Predictive factors for antipsychotic treatment adherence among first-episode psychosis patients in the first year after remission.

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Abstract

Background: Adherence rates to antipsychotic drugs in schizophrenia are low, while good adherence is important for achieving and maintaining remission. In patients with a 'First Episode of Psychosis' (FEP), early medication adherence can influence the further course of the illness. Identification of risk factors for non-adherence to antipsychotics in patients with an FEP in the first year after remission could prove useful.

Methods: This study was conducted with patients aged 16 to 55 years old, using antipsychotic medication, and in symptomatic remission of their first psychotic episode for 3-6 months. Medication adherence was determined with the Medication Possession Ratio (MPR) and validated with self-reported adherence rates. Covariate adjustment was performed to determine the influence of overlapping prescriptions on the MPR. The relationship between several patient- and environment-related factors with treatment adherence was assessed with linear regression.

Results: A total of 260 patients were included in the MPR calculation, of which 88,8% had a good treatment adherence. The MPR had a very weak correlation with the self-reported adherence rates ($p = 0.005$). Side effects ($p = 0.013$) were positively associated with treatment adherence while patients experiencing more self-stigma were less adherent ($p = 0.030$). Overlapping prescriptions accounted for 25% of the variance in the MPR. After covariate adjustment, only the duration of psychosis was associated with treatment adherence ($p = 0.001$).

Conclusion: The MPR is sensitive to prescribing behavior, therefore correction for overlapping prescriptions is advised. Intervention strategies focused on lowering self-stigma among FEP patients could improve their adherence rates.

Introduction

Psychotic disorders like schizophrenia are severe mental disorders that can cause a patient to have disorganized thoughts and abnormal perceptions often manifesting themselves as delusions and/or hallucinations [1]. Approximately 24 million people worldwide suffer from schizophrenia [2]. Patients diagnosed with a psychotic disorder are often prescribed an antipsychotic drug with the aim of managing their symptoms and ultimately, achieving and maintaining remission. For a good chance of achieving and maintaining remission, adequate pharmaceutical treatment (i.e. choice of antipsychotic, treatment regimen, and duration) is of great importance. Maintenance treatment with antipsychotic drugs in schizophrenia has clear advantages like reduced relapse and hospitalization rates, as displayed in an article by Ceraso et al. where 75 Randomized Controlled Trials (RCTs) comparing antipsychotic maintenance treatment with placebo were reviewed [3]. In addition, in 'First Episode of Psychosis' (FEP) cases early intervention with antipsychotic medication has been associated with better long-term clinical outcomes [4].

However, there is another factor weighing in on the success of pharmaceutical treatment of a psychotic episode and that is the patient's adherence to the prescribed treatment regimen. Since favorable effects of antipsychotic treatment can only be achieved if the medication is actually taken by the patient.

Non-adherence to medical treatment is a known problem among many different medication users. According to a report from the World Health Organization (WHO)[5], adherence to long-term therapies for different chronic illnesses was estimated to be around 50% and psychotic disorders like schizophrenia are no exception. A review article from Lacro et al. reported a mean non-adherence rate of 40.5% (s.d. 18,5%) for patients with schizophrenia [6].

There are several reasons, intentional or unintentional, for not taking medication the way it has been prescribed. Identification of factors with a (high) risk for non-adherence to antipsychotic medication during the first year of treatment after remission of the first episode of psychosis could prove useful for the treatment of future FEP patients. This way, healthcare providers know which patients are prone to non-adherence. These patients can be closely monitored which could prove useful in improving adherence rates and thereby improving treatment outcomes for these patients.
There have already been several studies looking into identifying risk factors for non-adherence to antipsychotics. Two systematic reviews (Lacro et al. (2002), and Velligan et al. (2017) investigating risk factors and specific reasons for non-adherence to antipsychotic medication found a wide array of factors associated with non-adherent behavior[6,7]. Factors linked with non-adherence in both articles were poor illness insight, negative attitude toward medication, substance abuse, and poor therapeutic alliance (i.e. relationship between patient and healthcare provider). Other factors linked to non-adherence were previous non-adherence, shorter illness duration, inadequate discharge planning or aftercare environment, medication side effects, cognitive impairment, family/social support, stigma, social functioning, depression, and access to mental health care.

While studies identifying risk factors for non-adherence to antipsychotics have already been conducted, evidence specifically for first-episode psychosis patients in their first year after remission is more scarce. Of the 36 studies included in the systematic review of Velligan et al., only six[8–13] were conducted with a cohort of FEP patients, with most of the studies only including one or at most 4 independent variables.
Therefore, the aim of this study was to determine the association of a combination of several patient-, disease-, treatment- and environment-related factors on non-adherence rates among patients with a first episode of psychosis in their first year after remission. In doing so, identifying risk factors associated with poor adherence to antipsychotic medication among this group of patients.

Method

Setting

This study was conducted from February through June of 2022, with data provided by the HAMLETT study [14]. The HAMLETT study is a multi-center pragmatic randomized controlled trial in the Netherlands, researching the effects of duration of antipsychotic treatment on personal and social functioning and symptom severity in FEP patients. Patients included in the HAMLETT study were aged between 16 and 55 years and diagnosed with a first psychotic episode of schizophrenia or schizophrenia-like psychotic disorder. The subjects were prescribed antipsychotic medication for this FEP and were in symptomatic remission for 3 to 6 months. Subjects were pseudonymized, only identified with a study number assigned by HAMLETT researchers.

Data collection

Data on medication dispensing was provided by a secondary database, the Foundation for Pharmaceutical Statistics (SFK). This foundation is a Dutch data source that registers and analyses data regarding medication dispensing in community pharmacies in the Netherlands. Data from this database consisted of a list with the dates on which an antipsychotic was dispensed, the name and dose of the dispensed drug, the prescribed dosage regimen, and the quantity of medication dispensed for each participant of the HAMLETT study.

Data on the independent variables was actively collected by HAMLETT-researchers by means of (self-report) questionnaires and assessments conducted during the baseline visit, which takes place 3-6 months after remission of the FEP.
The independent variables included in this study were grouped into four different categories, demographics, patient- and disease-related factors, social- and environment-related factors, and treatment-related factors.
Demographics consisted of age and gender. Patient- and disease-related factors included insight and depression both measured with subitems of the Positive And Negative Syndrome Scale [15](PANSS), cognitive impairment assessed with the Brief Assessment of Cognition in Schizophrenia [16] (BACS), lifetime illicit substance use based on hard- and soft drug use according to questions asked in the Comprehensive Assessment of Symptoms and History [17] (CASH) questionnaire, and the duration of the first psychosis.
Social- and environment-related factors consisted of family and social support measured with The Multidimensional Scale of Perceived Social Support [18] (MSPSS), the self-stigma around psychiatric disorders experienced by the participants using the Internalized Stigma of Mental Illness [19] (ISMI) scale,

and social functioning assessed with the World Health Organization's Disability Assessment Schedule [20] (WHO-DAS 2.0).
Treatment-related factors were made up of side effects measured with the total unpleasant effects subscale from the Subjective Reaction on Antipsychotics [21] (SRA) rating scale, mental healthcare visits defined as the number of consultations and home visits with mental healthcare professionals assessed in The Trimbos and iMTA 'Treatment Inventory Cost in Patients with a psychiatric disorder' [22] (TiC-P) questionnaire, attitude towards medication, and medication use preference (i.e. preference for continuing, discontinuing or no preference). For a more extensive description of the independent variables, see Appendix A.

Outcome measures

The primary dependent variable of this study was adherence to antipsychotic medication in the first year after remission of an FEP. This outcome was measured by calculating the Medication Possession Ratio (MPR), an adherence measure to determine the proportion of time for which a patient has access to medication, for each of the participants. The MPR was calculated by dividing the number of days for which the patients had collected medication during the total treatment period by the total number of days in this interval. Per individual dispensing moment, the number of days for which was dispensed was calculated by dividing the quantity of dispensed medication by the daily prescribed dose. By adding this number for all the dispensing moments within one year after remission the number of days for which medication was collected was calculated.

The intended treatment interval was 365 days but because the dispensing dates from the community pharmacies did not exactly line up with the remission- and one-year remission dates of the participants, the exact refill intervals varied. For each participant, the number of days between the first dispensing date after remission and the last dispensing date before one-year remission was calculated. The number of days for which medication was dispensed on the last dispensing date was subsequently added, giving the total treatment period for each participant.
For some participants, the one-year remission dates did not yet pass during the time of this study. For these cases, the last known dispensing moment after remission was used as the endpoint of the treatment period.
In addition, two other corrections to the total treatment periods were made. Firstly, hospitalization periods were deducted from the total treatment periods. This is because not every hospital in the Netherlands is connected to SFK, which would have led to dissimilarity in the MPR calculations among patients with a hospitalization. Furthermore, we can assume that patients were adequately administered their medication during this period.
Because the study design of the HAMLETT study required some participants to follow a dose reduction/early discontinuation treatment schedule, some participants stopped using antipsychotics within one year after remission. If participants stopped using antipsychotics within one year after remission and restarted their medication within this year, due to a relapse, the period between stop and restart was also deducted from the total treatment period.

MPR validation with self-reported adherence

Because dispensed medication is not automatically equal to ingested medication, an attempt was made to validate the dispensing data using self-reported medication adherence data by the participants. This self-reported data was collected at the baseline visit and consisted of a general question about medication adherence reporting the number of days, in the past two weeks, on which the participant did not take their antipsychotic medication. The answer to this question could range from 0 (equal to adherence of 100%) to 14 days (equal to an adherence of 0%), which was later converted to a percentage to compare to the percentages of the MPR. However, this data was not always completely filled out by the participants and as a result, this validation could not be performed for every participant.

Covariates

The MPR was studied as a function of two variables. The first covariate was the number of different antipsychotics, according to ATC codes determined by the WHO, used within the first year after remission of the FEP. The second covariate was the mean refill interval (in days) between dispensing moments in the community pharmacy according to SFK data. These covariates were added in an attempt to correct for unusual high MPR outcomes due to overlapping prescriptions.

Missing data and data imputation

Since not every community pharmacy in the Netherlands is affiliated with SFK, medication dispensing data could not be provided for all HAMLETT participants. Therefore participants with no or too little (dispensing data covering less than a month) SFK data were not included in this study (n = 60). The participants of the HAMLETT study were asked to fill out various questionnaires at home, before the baseline visit took place. However, not everyone completed all the questionnaires and some questionnaires were not filled out at all. This led to missing data among the independent variables. After excluding subjects that dropped out of the HAMLETT study before the baseline visit (N = 16), the remaining missing values were imputed using a machine learning algorithm (missRanger package, version 2.1.3[23]) specifically created for imputing missing data in mixed-type data sets by chained random forests.

Statistical analysis

To assess the sensitivity of the MPR outcome, a correlation test between the MPR and the self-reported medication adherence rates was performed. Because of the skewed distribution of the self-reported adherence rates, a spearman's rank correlation was performed.

A multivariate linear regression analysis was performed to find predictors of non-adherence. The independent variables were divided into three models. Model 1 consisted of the demographics, and the patient- and disease-related factors. In model 2 the social- and environment-related factors were added and in model 3 the treatment-related factors were added. Two different analyses were performed, the first without covariate adjustment and the second with the covariates included as a separate model. This was done to determine the influence of the high MPR values on the outcome of the analysis. To determine the impact of the different variable categories on the linear regression outcome, ANOVA analyses were performed.

Assumption testing was performed to determine the presence of multicollinearity, normality of the distribution, and homogeneity of the variance of the dataset. To assess the stability of the regression outcomes, two more regression analyses with trimmed datasets were performed. In these analyses, outliers with a standardized residual above 2.5 or below -2.5, according to the results of the assumption testing, were excluded.

The level of significance for the independent variables was set at 0.05 and all data analyses were performed using RStudio programming (version 1.3.1093) [24].

Results

Of the subjects included in the MPR calculation, the majority (71,5%) were males. The age of the subjects ranged from 17 to 59 years with a mean age of 28,6 years. Most of the subjects (53,1%) were aged between 20 and 30 years. Start dates for the first psychotic episodes were between 2008 and 2021 and the remission dates were between 2016 and 2021.

Prevalence of adherence

The MPR was calculated for a total of 260 subjects and ranged from 33.2%-186.7% (mean 101%, S.D. 21.9). Approximately half of the subjects included had an MPR value above 100% (121 out of 260) meaning that they had a medication supply covering more days than the number of days in their respective treatment period. An MPR ≥ 0.8 is often classified as good treatment adherence [25]. When employing this threshold, 88,8% of the subjects had a good treatment adherence.

Self-reported adherence rates were calculated for 208 out of the 260 subjects and could not exceed 100%. The values ranged from 50%-100% (mean 95.7%, S.D. 9.3). Results of the one-sided Spearman's rank correlation test ($r_s = 0.19$, df = 206, $p = 0.005$) indicate a very weak, but significant, positive association between the MPR and self-reported treatment adherence.

Factors associated with medication adherence

After the exclusion of 16 subjects that dropped out of the study before the baseline visit, 244 remained for inclusion in the multivariate regression analysis. These 16 subjects were included in the MPR calculation and for two of these subjects, self-reported adherence rates were also available.

Dataset without covariate adjustment

Model comparison with ANOVA, displayed in Table 1, showed that demographics, patient and environment-related factors were not significantly related to treatment adherence. The treatment-related factors did have a significant association with treatment adherence (model 3, $p = 0.024$) and improved model fit.

Table 1. Results of model comparison with ANOVA

	R^2	df	F	*p*-value
Dataset no adjustment				
1. Demographics + patient- and disease-related factors	0.025	-	-	-
2. Model 1 + social- and environment-related factors	0.037	3	1.043	0.374
3. Model 2 + treatment-related factors	0.083	4	2.876	**0.024***
Dataset adjusted for covariates				
1. Covariates	0.263	-	-	-
2. Model 1 + demographics + patient- and disease-related factors	0.313	7	2.380	**0.023***
3. Model 2 + social- and environment-related factors	0.319	3	0.677	0.567
4. Model 3 + treatment-related factors	0.327	4	0.700	0.593

df = degrees of freedom

****p < 0.001, **p < 0.01, *p < 0.05*

Model 3 also appeared to explain more of the variability in the MPR than models 1 and 2 (R^2 = 0.083 for model 3 compared to R^2 = 0.025 and R^2= 0.037 for models 1 and 2 respectively). However, even the R-squared for model 3 was very low, only explaining around 8% of the variance.

Of the 14 variables included in the multivariate regression analysis without covariate adjustment, side effects was the only variable with a significant association with treatment adherence (β = 0.253; p = 0.013). Subjects experiencing a higher number of antipsychotic medication side effects were more likely to be adherent to their prescribed medication regimen. For a complete overview of the results of the multivariate regression analysis and distribution of the patient characteristics see Table 2. The standardized estimated effect sizes obtained with regression analysis are presented in Figure 1.

The trimmed version of the dataset, in which six subjects were excluded, showed similar results. Side effects were still significantly associated with treatment adherence (see Appendix B). In addition, after exclusion of the outliers of the dataset stigma was also significantly associated with the MPR (β = -0.310; p = 0.030), indicating that subjects with a higher level of self-stigma surrounding mental illness, tend to be less adherent to their prescribed treatment regimen.

Results of assumption testing showed no multicollinearity. There was a linear relationship with constant variance between the MPR and the predictor variables, with the exception of some outliers at both ends of the spectrum. Results of a Q-Q test for normality showed that the data had a slight positive skew.

Dataset adjusted for covariates

Model comparison for the dataset with covariate adjustment showed that the addition of the environment- and treatment-related factors did not significantly change the fit of the dataset (Table 1). The patient- and disease-related factors did have a significant association with treatment adherence (model 2, p = 0.023). The two covariates alone appeared to explain more than 25% of the variability in the MPR (R^2 = 0.263). After the addition of the independent variable categories, this percentage increases by approximately six percent. This increase was mostly attributed to the addition of model 2 (R^2 = 0.313).

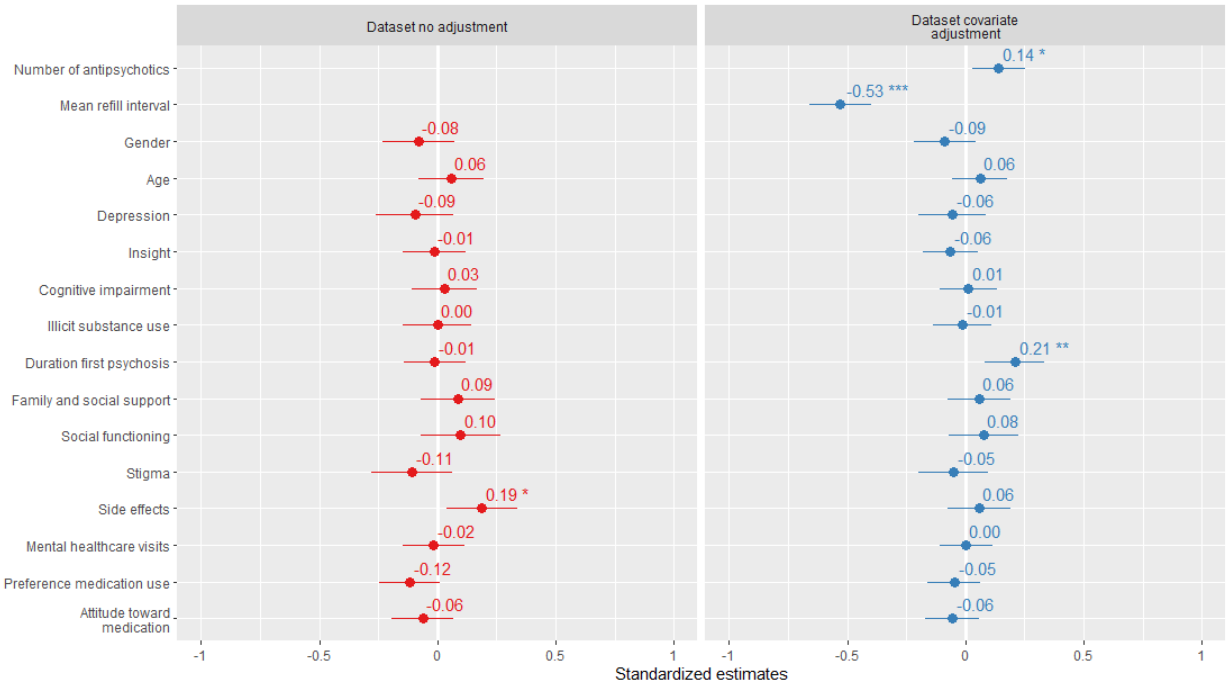
The results from the multivariate regression analysis (Table 2) showed that both covariates were significantly associated with the MPR (Number of APs, β = 5.333, p= 0.015 and mean refill interval, β = -0.681, p = 1.29E-13). A higher number of antipsychotics used in the year after remission of the FEP and a shorter mean refill interval were both associated with a higher MPR. Furthermore, the duration of the first psychosis was also significantly associated with treatment adherence (β = 0.310; p = 0.001). Subjects with a longer duration of the first psychosis were more adherent to their prescribed treatment regimen. The trimmed version of this dataset, listed in Appendix B, showed similar results.

Table 2. Results of multivariate regression analyses

		Dataset no adjustment (N = 244)		Dataset adjusted for covariates (N = 244)	
Variable	N	β	*p*	β	*p*
Number of APs					
Mean ± SD	1.3 ± 0.6	-	-	5.333	**0.015***
Range	1 - 3				
Mean refill interval (days)					
Mean ± SD	33.6 ± 16.5	-	-	-0.681	**1.29E-13*****
Range	4.8 - 177				
Gender					
Female	74	-3.765	0.291	-4.058	0.189
Male	174				
Age (years)					
Mean ± SD	28.6 ± 8.7	0.141	0.403	0.149	0.308
Range	17 - 59				
Depression					
Mean ± SD	6.0 ± 2.7	-0.746	0.253	-0.436	0.440
Range	3 - 15				
Insight					
Mean ± SD	1.6 ± 1.1	-0.292	0.830	-1.291	0.273
Range	1 - 7				
Cognitive impairment					
Mean ± SD	-1.0 ± 0.7	0.789	0.696	0.367	0.833
Range	-4.3 - 1.0				
Lifetime illicit substance use					
Yes	159	0.038	0.991	-0.556	0.843
No	85				
Duration first psychosis (months)					
Mean ± SD	6.9 ± 14.2	-0.017	0.861	0.310	**0.001****
Range	1 - 171				
Family/social support					
Mean ± SD	66.8 ± 13.2	0.138	0.277	0.094	0.391
Range	12 - 84				
Social functioning					
Mean ± SD	6.7 ± 5.7	0.362	0.257	0.283	0.303
Range	0 - 28				
Stigma					
Mean ± SD	58.3 ± 11.1	-0.204	0.219	-0.096	0.502
Range	37 - 90				
Side effects					
Mean ± SD	27.8 ± 15.8	0.253	**0.013***	0.077	0.390
Range	0 - 76				
Mental health care visits					
Mean ± SD	4.1 ± 3.6	-0.091	0.812	0.012	0.971
Range	0 - 34				
Preference medication use					
Continuing	13	-5.628	0.077	-2.298	0.406
Discontinuing	196				
No preference	35				
Attitude towards medication					
No advantages	79	-1.914	0.346	-1.730	0.322
Some advantages	122				
Strong advantages	43				

APs = antipsychotics, SD = Standard Deviation, β = estimated effect size

****p < 0.001, **p < 0.01, *p < 0.05*



****p < 0.001, **p < 0.01, *p < 0.05*

Figure 1. Standardized estimated effect size distribution of the independent variables on the MPR. On the left side, the results of the original dataset without covariate adjustment are presented. On the right side, the covariates (number of antipsychotics and mean refill interval) are included in the dataset.

In comparison with the model without the adjustment for the covariates, most of the independent variables actually had higher p-values. However, as a whole, the model with covariate adjustment had a better R-squared, while still on the lower side, and significant p-value (R^2 = 0.327; p = 8.506E-13 compared to R^2 = 0.083 and p = 0.117). Therefore, the model with covariate adjustment fit the data better and explained more of the variability of the MPR.

Discussion

This study aimed to find predictors for non-adherence to antipsychotics among first-episode psychosis patients in the first year after remission. Adherence was measured with the MPR. The mean MPR among 260 subjects was 101%, with 121 of the subjects having an adherence rate above 100%. The results of regression analyses showed that side effects, stigma, and the duration of the first psychosis were significantly associated with the MPR, and thus treatment adherence.

In this study, 88,8% of the subjects had a good treatment adherence. This is higher than previous findings, mostly reporting adherence rates in schizophrenia around 40-60% [6,26]. In an attempt to validate these results, the MPR was compared to self-reported adherence rates. The results showed a very weak, but significant, correlation between the two methods. This validation was not fully equivalent seeing that the MPR was calculated over a period of 1 year and the self-reported adherence rates covered a period of two weeks. Furthermore, the self-reported adherence rates couldn't exceed 100% whereas the MPR could. However, the significant correlation does provide a bit more assurance on the accuracy of the adherence rates.

A reason for the high MPRs found in this study could be overlapping prescriptions due to switching between antipsychotics and/or discontinuation of treatment. With an MPR exceeding 100% a patient had a medication supply covering more days than the number of days in the respective treatment period. This happens when a new prescription is dispensed before the previous one is completed, resulting in overlapping prescriptions.

Patients using antipsychotic drugs often switch between antipsychotics, for example when treatment response is inadequate or when disturbing side effects occur. Two American studies report that about one-third of their patient population switched at least once within one year of treatment with an antipsychotic [27,28].

The remaining medication from the previous prescription would then not be used, giving the false appearance of a high(er) adherence rate.
In addition, discontinuation of antipsychotics could also lead to leftover medication because this requires tapering of the medication with the help of a predefined schedule. Different doses of the drug are needed to adhere to this schedule, of which possibly not the whole prescription is used.
Another reason for overlapping prescriptions could be the somewhat disorganized nature of the patient group using antipsychotics. Cognitive dysfunction is a fundamental characteristic of schizophrenia, with deficits presenting in areas like attention and working memory, with big implications for daily functioning [29,30]. This could lead to problems with taking medication as prescribed (i.e. losing medication, taking the wrong dose, etc.) and possibly the need for overlapping prescriptions.

The positive association between side effects and the MPR, indicating a better treatment adherence among the patients experiencing more side effects, was not expected. The occurrence of more distressing side effects could be a reason to take less medication, as demonstrated by several studies connecting the occurrence of antipsychotic side effects to non-adherence [7,31,32]. A potential reason for this contrasting result is the fact that the independent variables were measured at baseline and the MPR was determined over a period of the first year after remission. Subjects experiencing distressing side effects could switch to a different antipsychotic after baseline subsequently causing an increase in adherence.
A higher level of self-stigma surrounding psychotic disorders was associated with a lower treatment adherence, which is in accordance with previous studies [33,34]. Self-stigma refers to negative feelings and experiences the patient has about their mental illness, including alienation, stereotype endorsement, perceived discrimination, social withdrawal, and stigma resistance [19]. With more negative feelings and experiences towards the mental illness, lower treatment adherence is to be expected.
In one of the analyses, the duration of psychosis also showed a significant association with the MPR. Previous studies have linked a longer duration of untreated psychosis to non-adherence in schizophrenia and FEP patients [35,36]. The association in this study shows an increased treatment adherence among patients with a longer duration of psychosis. However, the variable was included as the total duration of the first psychotic episode meaning that patients were partially treated with an antipsychotic during this period.
The mean total duration of psychosis was 6.9 months (SD 14.2). Because the untreated psychosis is a part of the total duration of the psychosis, the mean untreated psychosis in this study would most likely have been even shorter. The studies researching the duration of untreated psychosis reported mean durations of the untreated psychosis of 401.1 days and 2.9 years respectively [35,36].
Most of the patients included in this study were treated by early-intervention teams, established to treat patients with risk and/or proneness for the development of psychosis to prevent the condition from getting worse. This could be the reason for the difference in the mean duration of the psychotic episode and the association found between the duration of psychosis and treatment adherence. Patients with a longer duration of the first psychosis are possibly more aware of their situation and willing to take medication to reach remission.

This study worked with real-world data, representing a heterogeneous patient population in a real-life setting. In addition, the number of patients included in this study (N = 260) exceeded the number of participants for 15 out of 19 articles included in a recent comprehensive review of literature researching determinants of adherence to antipsychotic medication in FEP [37]. Moreover, this study looked at a combination of 14 potential risk factors, 16 out of the 19 studies in the comprehensive review had included fewer predictor variables [37]. Therefore, this study has a bigger ratio of patients to potential risk factors than many of the other studies on this topic.
The main limitation of this study was the sensitivity of the MPR calculation to prescribing behavior. In an attempt to determine the influence of overlapping prescriptions, the number of antipsychotics used in the treatment period and the mean refill interval between dispensing moments were included as covariates. With a higher number of different antipsychotics used, it stands to reason that there would be more overlapping prescriptions with leftover medication. In addition, the overall mean refill interval in this study was 33.6 days (i.e. a month), which is not an uncommon length for prescriptions in community pharmacies in the Netherlands. However, medication for chronic illnesses is often prescribed for longer periods of time such as 3 months per prescription [38]. A small refill interval could therefore mean that a patient is too early for their next prescription and be an indicator of overlapping prescriptions.

Both covariates were in fact significantly associated with a higher MPR and together explained more than 25% of the variance seen in the MPR. This calls into question the accuracy of the adherence rates found in this study.

Another shortcoming of working with dispensing data is the fact that it is unclear what patients do with their medication after they collect it from the pharmacy. The fact that a patient collected his or her medication does not mean that they will take the medication as prescribed.

Conclusions

Treatment adherence is difficult to measure, and there is no one right way to do it. Future research employing the MPR should consider the sensitivity of this calculation to prescribing behavior by correcting for overlapping prescriptions due to switching between antipsychotics and discontinuation.

Intervention strategies focused on lowering self-stigma among patients with a first episode of schizophrenia could lead to an increase in treatment adherence among FEP patients. By identifying patients with a high level of self-stigma early, healthcare providers know to exercise an extra level of vigilance around treatment adherence with these patients from the onset.

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Appendix A: Description of independent variables

Variable	Description
Insight	Better described as (lack of) awareness of illness and need for treatment was measured using item G12, of the Positive And Negative Syndrome Scale [15] (PANSS). The PANSS is a semi-structured interview used for measuring symptom severity in patients with schizophrenia. Items on this scale can be scored according to a rating scale from 1 to 7 where "1" classifies as the absence of that particular symptom and patients with rating scores "2-7" show increasing levels of symptom severity.
Depression	Also measured using the PANSS assessment. Depression was measured according to the 'five-factor model' of the PANSS, where depression is measured by not only PANSS item G6 (depression) but also items G2 an G3 (anxiety and guilt feelings). The scores of these three items were added together and used for the variable depression.
Cognitive impairment	Measured with the Brief Assessment of Cognition in Schizophrenia (BACS). The performances on the subtests of the BACS were adjusted for gender and age using the standardized norms of Keefe et al. (2004)[16]. Scores were then converted to individual z-scores and a composite z-score reflecting global cognitive function.
Lifetime (illicit) substance use	With the Comprehensive Assessment of Symptoms and History [17] (CASH) questionnaire information about lifetime hard- and soft drug use was obtained. Both questions were answered with a yes/no response or with 'no info' if this information was unknown, corresponding with a 1, 0, and -1 value, respectively. Participants with a score of 1 on either hard- or soft drug use or on both questions got assigned a cumulative score of 1 (illicit substance use during lifetime) and participants with a score of 0 or -1 on either question were assigned a cumulative score of 0 (no illicit substance use during lifetime).
Duration of first psychosis	By means of the date on which the first episode of psychosis started and the remission date, the duration of the FEP was calculated.
Family and social support	The total score of The Multidimensional Scale of Perceived Social Support [18] (MSPSS) was used for the variable family and social support. This self-report questionnaire measures the level of social support the participant perceives from family, friends, and his or her significant other.
Stigma	The total score of the Internalized Stigma of Mental Illness [19] (ISMI) scale was used for the variable stigma. This self-report questionnaire measures the experience of stigma among individuals with a psychiatric disorder.
Social functioning	The World Health Organization's Disability Assessment Schedule [20] (WHO-DAS 2.0) is an instrument to assess six different functioning domains, among others, in psychiatric patients. Social functioning is measured with domain 6 of this tool and will be used for the variable in this study. Computation of the item scores of domain 6 gave a total score for social functioning.
Side effects	With the total unpleasant effects subscale from the Subjective Reaction on Antipsychotics [21] (SRA) rating scale, the number of unpleasant side effects from the antipsychotic medication in use was measured.
Mental healthcare visits	The Trimbos and iMTA 'Treatment Inventory Cost in Patients with a psychiatric disorder' [22] (TiC-P) questionnaire is a Dutch tool used to estimate health care utilization. In this questionnaire, there is a section of questions in which the number of consultations and home visits in the past 4 weeks with different health care professionals is assessed. For the variable mental healthcare visits the number of visits with a doctor, a doctor in training, general practice-based nurse, psychologist, psychiatrist, and nurse practitioner were added together.
Attitude toward medication	The Subjective Reaction on Antipsychotics [21] (SRA) rating scale has a specific question asking if the advantages of the medication outweigh the disadvantages. The question is answered with one of three categories: no; yes, to some extent; yes, strongly, corresponding to scores 0, 1, and 2, respectively.
Medication use preference	With respect to the study design of the HAMLETT study, the participants were asked if they had a preference for the continuation or early discontinuation of their antipsychotic medication. The answer options were a preference for continuing, discontinuing, or no preference. This information is used for the variable medication use preference.

Appendix B: Results of the trimmed regression analyses

	Dataset without covariates (N = 238)		Dataset with covariates (N = 237)	
Variable	β	*p*	β	*p*
Number of APS	-	-	3.534	0.0522
Mean refill interval	-	-	-0.657	**<2E-16*** **
Gender	-4.395	0.155	-4.960	0.052
Age	0.137	0.337	0.127	0.282
Depression	-0.416	0.456	-0.284	0.536
Insight	-0.295	0.797	-0.764	0.422
Cognitive impairment	-0.053	0.975	-0.683	0.630
Lifetime illicit substance use	0.553	0.843	0.040	0.986
Duration first psychosis	-0.001	0.986	0.323	**4.71E-5*** **
Family/social support	0.006	0.956	0.013	0.888
Social functioning	0.354	0.192	0.267	0.237
Stigma	-0.310	**0.030***	-0.175	0.138
Side effects	0.182	**0.035***	0.028	0.700
Mental healthcare visits	-0.204	0.531	-0.060	0.823
Preference medication use	-4.823	0.073	-1.543	0.489
Attitude towards medication	-2.585	0.136	-2.031	0.156

****p < 0.001, **p < 0.01, *p < 0.05*