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## Research Article

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# Subjective well-being in early-phase schizophrenia patients using long-acting injectable versus oral antipsychotic drugs: Data from the European Long-acting Antipsychotics in Schizophrenia Trial (EULAST)

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## Abstract

**Background.** This analysis evaluated potential differences in subjective well-being (SW) among patients with early-phase schizophrenia (SZ) randomized to treatment with either long-acting injectable (LAI) or oral aripiprazole or paliperidone within the "European Long-acting Antipsychotics in Schizophrenia Trial" (EULAST).

**Methods.** A total of 478 patients were followed for up to 19 months. SW was measured using the Subjective Well-being under Neuroleptic Treatment scale (SWN). Linear mixed-effects models assessed treatment differences. Comprehensive analyses included age, sex, symptomatology (Positive and Negative Syndrome Scale [PANSS]), and side effects (Systematic Monitoring of Adverse Events Related to Treatments [SMARTS] and St. Hans rating scale [SHRS] for extrapyramidal syndromes) on SWN changes.

**Results.** Overall, SW improved over the course of the study. No significant differences emerged between LAI and oral administration ($p = 0.1533$) or between aripiprazole and paliperidone ($p = 0.2008$). Similarly, age and sex were not relevant in this regard. In contrast, negative, positive, and affective symptoms (all $p < 0.0001$) as well as the overall side effect burden (SMARTS sum-score, $p < 0.0001$) showed significant inverse associations with SW. Certain SHRS subscales correlated with SW in partial models, but associations disappeared in the fully adjusted model.

**Conclusions.** Patients with SZ initiating LAI or oral treatment with aripiprazole or paliperidone reported comparable SW improvements. Findings emphasize that treatment choice should be guided less by formulation or substance and more by individual patient needs, prioritizing symptom control while minimizing adverse effects. A patient-centered approach remains essential to optimize both clinical outcomes and subjective well-being in early-phase SZ.

## Introduction

The prevalence of psychotic disorders in the European Union is estimated at 1.2%, affecting around five million people [1]. Achieving personal recovery in schizophrenia (SZ) involves symptomatic remission, subjective well-being (SW), and psychosocial outcomes including quality of life (QOL) – key factors for adherence to antipsychotic maintenance therapy [2–4]. However, currently available antipsychotics lead to full remission in only 30% of patients, with 20–30% demonstrating drug resistance. This highlights a significant unmet need [5] and makes SZ one of the top 20 most disabling diseases globally [6].

SZ imposes a substantial economic burden requiring extensive healthcare services [7]. In 2010, the disorder's total cost in Europe was estimated at €29 billion [8]. Indirect costs resulting from reduced productivity, caregiver burden, and premature mortality account for 44% of this total [9]. Improving adherence to antipsychotic maintenance therapy is crucial for reducing these costs and enhancing patient care [10], and clearly, SW during treatment plays a critical role in this context [11–14].

Although SW partially overlaps with concepts such as QOL and personal recovery, it is more narrowly focused on self-reported assessments of one's mental functioning and emotional state, whereas QOL and personal recovery also encompass aspects of social connectedness and functioning [15, 16]. SW is closely tied to dopaminergic neuromodulation in the striatum

[17, 18], and as most antipsychotics target dopamine receptors, they often negatively impact SW at higher doses [19]. For example, in a positron emission tomography (PET) study by Kim et al. [20] a lower dopamine D2 receptor occupancy was associated with higher subjective well-being under neuroleptic treatment scale (SWN) [11] scores, though the SWN score did not show a significant correlation with the positive and negative syndrome scale (PANSS) [21] score. This suggests that minimizing D2 receptor occupancy by prescribing the lowest effective dose could enhance SW. Notably, early improvements in this area after treatment initiation are linked to better long-term outcomes [22–25], making it a key indicator of adherence and recovery [25–27].

Second-generation long-acting injectable antipsychotics (SGA-LAIs) represent an effective therapeutic option for the management of SZ, as their unique pharmacokinetics, reduced dosing frequency, and administration by healthcare providers promote treatment continuity compared to oral formulations [28–31]. While guidelines traditionally recommended SGA-LAIs for patients with poor adherence [32], they are increasingly considered for maintenance therapy in general and/or based on patient preference [22, 30, 32, 33]. Patients with early-phase SZ who often lack insight and acceptance of their condition [34] are particularly prone to poor adherence, high relapse rates, incomplete symptom remission [35], and self-harming behavior or suicide [36]. Although LAIs and oral antipsychotics show comparable efficacy, the former may offer advantages in this respect [37, 38] as well as in reducing mortality [36], and accordingly, they appear particularly suitable for patients with early-phase SZ.

In consideration of this, the current investigation sought to evaluate possible differences in SW changes in patients with early-phase SZ starting treatment with LAI or oral aripiprazole or paliperidone as part of the "European Long-acting Antipsychotics in Schizophrenia Trial" (EULAST) [39]. Using a series of linear mixed-effects models, we further investigate how demographics (age, sex), psychopathological symptom changes, and medication side effects contribute to SWN changes over the course of treatment. Additionally, we examine interaction effects between these variables and antipsychotic formulation (LAI versus oral) to explore potential differential treatment effects on SW.

## Methods

For a detailed description of the study design, the study population, and procedures performed, we refer to Winter-van Rossum et al. [39] and ClincalTrials.gov, trial number NCT02146547.

### *Study design and patient population*

The EULAST was a large-scale, open-label, randomized study conducted across 50 hospitals and psychiatric clinics in 15 European countries and Israel (2015–2020). The primary outcome was the time to all-cause discontinuation among patients assigned to an LAI versus oral antipsychotic treatment with aripiprazole or paliperidone over 19 months. Eligible participants were aged 18 or older, met Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV) criteria for SZ, and had an illness duration between 6 months and 7 years at study entry.

### *Procedures and clinical measurements*

Following written informed consent (visit 1), baseline assessment (visit 2) occurred within 10 days and participants were randomized (1:1:1:1) to LAI aripiprazole, LAI paliperidone, oral aripiprazole, or oral paliperidone. A 4-week cross-titration period transitioned patients from their pre-study antipsychotic to the study medication, adjusting to the optimal dose. Those assigned to LAI treatment first received oral medication. At the 4-week mark after study initiation (visit 3, month 1), the prestudy drug was discontinued and LAI patients received their first injection. Estimating all groups reached a steady state by 8 weeks after treatment initiation, an extensive evaluation (visit 4, week 8) was conducted, followed by assessments every 3–4 months. During the monthly visits between these expanded assessments, study evaluations were kept to a minimum. The data included in this report were collected during visit 2 and eight subsequent visits (visits 4, 5, 6, 7, 11, 15, 18, and 21). Visit 4 was performed 8 weeks after visit 2, with all subsequent visits taking place at a monthly interval.

#### Subjective well-being under neuroleptic treatment scale

The SWN [11] is a self-rating scale to evaluate SW over the past 7 days, with strong validity and reliability, and firmly established psychometric properties in SZ [40–42]. It comprises 20 items (10 positive, 10 negative) rated on a 1–6 Likert scale, yielding scores from 20 (poor well-being) to 120 (good well-being). A score ≥80 indicates adequate well-being, while scores <80 suggest poor well-being [27, 43, 44]. Initially, the SWN has been designed to assess subjective experience across five subscales (emotional regulation, self-control, physical and mental functioning, and social integration) [45]; however, subsequent research did not confirm this subscale structure [42, 46].

#### Systematic monitoring of adverse events related to treatments

The systematic monitoring of adverse events related to treatments (SMARTS) [47] is an expert-developed 11-item checklist asking patients to indicate whether they experience the following common side effects of antipsychotic drugs by circling them: parkinsonism, tremor, weight/appetite changes, sexual dysfunction, hyperprolactinemia, postural hypotension, sedation, akathisia, gastrointestinal issues, urinary symptoms, and affective/miscellaneous side effects. Patients can further indicate additional issues with an open-ended question. Example items are "Difficulties in your movement, such as shaking, stiffness, or muscle aches?" or "Problems with your concentration or memory?" Higher sum scores indicate a greater number and/or severity of adverse effects potentially related to medication.

#### St. Hans rating scale for extrapyramidal syndromes

The St. Hans rating scale (SHRS) for extrapyramidal syndromes [48] is a multi-dimensional rating scale designed to assess the severity of extrapyramidal symptoms, including parkinsonism (eight items), dyskinesia (eight items), akathisia (subjective/objective), and dystonia, each rated from 0 (absent) to 6 (severe). It represents an easy-to-complete, sensitive, valid, and reliable rating scale [48, 49].

#### Positive and negative syndrome scale

The positive and negative syndrome scale (PANSS) [21] is the most widely used expert-rated SZ symptom assessment tool [50], comprising 30 items rated from 1 (absent) to 7 (extreme). Analysis was based on the five-factor model by Marder et al. [51]: positive symptoms (PSs; items: P1, P3, P5, P6, N7, G1, G9, G12), negative symptoms (NSs; items: N1, N2, N3, N4, N6, G7, G16), disorganized thought (DT; items: P2, N5, G5, G10, G11, G13, G15), anxiety/depression (AD; items: G2, G3, G4, G6), and uncontrolled hostility/excitement (UHE; items: P4, P7, G8, G14). To provide

a comprehensive analysis regarding the final model, we followed the current European Psychiatric Association (EPA) guidance [52] for the NS dimension, including only the core NS items consistently loading on the negative factor (NS; items: N1, N2, N3, N4, N6). The other psychopathological dimensions, positive (PS; items: P1, P3, P5, G9), disorganized (DT; items: P2, N5, G11), excited (EX; items: P4, P7, G8, G14), and depressed (DEP; items: G2, G3, G6), were computed according to the factor model proposed by Wallwork et al. [53].

### Statistical analysis

For statistical analysis, *R* (version 4.4.1) and the *nlme* package (version 3.1–166) were used. The study population included the Intent-to-Treat (ITT) sample as defined in the protocol with the additional restriction that only the data of those patients were used for analysis who completed baseline SWN assessment. A linear mixed-effects analysis approach was employed for a series of models. All models included random intercepts for patients to account for repeated measurements within patients. Furthermore, the models were fitted using restricted maximum likelihood estimation, assuming a compound symmetry covariance matrix. Model estimates are reported as least-square means with standard errors, along with corresponding $t$ and $p$ values. For model comparison, we report Akaike Information Criterion and Bayesian Information Criterion. To address multiple comparisons, we applied the Benjamini-Hochberg correction procedure [54].

To estimate the causal effect of antipsychotic formulation, we first modeled SWN score changes over the study period (model 1.0) and then assessed differences between LAI and oral treatment groups (model 1.1) and drug types (aripiprazole/paliperidone, model 1.2). Furthermore, we evaluated whether treatment effects varied over time, thus including visit-by-formulation (model 1.1.1) and visit-by-drug (model 1.2.1) interaction terms. Possible formulation-by-drug interaction regarding SWN score changes was assessed with model 9, additionally providing a plot for visualization (Supplementary Figure S1).

Next, we investigated age (model 2.1), sex (model 2.2), psychopathological symptoms (PANSS dimensions, models 3.1–3.5), medication side effects (model 4.1), and severity of extrapyramidal syndromes (models 5.1–5.6) as potential effect modifiers, by including each dimension separately as a fixed effect. The impact of changes was analyzed, including interactions with treatment formulation for the PANSS dimensions (models 3.1.1–3.5.1), medication side effects (model 4.1.1), and severity of extrapyramidal symptoms (models 5.1.1–5.6.1) to explore whether symptom- and medication-related effects varied between LAI and oral treatments.

To account for shared variance and confounding effects, we developed multivariate models incorporating all variables from the respective scale (PANSS [model 6.1] and SHRS [model 7.1]) to minimize bias due to missing data and ensure a consistent analysis across different scales. Similarly, to the separated dimension model building procedure, we tested the formulation-by-symptom interactions (model 6.1.1 for PANSS, model 7.1.1 for SHRS). Because treatment assignment was randomized, confounding should be minimal. However, to increase precision and account for any imbalances, all multivariable models included age and sex as covariates.

Finally, a comprehensive model incorporating PANSS Marder factors, SHRS, SMARTS, age, and sex was developed (model 8), including the formulation-by-predictor interactions (model 8.1). These models allowed for an integrated evaluation of the most critical factors influencing changes in SW while controlling for confounders and shared variance. In line with model 8, we built model 10 including the PANSS NS dimension [52] and the PANSS factors according to Wallwork [53], and model 10.1 including the formulation-by-predictor interactions (Supplementary Table S2). Supplementary Table S1 depicts an overview of the variables included in each model.

## Results

### Sample characteristics

Demographics and clinical characteristics of the baseline study sample (visit 2) are provided in Table 1. A total of 478 patients of the EULAST study population were included in the ITT sample. The mean age was 30.7 years, 34% were female, and 81% were of white ethnicity. At visit 2, the mean SWN value was 79.7 (SD 19.2, 95% confidence interval [CI] [77.21, 82.19]) for the oral treatment group and 81.9 (SD 17.9, 95% CI [79.68, 84.12]) for the LAI treatment group, increasing to 95.4 (SD 16.7, 95% CI [91.81, 98.99]) for the oral group and 95.7 (SD 16.2, 95% CI [92.63, 98.77]) for the LAI treatment group at visit 21. T-test analyses revealed no statistically significant differences between both treatment groups and between types of drug within each treatment group. Mean PANSS total scores also did not differ significantly between groups, starting with 74.3 (SD 18.4, 95% CI [72.65, 75.95]) at baseline and declining to 52.9 (SD 15.1, 95% CI [50.73, 55.05]) at visit 21. Both groups experienced a reduction in sample size as the study progressed, starting with 249 (LAI) and 229 (oral) participants at visit 2 and dropping to 107 (LAI) and 83 (oral) by visit 21.

### SW during the study period

Over the course of treatment (visits 2–21), SWN scores did improve (Estimate = 11.14, 95% CI [9.46, 12.82]; $p < 0.0001$; model 1.0, Supplementary Table S2) and were overall comparable between LAI and oral treatment groups (Estimate = −1.314, 95% CI [−3.12, 0.49], $p = 0.1533$; model 1.1, Table 2). When considering the formulation-by-visit interactions, it becomes evident that after Benjamini-Hochberg correction there are differences at visits 4, 6, 11, and 15, indicating higher SWN improvements in the oral compared to the LAI group (model 1.1.1, Figure 1, Table 2).

The association between the assigned antipsychotic drug (aripiprazole/paliperidone) and SWN change did not differ over the study period (Estimate = −1.173, 95% CI [−2.97, 0.62], $p = 0.2008$; model 1.2, Table 2); however, when analyzing the drug-by-visit interactions, results indicated greater SWN improvements at visit 4 in patients treated with aripiprazole (model 1.2.1, Figure 2, Table 2). Analyzing the formulation-by-drug interaction (model 9, Supplementary Table S2) did not reveal significant differences regarding SWN changes.

#### Age, sex, and changes in SW

Results neither indicated a relevant association of SW changes with age (Estimate = 0.021, 95% CI [−0.07, 0.11], $p = 0.6602$; model 2.1, Supplementary Table S2) nor between sexes (Estimate = −1.056, 95% CI [−2.95, 0.83], $p = 0.2737$; model 2.2, Supplementary Table S2).

#### Changes in psychopathology and changes in SW

Analyzing the influence of changes in the five PANSS dimensions on SWN change (models 3.1–3.5, Supplementary Table S2)

**Table 1.** Demographics and clinical characteristics of the overall ITT sample, oral and LAI formulation groups at study baseline (visit 2)

| Characteristic | N | Overall, *N* = 478 | Formulation | |
|---|---|---|---|---|
| | | | Oral, *N* = 229 | LAI, *N* = 249 |
| Age, years | 478 | **30.7** (9.7)/*28* (23, 36) | **31** (10.1)/*28* (23, 38) | **30.5** (9.4)/*28* (24, 36) |
| **Sex** | | | | |
| Female | | 164/478 (34.3%) | 70/229 (30.6%) | 94/249 (37.8%) |
| Male | | 314/478 (65.7%) | 159/229 (69.4%) | 155/249 (62.2%) |
| **Ethnicity** | | | | |
| Asian | | 19/478 (4.0%) | 12/229 (5.2%) | 7/249 (2.8%) |
| Black | | 31/478 (6.5%) | 12/229 (5.2%) | 19/249 (7.6%) |
| Other | | 41/478 (8.6%) | 23/229 (10.0%) | 18/249 (7.2%) |
| White | | 387/478 (80.9%) | 182/229 (79.6%) | 205/249 (82.4%) |
| **SWN** | | | | |
| SWN total score | 478 | **80.8** (18.5)/*81.5* (66.1, 96) | **79.7** (19.2)/*81* (64, 95) | **81.9** (17.9)/*82* (68, 97) |
| **SMARTS** | | **1.68** (2.16)/*1* (0, 3) | **1.59** (2.07)/*1* (0, 3) | **1.76** (2.24)/*1* (0, 3) |
| Any side effects | | 259/472 (54.9%) | 122/227 (53.7%) | 137/245 (55.9%) |
| No side effects | | 213/472 (45.1%) | 105/227 (46.3%) | 108/245 (44.1%) |
| **SHRS parkinsonism** | | **1.91** (4.75)/*0* (0, 1) | **1.61** (3.91)/*0* (0, 1) | **2.17** (5.38)/*0* (0, 2) |
| Absent | | 254/360 (70.6%) | 124/168 (73.8%) | 130/192 (67.7%) |
| Present | | 106/360 (29.4%) | 44/168 (26.2%) | 62/192 (32.3%) |
| **SHRS dystonia** | | **0.08** (0.42)/*0* (0, 0) | **0.05** (0.29)/*0* (0, 0) | **0.11** (0.51)/*0* (0, 0) |
| Absent | | 343/357 (96.1%) | 163/168 (97.0%) | 180/189 (95.2%) |
| Present | | 14/357 (3.9%) | 5/168 (3.0%) | 9/189 (4.8%) |
| **SHRS akathisia subjective** | | **0.35** (0.93)/*0* (0, 0) | **0.33** (0.91)/0 (0, 0) | **0.36** (0.95)/*0* (0, 0) |
| Absent | | 301/358 (84.1%) | 141/168 (83.9%) | 160/190 (84.2%) |
| Present | | 57/358 (15.9%) | 27/168 (16.1%) | 30/190 (15.8%) |
| **SHRS akathisia objective** | | **0.28** (0.81)/*0* (0, 0) | **0.32** (0.84)/*0* (0, 0) | **0.25** (0.78)/*0* (0, 0) |
| Absent | | 310/357 (86.8%) | 142/168 (84.5%) | 168/189 (88.9%) |
| Present | | 47/357 (13.2%) | 26/168 (15.5%) | 21/189 (11.1%) |
| **SHRS dyskinesia passive** | | **0.51** (1.86)/*0* (0, 0) | **0.55** (2.00)/*0* (0, 0) | **0.47** (1.73)/*0* (0,03) |
| Absent | | 319/360 (88.6%) | 148/168 (88.1%) | 171/192 (89.1%) |
| Present | | 41/360 (11.4%) | 20/168 (11.9%) | 21/192 (10.9%) |
| **SHRS dyskinesia active** | | **0.45** (1.75)/*0* (0, 0) | **0.54** (1.98)/*0* (0, 0) | **0.38** (1.52)/*0* (0, 0) |
| Absent | | 323/360 (89.7%) | 148/168 (88.1%) | 175/192 (91.1%) |
| Present | | 37/360 (10.3%) | 20/168 (11.9%) | 17/192 (8.9%) |
| PANSS total score | 478 | **74.1** (18.3)/*73* (62, 87) | **74.5** (18.9)/*73* (62, 87) | **73.7** (17.8)/*73* (62, 84) |
| PANSS negative symptoms (MF) | 478 | **19.4** (6.8)/*19* (15, 24) | **19.5** (6.7)/*19* (15, 24) | **19.3** (6.9)/*19* (14, 24) |
| PANSS positive symptoms (MF) | 478 | **21.3** (6.7)/*21* (16, 26) | **21.5** (7.1)/*21* (17, 27) | **21.3** (6.5)/*21* (16, 26) |
| PANSS disorganized thoughts (MF) | 478 | **16.2** (5.1)/*16* (12, 20) | **16.1** (5.2)/*16* (12, 20) | **16.2** (5.0)/*16* (12, 19) |
| PANSS uncontrolled hostility/excitement (MF) | 478 | **7.1** (3.1)/*6* (4, 9) | **7.3** (3.2)/*6* (4, 9) | **7.0** (3.0)/*6* (5, 9) |
| PANSS anxiety/depression (MF) | 478 | **10.0** (3.7)/*10* (7, 12) | **10.2** (3.6)/*10* (8, 13) | **9.9** (3.8)/*10* (7, 12) |
| PANSS negative (EPA) | 478 | **14.4** (5.4)/*14* (10.2, 18) | **14.6** (5.2)/*15* (11, 18) | **14.3** (5.5)/*14* (10, 18) |
| PANSS positive (Wallwork) | 478 | **10.7** (4.3)/*10* (7, 14) | **10.8** (4.4)/*10* (7, 13) | **10.7** (4.2)/*10* (8, 14) |
| PANSS disorganized (Wallwork) | 478 | **8.1** (2.8)/*8* (6, 10) | **8.1** (2.8)/*8* (6, 10) | **8.1** (2.8)/*8* (6, 10) |

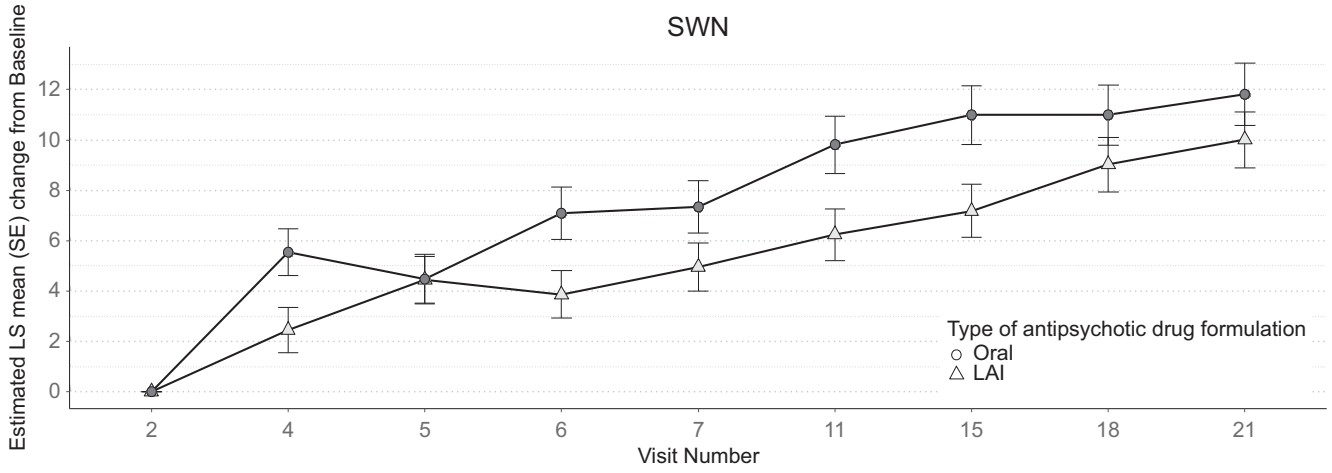
*Continued*

**Table 1.** *Continued*

| Characteristic | N | Overall, *N* = 478 | Formulation | |
|---|---|---|---|---|
| | | | Oral, *N* = 229 | LAI, *N* = 249 |
| PANSS excited (Wallwork) | 478 | **7.1** (3.1)/*6* (4.25, 9) | **7.3** (3.2)/*6* (4, 9) | **7.0** (3.0)/*6* (5, 9) |
| PANSS depressed (Wallwork) | 478 | **7.6** (3.1)/7 (5, 10) | **7.7** (3.0)/*7* (5, 10) | **7.6** (3.1)/7 (5, 9) |

Abbreviations: SD, standard deviation; CI, confidence interval; EPA, European Psychiatric Association; LAI, long-acting injectable; MF, Marder factor; SWN, subjective well-being under neuroleptic treatment scale; SMARTS, systematic monitoring of adverse events related to treatments; SHRS, St. Hans rating scale for extrapyramidal syndromes; PANSS, positive and negative syndrome scale.

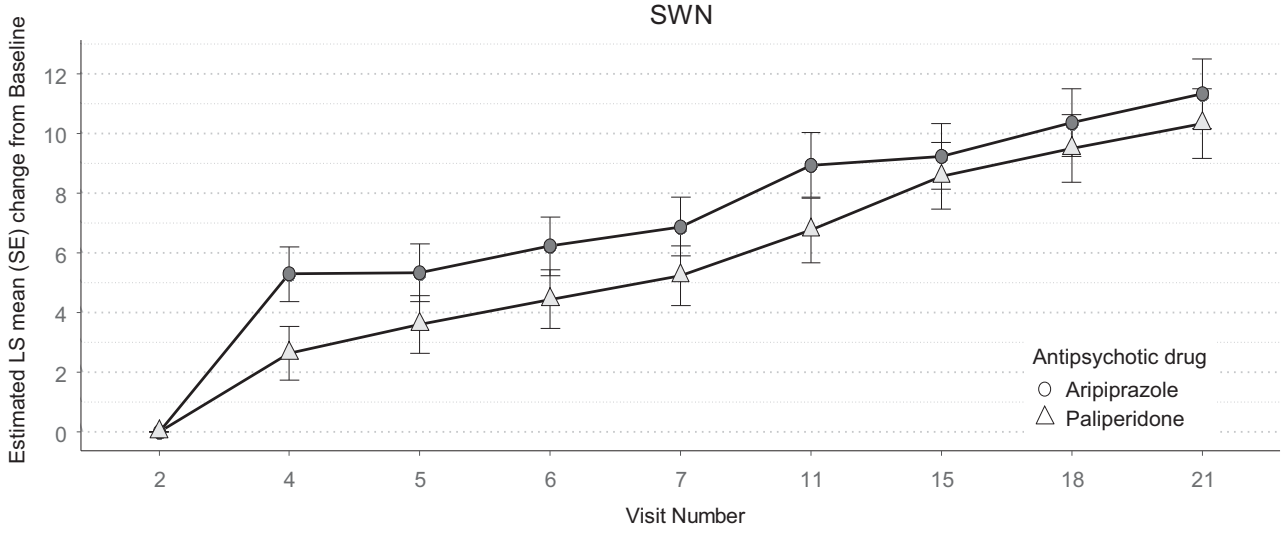
*Note:* Descriptive statistics for age, sex, ethnicity, SWN, SMARTS, SHRS and PANSS dimensions (Marder et al., Wallwork et al., and EPA guidance) for ITT sample at baseline (visit 2) for overall study population, oral and LAI formulation group. Data are presented as **mean** (standard deviation) and *median* (25th and 75th percentiles) for continuous variables and as frequency (percentage) for categorical variables. Additionally, frequency (percentage) is also reported for SHRS and SMARTS, despite being continuous variables.




Sample size (n) per visit and type of antipsychotic drug formulation

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| LAI | 249 | 188 | 170 | 164 | 154 | 133 | 122 | 116 | 107 |
| Oral | 229 | 176 | 149 | 132 | 130 | 104 | 95 | 89 | 83 |

**Figure 1.** Estimated least squares mean change in subjective well-being as measured by the subjective well-being under neuroleptic treatment scale from visits 2 to 21 among patients treated with long-acting injectable or oral antipsychotic drugs.




Sample size (n) per visit and type of antipsychotic drug

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Paliperidone | 241 | 186 | 158 | 148 | 139 | 118 | 107 | 101 | 93 |
| Aripiprazole | 237 | 178 | 161 | 148 | 145 | 119 | 110 | 104 | 97 |

**Figure 2.** Estimated least squares mean change in subjective well-being as measured by the subjective well-being under neuroleptic treatment scale from visits 2 to 21 among patients treated with aripiprazole or paliperidone.

**Table 2.** Results of the linear mixed-effects models for predicting the subjective well-being under neuroleptic treatment scale score

| Model | | Predictor | Timepoint | Estimate | SE | df | *t*-value | *p*-value | $p_{BH}$-value | BIC | AIC | *n* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Formulation | 1.1 | LAI versus oral (ref.) | main effect | −1.314 | 0.919 | 475 | −1.4301 | 0.1533 | – | 19,812.81 | 19,777.73 | 478 |
| Formulation × visit (interaction) | 1.1.1 | LAI versus oral (ref.) | Visit 2 | 0.597 | 1.142 | 475 | 0.522 | 0.6017 | 0.6351 | 19,624.77 | 19,496.27 | 478 |
| | | LAI versus oral × visit 4 | Visit 4 | −3.675 | 1.370 | 2068 | −2.682 | 0.0074 | 0.0117 | | | |
| | | LAI versus oral × visit 5 | Visit 5 | −0.629 | 1.435 | | −0.438 | 0.6614 | 0.6614 | | | |
| | | LAI versus oral × visit 6 | Visit 6 | −3.818 | 1.474 | | −2.590 | 0.0097 | 0.0131 | | | |
| | | LAI versus oral × visit 7 | Visit 7 | −2.980 | 1.492 | | −1.997 | 0.0459 | 0.0582 | | | |
| | | LAI versus oral × visit 11 | Visit 11 | −4.162 | 1.594 | | −2.611 | 0.0091 | 0.0131 | | | |
| | | LAI versus oral × visit 15 | Visit 15 | −4.408 | 1.643 | | −2.683 | 0.0073 | 0.0117 | | | |
| | | LAI versus oral × visit 18 | Visit 18 | −2.567 | 1.678 | | −1.530 | 0.1261 | 0.1498 | | | |
| | | LAI versus oral × visit 21 | Visit 21 | −2.391 | 1.721 | | −1.389 | 0.1650 | 0.1844 | | | |
| Antipsychotic drug | 1.2 | Paliperidone versus aripiprazole (ref.) | Main effect | −1.173 | 0.915 | 475 | −1.281 | 0.2008 | - | 19,813.22 | 19,778.14 | 478 |
| Antipsychotic drug × visit (interaction) | 1.2.1 | Paliperidone versus aripiprazole (ref.) | Visit 2 | 0.436 | 1.142 | 475 | 0.3815 | 0.7030 | 0.7030 | 19,636.18 | 19,507.68 | 478 |
| | | Paliperidone versus aripiprazole × visit 4 | Visit 4 | −3.083 | 1.373 | 2068 | −2.245 | 0.0249 | 0.0430 | | | |
| | | Paliperidone versus aripiprazole × visit 5 | Visit 5 | −2.187 | 1.437 | | −1 to 522 | 0.1281 | 0.1774 | | | |
| | | Paliperidone versus aripiprazole × visit 6 | Visit 6 | −2.225 | 1.472 | | −1.552 | 0.1307 | 0.1774 | | | |
| | | Paliperidone versus aripiprazole × visit 7 | Visit 7 | −2.089 | 1.492 | | −1.400 | 0.1616 | 0.2047 | | | |
| | | Paliperidone versus aripiprazole × visit 11 | Visit 11 | −2.634 | 1.589 | | −1.657 | 0.0976 | 0.1545 | | | |
| | | Paliperidone versus aripiprazole × visit 15 | Visit 15 | −1.093 | 1.638 | | −0.667 | 0.5048 | 0.5328 | | | |
| | | Paliperidone versus aripiprazole × visit 18 | Visit 18 | −1.299 | 1.672 | | −0.777 | 0.4373 | 0.4887 | | | |
| | | Paliperidone versus aripiprazole × visit 21 | Visit 21 | −1.441 | 1.716 | | −0.840 | 0.4010 | 0.4762 | | | |
| SMARTS (univariate) | 4.1 | LAI versus oral (ref.) | Main effect | −1.070 | 0.906 | 473 | −1.182 | 0.2377 | - | 19,601.17 | 19,560.27 | 476 |
| | | SMARTS | | −1.749 | 0.159 | 2072 | −10.997 | <0.0001 | - | | | |
| PANSS [Marder factors] (multivariable) | 6.1 | LAI versus oral (ref.) | Main effect | −1.112 | 0.808 | 472 | −1.377 | 0.1691 | 0.2114 | 19,130.24 | 19,054.24 | 477 |
| | | PANSS negative symptoms [MF] | | −0.547 | 0.053 | 2075 | −10.314 | <0.0001 | <0.0001 | | | |
| | | PANSS positive symptoms [MF] | | −0.214 | 0.058 | | −3.672 | 0.0002 | 0.0005 | | | |
| | | PANSS disorganized Thought [MF] | | −0.211 | 0.086 | | −2.457 | 0.0141 | 0.0235 | | | |
| | | PANSS uncontrolled hostility/ excitement [MF] | | 0.178 | 0.126 | | 1.417 | 0.1566 | 0.2114 | | | |
| | | PANSS anxiety/depression [MF] | | −1.248 | 0.092 | | −13.502 | <0.0001 | <0.0001 | | | |
| | | Age | | −0.011 | 0.042 | 472 | −0.251 | 0.8019 | 0.8019 | | | |
| | | Sex (male vs. female [ref.]) | | −0.414 | 0.869 | | −0.477 | 0.6338 | 0.7043 | | | |

*Continued*

**Table 2.** *Continued*

| Model | | Predictor | Timepoint | Estimate | SE | df | *t*-value | *p*-value | $p_{BH}$-value | BIC | AIC | *n* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SHRS (multivariable) | 7.1 | LAI versus oral (ref.) | Main effect | −1.450 | 1.012 | 419 | −1.432 | 0.1529 | 0.2803 | 16,446.43 | 16,367.19 | 424 |
| | | SHRS-dystonia | | 0.217 | 0.911 | 1693 | 0.239 | 0.8114 | 0.8114 | | | |
| | | SHRS-akathisia (subjective) | | −1.768 | 0.500 | | −3.534 | 0.0004 | 0.0012 | | | |
| | | SHRS-akathisia (objective) | | 0.180 | 0.650 | | 0.277 | 0.7817 | 0.8114 | | | |
| | | SHRS-dyskinesia (passive) | | 0.352 | 0.432 | | 0.816 | 0.4149 | 0.5705 | | | |
| | | SHRS-dyskinesia (active) | | −0.134 | 0.47 | | −0.284 | 0.7766 | 0.8114 | | | |
| | | SHRS-parkinsonism (total) | | −0.543 | 0.106 | | −5.106 | <0.0001 | <0.0001 | | | |
| | | Age | | 0.089 | 0.054 | 419 | 1.641 | 0.1016 | 0.2236 | | | |
| | | Sex (male versus female [ref.]) | | −1.006 | 1.085 | | −0.927 | 0.3542 | 0.5566 | | | |
| Final model [Marder factors] (multivariable) | 8 | LAI versus oral (ref.) | Main effect | −1.057 | 0.897 | 418 | −1.178 | 0.2395 | 0.3701 | 15,887.52 | 15,774.59 | 423 |
| | | PANSS negative symptoms [MF] | | −0.504 | 0.058 | 1676 | −8.739 | <0.0001 | <0.0001 | | | |
| | | PANSS positive symptoms [MF] | | −0.255 | 0.064 | | −3.983 | 0.0001 | 0.0002 | | | |
| | | PANSS disorganized Thought [MF] | | −0.143 | 0.094 | | −1.532 | 0.1257 | 0.2375 | | | |
| | | PANSS uncontrolled hostility/ excitement [MF] | | 0.355 | 0.143 | | 2.491 | 0.0129 | 0.0312 | | | |
| | | PANSS anxiety/depression [MF] | | −1.216 | 0.102 | | −11.872 | <0.0001 | <0.0001 | | | |
| | | SHRS dystonia | | 0.267 | 0.806 | | 0.331 | 0.7408 | 0.8995 | | | |
| | | SHRS akathisia (subjective) | | −0.708 | 0.445 | | −1.591 | 0.1118 | 0.2375 | | | |
| | | SHRS akathisia (objective) | | 0.128 | 0.575 | | 0.222 | 0.8245 | 0.9321 | | | |
| | | SHRS dyskinesia (passive) | | 0.044 | 0.382 | | 0.114 | 0.9092 | 0.9321 | | | |
| | | SHRS dyskinesia (active) | | −0.036 | 0.418 | | −0.085 | 0.9321 | 0.9321 | | | |
| | | SHRS parkinsonism (total) | | −0.119 | 0.097 | | −1.234 | 0.2175 | 0.3697 | | | |
| | | SMARTS | | −0.780 | 0.177 | | −4.398 | <0.0001 | <0.0001 | | | |
| | | Age | | 0.038 | 0.048 | 418 | 0.795 | 0.4270 | 0.6048 | | | |
| | | Sex (male versus female [ref.]) | | −0.699 | 0.962 | | −0.727 | 0.4679 | 0.6119 | | | |

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; df, degrees of freedom; n, sample size; SE, standard error; LAI, long-acting injectable; MF, Marder factor; SWN, subjective well-being under neuroleptic treatment scale; SMARTS, systematic monitoring of adverse events related to treatments; SHRS, St. Hans rating scale for extrapyramidal syndromes; PANSS, positive and negative syndrome scale; $p_{BH}$, Benjamini-Hochberg procedure corrected *p*-values.

revealed significant ($p < 0.0001$) associations for all dimensions, suggesting that a reduction in PANSS scores over time is associated with an improvement in SW. Concerning the formulation-by-dimension interaction for each dimension separately (models 3.1.1–3.5.1, Supplementary Table S2), results revealed stronger effects for NSs ($Estimate_{diff.} = 0.244$, 95% CI [0.058, 0.430]; $Estimate_{LAI} = -0.844$, $Estimate_{oral} = -1.088$), PSs ($Estimate_{diff.} = 0.378$, 95% CI [0.200, 0.556]; $Estimate_{LAI} = -0.629$, $Estimate_{oral} = -1.007$), and DT ($Estimate_{diff.} = 0.370$, 95% CI [0.107, 0.633]; $Estimate_{LAI} = -1.004$, $Estimate_{oral} = -1.374$; models 3.1.1, 3.2.1, 3.3.1) in the group treated with oral antipsychotics.

Evaluating the model including all PANSS dimensions, age, and sex (model 6.1, Table 2) confirmed associations between NS, PS, DT, and AD changes with SWN changes. Concerning the formulation-by-symptom interaction (model 6.1.1, Supplementary Table S2), differences ($Estimate_{diff.} = 0.355$, 95% CI [0.126, 0.584]) between LAI (Estimate = −0.052) and oral treatment (Estimate = −0.407) regarding the effect of changes in PS on changes in SWN score where apparent, indicating that in the oral antipsychotic group, greater reductions in positive symptoms are associated with larger improvements in SW.

Overall, there was a strong association between PANSS dimensions and SWN change throughout all models, especially for PS, NS, and AD.

### Side effects of medication and changes in SW

Exploring the influence of medication side effects as evaluated by the SMARTS on SWN change analyzed through the univariate model revealed that having more side effects was associated with lower SW over time (Estimate = −1.749, 95% CI [−2.50, −1.58], $p < 0.0001$; model 4.1, Table 2). This effect was comparable between treatment groups (model 4.1.1, Supplementary Table S2).

Analyzing the influence of the severity of extrapyramidal symptoms on SWN changes by including each SHRS subscale separately (models 5.1–5.6, Supplementary Table S2) revealed negative associations with subjective akathisia (Estimate = −1.872, 95% CI [−2.6, −1.14], $p < 0.0001$), objective akathisia (Estimate = −1.555, 95% CI [−2.10, −0.21], $p = 0.0013$), and parkinsonism (Estimate = −0.543, 95% CI [−0.73, −0.35], $p < 0.0001$). The formulation-by-dimension interaction for each subscale (models 5.1.1–5.6.1, Supplementary Table S2) was nonsignificant, suggesting that the impact of SHRS subscales on SWN changes was comparable across groups.

When evaluating the combined model by including all SHRS subscales, age, and sex (model 7.1, Table 2), subjective akathisia (Estimate = −1.768, 95% CI [−2.748, −0.788], $p_{BH} = 0.0012$) and parkinsonism (Estimate = −0.544, 95% CI [−0.751, −0.335], $p_{BH} < 0.0001$) remained predictors of changes in SWN scores. However, other SHRS subscales did not reach significance in the multivariate model, likely due to shared variance or the relative strength of subjective akathisia and parkinsonism effects. Possible formulation-specific differences in these associations (model 7.1.1, Supplementary Table S2) did not prove to be significant.

To summarize, the SMARTS sum-score and SHRS subscales parkinsonism and (subjective) akathisia appeared as predictors of SWN change in univariate as well as multivariate models with no differences between treatment groups.

### Comprehensive model explaining changes in SW

To assess the combined influence of all predictor variables on changes in SW, we estimated a comprehensive model (model 8, Table 2). Consistent with the multivariable PANSS model 6.1, improvements in NS, PS, and AD scores predicted higher SWN scores. Contrary to the previous results, DT was no longer a significant predictor. Furthermore, uncontrolled hostility/excitement (UHE) became a significant predictor (Estimate = 0.355, 95% CI [0.075, 0.635], $p_{BH} = 0.0321$), indicating that increasing scores were associated with improvements in SW.

Regarding the PANSS dimensions proposed by EPA and Wallwork, model 10 yielded similar patterns of associations regarding the NS, PS, and DEP dimensions. Contrary to model 8, the DT dimension was significantly associated with SW, indicating reductions in DT scores predict higher SWN scores. Moreover, the excitement dimension was not significantly associated with SW.

SMARTS continued to be associated with reduced SWN scores. However, in the comprehensive model, neither subjective akathisia nor parkinsonism (SHRS) remained significant predictors, potentially due to their shared variance with PANSS dimensions or SMARTS side effects. Evaluating model 8.1, including the formulation-by-predictor variables interaction, showed differences between LAI and oral treatment regarding NS ($Estimate_{diff.} = 0.257$, 95% CI [0.032, 0.482]; $Estimate_{LAI} = -0.371$; $Estimate_{oral} = -0.628$), and PS ($Estimate_{diff.} = 0.308$, 95% CI [0.057, 0.533]; $Estimate_{LAI} = -0.110$; $Estimate_{oral} = -0.418$), which did not remained after Benjamini-Hochberg correction. In model 10.1, which includes the PANSS dimensions according to EPA and Wallwork, similar results were observed for negative symptoms. Different associations ($Estimate_{diff.} = 0.308$, 95% CI [0.038, 0.578]) were found for LAI (Estimate = −0.424) and oral (Estimate = −0.732) treatment. However, after applying Benjamini-Hochberg correction, no differences remained.

## Discussion

This analysis did not reveal relevant differences over the study period in the effect of LAI versus oral antipsychotic treatment and between treatment with aripiprazole or paliperidone on changes in SW, suggesting similar subjective tolerability. This supports earlier findings from Vothknecht et al. [44], who reported improved SW across most SZ treatments with dosage playing a more critical role than the type of antipsychotic.

Previous studies indicate that striatal dopamine D2 receptor occupancy rates between 60% and 70% are associated with improved SW compared higher occupancy rates, which are often associated with more dose-dependent side effects [55, 56]. As reported by Winter-van Rossum et al. [39], EULAST drug dosages and plasma levels were in the low-to-medium range according to therapeutic drug monitoring guidelines [57], potentially contributing to the overall high SW in study participants. However, precise dopamine D2 receptor occupancy data were unavailable, as PET was not performed.

In general, LAIs can improve treatment adherence via easier monitoring as missed injections, indicating a lack of adherence, are readily detected at an early stage. In addition, their prolonged half-lives delay relapse, providing more time to recommence treatment [28–31]. However, in randomized controlled trials like the EULAST where adherence is monitored, LAI benefits may be less pronounced than in real-world settings, emphasizing the impact of the research design on treatment outcomes [58]. In this respect, we cannot rule out the possibility that comparing the impact of LAI and oral antipsychotic treatment on SW in an observational study would have led to different results.

Age and sex did not significantly impact SWN changes, which corroborates the findings of previous studies [16, 43, 50]. However, other research suggests that older individuals may report greater

well-being due to evolving coping strategies and acceptance of limitations among other factors [59–61].

A strong inverse relationship was observed between symptom severity and SW, reinforcing earlier findings [24, 25, 27, 62, 63]. The positive correlation between increasing scores in UHE and higher SWN scores over time may be a chance finding, which will have to be tested in future controlled clinical trials.

As expected and in line with the findings of previous studies [26, 63–65], medication side effects, particularly extrapyramidal symptoms, negatively impacted SW. Significant negative correlations were observed between both akathisia and parkinsonism and SWN scores, indicating that these symptoms are strong predictors of treatment satisfaction as extrapyramidal symptoms may impair daily functioning and QOL [2, 66] and thereby increase the risk of treatment discontinuation [67].

Concerning the differences between oral and LAI treatment regarding the effect of changes in positive symptoms on changes in SWN scores, patients receiving oral treatment may experience greater fluctuations in symptoms, making improvements more noticeable in their subjective well-being. On the other hand, those treated with LAIs, having a more stable medication delivery, may not experience as pronounced SW changes despite symptom improvement. If oral formulations have a stronger effect on SW through symptom reduction, there may be a mediation pathway where PANSS symptom reduction mediates the effect of treatment formulation on SWN.

There are several strengths and limitations to this study. As a major advantage, the pragmatic and naturalistic study design of EULAST attempted to capture more real-world clinical conditions and the large patient population allowed for sufficient power in detecting small effect sizes in statistical analysis. However, regarding the study sample, predictive SWN cutoff scores classify patients into stable high (SWN > 80) and stable low (SWN < 60) clusters, which aid in early outcome prediction and treatment planning [43, 44]. Accordingly, the EULAST study population was on average already attributable to the stable high cluster at baseline (mean SWN value of 80.8), which is also complemented by a generally low level of symptoms at this time (mean PANSS total score of 74.1). This clearly limits the generalizability of our findings, as more severely ill patients with a lower baseline level of SW did not participate in this study. It also remains unclear to what extent our findings apply to SZ patients with a longer duration of illness and whether various personal characteristics, including personality traits, cognitive abilities, self-esteem, and neurobiological factors known to influence SW alongside environmental and therapeutic factors [62, 68, 69], may have impacted our findings. However, as these factors were not analyzed as part of the EULAST, their potential effect on our results cannot be assessed. Also due to the naturalistic study design, oral and LAI medication dosages were not dose equivalent and therefore not directly comparable, but rather oriented more closely to common dosages implemented in clinical practice. Furthermore, the five-factor model by Marder et al. (M5M) is currently under discussion, and a 2025 review of the Marder factor solution and other factor models concluded that due to insufficient structural validity the M5M should not be used [70]. However, other models, such as that of Wallwork et al. [53], require further evaluation. For this reason, it has been recommended to continue taking into account the results achieved with the M5M [70]. In line with this, we report our analyses according to the M5M as well as to the model proposed by Wallwork et al., applying the EPA guidance, which yielded similar results. With respect to subjective well-being, the negative factor of the PANSS focuses more on the patient's behavior, thereby neglecting internal experiences, which are a substantial element influencing subjective well-being [16].

Our analysis followed an ITT approach as outlined in the study protocol. Since then, the ICH E9(R1) addendum on estimands and sensitivity analyses [71] has been published, providing a structured framework for defining treatment effects in clinical trials. This highlights the importance of specifying an estimand aligned with the study objective, particularly in handling intercurrent events such as treatment discontinuation or nonadherence. While our analysis was not explicitly aligned with a specific strategy, the linear mixed-effects model included all available data at each assessment. Under a missing at random (MAR) assumption, this corresponds to a hypothetical strategy, estimating effects as if intercurrent events had not occurred. If missingness was not MAR (e.g., dropout due to treatment-related factors), the analysis aligns more with a while-on-treatment strategy, estimating effects only for those who remained in the study. Depending on the objective, alternative strategies – such as a treatment policy or while-on-treatment approach – could have enhanced interpretability of treatment effects.

Analyses of self-report questionnaire data in schizophrenia research may also benefit from the SISAQOL-IMI guidelines [72], which offer methodological recommendations for patient-reported outcomes (PROs). Given the relapsing nature of schizophrenia, treatment changes are common and can affect PROs. However, our main study [39] found no difference in discontinuation rates between LAI and oral treatments, suggesting that adherence may be also influenced by factors like treatment response, side effects, or patient preference. Future studies should apply the estimand framework to PROs for more accurate interpretation of LAI and oral treatment effects on SW and long-term outcomes.

To summarize, our findings do not allow for a clear treatment recommendation statement but rather demand a patient-centered approach. A collaborative psychosocial process, including extensive education on the disease and possible benefits of LAIs, as well as the inclusion of patients and family members in treatment decisions and choice of antipsychotic medication based on individual needs are critical to achieve optimal clinical outcomes [37, 39, 73, 74]. Notably, family psychoeducation has been shown to significantly reduce relapse rates [75, 76], and multifamily group psychoeducation in addition to antipsychotic medication leads to an approximate increase of 100% in effect size compared to medication alone [75, 76]. A patient-centered approach including a broad support network, extensive disease education, and a process of shared decision-making can empower patients to impact and improve subjective well-being, QOL, and personal recovery during all stages of the illness [77, 78].

In conclusion, our findings highlight the complex and multifaceted nature of personal recovery in SZ, wherein advancements in SW hinge upon effective symptom management, the tolerability of side effects, and the adaptability to meet individual patient needs. By aligning therapeutic strategies with these insights, clinicians are better positioned to support treatment adherence, mitigate the risk of relapse, and facilitate enduring recovery.

**Supplementary material.** The supplementary material for this article can be found at http://doi.org/10.1192/j.eurpsy.2025.10086.

**Data availability statement.** A request for receipt of the study data, the data dictionary, study protocol, and informed consent can be submitted for review and approval by the Study Management Group, through the corresponding author.

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