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Medication adherence in first episode psychosis: The role of pre-onset sub-threshold symptoms.

Jean-Gabriel Daneault, MD,FRCPC^{1,2}, Anika Maraj, MD¹, Martin Lepage, PhD^{1,3,4}, Ashok Malla, MBBS,FRCPC^{1,4}, Norbert Schmitz, PhD⁴, Srividya N. Iyer, PhD^{1,4}, Ridha Joober, MD,PhD^{1,4}, and Jai L. Shah, MD,FRCPC^{1,3,4}

¹Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), Douglas Mental Health University Institute, Montreal, Quebec, Canada

²Clinique J.-P. Mottard, Hôpital en santé mentale Albert-Prévost, Département de psychiatrie, Université de Montréal, Montreal, Quebec, Canada

³Integrated Program in Neuroscience, McGill University, Montreal, Quebec, Canada

⁴Department of Psychiatry, McGill University, Montreal, Quebec, Canada

Abstract

Objective: The experience of pre-onset sub-threshold psychotic symptoms (STPS, signifying a clinical high-risk state) in first episode psychosis (FEP) predicts poorer outcomes during treatment, possibly through differential adherence to medication. We explored whether adherence differs between FEP patients with and without pre-onset STPS.

Methods: Antipsychotic medication adherence was compared in 263 STPS+ and 158 STPS- subjects in a specialized early intervention program for FEP. Data were gathered from a larger observational study conducted between 2003–2016. STPS status, sociodemographic and baseline clinical variables were tested as predictors of nonadherence using univariate and multivariate logistic regressions. Time to onset of nonadherence was analyzed using Kaplan-Meier curves. The same predictors were tested as predictors of time to onset of nonadherence using Cox regression models.

Results: Medication nonadherence was higher in STPS+ participants (78.9% vs 68.9%). STPS status (OR 1.709), substance use disorder (OR 1.767) and milder positive symptoms (OR 0.972) were significant baseline predictors of nonadherence. Substance use disorder (HR 1.410), milder positive symptoms (HR 0.990) and lack of contact between the clinical team and relatives (HR 1.356) were significant baseline predictors of time to nonadherence. STPS status was not a significant predictor of time to nonadherence.

Conclusion: FEP patients who experience pre-onset STPS are more likely to be nonadherent to antipsychotic medication over two years of intervention. FEP programs should routinely evaluate pre-onset symptomatology to deliver more personalized treatments, with emphasis on engaging both patients and family members from the beginning of care.

Keywords

symptomatology; clinical high-risk; substance use disorder; family involvement

Introduction

Over the past twenty years, the dual objectives of early intervention paradigms – reduction of delays in treatment and provision of phase specific interventions – have been shown to improve outcomes in psychosis^{1–5}. Early identification requires a refined understanding of the period surrounding the onset of psychosis.^{6,7} Thus, in an effort to ‘close in’ on those most likely to develop a first episode psychosis (FEP)⁸, help-seeking individuals with subthreshold psychotic symptoms (STPS) are now routinely identified as being at ultra or ‘clinical’ high-risk (CHR) for the illness^{9,10}.

Treatment implications of CHR states on later-stage (FEP) outcomes have also been investigated. Although the results of these studies^{11,12} have been inconsistent, previous efforts comparing patients entering FEP services de novo (versus those who entered after receiving interventions during the CHR phase) presume that the former group would have invariably experienced STPS. Yet recent reports indicate that only 46–68% of FEP patients report STPS before their psychosis^{13,14} and that these symptom trajectories predict differential clinical and functional outcomes over time¹⁵.

A putative explanation for these differential treatment outcomes is that the experience of STPS is associated with diminished insight^{16–18}, and that this in turn affects adherence to medication. In other words, although medication adherence is a complex phenomenon – influenced by factors related to the patient, illness characteristics, medication and the environment¹⁹ – the experience of the CHR state may itself leave an imprint on subsequent adherence to antipsychotic medication in those who convert to FEP. Furthermore, symptomatology, functioning and many other clinical outcomes – poor quality of life^{20,21}, psychotic relapse or hospitalization^{22–28}, increased risk of suicide^{22,29} and violence^{30,31}, deterioration of functioning^{21,32} and possible development of resistance to treatment³³ – have repeatedly been associated with medication nonadherence. Discontinuation of antipsychotic medication in a remitted first episode psychosis sample was found to confer a five-fold increase in risk of psychotic relapse over a five-year period³⁴.

Antipsychotic medication adherence has been studied in CHR populations even though its use to treat CHR patients is controversial³⁵: a naturalistic study³⁶ found that adolescents at CHR were more likely to discontinue antipsychotic medications, potentially due to poor insight and worsening symptomatology. However, despite increasing attention recently directed towards early intervention in psychosis, to the best of our knowledge there have been no investigations of the impact of CHR syndromes on medication adherence during a later (FEP) stage.

Aims of the Study

Our objective in the present analysis is, therefore, to understand whether and why medication adherence differs between FEP patients with and without pre-onset STPS. We hypothesized that STPS+ subjects would have higher rates of nonadherence, and that this would emerge earlier in STPS+ than in STPS– participants. We also examined whether other baseline predictors contribute to adherence among FEP patients.

Methods

Setting

This study was carried out at the Prevention and Early Intervention Program for Psychoses (PEPP) in Montreal, Canada. PEPP is the only FEP service in its catchment area, offering early and rapid access to phase specific treatment and follow-up with case management, medication management, and psychosocial interventions (group interventions, family psychoeducation, support for work and school, etc.)³⁷.

Study population

Between 2003 and June 2016, 780 patients were admitted to PEPP. Inclusion criteria for the program were: age 14 to 35 years old, diagnosed with an affective or nonaffective psychotic disorder according to the Structured Clinical Interview for DSM-IV-TR (SCID)³⁸, no more than 30 days of prior antipsychotic medications, and fluency in either English or French. Exclusion criteria were IQ <70, psychotic disorder solely related to substance intoxication or withdrawal or to a medical disorder. Patients with a concurrent substance use disorder were not excluded. A large majority (626 or 80.3%) provided consent for the overall PEPP research protocol. Those under age 18 provided consent signed by a parent or guardian. All patients included in this analysis signed informed consent. This analysis is part of a larger study approved by the Research Ethics Board at the Douglas Mental Health University Institute.

Twenty-three patients had received care at the Clinic for Assessment of Youth at Risk (CAYR) before admission to PEPP. CAYR is a specialized service for identification, monitoring and treatment of young individuals at CHR for psychosis³⁹. These patients were excluded from the analysis since our goal was to evaluate the impact of untreated STPS on clinical outcomes during FEP treatment, which would be confounded by inclusion of those who received CHR services.

STPS status

Within the first 3 months of entry into PEPP, patients were evaluated with the Topography of Psychotic Episode (TOPE)^{6,14,40}, a retrospective assessment of 27 potential early signs and symptoms of psychosis. The TOPE is part of the Circumstances of Onset and Relapse Schedule (CORS), which determines pathways to care through detailed interviews with the patient and, when available, his or her relative(s), and review of all health and educational records. For each patient, a synthesized CORS narrative with this information was generated by research assistants with at least an undergraduate degree and rigorous training (with videotapes' rating, role playing, and interviews under supervision). Consensus was reached

on dates and early symptoms during regular team meetings chaired by a research psychiatrist. Interrater reliability, based on 12 randomly selected cases evaluated separately by three raters, was excellent (with intraclass correlation coefficients between 0.81 and 0.98).

Of the 27 TOPE items, 9 were identified as “*attenuated positive symptoms/subthreshold psychotic symptoms, if they appeared at a time when an individual would not have met criteria for a syndromal level psychotic episode*” by experts in the early intervention field¹⁴. If a patient had one or more of these items, he or she was considered to have experienced STPS (STPS+)¹⁴.

Baseline sociodemographic and clinical data

We examined sociodemographic and baseline clinical variables that were previously shown to be associated with poor medication adherence in the literature on FEP and on severe and persistent mental illness^{41–46}. These included duration of untreated psychosis until start of adequate treatment⁴⁷, using the Circumstances of Onset and Relapse Schedule (CORS)⁴⁸; age of onset of psychosis^{20,23}; age at entry into the FEP program^{20,49,50}; education level at baseline⁷ (completed high school or not); vocational status during the last 4 weeks before entry at PEPP²⁶ (working or studying/not working or studying); substance use disorder at baseline^{20,47,51–54} based on SCID³⁸ (yes/no); severity of positive psychotic symptoms at baseline^{49,54–56} according to the Scale for the Assessment of Positive Symptoms (SAPS)⁵⁷; severity of negative symptoms at baseline^{58,59} according to the Scale for the Assessment of Negative Symptoms (SANS)⁶⁰; level of functioning at baseline⁶¹ according to the Social and Occupational Functioning Assessment Scale (SOFAS)⁶²; insight at baseline^{20,47,50,51,63} according to item G12 of the Positive And Negative Symptoms Scale (PANSS)⁶⁴; and whether the clinical team was in contact with relatives at baseline^{20,50} (yes/no). We also included premorbid adjustment^{20,51}, measured by the Premorbid Adjustment Scale⁶⁵, which estimates functioning at various developmental stages. Only childhood and early adolescence ratings were retained in our analysis, to avoid potential overlap with the CHR period^{66,67}.

Medication adherence

Medication adherence was based on the estimated percentage of full doses taken over the previous month. This method of estimation draws on previous work comparing adherence estimates based on pill count, patient reports, clinician reports, and family reports⁶⁸. In that study, patient or clinician reports provide a reasonable estimate of medication adherence in FEP, but patients reported higher rates of medication adherence than did the other methods. If different sources had diverging opinions, research evaluators used all possible sources of information (notes, client reports, clinician opinion) to converge on a consensus rating. Ultimately, most records in the current study were based exclusively on patient reports (with their relatively high estimates of adherence) at eight timepoints: months 1, 2, 3, 6, 9, 12, 18, and 24. If the subject was prescribed multiple antipsychotics, an integrated score was calculated⁵². Medication adherence was defined as 76–100% of full doses taken over the previous month and nonadherence as <76% (0–75%) of full doses taken over the previous month^{54,66,68,69}. Adherence during follow-up was defined as adherence at *all* timepoints;

nonadherence during follow-up was defined as nonadherence at *any* timepoint. Continuous antipsychotic treatment is associated with a decreased risk of psychotic relapse and increased time to psychotic relapse when compared to intermittent antipsychotic treatment^{70,71}. In addition, for some patients, it only takes a few missed doses to precipitate a psychotic relapse⁷². Time to onset of nonadherence was recorded as the time from program entry to the first month of nonadherence. Patients who completed the two-year program were censored at 24 months. Patients with missing data before 24 months or before reaching nonadherence were excluded from the calculation of time to onset of nonadherence.

Statistical analysis

Sociodemographic and baseline clinical variables are presented as frequencies and means. Two-tailed t-tests and chi-squared tests were used to assess group differences between adherent and nonadherent participants when the data was deemed normally distributed; Mann-Whitney U tests were used for non-parametric data. For our first aim, adherence and nonadherence rates were compared between STPS+ and STPS- subjects using the chi-squared test. STPS status, sociodemographic and baseline clinical variables were tested as predictors of nonadherence using univariate logistic regressions. Multivariate logistic regression was subsequently used to describe how variables found to be significantly associated ($p < 0.05$) with medication nonadherence in the univariate analyses jointly impacted nonadherence. Kaplan-Meier time-to-event curves were then plotted for STPS+ and STPS- groups to demonstrate survival patterns to medication nonadherence. Patients ($n=8$) who moved or were transferred were censored as of that time.

For our second aim, univariate Cox proportional hazards regression analyses were used to determine the predictive value of all selected sociodemographic and baseline variables on time to onset of medication nonadherence. Multivariate Cox analyses were subsequently used to describe how variables found to be significantly associated ($p < 0.05$) with time to medication nonadherence in the univariate analyses jointly impacted time to nonadherence. Results are presented as hazard ratios (HR) with 95% confidence intervals (CI). All analyses were performed using SPSS software, version 20⁷³.

Results

Sample characteristics

Of 780 potential patients admitted to PEPP-Montréal between 2003–2016, 626 provided informed consent for the comprehensive research protocol. Of these, 23 patients were excluded because they received care at CAYR; of the remaining 603 patients, 421 (69.8%) completed assessments regarding early signs and symptoms prior to a FEP and could be assigned to STPS+ or STPS- groups. Those who did not complete these assessments ($n=182$, 30.2%) had less education (56.4% graduated high school vs 66.8% in the completers group, $\chi^2(1, n=444) = 3.896$, $p=0.048$), had lower social and occupational functioning at baseline (median SOFAS score of 35 vs 40 in the completers group, $U=35504$, $p<0.001$), and had lower insight at baseline (with a mean PANSS G12 score of 4.4 vs 4.1 in the completers groups, $U=26674.5$, $p=0.019$) (see Table 1). The 182 non-completers were also less adherent

to antipsychotic medication (13.5% adherent throughout vs 24.6% in the completers group, $\chi^2(1, n=468) = 6.667, p=0.010$).

Sociodemographic and clinical information of the 421 STPS+ and STPS- participants are presented in Table 2. 263 (62.5%) of the participants were considered STPS+ and 158 (37.5%) were considered STPS-. Of note, STPS+ participants had longer median DUP (median 18 weeks vs 12 weeks, $U=19623, p=0.001$), and fewer days of antipsychotic medication treatment prior to entry in the program (median 10 days vs 15 days, $U=14407, p=0.032$). Both groups had equivalent levels of insight (both groups had a median of 4, $U=15090, p=0.160$).

Overall medication adherence

The 421 participants had an overall rate of nonadherence of 75.4% over 24 months of FEP treatment. Of the 23 FEP patients who previously received care at the CAYR clinic, 76.5% were nonadherent to antipsychotic medication over 24 months. This was not significantly different from the rest of the sample ($\chi^2(1, n=485) = 0.037; p=0.848$).

Among participants, STPS+ subjects had a higher proportion of individuals who were nonadherent (78.9% vs 68.9% in STPS-, $\chi^2(1, n=342) = 4.201, p=0.040$). Participants who were adherent throughout had more days of antipsychotic medication treatment prior to entry in the program (median 15 days vs 10 days for the nonadherent group, $U=13986.5, p=0.003$), fewer comorbid substance use disorders (46.9% vs 59.2% for the nonadherent group, $\chi^2(1, n=436) = 4.624, p=0.032$), and more severe positive symptoms at baseline (median SAPS score 36.0 vs 32 for the nonadherent group, $U=14622, p=0.008$).

Baseline predictors of medication nonadherence

Using univariate logistic regressions, we found a higher likelihood of medication nonadherence in STPS+ participants, in those with comorbid substance use disorder at baseline, and in those with less severe positive symptoms at baseline. These variables each remained significantly associated with the outcome in the multivariate logistic regression model, with a higher likelihood of medication nonadherence in STPS+ participants (OR 1.709, 95% CI 1.008–2.899; meaning that with STPS+ status, the odds of nonadherence are increased by 70.9%), in those with comorbid substance use disorder (OR 1.767, 95% CI 1.046–2.984; meaning that with comorbid baseline substance use disorder, the odds of nonadherence are increased by 76.7%), and in those with less severe positive symptoms at baseline (OR 0.972, 95% CI 0.956–0.989; meaning that with each decrease of 10 points on the SAPS scale, the odds of nonadherence are increased by 28%) (see Table 3).

Time to onset of medication nonadherence

Data on time to onset of medication nonadherence was available for 215 STPS+ participants and 110 STPS- participants. Mean time to onset of medication nonadherence was not statistically different between STPS+ and STPS- groups (10.4 months vs 8.9 months for STPS+ subjects, $\chi^2(1, n=325) = 3.440, p=0.064$) (see Figure 1).

Baseline predictors of time to onset of medication nonadherence

Using Cox univariate proportional hazards regression, we found a significantly faster onset of medication nonadherence in participants with comorbid substance use disorders at baseline, less severe positive symptoms at baseline, and lack of clinical contact with relatives at baseline. These variables were still significantly associated with the outcome in the Cox multivariate proportional hazards regression model, with a significantly faster onset of nonadherence in participants with comorbid substance use disorder at baseline (HR 1.410, 95% CI 1.007–1.785; meaning that with substance use disorder at baseline, there was a 41% increase in risk of becoming nonadherent over 24 months), less severe positive symptoms at baseline (HR 0.990, 95% CI 0.983–0.998; meaning that with each decrease of 10 points on the SAPS scale, there was a 10% increase in risk of becoming nonadherent over 24 months), and lack of clinical contact with relatives at baseline (HR 1.356, 95% CI 1.019–1.806; meaning that with no clinical contact at baseline, there was a 35.6% increase in risk of becoming nonadherent over 24 months). In the univariate regression, STPS status was not a significant predictor of time to onset of medication nonadherence (HR 0.791, 95% CI 0.601–1.041) (see Table 4).

Discussion

This study suggests that the experience of pre-onset sub-threshold psychotic symptoms is associated with antipsychotic medication nonadherence during treatment of a first episode of psychosis. In addition, we found that substance use disorder, milder positive symptoms, and having no contact with relatives were significant baseline predictors of subsequent medication nonadherence over 24 months. However, there was no difference in time to onset of nonadherence between the STPS+ and STPS- groups.

Our findings regarding two potentially modifiable factors – presence of substance use disorder and involvement of relatives at baseline – being associated with positive outcomes are consistent with some, but not all^{74,75} previous literature.

The experience of STPS may leave a differential imprint on subsequent antipsychotic medication adherence. STPS+ participants are by definition gradually exposed to psychotic symptoms (first at a sub-threshold level, then at a threshold level). STPS+ subjects who endure more severe positive symptoms might find these more jarring and could therefore be more likely to consider medication options. In contrast, those enduring milder threshold-level psychotic symptoms might consider these to be consistent with their longer-term (pre-onset) symptoms, or might (because of their mild symptoms) experience only a minor decrease in positive symptoms with antipsychotic treatment – and would therefore be less likely to consider medications. Relatives and carers might similarly see less need for patients to take medications, and clinicians might be less insistent on the need for antipsychotic medication, which may explain why these differences occur despite similar levels of insight between STPS+ and STPS- groups. STPS- participants (who recalled no subthreshold psychotic symptoms before their FEP onset) may experience psychotic symptoms as being more abrupt in onset (regardless of severity) and could thus be more likely to continue their medications. These results are also consistent with previous literature on the association between insidious onset of psychosis and poorer outcomes^{3,76–79}; our work complements

this literature by reflecting symptoms that have been operationalized through the CHR construct.

Overall, this work underscores the potential value of evaluating pre-onset symptomatology in FEP patients to deliver more personalized interventions. For example, FEP patients who experienced pre-onset STPS and have comorbid substance use disorder and milder positive symptoms at baseline might benefit from encouragement or psychoeducation around adherence, or even neutral approaches such as motivational interviewing which attempts to identify sources of ambivalence^{80,81}. And regardless of STPS status, efforts made by FEP services to engage relatives from the beginning of treatment may contribute to medication adherence^{3,76–79}.

Several aspects strengthen the relevance of our results, including the use of a naturalistic design, a relatively large and well-characterized sample situated in a defined geographic catchment area, and routine (rather than selective) assessments of STPS status and outcome. Our measure of medication adherence was rigorous and representative of real-life adherence, has been shown to provide a reasonable estimate of adherence in FEP patients⁶⁸, occurred at regular timepoints over 24 months, and corresponds to the common clinical experience of patients frequently stopping their prescribed medication over time. Our rates of nonadherence are also consistent with previous literature, in which 60% or more patients stopped their antipsychotic medications for at least one week or self-reported poor medication adherence^{59,61,82}. While there was a statistically significant difference between the number of days of antipsychotic treatment prior to entry in the program between STPS+ and STPS-, this difference was small and not clinically meaningful. Nonetheless, it should be noted that (based on the program's inclusions/exclusion criteria) participants received no more than 30 days of antipsychotic medication prior to intake in the clinical service (median 10 days and 15 days for STPS+ and STPS- participants, respectively), indicating that our measures of medication adherence capture early *and* delayed adherence to antipsychotic medications, from within a month of first prescription. Finally, in our analysis of predictors of nonadherence, we controlled for several potentially confounding variables by following up our univariate analyses with multivariate analyses.

Limitation of this work include the fact that a proportion of the 626 patients who were admitted to PEPP between 2003 and 2016 and who provided consent for research were not included in our analysis, because they received treatment at CAYR or did not complete assessments required for assignment of STPS status. The latter group had greater nonadherence during follow-up, less education, lower social and occupational functioning, and diminished insight at baseline, and their assignment to STPS status (if data were available) could have affected our results. Another limitation is the recall bias inherent in the use of retrospective instruments such as the CORS and TOPE. While these are based on recollection of symptoms and behaviors, we attempted to reduce potential bias via the use of multiple sources and multiple probes and anchors (birthdays, milestones, and major events). Additionally, some studies have shown that persistent rather than baseline substance use was associated with poor outcomes (including nonadherence)⁸³. Finally, the choice of the PANSS-G12 item about judgment and insight was convenient as it is short and easy to use, but may conflate several concepts (including compliance to treatment) in a one-dimensional

measure⁸⁴. Nonetheless, PANSS-G12 scores have shown significant correlations with scores on the awareness of mental disorder subscale (from the Scale of Unawareness of Mental Disorder, a more comprehensive scale on insight)⁸⁴.

In this detailed examination of antipsychotic medication adherence, we found higher levels of antipsychotic medication nonadherence in FEP patients who experienced pre-onset STPS. Along with capturing this symptomatology and its relevance for clinical outcomes⁷⁹, FEP programming should pay particular attention to two modifiable predictors of medication nonadherence: involvement of relatives and addressing comorbid substance use disorders. Future work should investigate the potential role of medication adherence as a mediator in the relationship between STPS status and longitudinal symptomatic and functional outcomes¹⁵. Finally, adherence is only one dimension of treatment engagement: a broader and more comprehensive understanding of the influence of early symptoms on engagement could ultimately lead to interventions to improve clinical and functional outcomes.

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Significant outcomes:

- 1- The experience of pre-onset sub-threshold psychotic symptoms (STPS) was associated with higher rates of antipsychotic medication nonadherence over the first two years of treatment in a specialized early intervention program for first episode psychosis (FEP).
- 2- There was no difference in insight at baseline between FEP patients who had experienced pre-onset STPS and those who had not.
- 3- Substance use disorder at baseline, milder positive symptoms at baseline, and lack of contact between the clinical team and relatives at baseline were also associated with nonadherence.

Limitations:

- 1- Some (n=182) patients provided consent for research but did not complete assessments required for assignment of STPS status and thus could not be included in the analyses. These may represent a subset of patients who are less engaged in services and less adherent to medication.
- 2- As with all retrospective instruments, the CORS and TOPE (used to determine STPS status) are potentially susceptible to recall bias.
- 3- The PANSS-G12, used to measure insight, may conflate several concepts in a one-dimensional measure.

Figure 1:
Time to medication nonadherence curves

Table 1:

Comparison between participants who completed the CORS and TOPE assessments (completers) and those who did not (non-completers)

Variables	Completers (n=421, 69.8%)		Non-completers (n=182, 30.2%)		p
	M/N	SD/%	M/N	SD/%	
Gender					0.292 [†]
Male	287	68.17%	134	73.6%	
Female	132	31.35%	48	26.4%	
Other	2	0.48%	0	0.0%	
Premorbid adjustment [¶]	0.24	0.14	0.24	0.14	0.838 [§]
Duration of untreated psychosis (weeks)	54.4	117.0	50.9	93.9	0.720 [§]
	Median 15		Median 14		
Age of onset of psychosis	22.7	4.6	23.0	5.3	0.390 [‡]
Days of antipsychotic medication treatment prior to entry in program	13.9	64.5	15.5	52.9	0.765 [§]
	Median 12		Median 12		
Age at entry in program	23.5	4.4	24.1	5.2	0.149 [‡]
Proportion of early-onset psychosis					0.977 [†]
Onset before 18 years old	62	14.7%	24	14.6%	
Onset after 18 years old	359	85.3%	14	85.4%	
Education at baseline					0.048 ^{**‡}
High school not completed	111	33.2%	48	43.6%	
High school completed	223	66.8%	62	56.4%	
Vocational status during the last 4 weeks before entry in program					0.063 [†]
Student, or working, or homemaker	147	36.6%	45	28.3%	
Not working nor studying	255	63.4%	114	71.7%	
Diagnosis at baseline					0.168 [†]
Non affective psychosis	254	73.8%	71	67.0%	
Affective psychosis	90	26.2%	35	33.0%	
Substance use disorder at baseline					0.678 [†]
No	190	47.0%	63	45.0%	
Yes	214	53.0%	77	55.0%	
Positive symptoms at baseline ^{†‡}	33.9	15.6	34.3	14.3	0.501 [§]
	Median 32		Median 33		
Negative symptoms at baseline ^{‡‡}	26.5	14.5	26.4	14.3	0.946 [‡]
Functioning at baseline ^{§§}	42.5	13.2	38.1	12.4	<0.001 ^{***§}
	Median 40		Median 35		

Variables	Completers (n=421, 69.8%)		Non-completers (n=182, 30.2%)		p
Insight at baseline ^{¶¶}	4.1	1.6	4.4	1.5	0.019 ^{*§}
	Median 4		Median 4		
Team in contact with relatives at baseline					0.364 [†]
Yes	343	83.9%	134	80.7%	
No	66	16.1%	32	19.3%	
Medication adherence					0.010 ^{*†}
Adherent throughout	84	24.6%	17	13.5%	
Nonadherent at any of the 8 timepoints	258	75.4%	109	86.5%	

* p<0.05

** p<0.01

*** p<0.001

[†] Pearson chi-squared test

^{††} Independent samples t-test

[§] Independent samples Mann-Whitney U test

[¶] Sum of the childhood (up to age 11) and early adolescence (12 to 15 years old) scores on the Premorbid Adjustment Scale (lower scores indicating better premorbid functioning)

^{††} Total score on the Scale for the Assessment of Positive Symptoms (SAPS), with a range of 0 to 150 (higher scores indicating more severe positive symptoms)

^{†††} Total score on the Scale for the Assessment of Negative Symptoms (SANS), with a range of 0 to 90 after removal of items for attention (higher scores indicating more severe negative symptoms)

^{§§} Score on the Social and Occupational Functioning Assessment Scale (SOFAS), with a range of 0 to 100 (higher scores indicating better functioning)

^{¶¶} Score on the G12 item of the Positive And Negative Symptoms Scale (PANSS), with a range of 1 to 7 (higher scores indicating poorer insight)

Table 2:

Comparison between STPS+ and STPS– participants

Variables	STPS+ (n=263, 62.5%)		STPS– (n=158, 37.5%)		p
	M/N	SD/%	M/N	SD/%	
Gender					0.696 [†]
Male	183	69.6%	104	65.8%	
Female	79	30.0%	53	33.5%	
Other	1	0.4%	1	0.6%	
Premorbid adjustment [¶]	0.25	0.14	0.23	0.13	0.462 [‡]
Duration of untreated psychosis (weeks)	64.8	133.7	36.9	79.2	0.001 ^{**§}
	Median 18		Median 12		
Age of onset of psychosis	22.4	4.4	23.0	4.8	0.233 [‡]
Days of antipsychotic medication treatment prior to entry in program	11.1	36.7	18.7	94.2	0.022 ^{*§}
	Median 10		Median 15		
Age at entry in program	23.4	4.3	23.7	4.7	0.563 [‡]
Education at baseline					0.847 [†]
High school not completed	75	32.9%	36	34.0%	
High school completed	153	67.1%	70	66.0%	
Vocational status during the last 4 weeks before entry in program					0.745 [†]
Student, or working, or homemaker	91	36.0%	56	37.6%	
Not working nor studying	162	64.0%	93	62.4%	
Substance use disorder at baseline					0.186 [†]
No	114	44.5%	76	51.4%	
Yes	142	55.5%	72	48.6%	
Positive symptoms at baseline ^{††}	34.1	15.8	32.9	15.3	0.285 [§]
	Median 33		Median 30		
Negative symptoms at baseline ^{‡‡}	26.6	14.5	26.4	14.6	0.860 [‡]
Functioning at baseline ^{§§}	42.8	13.6	42.0	12.5	0.825 [§]
	Median 40		Median 40		
Insight at baseline ^{¶¶}	4.0	1.5	4.2	1.6	0.160 [§]
	Median 4		Median 4		
Team in contact with relatives at baseline					0.214 [†]
Yes	220	85.6%	123	80.9%	
No	37	14.4%	29	19.1%	
Medication adherence					0.040 ^{*‡}
Adherent throughout	47	21.1%	37	31.1%	

Variables	STPS+ (n=263, 62.5%)		STPS- (n=158, 37.5%)		p
	M/N	SD/%	M/N	SD/%	
Nonadherent at any of the 8 timepoints	176	78.9%	82	68.9%	

*
p<0.05

**
p<0.01

p<0.001

†
Pearson chi-squared test

‡
Independent samples t-test

§
Independent samples Mann-Whitney U test

¶
Sum of the childhood (up to age 11) and early adolescence (12 to 15 years old) scores on the Premorbid Adjustment Scale (lower scores indicating better premorbid functioning)

††
Total score on the Scale for the Assessment of Positive Symptoms (SAPS), with a range of 0 to 150 (higher scores indicating more severe positive symptoms)

‡‡
Total score on the Scale for the Assessment of Negative Symptoms (SANS), with a range of 0 to 90 after removal of items for attention (higher scores indicating more severe negative symptoms)

§§
Score on the Social and Occupational Functioning Assessment Scale (SOFAS), with a range of 0 to 100 (higher scores indicating better functioning)

¶¶
Score on the G12 item of the Positive And Negative Symptoms Scale (PANSS), with a range of 1 to 7 (higher scores indicating poorer insight)

Table 3:

Predictors of medication nonadherence

Variables	Medication nonadherence		
	OR	95% CI	p
Univariate logistic regressions			
Premorbid adjustment [†]	1.464	0.212–10.131	0.699
STPS status			
STPS+	1.690	1.021–2.798	0.041 [*]
STPS-	Reference		
Duration of untreated psychosis (weeks)	1.002	0.999–1.004	0.249
Age at onset of psychosis	1.026	0.977–1.077	0.299
Age at entry in program	1.041	0.990–1.094	0.114
Education at baseline			
High school completed	Reference		
High school not completed	1.230	0.743–2.034	0.421
Vocational status during the last 4 weeks before entry at PEPP			
Student, or working, or homemaker	Reference		
Not working nor studying	1.065	0.663–1.711	0.794
Substance use disorder at baseline			
Yes	1.638	1.042–2.575	0.032 [*]
No	Reference		
Positive symptoms at baseline [‡]	0.977	0.963–0.991	0.002 ^{**}
Negative symptoms at baseline ^{§§}	0.991	0.975–1.006	0.231
Functioning at baseline ^{¶¶}	1.003	0.984–1.022	0.779
Insight at baseline ^{††}	0.991	0.858–1.145	0.905
Team in contact with relatives at baseline			
Yes	Reference		
No	1.848	0.959–3.560	0.066
Multivariate logistic regression			
STPS status			
STPS+	1.709	1.008–2.899	0.047 [*]
STPS-	Reference		
Substance use disorder at baseline			
Yes	1.767	1.046–2.984	0.033 [*]
No	Reference		
Positive symptoms at baseline [‡]	0.972	0.956–0.989	0.001 ^{**}

* p<0.05

**
p<0.01

p<0.001

[†] Sum of the childhood (up to age 11) and early adolescence (12 to 15 years old) scores on the Premorbid Adjustment Scale (lower scores indicating better premorbid functioning)

[‡] Total score on the Scale for the Assessment of Positive Symptoms (SAPS), with a range of 0 to 150 (higher scores indicating more severe positive symptoms).

[§] Total score on the Scale for the Assessment of Negative Symptoms (SANS), with a range of 0 to 90 after removal of items for attention (higher scores indicating more severe negative symptoms).

[¶] Score on the Social and Occupational Functioning Assessment Scale (SOFAS), with a range of 0 to 100 (higher scores indicating better functioning).

^{††} Score on the G12 item of the Positive And Negative Symptoms Scale (PANSS), with a range of 1 to 7 (higher scores indicating poorer insight).

Table 4:

Predictors of time to onset of medication nonadherence

Predictor	Time to onset of poor medication adherence		
	HR	95% IC	p-value
Univariate Cox regressions			
Premorbid adjustment [†]	1.433	0.564–3.641	0.450
STPS status			
STPS+	Reference		
STPS-	0.791	0.601–1.041	0.094
Duration of untreated psychosis (weeks)	1.001	1.000–1.002	0.111
Age at onset of psychosis	1.006	0.983–1.030	0.596
Age at entry in program	1.012	0.989–1.036	0.303
Education at baseline			
High school completed	Reference		
High school not completed	0.995	0.783–1.265	0.971
Vocational status during the last 4 weeks before entry at PEPP			
Student, or working, or homemaker	Reference		
Not working nor studying	1.046	0.826–1.322	0.709
Substance use disorder at baseline			
Yes	1.322	1.051–1.661	0.017 [*]
No	Reference		
Positive symptoms at baseline [†]	0.990	0.983–0.988	0.010 [*]
Negative symptoms at baseline [‡]	0.996	0.988–1.004	0.297
Functioning at baseline [§]	1.001	0.993–1.010	0.756
Insight at baseline [¶]	1.009	0.941–1.083	0.795
Team in contact with relatives at baseline			
Yes	Reference		
No	1.328	1.007–1.753	0.045 [*]
Multivariate Cox regression			
Substance use disorder at baseline			
Yes	1.410	1.113–1.785	0.004 ^{**}
No	Reference		
Positive symptoms at baseline [†]	0.990	0.983–0.998	0.010 [*]
Team in contact with relatives at baseline			
Yes	Reference		
No	1.356	1.019–1.806	0.037 [*]

* p<0.05

**
p<0.01

p<0.001

[†] Sum of the childhood (up to age 11) and early adolescence (12 to 15 years old) scores on the Premorbid Adjustment Scale (lower scores indicating better premorbid functioning)

[‡] Total score on the Scale for the Assessment of Positive Symptoms (SAPS), with a range of 0 to 150 (higher scores indicating more severe positive symptoms).

[§] Total score on the Scale for the Assessment of Negative Symptoms (SANS), with a range of 0 to 90 after removal of items for attention (higher scores indicating more severe negative symptoms).

[¶] Score on the Social and Occupational Functioning Assessment Scale (SOFAS), with a range of 0 to 100 (higher scores indicating better functioning).

^{††} Score on the G12 item of the Positive And Negative Symptoms Scale (PANSS), with a range of 1 to 7 (higher scores indicating poorer insight).