysis for the risk set of 122 FEP patients who were adherent at month 6, setting medication non-adherence as the endpoint. Medication adherence was estimated by analyzing the complete medical record of each individual patient over each 6-month treatment period, specifically tracking phrases such as "adherence," "compliance," "taking medication," and their antonyms. After a preliminary review of charts showed that clinical documentation lacked the specificity to confidently report more precise estimates, medication adherence was dichotomized into adherent (≥ 90%) or non-adherent (< 90%) by the clinician reviewing each patient chart. Any documented period of clinically significant medication non-adherence (ie, more than the patient missing a dose or two of medication) was coded as < 90% adherence for that 6-month interval. While

Figure 1.
Patient Flow Diagram



Abbreviations: FEAP = first-episode affective psychosis, FEPP = first-episode primary psychotic disorders, NMDA = *N*-methyl-D-aspartate, NOS = not otherwise specified.

90% adherence is a higher benchmark for adherence in schizophrenia than in some studies, such as those that use thresholds of 75%[18,19,22] or 80%,[31,32] our adherence threshold is consistent with those of other studies[33] and may provide a more accurate estimate, given that self-report measures of adherence tend to overestimate actual adherence.[34,35] Fifteen patients had missing adherence data for a single 6-month interval occurring prior to a non-adherence event or dropout. We imputed the adherence value at the missing time point as adherent if both the time points immediately preceding and following the missing time point were documented as adherent.

In the Cox model, we included a priori selected clinical and demographic predictors of non-adherence, including age, race, sex, diagnostic category (FEPP or FEAP), insight, substance use, use of a first-generation antipsychotic (FGA) or second-generation antipsychotic (SGA), antipsychotic medication dosage as calculated by chlorpromazine (CPZ) equivalents, presence of a mood stabilizer, total number of psychotropic medications, and maximum daily psychotropic frequency. For race, we used the following categories: White, Black, American Indian/Alaska Native, Asian/Pacific Islander, and Other. As the numbers of patients in racial categories other than White were small, we grouped patients into two broad categories: White and non-White. Given diagnostic shifts over the study period,[36] we used the diagnosis given to each patient during their final visit in the clinic. Those

Table 1.

Baseline Characteristics of First-Episode Patients (FEP) Who Were Medication Adherent vs Those Who Were Non-Adherent at Month 6[a]

Characteristic	Adherent at Month 6 (n = 122)	Non-Adherent at Month 6 (n = 65)	Statistic	*P* Value
Age, mean ± SD, y	21.9 ± 3.5	21.4 ± 3.3	$t = -0.908$	.365
Female	32 (26.2)	14 (21.5)	$\chi^2 = 0.503$	.478
Race[b]			$\chi^2 = 2.813$	.245
White	92 (81.4)	43 (82.7)		
Black	7 (6.2)	6 (11.5)		
Asian	14 (12.4)	3 (5.8)		
Married	6 (4.9)	6 (9.2)	$\chi^2 = 0.080$	.777
Referral source[b]			$\chi^2 = 2.393$	.664
Inpatient	71 (61.2)	42 (68.9)		
Partial	20 (17.2)	8 (13.1)		
Outpatient	12 (10.3)	6 (9.8)		
Family	10 (8.6)	5 (8.2)		
Other	3 (2.6)	0		
Total hospitalizations, mean ± SD	1.5 ± 1.0	1.6 ± 1.0	$t = 0.484$	.629
History of at least 1 suicide attempt	4 (3.3)	5 (7.7)	$\chi^2 = 1.874$	.171
No. of antipsychotic trials, mean ± SD	1.9 ± 1.1	1.7 ± 0.8	$t = -1.123$	.263
History of trauma[b]	36 (31.3)	17 (29.3)	$\chi^2 = 0.0721$	.788

[a]Values are shown as n (%) unless otherwise noted.
[b]The total n values used in the calculations differed from those listed in the column headings due to missing data for some patients.

documented as having schizophrenia, schizoaffective disorder, psychosis not otherwise specified (NOS), or brief psychotic disorder were labeled as FEPP, while those with bipolar disorder or major depressive disorder with psychotic features were labeled as FEAP. Patients diagnosed with substance-induced psychosis (n = 2), and *N*-methyl-D-aspartate (NMDA) receptor encephalitis (n = 1) were considered to be psychotic and thus not excluded from the risk pool but were considered neither FEAP nor FEPP. Substance use was coded as a binary variable reflecting the documentation of any substance use over the prior 6-month period. Insight was extracted from the documented mental status examination and coded as a dichotomous variable. For both substance use and insight, we used data documented during the interval just prior to the non-adherence event (ie, last interval of adherence), or the final interval in clinic for censored patients, as we could not otherwise ascertain if they changed as a consequence of non-adherence.

For medication-related variables, pharmacology notes from each 6-month interval were reviewed to determine if the patient was prescribed a FGA, SGA, or mood stabilizer. We did not include topiramate as a mood stabilizer, since it is rarely used clinically for this purpose, though topiramate was included when counting the total number of psychotropic medications. Total number of psychotropic medications tallied all prescribed psychotropic medications, inclusive of antipsychotics, mood stabilizers, antidepressants, stimulants, and sedative-hypnotics. Medication frequency was calculated as the maximum daily frequency of any psychotropic medication per day (eg, daily, twice daily, 3 times daily). CPZ equivalents were determined based on established conversion ratios.[37] We also extracted data on the use of long-acting injectable (LAI) medications; however, because only 3 patients in our risk pool had LAI use in the final 6-month interval, we did not include LAI use as a variable in our model. For medication-related variables in our Cox model, we used the values concurrent with the first non-adherence interval (ie, failure event). For censored patients, we used values from the final interval prior to termination in the clinic.

We used the Efron method for handling ties in the Cox model. We assessed proportional hazards by visualizing log-log plots and also with Schoenfeld residual tests. The *P* value for age in the Schoenfeld residual test was .02; with this exception, we found no evidence of a violation of the proportional hazards assumption in the global test or for the other 11 covariates ($P > .05$), suggesting that the log hazard ratio function is generally constant over time. We report the Wald *P* value for each variable of interest. To assess the degree to which LAI use might impact findings, we also ran the Cox proportional hazards excluding the 3 individuals with LAI use in the final 6 months.

RESULTS

Overall Rates of Adherence

Six months after clinic entry, 55.7% (122 of all 219 patients in the clinic) were documented as medication adherent. At 12 and 24 months after clinic entry, 56.6% (n = 98 of 173 of patients still in the clinic) and 51.0% (n = 52 of 102 patients still in the clinic), respectively, were adherent.

Baseline Characteristics of Adherent Versus Non-Adherent Patients

There were no significant differences between the patients who were (n = 122) versus were not adherent (n = 65, excluded from survival analysis) at 6 months in age, sex, race, marital status, referral source, total number of psychiatric hospitalizations, history of suicide attempt, prior number of antipsychotic trials, or history of trauma at baseline (Table 1).

Survival Analysis

Of the risk pool of 122 adherent patients, 37 (30%) had documented non-adherence events. Figure 2 shows the Kaplan-Meier curve for time to medication non-adherence. The cumulative risk of non-adherence at the 18-, 24-, 30-, and 36-month time points was 0.30 (95% CI, 0.21–0.40), 0.35

Figure 2.

Survival Curve of Time to Medication Non-Adherence From Clinic Entry Among Patients With First-Episode Psychosis Who Are Medication Adherent at 6 Months (n = 122)

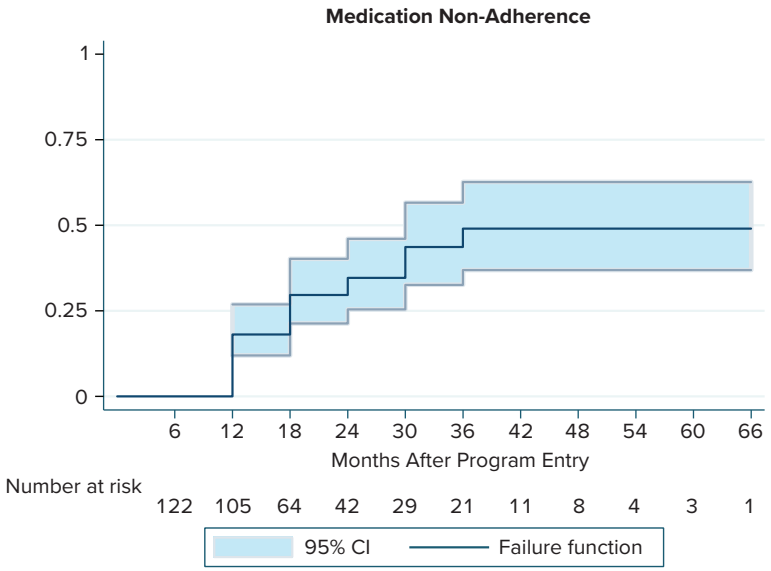


Table 2.

Cox Proportional Hazards Model for Medication Non-Adherence in a First-Episode Psychosis Clinic[a]

Variable	Hazard Ratio	Standard Error	*z*-Statistic	*P* Value	95% CI
Age	1.09	0.067	1.55	.122	0.97–1.24
Female	0.87	0.460	−0.26	.796	0.31–2.45
Race (non-White)	3.69	1.614	2.99	**.003**	1.57–8.70
FEAP (versus FEPP)	0.86	0.407	−0.31	.757	0.34–2.17
FGA	1.53	1.089	0.60	.547	0.38–6.17
SGA	1.05	0.608	0.09	.927	0.34–3.27
CPZ equivalent	1.00	0.00126	−1.65	.100	0.995–1.000
Mood stabilizer	0.72	0.348	−0.68	.497	0.28–1.85
Maximum psychotropic daily frequency	1.22	0.439	0.54	.586	0.60–2.47
Total psychotropics	0.74	0.217	−1.02	.308	0.42–1.32
Substance use	2.58	1.069	2.29	**.022**	1.15–5.81
Lack of insight	3.24	1.354	2.82	**.005**	1.43–7.35

[a]**Boldface** is used to denote *P* values < .05.
Abbreviations: CPZ = chlorpromazine, FEAP = first-episode affective psychosis, FEPP = first-episode primary psychotic disorders, FGA = first-generation antipsychotic, SGA = second-generation antipsychotic.

(0.25–0.46), 0.44 (0.33–0.57), and 0.49 (0.37–0.63), respectively, with the curve flat after 36 months.

In our Cox model, adjusting for all other variables, non-White race (HR = 3.69; *P* = .003; 95% CI, 1.57–8.70), lack of insight in the prior 6 months (HR = 3.24; *P* = .005; 95% CI, 1.43–7.35), and substance use in the prior 6 months (HR = 2.58; *P* = .022; 95% CI, 1.15–5.81) were significantly associated with non-adherence. None of the other covariates (age, sex, FEPP versus FEAP diagnosis, use of FGA, use of SGA, CPZ equivalents, presence of a mood stabilizer, and maximum daily psychotropic frequency) had significant effects (Table 2). Non-White race (HR = 3.54; *P* = .003; 95% CI, 1.53–8.20), lack of insight in the prior 6 months (HR = 3.69; *P* = .002; 95% CI, 1.60–8.48), and substance use in the prior 6 months (HR = 2.71; *P* = .014; 95% CI, 1.23–5.98) remained significantly associated with non-adherence when we reran the model excluding the 3 patients who were using LAIs.

DISCUSSION

In this study, we examined factors that may contribute to medication non-adherence in a real-world sample of patients in a FEP clinic followed longitudinally for up to 66 months. Aside from demographic variables and diagnosis, we focused largely on medication-related factors that are modifiable by the clinician (eg, type of medication used, medication dosage and frequency, total number of medications) or potentially modifiable clinical factors (eg, substance use, insight). We found that non-White race, lack of insight in the prior 6 months, and substance use in the prior 6 months were associated with medication non-adherence in our overall model.

Medication adherence has been shown to lead to improved clinical outcomes, particularly in first-episode psychosis.[5–7] Individuals with early psychosis are also often at critical junctures in their academic and occupational development, further increasing the importance of timely, appropriate, and effective psychiatric care. Although periods of non-adherence are common among patients with psychotic disorders in general, maintaining adherence early in the disease course is an important goal.

Contrary to our expectations, factors related to medication burden, whether in dosage, frequency, quantity, or medication class, were not found to be associated with adherence. This was surprising, given that patients may cite such medication-related factors as deterrents to adherence. Moreover, psychiatrists may feel that simplifying or reducing a medication regimen is a concrete and easily achievable approach to gaining alliance and supporting adherence. It is worth noting, however, that our study does not capture the rationale for medication changes and thus may not account for reductions to medication burden by clinicians made during periods of adherence that successfully prevent future non-adherence. The effect of medication-related factors is worth further exploration in future studies.

In our analysis, race was the variable most strongly associated with medication non-adherence. Identification with non-White race was associated with a 3.7-times greater risk of non-adherence after controlling for other clinical and demographic variables. Our findings are consistent with those of prior studies that have shown lower medication adherence in non-White populations.[38,39] However, the literature is mixed, and a link between race or ethnicity and non-adherence in psychotic disorders has not always been observed.[23,40] There are multiple factors that may inform our observed racial differences in medication adherence. These include familial and cultural beliefs and mistrust of medical institutions[41] that should be considered in the context of minority mistreatment and experimentation throughout medical history in the United States. Furthermore, poor communication with non-White patients may be more common in settings where the majority of clinicians are White,[39] and there is evidence that physician training in communication skills may improve patient medication adherence.[42]

Poor insight in the prior 6-month period was another significant predictor of medication non-adherence, increasing non-adherence risk by 3.2-fold after controlling for other factors. Lack of insight is a common though not universal feature of psychotic disorders[43] and has been used as justification for the use of involuntary psychiatric hospitalization and treatment.[44] Insight can be categorized as clinical insight (related to awareness of illness, ability to relabel psychotic experiences as abnormal, attribution of symptoms to a mental disorder, and treatment compliance)[45,46] and cognitive insight (related to self-reflectiveness, ability to consider alternate explanations, and a person's confidence in their interpretations of experiences).[47,48] While our study most likely captured the clinician's assessment of patients' clinical insight, both clinical and cognitive insight have been shown to correlate with medication adherence when researchers have used validated measures. Specifically, poorer scores on the Scale to Assess Unawareness of Mental Disorder[46] (SUMD; a clinical insight measure) and the Beck Cognitive Insight Scale[47] (BCIS; a cognitive insight measure) have been shown across multiple studies of individuals with psychotic disorders to portend worse medication adherence.[49–51] Interestingly, one study showed that the SUMD and BCIS scores more robustly predicted medication adherence than did psychopathology as measured by the Positive and Negative Syndrome Scale.[51] In clinical practice, insight is sometimes used as a proxy for uptake of recommended behaviors and treatments, while poor insight suggests a departure from the clinician's perspective or recommendations. Even with a broad definition of insight, the reason a person with a psychotic illness may lack insight is not uniform. Poor insight may be a pathological feature of disease (ie, "anosognosia"), be associated with cognitive impairments (which are common in psychotic disorders), reflect lack of awareness of distress or aberrance (such as in mania), and/or be influenced by stigma and other negative attitudes about mental health conditions and institutions. Moreover, there are both "trait" and "state" elements of insight.[52] While some amount of insight may be static, other elements may vary with severity of psychotic symptoms.[43] Whether insight can be modified through treatment is an open question. A meta-analysis[53] found that cognitive-behavioral therapy, adherence therapy (motivational interviewing approach), and psychoeducation had small to moderate benefit in improving insight, though none met the threshold for statistical significance.

Finally, we found that substance use in the prior 6-month period increased the risk of non-adherence approximately 2.5-fold. The association between substance use and non-adherence has been reported in multiple[9,17,21,24] though not all[25,26] studies. While the mechanisms for this association are not entirely clear, substance use in people with psychotic illness can lead to

exacerbation of symptoms,[54,55] which may in turn change attitudes toward medications or disrupt daily routines, including taking medications. For example, substance use may make it more difficult to perceive benefit from medication.[21] Although substance use disorders can be difficult to treat, substance use stands out as the most clearly modifiable risk factor of those found to be associated with non-adherence in this analysis.

The strengths of this study include use of a broad definition of FEP to include both non-affective and affective psychoses, longitudinal follow-up for up to 66 months (5.5 years) in a real-world FEP sample, and our focus on clinically related and potentially modifiable variables. However, the study also had a number of limitations. In addition to the moderate sample size, the lack of information on censored patients was a limitation. It is unclear how the different reasons for disengagement from the clinic might have influenced the results. It is important to note, however, that clinic discontinuation was not always synonymous with discontinuation of treatment in general. The primary goal of the OnTrack clinic is to provide intensive intervention in the early course of illness; even if the program accommodated patients who wished to continue care in the clinic beyond 2 years, it was not the expectation or standard for patients to stay in OnTrack beyond 2 years, and many patients transitioned their care to other providers with the support of their OnTrack clinicians. Nevertheless, the high number of patients who were lost to follow-up could have introduced attrition bias. Another limitation is that the current project involved secondary analysis of data extracted for a study not directly related to medication adherence, and data were extracted in 6-month intervals, which may not provide the optimal temporal granularity to examine non-adherence. In addition, this study relied on medical record reviews, and such data are restricted to what clinicians document in their notes and did not utilize standardized rating measures. For example, insight was determined through clinical assessment rather than with validated insight scales such as the SUMD and BICS. Moreover, our study did not contain a sufficient sample size of participants using LAIs to include LAI use as a variable in our model. However, when we reran our analysis excluding the patients on LAIs, the overall findings remained essentially unchanged. Finally, the racial composition of the patient sample consisted of a White majority, and we also did not have a large enough Hispanic population to include a variable for ethnicity (Hispanic vs non-Hispanic). The link between race/ethnicity and medication adherence among FEP should be further investigated in samples with more diverse racial/ethnic representation.

CONCLUSION

Medication adherence is an important component of successful treatment of psychotic disorders and has particular valence in first-episode psychosis. This study suggests that non-White race, poor insight, and substance use have the strongest association with medication non-adherence in FEP, while factors related to medication type, quantity, and frequency were not associated with adherence in our sample. To minimize the risk of medication non-adherence in FEP and thus increase the chance of positive outcomes, clinicians should consider ways in which they can improve understanding of race- and culture-related factors that might impede the development of therapeutic alliance with a patient, improve skills in communicating with patients, help patients develop greater insight and awareness into their illness, and encourage reduced substance use.

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