Psychiatry Research 354 (2025) 116780

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Treatment adherence in first-episode psychosis: A one-year follow-up study comparing self-reported adherence, pharmacy refill data, and therapeutic drug monitoring

Juhani Leijala [a,b,c,d,*], Olli Kampman [a,d,e,f], Teemu Gunnar [g], Jaana Suvisaari [c]

[a] University of Turku, Faculty of Medicine, Department of Clinical Medicine (Psychiatry), Turku, Finland
[b] The Wellbeing Services County of South Ostrobothnia, Department of Psychiatry, Seinäjoki, Finland
[c] Finnish Institute for Health and Welfare, Mental Health Unit, Helsinki, Finland
[d] The Wellbeing Services County of Ostrobothnia, Department of Psychiatry, Vaasa, Finland
[e] Department of Clinical Sciences, Psychiatry, Umeå University, Umeå, Sweden
[f] The Wellbeing Services County of Pirkanmaa, Department of Psychiatry, Tampere, Finland
[g] Finnish Institute for Health and Welfare, Forensic Chemistry Unit, Helsinki, Finland

ARTICLE INFO

Keywords:
Adherence
Schizophrenia
First episode psychosis
Psychotic disorder
Attitudes toward neuroleptic treatment scale

ABSTRACT

Background: This study evaluates the accuracy of different adherence assessment methods in first-episode psychosis (FEP), where long-term adherence is essential for relapse prevention. We compared self-reported adherence, pharmacy refill data, and therapeutic drug monitoring (TDM).
Methods: In this one-year follow-up study, 78 FEP patients were assessed for adherence at two and twelve months using the Attitudes towards Neuroleptic Treatment (ANT) scale (self-report), pharmacy refill data (≥1 or ≥2 purchases in four months), and TDM as the reference standard. Statistical analyses included McNemar's test, sensitivity, specificity, Cohen's kappa, and Receiver Operating Characteristic (ROC) analysis.
Results: At two months, adherence was 50.0% based on TDM, decreasing to 41.5% at twelve months. At two months, adherence rates were 73.3% for the ANT scale, 84.6% for at least one pharmacy refill, and 55.8% for at least two refills; by twelve months, these were 68.8%, 91.2%, and 52.9%, respectively. The ANT-attitude variable had weak predictive value for adherence (AUC: 0.607 at two months, 0.671 at twelve months). The ANT scale showed high sensitivity but low specificity, leading to adherence overestimation. Pharmacy refill adherence was more reliable, particularly when defined as at least two purchases within four months.
Conclusion: Medication non-adherence is common in FEP. Pharmacy refill data provided a more accurate adherence measure than self-report. Enhancing adherence requires psychoeducation, follow-up, and proactive monitoring. Measuring drug concentrations after hospital discharge could help detect early non-adherence and optimize treatment.

1. Introduction

Antipsychotics effectively treat acute psychosis and prevent relapses and hospitalizations (Leucht et al., 2012, 2013; Tiihonen et al., 2011). Medication adherence is crucial for therapeutic efficacy, and discontinuation is a major risk factor for symptom exacerbation and relapse in psychosis (Robinson et al., 1999). Adherence rates among patients with psychotic disorders vary widely across studies, ranging from as low as 6 % to as high as 95 % (Lacro et al., 2002; Ljungdalh, 2017; Sendt et al., 2015). This variability may be partially attributed to the diverse methodologies used to assess adherence. These methods range from self-reported measures and pill counts to electronic medication monitoring (Velligan et al., 2007).

Self-report questionnaires are widely utilized due to their low cost and ease of administration, although they pose a risk of overestimating adherence (Velligan et al., 2020). These instruments typically require patients to self-report their medication-taking behavior over a specified period. Several self-report scales also include questions based on the Health Belief Model (Becker et al., 1978; Becker and Maiman, 1975), which address attitudes towards medication adherence (Hogan et al., 1983; Kampman et al., 2000; Morisky et al., 1986; Thompson et al.,

* Corresponding author at: Department of Psychiatry, South Ostrobothnia Wellbeing Services County, Hanneksenrinne 7, 60220 Seinäjoki, Finland.
E-mail address: juhani.m.leijala@utu.fi (J. Leijala).

https://doi.org/10.1016/j.psychres.2025.116780
Received 24 March 2025; Received in revised form 14 October 2025; Accepted 19 October 2025
Available online 20 October 2025

Abbreviations

ANT	Attitudes towards Neuroleptic Treatment scale
AUC	Area Under the Curve
BPRS	Brief Psychiatric Rating Scale
CI	Confidence Intervals
DAI-10	Drug Attitude Inventory
DDD	Defined Daily Doses
DRRR	Dose-Related Reference Ranges
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
FEP	First-episode psychosis
+LR	positive likelihood ratio
-LR	negative likelihood
MEMS	Medication Event Monitoring System
NVP	negative predictive value
PPV	positive predictive value
ROC	Receiver Operating Characteristic
SOFAS	Social and Occupational Functioning Assessment Scale
SPSS	Statistical Package for Social Sciences
TDM	Therapeutic drug monitoring;

2000). Research has consistently shown that attitudes significantly influence adherence (Baloush-Kleinman et al., 2011; Brain et al., 2013; Lacro et al., 2002).

The use of medication dispensing registry data to assess adherence has become more common (Velligan et al., 2020). A recent Finnish study using registry data found that 31 % of 29,956 patients were classified as non-adherent (Lieslehto et al., 2022). The absence of pharmacy refills clearly indicates complete non-adherence, as the medication is not being purchased. While possession of medication, as indicated by pharmacy refills, suggests adherence, it does not confirm that patients are taking the medication as prescribed. This issue can be further investigated by comparing pharmacy refill data with drug concentration measurements (Osula et al., 2022).

When adherence is assessed using drug concentration measurements, several thresholds can be applied, including the therapeutic range, the dose/concentration ratio, or a dose-related reference range (DRRR) (Beebe et al., 2016; Brasso et al., 2021; Jónsdóttir et al., 2012). Therapeutic drug monitoring (TDM) and DRRR-based assessment methods provide a more reliable estimate when plasma concentrations accurately reflect the administered dose (Brasso et al., 2021; Hiemke et al., 2018). This approach is particularly beneficial for patients with first-episode psychosis, as their antipsychotic treatment is typically initiated at lower doses.

Numerous adherence studies have been conducted over the past decades (Velligan et al., 2020). However, only a few have systematically validated and compared the sensitivity and specificity of different adherence assessment methods in longitudinal studies. The use of pharmacy dispensing records as an adherence assessment method has gained popularity due to its distinct advantages (Lieslehto et al., 2022; Velligan et al., 2020). Nonetheless, this method requires further validation against more robust measures of medication adherence. Ensuring adherence in first-episode psychosis is critical, as non-adherence not only increases relapse risk but also worsens long-term prognosis, functional capacity, and mortality (Harvey and Strassnig, 2012; Huhn et al., 2019; Murray and Lopez, 1997; Suvisaari et al., 2013).

In this study, we assess treatment adherence in a cohort with first-episode psychoses and compare different methods of measuring adherence and detecting non-adherence. Our primary research question is: How do adherence measurements based on the Attitudes towards Neuroleptic Treatment (ANT) scale and pharmacy refill data compare to drug concentration-based adherence in terms of sensitivity and specificity? The null hypothesis states that there is no significant difference in the measurement of medication adherence when comparing the ANT scale (H0_1) and pharmacy refill adherence (H0_2) to drug concentration-based medication adherence.

2. Methods

In the Helsinki Early Psychosis Study, conducted between December 2010 and July 2016, we included 78 adult first-episode psychosis (FEP) patients for whom blood samples and medication data were available to determine adherence to treatment based on medication concentrations. The patients were recruited from in- and outpatient units of the University Hospital District of Helsinki and Uusimaa and the city of Helsinki. Each patient underwent three assessments. The baseline assessment took place once the patient had entered treatment and could provide informed consent, as determined by the treating personnel. Follow-up assessments were conducted at two and 12 months (Keinänen et al., 2015; Mäntylä et al., 2015).

Diagnostic assessment was conducted using the Research Version of the Structured Clinical Interview for DSM-IV Disorders – Axis I (SCID-I) (First et al., 2002),supplemented by a comprehensive review of symptoms from medical records up to the 12-month follow-up. To evaluate medication treatment, patients were asked to bring their prescriptions or current medications to the interview. In cases where this was not possible or when patients were unable to accurately recall the names or doses of their medications, the information was verified using medical records. Additionally, medical records were reviewed retrospectively to document the precise timing of any dosage adjustments. In cases where discrepancies arose between self-reported medication use and medical records, self-reported information was prioritized.

The study was conducted in accordance with the ethical principles outlined in the Code of Ethics of the World Medical Association (Declaration of Helsinki). The study protocol was approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa (257/12/03/03/2009 and 226/13/03/03/2013), as well as by the institutional review boards of the Finnish Institute for Health and Welfare (THL) and the University of Helsinki. All participants provided written informed consent prior to study enrollment.

2.1. Measures

Patients' adherence to antipsychotic medication was measured through self-reports, pharmacy refill data, and plasma level concentrations. For self-assessment, we used the Attitudes towards Neuroleptic Treatment Scale (ANT) (Kampman et al., 2000). The ANT includes measurements of patient adherence and attitudes toward antipsychotic treatment. We created a continuous ANT attitude variable from the mean attitude scores and defined a dichotomous ANT adherence variable using a 75 % medication use cutoff (Leijala et al., 2021).

Based on the method described in the Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology, we calculated dose-related reference ranges (DRRR) for the antipsychotics measured in blood samples (Hiemke et al., 2018). Patients were classified as adherent (TDM_DRRR) if their medication concentration fell within the DRRR or the established therapeutic range. As an alternative and slightly more permissive TDM-based measure of adherence, we utilized the TDM_Detectable_Level variable. This variable includes all patients with detectable plasma levels of medication, ensuring that e.g. patients with unusually rapid metabolism are also classified as adherent. TDM was conducted retrospectively, meaning results were not available to clinicians or patients during follow-up, ensuring adherence classification was not influenced by knowledge of drug levels.

In Finland, pharmacies are permitted to dispense a maximum of a three-month supply based on the prescribed dosage. To assess adherence based on pharmacy purchases, we retrieved data from the national electronic prescription archive for the four months preceding each

follow-up point. First, individuals who did not purchase any medication were classified as completely non-adherent. Second, individuals who made at least one purchase during the study period were considered at least partially adherent, even if the supply did not cover the entire four months, unless the dosage had been reduced and based on it the individual could be considered as adherent. Full adherence, in contrast, required at least two purchases within the study period to ensure coverage of the prescribed dosage. These classifications were used to create pharmacy refill-based adherence variables (≥1 purchase and ≥2 purchases within the observation period).

The study employed additional psychiatric measures, including the 24-item version of the Brief Psychiatric Rating Scale (BPRS) (Ventura et al., 1993), and assessed levels of functioning using the Social and Occupational Functioning Assessment Scale (SOFAS) (APA, 2000). To standardize antipsychotic dosage across different medications, doses were converted to Defined Daily Doses (DDD) (WHO, 2024).

2.2. Laboratory analytical methods

All laboratory analyses were performed at the Forensic Chemistry Unit of the Finnish Institute for Health Welfare (THL) in Helsinki, Finland. Patients' blood plasma samples (0.5 ml) were screened and positive findings quantified by using liquid-liquid extraction (LLE) in sample preparation before sensitive ultra-high performance liquid chromatography triple quadrupole tandem mass spectrometric methodology (UHPLC-QQQ-MS/MS) (Gunnart and Ariniemi, 2013). UHPLC-QQQ-MS/MS analysis (1290II Infinity LC system and 6460A mass spectrometer) was performed using multiple reaction monitoring (MRM) with at least two MRM transitions in the electrospray ionization (ESI) positive ion mode. Calibration curves were prepared for each analyte by using multiple concentration points and internal standardization. The following antipsychotics were screened and quantified with the following limit of quantification (LOQ) in the study: clozapine (10 ng ml^{-1}), chlorpromazine (10), chlorprothixene (10), olanzapine (Zyprexa), quetiapine (10), risperidone (Risperdal), 9-OH-risperidone (Risperdal) (1), sertindole (2), aripiprazole (10), perphenazine (0.2) and ziprasidone (10). The latter three were separately quantified after initial semi-quantitative screening methodology for those analytes by LLE followed by UHPLC-QQQ-MS/MS analysis in the MRM mode applying ESI in the positive ion mode (Agilent 1200 UHPLC and Sciex 4000QTRAP mass spectrometer). All samples were kept at −80 °C until analyses.

2.3. Statistical methods

Statistical analyses and data visualization were performed using IBM SPSS Statistics for Windows, Version 29.0 (IBM Corp., 2023) and RStudio, Version 2022.7.2.576 (RStudio Team, 2022). Descriptive statistics were used to summarize the demographic and clinical characteristics of the sample. To evaluate the comparative accuracy of different adherence measurement techniques, we employed McNemar's test for paired nominal data, Cohen's kappa coefficient for inter-rater agreement, and sensitivity/specificity analyses to assess the diagnostic performance of each method. When assessing diagnostic performance, the adherence variable based on Therapeutic Drug Monitoring (TDM) was used as the reference standard. Binomial proportion confidence intervals were calculated using the Clopper-Pearson exact method. The Receiver Operating Characteristic (ROC) curve was used to evaluate the performance of the continuous ANT-attitude variable in predicting adherence. All statistical tests were conducted at a 5 % level of significance (two-tailed). Differences in baseline characteristics between completers and patients lost to follow-up were examined using chi-square tests for categorical variables and Mann–Whitney U tests for continuous variables.

3. Results

Fig. 1. The flow of participants throughout the study is shown in

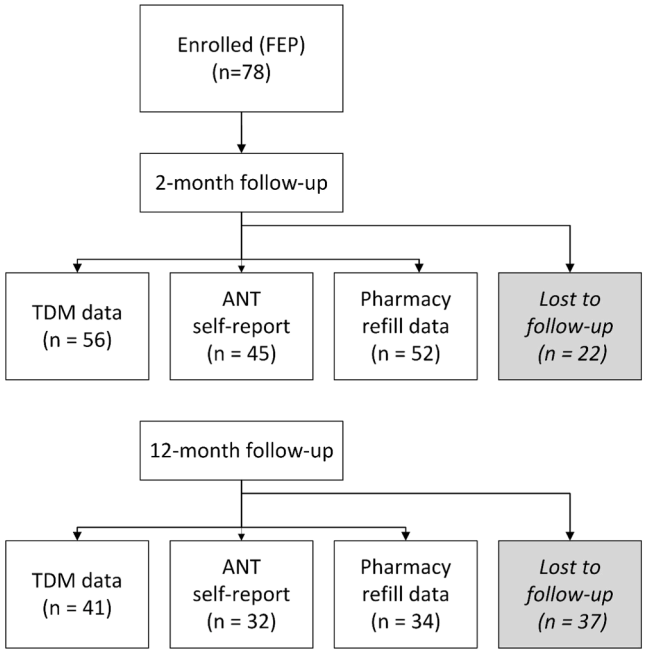

Fig. 1. Participant flow diagram. The diagram illustrates the number of participants with first-episode psychosis (FEP) enrolled (n = 78) and data availability at the 2-month and 12-month follow-ups for therapeutic drug monitoring (TDM), self-reported adherence assessed with the Attitudes towards Neuroleptic Treatment Scale (ANT), and pharmacy refill data. Participants lost to follow-up or with missing data are shown separately at each time point.

Fig. 1. The baseline sociodemographic and clinical characteristics of all subjects are outlined in Table 1. The majority of participants were male (66.7 %), with schizophrenia being the most common diagnosis. At baseline, self-reported adherence to antipsychotic medication was 97.4

Table 1
Sociodemographic and clinical characteristics of the sample.

Variables	Total (n = 78)
	Mean or *n (%, S.D.)*
Age	26.9 (5.9)
Sex (male)	52 (66.7 %)
Married or cohabitating	15 (19.2 %)
Employed or student	49 (63.6 %)
BPRS	43.2 (10.3)
Defined Daily Dose	1.2 (0.8)
Patient on antipsychotic medication	76 (97.4 %)
Sofas	40.2 (8.6)
Smoking (current) [a]	16 (20.5 %)
Alcohol use disorder (current)	4 (5.1 %)
Alcohol use disorder (lifetime)	5 (6.4 %)
Substance use disorder (current)	9 (11.5 %)
Substance use disorder (lifetime)	10 (12.8 %)
Diagnoses (DSM-IV)	78 (100 %)
Substance-induced psychotic disorder	2 (2.6 %)
Schizophrenia	28 (35.9 %)
Schizophreniform disorder	21 (26.9 %)
Schizoaffective disorder	2 (2.6 %)
Bipolar disorder type I	7 (8.9 %)
Psychotic depression	4 (5.1 %)
Delusional disorder	1 (1.3 %)
Brief psychotic disorder	3 (3.8 %)
Psychotic disorder not otherwise specified	10 (12.8 %)
Hospitalized	47 (60.3 %)
TDM_DRRR based adherence (adherent)	44 (56.4)
TDM_Detectable_Level	72 (92.3 %)

BPRS, Brief Psychiatric Rating Scale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; SOFAS, Social and Occupational Functioning Assessment Scale; TDM, Therapeutic drug monitoring.
footnote: [a] Missing data 10 (12.8 %).

%. However, only 56.4 % were classified as adherent based on TDM_DRRR.

Of the 78 patients, 37 (47.4 %) were lost to follow-up. Dropouts did not differ from completers in baseline age, symptom severity (BPRS, SANS), functioning (SOFAS), insight (SAI-E), antipsychotic dose, or hospitalization status. The only significant difference was sex: males were more likely to be lost to follow-up (83.8 % vs. 51.2 %, $p = 0.004$).

During the 2-month follow-up phase, TDM_DRRR-based adherence data were available for 56 patients, with 50.0 % demonstrating adherence. Among these, 7 patients (12.5 %) were hospitalized at the 2-month follow-up. At the 12-month follow-up, TDM_DRRR data were available for 41 patients, with 41.5 % classified as adherent, including one patient (2.4 %) who was hospitalized at the time of data collection (Table 2).

Adherence variables based on the ANT scale and pharmacy refill data were compared using TDM_DRRR-based adherence as the reference standard (Table 3). The ANT scale showed high sensitivity, whereas pharmacy refill adherence demonstrated higher specificity. However, all accuracy rates remained below 70 %. The highest positive likelihood ratio (2.10) was observed for pharmacy refill adherence at 12 months. The lowest negative likelihood ratio (0.00) was associated with pharmacy refill adherence (≥ 1 purchase) at 2 months, reflecting the absence of false negatives in this category.

A significant disagreement was observed between the reference standard (TDM_DRRR) and the ANT scale ($p = 0.007$ and $p = 0.022$, McNemar test) as well as pharmacy refill adherence (≥ 1 purchase) ($p < 0.001$, McNemar test). In contrast, pharmacy refill adherence (≥ 2 purchases) demonstrated modest agreement (kappa = 0.38 and 0.36 at 2 and 12 months, respectively). Additionally, the kappa value (0.30) for ANT scale adherence at 2 months indicated statistically significant but weak agreement.

The Receiver Operating Characteristic (ROC) analysis was employed to evaluate the predictive capability of ANT-attitude scores for adherence, using TDM_Detectable_Level-based adherence as the reference standard (Fig. 2). The Area Under the Curve (AUC) was 0.604 (95 % CI 0.323–0.884) at the 2-month follow-up and 0.671 (95 % CI 0.477–0.865) at the 12-month follow-up. Fig. 2.

4. Discussion

The results indicate that the first null hypothesis (H0_1) can be rejected, showing a significant difference between ANT scale– and TDM_DRRR–based adherence assessments. Attitudes measured by the ANT scale did not reliably predict treatment adherence. Self-report clearly overestimated adherence, as reflected in its high sensitivity but low specificity. At two months, the ANT scale showed a low negative predictive value, suggesting that self-reported non-adherence was more credible than self-reported adherence. Changes in ANT scores over time may reflect attrition or response bias, whereby patients modify answers to align with perceived clinical expectations.

The ROC analysis of the ANT-attitude variable revealed weak but gradually improving discriminatory ability over time, although it remained below the threshold for moderate prediction. This is consistent with Brain et al., who also found limited predictive power using a related attitude scale (DAI-10) and electronic adherence monitoring (MEMS) (Brain et al., 2013). Methodological differences, including the definition of adherence and measurement tools, may partly explain the divergence in results. Therefore, although the ANT-attitude measure may provide useful information about patient perceptions, it cannot be recommended as a standalone tool for adherence monitoring in clinical practice.

Pharmacy refill–based assessment showed higher reliability, particularly when adherence was defined as at least two purchases within four months, supporting the second null hypothesis (H0_2). Yet, the modest kappa values (<0.4) indicate limited agreement. Clinically, patients who regularly refill prescriptions are more likely to take their medication, although refills alone do not guarantee adherence to the prescribed regimen.

Although healthcare systems differ across countries, Finland's nationwide electronic prescription and pharmacy database system (Kanta) is broadly comparable to those implemented in other high-income countries, including the other Nordic countries, EU member states, the United States, and Australia. The Finnish model is highly integrated and centralized, with all prescription data stored in a single national database accessible across care providers and pharmacies (Peltoniemi et al., 2021). Therefore, our findings regarding pharmacy refill data are likely to be applicable to other comparable healthcare settings.

This study has several limitations. High attrition during follow-up reduced statistical power and may have biased the results, thereby limiting generalizability (Higashi et al., 2013). Subgroup analyses by diagnostic subtype or hospitalization status were not conducted, as the small sample size would have provided insufficient power. This limits our ability to determine whether adherence patterns differ across these clinically relevant subgroups and underscores the need for larger future studies.

Although TDM was used as the reference standard, pharmacogenetic data were unavailable, preventing adjustment for interindividual differences in metabolism. Consequently, some fast metabolizers may have been misclassified as non-adherent. To partly address this, we also applied the TDM_Detectable_Level variable when examining the role of attitudes in adherence. Moreover, TDM itself has inherent limitations. Plasma concentrations reflect medication intake retrospectively, and blood sampling was not standardized with respect to dosing time. Intra-individual pharmacokinetic variability may further complicate interpretation. Thus, while TDM remains the most objective available reference standard, it should not be considered flawless (Hiemke et al., 2018). Nevertheless, these methodological constraints do not diminish the clinical relevance of objective adherence monitoring, which remains essential for optimizing treatment in psychotic disorders.

In clinical practice, TDM remains the most accurate method for verifying medication-taking behavior, as self-reports tend to overestimate true adherence. However, the costs associated with TDM limit its routine use (Laux et al., 2018). In everyday settings where TDM is not feasible for all patients, systematic review of pharmacy refill records can serve as a first-line screen to flag potential nonadherence, and more importance should be given to this method in clinical practice. In such cases, targeted TDM provides confirmatory, objective evidence and can guide clinical decision-making regarding dose adjustment, psychoeducation, or medication switching. Post-discharge TDM monitoring may help optimize pharmacotherapy in psychotic disorders, while refill tracking offers a pragmatic and cost-effective alternative for longer-term

Table 2
Hospitalization and treatment adherence variables at 2 months and 12 months follow-up.

Hospitalization and treatment adherence variables	2 months		12 months	
	n[a]	Mean or n (%, S.D.)	n[a]	Mean or n (%, S.D.)
Hospitalized	56	7 (12.5 %)	41	1 (2.4 %)
TDM_DRRR based adherence (adherent)	56	28 (50.0 %)	41	17 (41.5 %)
TDM_Detectable_Level based adherence (adherent)	78	51 (65.4 %)	78	32 (41.0 %)
ANT scale adherence (adherent)	45	33 (73.3 %)	32	22 (68.8 %)
ANT scale attitude	43	63.9 (15.1)	32	63.5 (19.8)
Pharmacy refill adherence (≥ 1 purchase)	52	44 (84.6 %)	34	31 (91.2 %)
Pharmacy refill adherence (≥ 2 purchase)	52	29 (55.8 %)	34	18 (52.9 %)

ANT, Attitudes towards Neuroleptic Treatment scale; DRRR, dose-related reference ranges; TDM, Therapeutic drug monitoring.
footnote: [a] Number of subjects with data available.

Table 3
Diagnostic performance of ANT scale and pharmacy refill adherence versus TDM based treatment adherence.

	n	Sensitivity (0.95CI)	Specificity (0.95 CI)	Accuracy (0.95 CI)	PPV (0.95 CI)	NPV (0.95 CI)	+LR (0.95 CI)	-LR (0.95 CI)	McNemar *p*-value	Kappa value	Kappa *p*-value
2M_ANT_adherence	42	0.90 (0.70, 0.99)	0.38 (0.18, 0.62)	0.64 (0.48, 0.78)	0.59 (0.41, 0.76)	0.80 (0.44, 0.97)	1.46 (1.02, 2.10)	0.25 (0.06, 1.04)	0.007	0.3	0.03
12M_ANT_adherence	26	0.80 (0.44, 0.97)	0.31 (0.11, 0.59)	0.50 (0.30, 0.70)	0.42 (0.20, 0.67)	0.71 (0.29, 0.96)	1.16 (0.74, 1.83)	0.64 (0.15, 2.69)	0.022	0.096	0.529
2M_Pharmacy refill adherence (≥ 1 purchase)	49	0.96 (0.80, 1.00)	0.26 (0.10, 0.48)	0.63 (0.48, 0.77)	0.60 (0.43, 0.74)	0.86 (0.42, 1.00)	1.30 (1.01, 1.68)	0.15 (0.02, 1.14)	<0.001	0.232	0.026
12M_Pharmacy refill adherence (≥ 1 purchase)	34	1.00 (0.78, 1.00)	0.16 (0.03, 0.40)	0.53 (0.35, 0.70)	0.48 (0.30, 0.67)	1.00 (0.29, 1.00)	1.19 (0.98, 1.44)	0.00 (0.00, 0.00)	<0.001	0.142	0.107
2M_Pharmacy refill adherence (≥ 2 purchase)	49	0.73 (0.52, 0.88)	0.65 (0.43, 0.84)	0.69 (0.55, 0.82)	0.70 (0.50, 0.86)	0.68 (0.45, 0.86)	2.10 (1.15, 3.85)	0.41 (0.20, 0.83)	1.00	0.384	0.007
12M_Pharmacy refill adherence (≥ 2 purchase)	34	0.73 (0.45, 0.92)	0.63 (0.38, 0.84)	0.68 (0.49, 0.83)	0.61 (0.36, 0.83)	0.75 (0.48, 0.93)	1.99 (1.03, 3.86)	0.42 (0.17, 1.05)	0.549	0.357	0.034

Therapeutic drug monitoring results were used as reference standards. (0.95 CI), CI: confidence interval; NVP: negative predictive value; PPV: positive predictive value; +LR: positive likelihood ratio; -LR: negative likelihood.

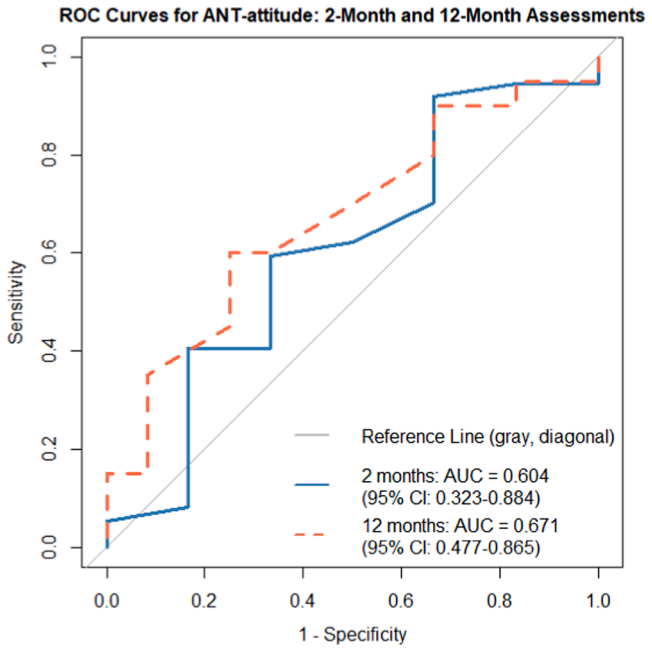

Fig. 2. ROC Curve ANT scale attitude score using TDM_Detectable_Level based adherence as reference standard. ANT, Attitudes towards Neuroleptic Treatment scale; AUC, area under the curve; CI, confidence interval; ROC, Receiver Operating Characteristic; TDM, Therapeutic drug monitoring.

management. Although predicting adherence based on patient attitudes remains challenging, regular discussion of medication beliefs and psychoeducation should remain integral to comprehensive care (Xia et al., 2011). In first-episode psychosis, where early adherence is critical for prognosis, considering routine or low-threshold TDM during the stabilization phase may be warranted, while continuing to monitor refill data longitudinally.

5. Conclusion

This study provides important insights into treatment adherence among patients with first-episode psychosis and evaluates different methods for assessing adherence in this population. Accurate assessment of medication adherence is essential for improving long-term outcomes in psychosis. Self-report proved unreliable, whereas pharmacy refill data provided a more objective and consistent measure. Combining self-report, refill data, and TDM may offer the most comprehensive understanding of adherence and treatment attitudes in first-episode psychosis.

Funding

The preparation of this manuscript was supported by a grant from the Ostrobothnia (2024, Leijala Juhani) and South Ostrobothnia Well-being Services Counties (1052, OMA24, Leijala Juhani). The funding sources had no role in the study design; data collection, analysis, or interpretation; manuscript writing; or the decision to submit the paper for publication.

CRediT authorship contribution statement

Juhani Leijala: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Olli Kampman:** Writing – review & editing, Supervision, Investigation, Formal analysis, Conceptualization. **Teemu Gunnar:** Writing – review & editing, Methodology, Investigation. **Jaana Suvisaari:** Writing – review & editing, Supervision, Resources, Project administration, Data curation.

Declaration of competing interest

All authors declare that they have no conflicts of interest.

Acknowledgements

We thank Marjut Grainger of the Finnish Institute for Health and Welfare (THL) for data management and Raimo Ketola (THL) for contributing to the laboratory analyses.

References

APA, 2000. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. American Psychiatric Association.

Baloush-Kleinman, V., Levine, S.Z., Roe, D., Shnitt, D., Weizman, A., Poyurovsky, M., 2011. Adherence to antipsychotic drug treatment in early-episode schizophrenia: a six-month naturalistic follow-up study. Schizophr. Res. 130, 1–3. https://doi.org/10.1016/j.schres.2011.04.030.

Becker, M.H., Maiman, L.A., 1975. Sociobehavioral determinants of compliance with health and medical care recommendations. Med. Care 13 (1). https://journals.lww.

com/lww-medicalcare/fulltext/1975/01000/sociobehavioral_determinants_of_compliance_with.2.aspx.
Becker, M.H., Radius, S.M., Rosenstock, I.M., Drachman, R.H., Schuberth, K.C., Teets, K. C., 1978. Compliance with a medical regimen for asthma: a test of the health belief model. Public Health Rep. 93 (3).
Beebe, L.H., Smith, K., Phillips, C., 2016. Descriptions and correlates of medication adherence, attitudes, and self-efficacy in outpatients with Schizophrenia spectrum disorders (SSDs). Arch. Psychiatr. Nurs. 30 (3). https://doi.org/10.1016/j.apnu.2016.01.010.
Brain, C., Allerby, K., Sameby, B., Quinlan, P., Joas, E., Karilampi, U., Lindstrom, E., Eberhard, J., Burns, T., Waern, M., 2013. Drug attitude and other predictors of medication adherence in schizophrenia: 12 months of electronic monitoring (MEMS ((R))) in the Swedish COAST-study. Eur. Neuropsychopharmacol. 23 (12), 1754–1762. https://doi.org/10.1016/j.euroneuro.2013.09.001 [doi].
Brasso, C., Cisotto, M., Ghirardini, C., Pennazio, F., Villari, V., Rocca, P., 2021. Accuracy of self-reported adherence and therapeutic drug monitoring in a psychiatric emergency ward. Psychiatry Res. 305. https://doi.org/10.1016/j.psychres.2021.114214.
First, M., Spitzer, R.L., Gibbon, M.L., Williams, J., 2002. Structured clinical interview for DSM-IV-TR Axis I Disorders, Research Version, non-patient edition. In (SCID-I/P).
Gunnart, T., Ariniemi, K., 2013. UHPLC-MS/MS for targeted screening and simultaneous semiquantification/quantification of over 150 drugs in whole blood. In: The 51st Annual Meeting of The International Association of Forensic Toxicologists (TIAFT).
Harvey, P.D., Strassnig, M., 2012. Predicting the severity of everyday functional disability in people with schizophrenia: cognitive deficits, functional capacity, symptoms, and health status. World Psychiatry 11 (2). https://doi.org/10.1016/j.wpsyc.2012.05.004.
Hiemke, C., Bergemann, N., Clement, H.W., Conca, A., Deckert, J., Domschke, K., Eckermann, G., Egberts, K., Gerlach, M., Greiner, C., Gründer, G., Haen, E., Havemann-Reinecke, U., Hefner, G., Helmer, R., Janssen, G., Jaquenoud, E., Laux, G., Messer, T., Baumann, P., 2018. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. In Pharmacopsychiatry 51, 1–2. https://doi.org/10.1055/s-0043-116492. Issues.
Higashi, K., Medic, G., Littlewood, K.J., Diez, T., Granstrom, O., De Hert, M., 2013. Medication adherence in schizophrenia: factors influencing adherence and consequences of nonadherence, a systematic literature review. Ther. Adv. Psychopharmacol. 3 (4), 200–218. https://doi.org/10.1177/2045125312474019 [doi].
Hogan, T.P., Awad, A.G., Eastwood, R., 1983. A self-report scale predictive of drug compliance in schizophrenics: reliability and discriminative validity. Psychol. Med. 13 (1), 177–183. https://doi.org/10.1017/s0033291700050182.
Huhn, M., Nikolakopoulou, A., Schneider-Thoma, J., Krause, M., Samara, M., Peter, N., Arndt, T., Bäckers, L., Rothe, P., Cipriani, A., Davis, J., Salanti, G., Leucht, S., 2019. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet 394 (10202). https://doi.org/10.1016/S0140-6736(19)31135-3.
IBM Corp. (2023). IBM SPSS statistics for windows, Version 29.0. IBM Corp.
Jónsdóttir, H., Opjordsmoen, S., Birkenaes, A.B., Simonsen, C., Engh, J.A., Ringen, P.A., Vaskinn, A., Friis, S., Sundet, K., Andreassen, O.A., 2012. Predictors of medication adherence in patients with schizophrenia and bipolar disorder. Acta Psychiatr. Scand. 127 (1). https://doi.org/10.1111/j.1600-0447.2012.01911.x.
Kampman, O., Lehtinen, K., Lassila, V., Leinonen, E., Poutanen, O., Koivisto, A.M., 2000. Attitudes towards neuroleptic treatment: reliability and validity of the Attitudes towards Neuroleptic treatment (ANT) questionnaire. Schizophr. Res. 45 (3). https://doi.org/10.1016/S0920-9964(99)00204-2.
Keinänen, J., Mantere, O., Kieseppä, T., Mäntylä, T., Torniainen, M., Lindgren, M., Sundvall, J., Suvisaari, J., 2015. Early insulin resistance predicts weight gain and waist circumference increase in first-episode psychosis - A one year follow-up study. Schizophr. Res. 169, 1–3. https://doi.org/10.1016/j.schres.2015.11.002.
Lacro, J.P., Dunn, L.B., Dolder, C.R., Leckband, S.G., Jeste, D.V., 2002. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. J. Clin. Psychiatry 63 (10), 892–909.
Laux, G., Hiemke, C., Zur Capellen, K.M., Assion, H.J., Messer, T., 2018. Therapeutic Drug-Monitoring in Psychiatric Hospitals - Results of a Survey of the Conference of National Directors of German Hospitals of Psychiatry and Psychotherapy, 25. Psychopharmakotherapie.
Leijala, J., Kampman, O., Suvisaari, J., Eskelinen, S., 2021. Daily functioning and symptom factors contributing to attitudes toward antipsychotic treatment and treatment adherence in outpatients with schizophrenia spectrum disorders. BMC Psychiatry 21 (1). https://doi.org/10.1186/s12888-021-03037-0.
Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Orey, D., Richter, F., Samara, M., Barbui, C., Engel, R.R., Geddes, J.R., Kissling, W., Stapf, M.P., Lassig, B., Salanti, G., Davis, J.M., 2013. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet (Lond. Engl.) 382 (9896), 951–962. https://doi.org/10.1016/S0140-6736(13)60733-3 [doi].
Leucht, S., Tardy, M., Komossa, K., Heres, S., Kissling, W., Salanti, G., Davis, J.M., 2012. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. Lancet (Lond. Engl.) 379 (9831), 2063–2071. https://doi.org/10.1016/S0140-6736(12)60239-6 [doi].
Lieslehto, J., Tiihonen, J., Lähteenvuo, M., Tanskanen, A., Taipale, H., 2022. Primary nonadherence to antipsychotic treatment among persons with schizophrenia. Schizophr. Bull. 48 (3). https://doi.org/10.1093/schbul/sbac014.
Ljungdalh, P.M., 2017. Non-adherence to pharmacological treatment in schizophrenia and schizophrenia spectrum disorders – an updated systematic literature review. In Eur. J. Psychiatry 31 (4). https://doi.org/10.1016/j.ejpsy.2017.08.001.
Mäntylä, T., Mantere, O., Raij, T.T., Kieseppä, T., Laitinen, H., Leiviskä, J., Torniainen, M., Tuominen, L., Vaarala, O., Suvisaari, J., 2015. Altered activation of innate immunity associates with white matter volume and diffusion in first-episode psychosis. PLoS ONE 10 (5). https://doi.org/10.1371/journal.pone.0125112.
Morisky, D.E., Green, L.W., Levine, D.M., 1986. Concurrent and predictive validity of a self-reported measure of medication adherence. Med. Care 24 (1), 67–74. https://doi.org/10.1097/00005650-198601000-00007 [doi].
Murray, C.J.L., Lopez, A.D., 1997. Global mortality, disability, and the contribution of risk factors: global burden of disease study. Lancet 349 (9063). https://doi.org/10.1016/S0140-6736(96)07495-8.
Osula, D., Wu, B., Schesing, K., Das, S.R., Moss, E., Alvarez, K., Clark, C., Halm, E.A., Brown, N.J., Vongpatanasin, W., 2022. Comparison of pharmacy refill data with chemical adherence testing in assessing medication nonadherence in a safety net hospital setting. J. Am. Heart Assoc. 11 (19). https://doi.org/10.1161/JAHA.122.027099.
Peltoniemi, T., Suomi, R., Peura, S., Lähteenoja, M.N.Y., 2021. Electronic prescription as a driver for digitalization in Finnish pharmacies. BMC Health Serv. Res. 21 (1). https://doi.org/10.1186/s12913-021-07003-0.
Robinson, D., Woerner, M.G., Alvir, J.M., Bilder, R., Goldman, R., Geisler, S., Koreen, A., Sheitman, B., Chakos, M., Mayerhoff, D., Lieberman, J.A., 1999. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. Arch. Gen. Psychiatry 56 (3), 241–247.
RStudio Team, 2022. RStudio: Integrated Development For R (2022.7.2.576). RStudio, PBC.
Sendt, K.V., Tracy, D.K., Bhattacharyya, S., 2015. A systematic review of factors influencing adherence to antipsychotic medication in schizophrenia-spectrum disorders. Psychiatry Res. 225, 1–2. https://doi.org/10.1016/j.psychres.2014.11.002. Issues.
Suvisaari, J., Partti, K., Perala, J., Viertio, S., Saarni, S.E., Lonnqvist, J., Saarni, S.I., Harkanen, T., 2013. Mortality and its determinants in people with psychotic disorder. Psychosom. Med. 75 (1), 60–67. https://doi.org/10.1097/PSY.0b013e31827ad512 [doi].
Thompson, K., Kulkarni, J., Sergejew, A.A., 2000. Reliability and validity of a new medication adherence rating scale (MARS) for the psychoses. Schizophr. Res. 42 (3), 241–247 [pii].
Tiihonen, J., Haukka, J., Taylor, M., Haddad, P.M., Patel, M.X., Korhonen, P., 2011. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am. J. Psychiatry 168 (6), 603–609. https://doi.org/10.1176/appi.ajp.2011.10081224 [doi].
Velligan, D.I., Maples, N.J., Pokorny, J.J., Wright, C., 2020. Assessment of adherence to oral antipsychotic medications: what has changed over the past decade? In Schizophr. Res. 215. https://doi.org/10.1016/j.schres.2019.11.022.
Velligan, D.I., Wang, M., Diamond, P., Glahn, D.C., Castillo, D., Bendle, S., Lam, Y.W.F., Ereshefsky, L., Miller, A.L., 2007. Relationships among subjective and objective measures of adherence to oral antipsychotic medications. Psychiatr. Serv. 58 (9). https://doi.org/10.1176/ps.2007.58.9.1187.
Ventura, J., Lukoff, D., Nuechterlein, K., Liberman, R.P., Green, M., Shaner, A., 1993. Brief Psychiatric rating Scale expanded version 4.0: scales anchor points and administration manual. Int. J. Meth. Psychiatr. Res. 13, 221–244.
WHO. (2024). ATC/DDD Index 2024. https://atcddd.fhi.no/atc_ddd_index_and_guidelines/atc_ddd_index/.
Xia, J., Merinder, L.B., & Belgamwar, M.R. (2011). Psychoeducation for schizophrenia. The Cochrane Database of Systematic Reviews, (6):CD0028(6), CD002831. https://doi.org/10.1002/14651858.CD002831.pub2.