Schizophrenia Research 288 (2026) 38–46

Contents lists available at ScienceDirect

Schizophrenia Research

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

Pharmacokinetic correlates of clinical response in a retrospective naturalistic cohort of patients treated with long-acting injectable antipsychotics

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ARTICLE INFO

Keywords:
Long-acting injectable antipsychotics
Therapeutic drug monitoring
Treatment response
Pharmacokinetics
Schizophrenia

ABSTRACT

Objective: To investigate the pharmacokinetic correlates of clinical response to long acting injectable (LAI) antipsychotics in a naturalistic outpatient sample.
Methods: We conducted a retrospective cohort study of LAI-treated outpatients. Steady-state trough antipsychotic plasma concentrations were classified as subtherapeutic, within, or supratherapeutic based on established therapeutic reference ranges (TRRs). Clinical response was defined as Clinical Global Impression Improvement score ≤ 2. Generalized linear mixed models were used to analyze predictors of treatment response.
Results: In a total of 158 LAI-treated outpatients, responders (42.4 %) were significantly younger (50.5 vs. 55.6 years, $p = 0.002$) and more often treated with monotherapy (64.2 % vs. 44.0 %, $p = 0.01$). Half of the responders (51.1 %) had antipsychotic levels below the TRR (51.1 %), and 42.2 % had levels within TRR, while there were no responders with supratherapeutic concentrations ($p = 0.01$). After controlling for age, sex, body mass index, smoking, LAI monotherapy, and symptom severity, patients with subtherapeutic plasma concentrations (adjusted odds ratio (aOR): 31.97, 95 % confidence interval (CI): 1.74–588.55, $p = 0.02$) and with levels within the TRR (aOR: 23.01, 95 % CI: 1.28–414.48, $p = 0.03$) had higher probability of treatment response compared to those with supratherapeutic concentrations, while these estimates were limited by the small group size ($n = 9$). Younger age (aOR: 0.97, 95 % CI: 0.94–0.99, $p = 0.04$) and LAI monotherapy (aOR = 3.77, 95 % CI = 2.19–6.51, $p = 0.001$) were associated with better treatment response.
Conclusions: Assessing antipsychotic concentrations combined with clinical characteristics such as LAI monotherapy and age may be useful for guiding pharmacotherapy with LAIs.

1. Introduction

The development of long-acting injectable (LAI) antipsychotics has marked a significant advancement in the pharmacological treatment of schizophrenia and other psychotic disorders (Brissos et al., 2014). Since the introduction of first-generation LAI antipsychotics in the 1960s with fluphenazine enanthate, the field has evolved substantially with LAI formulations of second-generation antipsychotics in the 2000s as well as third-generation compounds in recent years being available (VandenBerg, 2022). LAI formulations employ various approaches to

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https://doi.org/10.1016/j.schres.2025.12.012
Received 16 July 2025; Received in revised form 9 December 2025; Accepted 15 December 2025
Available online 23 December 2025

achieve sustained drug release, such as highly lipophilic salt complexes, biodegradable microspheres, or nanocrystals enabling extended release through altered dissolution properties (Lee et al., 2019), or leveraging a prodrug biotransformation mechanism (Hard et al., 2017). Compared to oral formulations, LAIs are associated with an improved treatment adherence, lower rates of treatment discontinuation, relapse, and hospitalization, as well as enhanced functioning and quality of life (Aprile et al., 2025; Rubio et al., 2020). Moreover, unlike oral formulations requiring daily administration and producing marked peak-to-trough fluctuations, LAI antipsychotics exhibit distinct absorption and distribution patterns (Schoretsanitis et al., 2021a). Nevertheless, pharmacokinetic knowledge from oral formulations is frequently extrapolated to LAIs (Samtani et al., 2016).

Therapeutic drug monitoring (TDM) currently represents a cornerstone of personalized medicine in psychiatry, enabling clinicians to optimize pharmacotherapy based on drug bioavailability (Hart et al., 2024). Through measurement of drug concentrations in biological fluids, typically blood serum or plasma, TDM facilitates the assessment of pharmacokinetic variability among patients, assessing the relationship between drug exposure and clinical effects (Hiemke et al., 2018). The use of TDM is based on a so-called therapeutic reference range (TRR), which refers to blood concentration ranges of medications that are associated with the optimal balance between effectiveness and safety outcomes (Grundmann et al., 2014).

Despite the distinct pharmacokinetics of LAI antipsychotics compared to their oral counterparts, the clinical role of TDM in LAI antipsychotic therapy remains largely unexplored. This is particularly noteworthy given that pharmacokinetic data are part of approval processes for LAI antipsychotics (Harlin et al., 2023; Kramer et al., 2010; Si et al., 2014). Moreover, TDM is well-established for oral antipsychotics, with defined therapeutic reference ranges and dose adjustment protocols (Hiemke et al., 2018). The use of TDM for LAI formulations in the clinical routine is currently more or less limited to switching an oral antipsychotic to its LAI formulation and vice versa (Schoretsanitis et al., 2021a). An emerging volume of studies has begun to explore the role of TDM in LAI antipsychotics and its relationship to clinical outcomes (D'Anna et al., 2022; Schoretsanitis et al., 2021b, 2021c). D'Anna et al. (2022) investigated 48 patients with schizophrenia spectrum disorders under therapy with LAI formulation of aripiprazole, paliperidone or olanzapine. Ten patients relapsed, and it was found that subtherapeutic concentrations of the drugs in blood were predictive for relapse. Zipursky et al. (2025) found in 21 patients that higher plasma levels paliperidone were associated with elevated prolactin levels and reduced sexual desire (Zipursky et al., 2025). The authors concluded that measurement of paliperidone levels in patients treated with paliperidone palmitate has the potential to minimize the dose of the antipsychotic medication prescribed and consequently the severity of sexual side effects. A few observational studies suggest that lower levels are achieved during maintenance therapy than during acute therapy (Baldelli et al., 2017; Hýža et al., 2021). These few reports give evidence that monitoring drug levels has potential benefits during long-term maintenance treatment with LAI antipsychotics. For practical purposes, however, uncertain therapeutic reference ranges of LAI antipsychotics are a major limitation, as the target range is an essential parameter for the use of TDM.

Overall, the evidence remains surprisingly scarce, especially considering the prescription patterns of LAI antipsychotics (Verdoux et al., 2016) and the potential benefits of monitoring antipsychotic drug concentrations during the long-term maintenance treatment (Schoretsanitis et al., 2021a). Thus, there is a critical need to generate TDM data for LAI antipsychotics in context of clinical outcomes. The present study addressed the knowledge gaps by assessing pharmacokinetic parameters of various LAI antipsychotics under steady-state conditions and their association with treatment response in a retrospective cohort of outpatients in a real-world clinical setting.

2. Materials and methods

Reporting adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Cuschieri, 2019) (Supplementary table 1).

2.1. Population and study design

The study was performed as a retrospective observational cohort study of psychiatric patients treated in 10 outpatient services of the Department of Psychiatry (SABES-ASDAA), Teaching Hospital of Medical University of Innsbruck, Innsbruck, Austria, and the Paracelsus Medical Private University (PMU), Bolzano, Italy, between November 2021 and June 2023. The data for this study was obtained through the standardized extraction using medical record from the hospital management system, ensuring comprehensive and accurate collection of relevant patient information. Patients treated with LAI antipsychotics were included in the study. Patients without plasma concentration assessments were excluded. We also excluded patients receiving comedication with the oral counterpart of the LAI to ensure that the assessed pharmacokinetic parameters solely reflected LAI pharmacokinetics. Further, we excluded patients treated with clozapine, i.e. patients with treatment-resistant schizophrenia, where response to antipsychotics needs to be investigated separately. The use of TDM followed various clinical reasons, e.g. management of adverse drug-related reactions (ADR), adherence assessment or suspected drug-drug interactions (Kuzin et al., 2023a, 2023b; Schoretsanitis et al., 2023). The retrospective analysis of clinical data was in accordance with the 1964 Declaration of Helsinki and its later amendments and was waived by the local regulatory authority of RWTH Aachen University hospital, Aachen, Germany. For this type of study, no formal patient consent was required.

2.2. Quantification of antipsychotics

Blood sampling was performed to assess trough concentration at a steady state (> 9 elimination half-lives under the same drug dose of LAI) (Schoretsanitis et al., 2021c). Trough concentration was defined as the concentration of drug in blood immediately before the next dose administration (McCoy and Cipolle, 1983). Patients whose LAI plasma concentration was measured outside of a trough condition were excluded. Blood samplings performed up to 25 % of the respective LAI application interval earlier were tolerated. Median deviation from the trough concentration sampling timepoint was 0 days with interquartile range (IQR) of 0 to 3 days and median sampling time precision of 100 % (IQR 90 % – 100 %).

Serum concentrations of antipsychotic drugs were assessed by ultra performance liquid chromatography coupled with a triple-quadrupole mass spectrometer (ACQUITY UPLC I-Class Xevo TQ-S micro, Waters) using a commercially available kit (MassTox Neuroleptics 1/EXTENDED and Neuroleptics 2/EXTENDED2, Chromsystems, Munich, Germany), following the manufacturers' protocol. Briefly, 50 µl of human serum sample were mixed with 25 µl of extraction buffer. After vortexing, 250 µl of a mixture, composed by the internal standard and the precipitation reagent (ratio 1:15), was added. The solution was then vortexed again before centrifuging for 5 min. The supernatant was then diluted at 1:40 (NL1: aripiprazole, haloperidol, olanzapine, risperidone, and 9-OH-risperidone) and 1:10 (NL2: zuclopenthixol), respectively, and 20 µl of NL1 sample or 40 µl of NL2 sample were injected into the HPLC system. A 3-point calibration curve using Chromsystems calibrator standards allowed for the quantification of each drug. The analysis of internal QC (MassCheck Neuroleptics 1/EXTENDED 1 Plasma Controls and MassChec Neuroleptics 2/EXTENDED 2 Plasma Controls, Chromsystems) was within acceptable limits. LC-MS/MS analyses were performed in an ISO 15189 accredited laboratory that participates in the INSTAND external quality assessment scheme.

2.3. Statistical analysis

Continuous variables are presented as median and IQR, and categorical variables as numbers and percentages as well as odds ratios with 95 % confidence interval (95 % CI). Normality and homogeneity of variance were assessed using the Shapiro Wilk test, and the Levene's test respectively. A 2-sided *p*-value of 0.05 was considered statistically significant. Holm-Bonferroni step-down multiple comparison correction procedure was performed when appropriate, ordering *p*-values from smallest to largest and comparing them to the iteratively adjusted threshold until first non-significant comparison. Different outpatient services were treated as separate recruitment sites. All analyses were performed with R (Chan, 2018). For the integrative clinical assessment, we used the Clinical Global Impression scales (Busner and Targum, 2007). Clinical Global Impression – Severity (CGI—S) scale is a 7-point clinician-rated instrument that measures the severity of illness, ranging from 1 ("not at all ill") to 7 ("among the most extremely ill"). Clinical Global Impression-Improvement (CGI-I) is a 7-point scale that assesses the change in patient's condition relative to baseline, where 1 represents "very much improved", and 7 represents "very much worse" (Busner and Targum, 2007). According to a local LAI treatment standard, baseline CGI-S assessment was performed systematically before or shortly after the initiation of the LAI treatment, while follow-up CGI-S as well as CGI-I scores were obtained at the timepoint of the blood sampling. Our primary outcome was CGI-I ratings. Parameters included in the analysis are listed in Tables 1–3.

2.3.1. Responders vs. non-responders

Patients were categorized as responders and non-responders and compared; clinical response was defined as CGI-I score ≤ 2 ("very much improved" or "much improved"). Daily doses of LAIs were calculated by dividing the injection doses by the number of the injection interval days (Schoretsanitis et al., 2018). For risperidone microspheres, the plasma concentration of the active moiety (the sum of the parent compound and the active metabolite) was used (Hiemke et al., 2018). Comparisons of continuous variables were performed using Mann-Whitney *U* test. Categorical variables were compared using Pearson's Chi-square test or Fisher's Exact, when appropriate.

2.3.2. TRR groups

Patients were categorized into three groups and compared based on their substance-specific TRRs: patients with antipsychotic concentrations below (subtherapeutic) vs. within vs. above the TRR (supratherapeutic); we utilized well established international TRRs, previously provided by the Therapeutic Drug Monitoring Task Force of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) (Hiemke et al., 2018). Comparisons of continuous variables were performed using Kruskal-Wallis *H*-Test with *post-hoc* pairwise analyses using Dunn's test with Holm-Bonferroni correction for multiple comparisons. Categorical variables were compared using Pearson's Chi-square tests or likelihood ratio tests, when appropriate, with *post-hoc* analysis of adjusted residuals (Agresti, 2002).

2.3.3. Predictors of treatment response

The association between LAI pharmacokinetics and treatment response was analyzed using generalized linear mixed models (GLMM). A binary GLMM with logit link function was fitted to analyze predictors of treatment response, defined as CGI-*I* ≤ 2. Fixed effects included age, sex, body mass index (BMI), smoking status, LAI monotherapy, and CGI—S. We added both baseline and follow-up CGI-S scores as repeated measurements with heterogenous compound symmetry thus controlling for both the baseline disease severity as well as the intrinsic covariation of the follow-up CGI-S and CGI-I scores. To account for potential clustering, we included patient recruitment site as a random effect. The role of pharmacokinetics was evaluated by adding to fixed effects either the LAI therapeutic reference range groups (below vs. within vs. above; Model 1a), or the LAI daily dose (Model 1b), or the LAI plasma concentration (Model 1c), or the LAI plasma concentrations adjusted by the calculated daily dose of the LAI, so called C/D ratios (Hiemke et al., 2018) (Model 1d), all nested within each LAI. Fixed model parameters were evaluated using Wald tests and presented as adjusted ORs (aORs). Random variance components were expressed as median odds ratios (mOR) (Yarnell et al., 2019) and evaluated using maximum likelihood ratio test.

Table 1
Patients' demographic and clinical characteristics in responders vs. non-responders based on Clinical Global Impression – Improvement (CGI—I) score ≤ 2.

Variable	Total sample ($n = 158$)	Responders ($n = 67$)	Non-responders ($n = 91$)	*p* value
Demographic characteristics				
[a] Age, years, median (IQR)	54.1 (42.0–61.2)	50.5 (34.8–57.7)	55.6 (44.7–64.1)	0.002
[a] Sex, male, n (%)	96 (61.5)	45 (68.2)	51 (56.7)	0.1
Body mass index (kg/m^2), median (IQR)	28.1 (25.0–31.9)	27.9 (25.5–32.9)	28.3 (24.4–31.3)	0.5
[b] Smokers, n (%)	76 (48.4)	29 (43.3)	47 (52.2)	0.3
Clinical characteristics				
[a] Diagnoses according to ICD-10:				
SCZ disorders (ICD-10: F2x), n (%)	118 (75.6)	48 (72.7)	70 (77.8)	0.5
Affective disorders (ICD-10: F3x), n (%)	24 (15.4)	10 (15.2)	14 (15.6)	1.0
Other diagnoses, n (%)	14 (9.0)	8 (12.1)	6 (6.7)	0.2
[c] CGI-S baseline, median (IQR)	4.0 (3.0–5.0)	4.0 (3.0–4.0)	4.0 (3.5–5.0)	0.2
CGI-S follow-up, median (IQR)	4.0 (3.0–4.0)	3.0 (2.0–4.0)	4.0 (3.0–4.0)	0.001
Concomitant medication:				
LAI monotherapy, n (%)	83 (52.5)	43 (64.2)	40 (44.0)	0.01
Other antipsychotics, n (%)	31 (19.6)	8 (11.9)	23 (25.3)	0.04
Antidepressants, n (%)	25 (15.8)	6 (9.0)	19 (20.9)	0.04
Mood stabilizers, n (%)	16 (10.1)	5 (7.5)	11 (12.1)	0.3
BDZ/Z/GABA, n (%)	39 (24.7)	11 (16.4)	28 (30.8)	0.04
Anticholinergics, n (%)	12 (7.6)	2 (3.0)	10 (11.0)	0.1
LAI characteristics:				
[d] LAI duration, months, median (IQR)	38.9 (21.2–87.0)	35.8 (17.8–63.5)	41.6 (24.2–99.7)	0.1
Aripiprazole monohydrate, n (%)	45 (28.5)	24 (35.8)	21 (23.1)	0.1
Haloperidol decanoate, n (%)	25 (15.8)	9 (13.4)	16 (17.6)	0.5
Olanzapine pamoate, n (%)	11 (7.0)	6 (9.0)	5 (5.5)	0.4
Paliperidone palmitate 1 Month, n (%)	32 (20.3)	11 (16.4)	21 (23.1)	0.3
Paliperidone palmitate 3 Months, n (%)	20 (12.7)	9 (13.4)	11 (12.1)	0.8
Risperidone microspheres, n (%)	16 (10.1)	4 (6.0)	12 (13.2)	0.1
Zuclopenthixol decanoate, n (%)	9 (5.7)	4 (6.0)	5 (5.5)	0.9

BDZ/Z/GABA: benzodiazepines or *Z*-substances or GABA analogues.
CGI-I: Clinical Global Impression-Improvement.
CGI-S: Clinical Global Impression-Severity.
ICD-10: International Classification of Diseases.
IQR: interquartile range.
LAI: long acting injectables.
SCZ: schizophrenia spectrum.
[a] Data was missing for 2 (1.2 %) patients.
[b] Data was missing for 1 (0.6 %) patient.
[c] Data was missing for 40 (25.0 %) patients.
[d] Data was missing for 3 (1.8 %) patients.

Table 2
Differences in pharmacokinetic characteristics in responders vs. non-responders based on Clinical Global Impression – Improvement (CGI—I) score ≤ 2.

Variable	Total sample	Responders	Non-responders	p value
Daily dose, mg/d, median (IQR)				
Aripiprazole monohydrate	13.3 (10.0–13.3)	13.3 (13.3–13.3)	13.3 (10.0–13.3)	0.2
Haloperidol decanoate	2.7 (1.8–3.6)	2.7 (1.7–3.6)	2.7 (1.8–4.5)	0.8
Olanzapine pamoate	14.5 (14.5–14.5)	14.5 (12.7–14.5)	14.5 (14.0–16.9)	0.6
Paliperidone palmitate 1-month	3.5 (2.5–3.6)	2.7 (2.5–5.4)	3.6 (2.7–3.6)	0.6
Paliperidone palmitate 3-months	3.9 (2.9–3.9)	3.9 (2.4–3.9)	3.9 (3.9–3.9)	0.3
Risperidone microspheres	3.6 (2.0–3.6)	3.1 (2.0–3.6)	3.6 (2.0–3.6)	1.0
Zuclopenthixol decanoate	7.1 (6.9–12.5)	6.9 (5.2–17.9)	7.1 (7.1–12.5)	0.4
Plasma concentration, ng/mL, median (IQR)				
Aripiprazole monohydrate	174.3 (95.7–249.1)	147.4 (85.5–240.8)	178.4 (122.1–260.8)	0.3
Haloperidol decanoate	2.9 (1.3–4.7)	2.7 (1.3–4.7)	3.1 (1.2–5.1)	0.9
Olanzapine pamoate	18.3 (9.3–30.5)	12.1 (8.0–19.1)	30.5 (12.7–35.3)	0.1
Paliperidone palmitate 1-month	32.0 (21.9–42.1)	24.8 (17.5–39.7)	32.6 (22.2–48.1)	0.3
Paliperidone palmitate 3-months	22.0 (16.6–30.9)	23.5 (18.9–30.8)	17.7 (16.0–31.0)	0.3
*Risperidone microspheres	22.6 (12.5–33.5)	17.2 (8.1–28.5)	24.5 (13.2–36.1)	0.3
Zuclopenthixol decanoate	5.3 (3.7–6.1)	5.4 (2.8–8.4)	4.1 (3.7–6.1)	1.0
C/D ratio, (ng/mL)/(mg/d), median (IQR)				
Aripiprazole monohydrate	13.7 (8.0–21.0)	12.0 (6.6–21.5)	16.2 (9.2–21.0)	0.3
Haloperidol decanoate	0.8 (0.5–1.7)	0.8 (0.5–1.7)	0.9 (0.5–1.7)	1.0
Olanzapine pamoate	1.2 (0.4–1.6)	1.1 (0.6–1.3)	1.6 (0.3–2.1)	0.5
Paliperidone palmitate 1-month	9.6 (6.7–14.9)	7.4 (5.5–14.3)	10.0 (7.4–15.5)	0.3
Paliperidone palmitate 3-months	7.3 (4.2–9.2)	8.0 (6.8–9.7)	4.6 (4.1–8.0)	0.2
*Risperidone microspheres	7.2 (5.2–11.6)	5.6 (2.3–15.1)	8.0 (6.1–11.6)	0.4
Zuclopenthixol decanoate	0.5 (0.4–0.8)	0.6 (0.3–1.0)	0.5 (0.4–0.7)	1.0
TRR, n (%)				
Below	47 (29.7)	24 (35.8)	23 (25.3)	0.2
Within	102 (64.6)	43 (64.2)	59 (64.8)	0.9
Above	9 (5.7)	0 (0.0)	9 (9.9)	**0.006**

Bold values indicate a statistically significant difference after multiple comparisons correction.
ADR: adverse drug reaction.
C/D ratio: concentration to (daily) dose ratio.
IQR: interquartile range.
TRR: therapeutic reference range.
* Concentration of active moiety was used.

2.3.4. Sensitivity analysis: comparison of the LAI plasma concentrations in responders with therapeutic reference ranges

We compared the IQRs of studied LAI antipsychotics in responders with the established TDM reference ranges (Hiemke et al., 2018). For aripiprazole and paliperidone, the 25th to 75th percentiles of the LAI plasma concentrations in responders were used to define preliminary therapeutic reference ranges for LAI formulations in accordance with the recent recommendations of the TDM Task Force of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) (Hart et al., 2025).

2.3.5. Sensitivity analysis 2: patients with schizophrenia spectrum disorders

In a second sensitivity analysis, we included only patients diagnosed with schizophrenia spectrum disorders. We compared responders vs. non-responders as well as patients with subtherapeutic vs. within TRR vs. supratherapeutic LAI concentration as in the main analysis.

3. Results

The study included 158 patients with a median age of 54.1 years (IQR = 42.0–61.2) and 61.5 % (n = 96) males. Most patients were diagnosed with schizophrenia spectrum disorders (ICD-10: F2.x; 75.6 %), followed by affective disorders (ICD-10: F3.x; 15.4 %). Median treatment duration with LAI was 38.9 months (IQR: 21.2–87.0 months). Patients were treated with aripiprazole monohydrate (28.5 %), paliperidone palmitate 1-month (20.3 %), followed by haloperidol decanoate (15.8 %), paliperidone palmitate 3-months (12.7 %), risperidone microspheres (10.1 %), olanzapine pamoate (7.0 %), and zuclopenthixol decanoate (5.7 %). Approximately half of the patients (52.5 %) received LAI monotherapy; no patient received more than one LAI concurrently (Table 1).

3.1. Demographic, clinical and pharmacokinetic characteristics

Almost 42.4 % of the patients (n = 67) were classified as responders (Table 1). Responders were significantly younger (50.5 vs. 55.6 years, p = 0.002), while no differences were reported regarding sex distribution (68.2 % vs. 56.7 % males, OR = 1.60, 95 % CI = 0.83–3.09, p = 0.1), BMI (27.9 vs. 28.3 kg/m^2, p = 0.5), or smoker status (43.3 % vs. 52.2 %, OR = 0.71, 95 % CI = 0.38–1.35, p = 0.3). The distributions of psychiatric diagnoses were also similar between the groups for schizophrenia spectrum disorders (72.7 % vs. 77.8 %, OR = 0.76, 95 % CI = 0.37–1.56, p = 0.5), affective disorders (15.2 % vs. 15.6 %, OR = 0.96, 95 % CI = 0.40–2.33, p = 1.0), and other diagnoses (12.1 % vs. 6.7 %, OR = 1.92, 95 % CI = 0.63–5.83, p = 0.2).

The median duration of LAI treatment did not differ between responders and non-responders (35.8 vs. 41.6 months, p = 0.1). While baseline disease severity was similar (median CGI-S score 4.0 vs. 4.0, p = 0.2), responders at follow-up showed significantly lower CGI-S scores (median 3.0 vs. 4.0, p = 0.001). Regarding concomitant medications, responders were more frequently treated with LAI monotherapy (64.2 % vs. 44.0 %, OR = 2.28, 95 % CI = 1.19–4.37, p = 0.01) and less likely to receive co-medication with other antipsychotics (11.9 % vs. 25.3 %, OR = 0.40, 95 % CI = 0.17–0.96, p = 0.04), antidepressants (9.0 % vs. 20.9 %, OR = 0.37, 95 % CI = 0.14–0.99, p = 0.04), or benzodiazepines/Z-drugs/GABA analogues (16.4 % vs. 30.8 %, OR = 0.44, 95 % CI = 0.20–0.97, p = 0.04; Table 1). The frequency of co-medication with mood stabilizers (7.5 % vs. 12.1 %, OR = 0.59, 95 % CI = 0.19–1.78) and anticholinergics (3.0 % vs. 11.0 %, OR = 0.25, 95 % CI = 0.05–1.18) did not differ between groups (both $p > 0.05$).

The calculated daily doses did not differ between responders and non-responders for any of the LAIs (all p > 0.05). Similarly, plasma concentrations and C/D ratios did not differ between responders and non-responders across all LAI medications (all p > 0.05), although responders had numerically lower levels for most LAIs compared to non-responders (Table 2). Two thirds of patients (64.6 %, n = 102) had LAI plasma concentrations within the TRRs, while 29.7 % (n = 47) were below and 5.7 % (n = 9) were above the TRRs. When comparing responders to non-responders, similar proportions were found for patients with concentrations below (35.8 % vs. 25.3 %, OR = 1.65, 95 % CI = 0.83–3.28, p = 0.1) and within the TRRs (64.2 % vs. 64.8 %, OR = 0.97, 95 % CI = 0.50–1.88, p = 0.9). Notably, no patients with supratherapeutic concentrations were classified as responders (0.0 % vs. 9.9

Table 3
Patients' demographic and clinical characteristics in patients with subtherapeutic, within the TRR and supratherapeutic LAI plasma concentrations.

Variable	Subtherapeutic levels (n = 47)	Within TRR (n = 102)	Supratherapeutic levels (n = 9)	p value
Demographic characteristics				
[a] Age, years, median (IQR)	49.8 (34.1–57.4)	55.6 (44.0–61.9)[†]	52.2 (30.0–60.3)	**0.02**
[a] Sex, male, n (%)	33 (71.7)	56 (55.4)	7 (77.8)	0.1
Body mass index (kg/m^2), median (IQR)	26.6 (24.4–30.8)	29.0 (25.5–32.4)	23.8 (23.2–34.4)	0.1
[b] Smokers, n (%)	27 (58.7)	45 (44.1)	4 (44.4)	0.3
Clinical characteristics				
[a] Diagnoses according to ICD-10:				
SCZ disorders (ICD-10: F2x), n (%)	34 (73.9)	78 (77.2)	6 (66.7)	0.7
Affective disorders (ICD-10: F3x), n (%)	7 (15.2)	15 (14.9)	2 (22.2)	0.8
Other diagnoses, n (%)	5 (10.9)	8 (7.9)	1 (11.1)	0.8
[c] CGI-S baseline, median (IQR)	4.0 (3.0–5.0)	4.0 (3.0–5.0)	3.5 (2.3–4.0)	0.4
CGI-S follow-up, median (IQR)	3.0 (2.0–4.0)	4.0 (3.0–4.0)	4.0 (3.0–5.0)	0.3
Concomitant medication:				
LAI monotherapy, n (%)	27 (57.4)	51 (50.0)	5 (55.6)	0.7
Other antipsychotics, n (%)	6 (12.8)	23 (22.5)	2 (22.2)	0.4
Antidepressants, n (%)	6 (12.8)	18 (17.6)	1 (11.1)	0.7
Mood stabilizers, n (%)	6 (12.8)	9 (8.8)	1 (11.1)	0.8
BDZ/Z/GABA, n (%)	8 (17.0)	30 (29.4)	1 (11.1)	0.2
Anticholinergics, n (%)	3 (6.4)	8 (7.8)	1 (11.1)	0.9
LAI characteristics:				
[d] LAI duration, months, median (IQR)	34.1 (13.7–86.4)	40.0 (24.4–87.5)	41.2 (16.0–51.9)	0.5
Aripiprazole monohydrate, n (%)	11 (23.4)	32 (31.4)	2 (22.2)	0.6
Haloperidol decanoate, n (%)	4 (8.5)	19 (18.6)	2 (22.2)	0.3
Olanzapine pamoate, n (%)	6 (12.8)	4 (3.9)	1 (11.1)	0.1
Paliperidone palmitate 1 Month, n (%)	7 (14.9)	23 (22.5)	2 (22.2)	0.6
Paliperidone palmitate 3 Months, n (%)	9 (19.1)	9 (8.8)	2 (22.2)	0.1
Risperidone microspheres, n (%)	7 (14.9)	9 (8.8)	0 (0.0)	0.3
Zuclopenthixol decanoate, n (%)	3 (6.4)	6 (5.9)	0 (0.0)	0.7
Outcomes:				
CGI-I, median (IQR)	2.0 (1.0–4.0)	3.0 (1.8–4.0)	3.0 (3.0–4.0)	0.3
Responders (GCI-I ≤ 2), n (%)	24 (51.1)	43 (42.2)	0 (0.0)[‡]	**0.01**

Bold values indicate a statistically significant difference after multiple comparisons correction.
BDZ/Z/GABA: benzodiazepines or Z-substances or GABA analogues.
CGI-I: Clinical Global Impression-Improvement.
CGI-S: Clinical Global Impression-Severity.
ICD-10: International Classification of Diseases.
IQR: interquartile range.
LAI: long acting injectable.
SCZ: schizophrenia spectrum.
TRR: therapeutic reference range.
[†] Statistically significant difference in pairwise comparison with subtherapeutic levels.
[‡] Statistically significant difference in pairwise comparison with subtherapeutic levels and within TRR.
[a] Data was missing for 2 (1.2 %) patients.
[b] Data was missing for 1 (0.6 %) patient.
[c] Data was missing for 42 (25.0 %) patients.
[d] Data was missing for 3 (1.8 %) patients.

%, OR: not available, $p = 0.006$).

3.2. TRR groups

Patients with LAI plasma concentration within the TRR were older compared to patients below TRR but not to those above TRR (median age: below: 49.8, within: 55.6, above: 52.2 years, $p = 0.02$; Table 3). There were no differences regarding sex distribution (71.7 % vs. 55.4 % vs. 77.8 % of males, respectively; p = 0.1), BMI (26.6 vs. 29.0 vs. 23.8 kg/m^2; p = 0.1) and smoking status (58.7 % vs. 44.1 % vs. 44.4 % smokers; $p = 0.3$). The distribution of psychiatric diagnoses was similar across groups (all $p > 0.7$). The median duration of LAI treatment was also comparable (34.1 vs. 40.0 vs. 41.2 months, $p = 0.5$), and the distribution of specific LAI medications also showed no significant differences between the groups (all $p > 0.1$). Similarly, no significant differences were found regarding concomitant medication rates (all p > 0.1).

While both baseline CGI-S scores (4.0 vs. 4.0 vs. 3.5; $p = 0.4$) and follow-up CGI-S scores (3.0 vs. 4.0 vs. 4.0; p = 0.3) did not differ across the groups, the proportion of responders (CGI-$I \leq 2$) was the highest in the group of patients with LAI plasma concentrations below the TRR (51.1 %), followed by the group of patients within TRR (42.2 %), while there were no responders with supratherapeutic LAI plasma concentrations ($p = 0.01$).

3.3. Predictors of treatment response

Four GLMMs were fitted to analyze predictors of treatment response (Table 4), all showing robust predictive performance with high accuracy (range: 83–85 %), good sensitivity (range: 77–82 %), and excellent specificity (range: 87–90 %; Table 4). Across all models, LAI monotherapy consistently predicted response with adjusted odds ratios ranging from 2.38 to 3.77 (all $p \leq 0.02$). Random effects were significant in all 4 models (range of mORs: 3.64–3.96), indicating differences between recruiting sites.

In model 1a, we reported that younger age (aOR: 0.97 per year, 95 % CI = 0.94–0.99, $p = 0.04$) and LAI monotherapy (aOR = 3.77, 95 % CI = 2.19–6.51, $p = 0.001$) were associated with higher probability of better treatment response. Notably, patients with subtherapeutic LAI plasma concentrations (aOR = 31.97, 95 % CI = 1.74–588.55, $p = 0.02$) and within TRR (aOR = 23.01, 95 % CI = 1.28–414.48, $p = 0.03$) showed higher probability of better treatment response compared to patients

Table 4
Factors Associated with response defined as Clinical Global Impression – Improvement score ≤ 2.

Variable	Adjusted odds ratio	95 % Confidence interval	p value
Model 1a: accuracy 85.2 %, sensitivity 81.8 %, specificity 87.6 %			
Fixed effects			
Age (per year)	0.97	0.94–0.99	**0.04**
Sex, male	0.99	0.44–2.23	0.1
Body mass index (per kg/m^2)	0.98	0.92–1.05	0.6
Smoker	0.48	0.23–1.02	0.1
*CGI-S (per unit)	1.00	1.00–1.00	1.0
LAI monotherapy	3.77	2.19–6.51	**0.001**
Sub- vs. supratherapeutic concentrations	31.97	1.74–588.55	**0.02**
Within TRR vs. supratherapeutic concentrations	23.01	1.28–414.48	**0.03**
Random effects			
Recruitment site (median odds ratio)	3.64	2.37–6.97	**0.02**
Model 1b: accuracy 83.2 %, sensitivity 77.3 %, specificity 87.6 %			
Fixed effects			
Age (per year increase)	0.97	0.94–1.00	0.1
Sex, male	0.99	0.41–2.41	1.0
Body mass index (per kg/m^2)	0.99	0.93–1.05	0.7
Smoker	0.51	0.23–1.10	0.1
*CGI-S (per unit)	1.00	1.00–1.00	1.0
LAI monotherapy	2.38	1.23–5.85	**0.01**
Random effects			
Recruitment site (median odds ratio)	3.96	2.50–7.86	**0.02**
LAI daily dose-specific effects (per mg/d)			
Aripiprazole monohydrate	0.99	0.89–1.10	0.8
Haloperidol decanoate	0.93	0.59–1.48	0.8
Olanzapine pamoate	0.99	0.88–1.12	0.9
Paliperidone palmitate 1-month	0.89	0.59–1.35	0.6
Paliperidone palmitate 3-months	0.85	0.56–1.29	0.4
Risperidone microspheres	0.84	0.50–1.41	0.5
Zuclopenthixol decanoate	0.86	0.73–1.00	0.1
Model 1c: accuracy 85.2 %, sensitivity 78.8 %, specificity 89.9 %			
Fixed effects			
Age	0.97	0.94–0.99	**0.04**
Sex, male	1.00	0.42–2.38	1.0
Body mass index	0.99	0.93–1.05	0.7
Smoker	0.44	0.21–0.96	**0.04**
*CGI-S (per unit increase)	1.00	1.00–1.00	1.0
LAI monotherapy	2.76	1.28–5.97	**0.01**
Random effects			
Recruitment site (median odds ratio)	3.88	2.48–7.56	**0.01**
LAI plasma concentration-specific effects (per 10 ng/mL)			
Aripiprazole monohydrate	0.97	0.93–1.02	0.2
Haloperidol decanoate	0.78	0.37–1.67	0.5
Olanzapine pamoate	0.67	0.36–1.26	0.2
Paliperidone palmitate 1-month	0.85	0.63–1.14	0.3
Paliperidone palmitate 3-months	0.73	0.52–1.03	0.1
Risperidone microspheres	0.69	0.43–1.11	0.1
Zuclopenthixol decanoate	0.03	0.01–0.48	**0.01**
Model 1d: accuracy 82.6 %, sensitivity 77.3 %, specificity 86.5 %			
Fixed effects			
Age	0.97	0.94–0.99	**0.04**
Sex, male	0.89	0.37–2.13	0.8
Body mass index	1.00	0.94–1.07	1.0
Smoker	0.47	0.22–1.04	0.1
*CGI-S (per unit increase)	1.00	1.00–1.00	1.0
LAI monotherapy	2.52	1.17–5.45	**0.02**
Random effects			
Recruitment site (median odds ratio)	3.83	2.41–7.75	**0.02**
LAI C/D ratio specific effects, (per (ng/mL) / (mg/d))			
Aripiprazole monohydrate	0.98	0.94–1.02	0.4
Haloperidol decanoate	0.95	0.78–1.02	0.4
Olanzapine pamoate	0.94	0.36–2.47	0.9
Paliperidone palmitate 1-month	0.98	0.90–1.06	0.6
Paliperidone palmitate 3-months	0.95	0.85–1.07	0.4
Risperidone microspheres	0.95	0.84–1.07	0.4
Zuclopenthixol decanoate	0.15	0.02–1.45	0.1

Bold values indicate a statistically significant difference.
ADR: adverse drug reaction.
C/D ratio: concentration to dose ratio.
CGI-I: clinical global impression-improvement.
CGI-S: clinical global impression-severity.
LAI: long acting injectable.
TRR: therapeutic reference range.
* Repeated measurements with compound symmetry covariance.

with supratherapeutic LAI plasma concentrations, when controlled for age, sex, BMI, smoking status, LAI monotherapy, and symptom severity. In the model 1b, after controlling for the same demographic and clinical variables, we reported the same effects for LAI monotherapy (aOR = 2.38, 95 % CI = 1.23–5.85, p = 0.01), with no other predictors being significantly associated with a treatment response. In model 1c, younger age (aOR = 0.97, 95 % CI = 0.94–0.99, p = 0.04), non-smoking status (aOR = 0.44, 95 % CI = 0.21–0.96, p = 0.04), and LAI monotherapy (aOR = 2.76, 95 % CI = 1.28–5.97, p = 0.01) were again associated with better response, although no LAI plasma concentration except of zuclopenthixol decanoate (aOR = 0.03, 95 % CI = 0.01–0.48, p = 0.01) were predictive for response, when controlled for age, sex, BMI, smoking status, LAI monotherapy, and disease severity. In model 1d, evaluating C/D ratios while controlling for the same set of variables, younger age (aOR = 0.97, 95 % CI = 0.94–0.99, p = 0.04) and LAI monotherapy (aOR = 2.52, 95 % CI = 1.17–5.45, p = 0.02) were associated with better treatment response, while smoking status was no longer predictive (p = 0.1). C/D ratios were also not associated with response.

3.4. Sensitivity analysis: comparison of the LAI plasma concentrations in responders with therapeutic reference ranges

In responders, the IQRs of LAI antipsychotics studied were found comparable with the respective established TRRs for oral antipsychotics, with a clear-cut trend towards lower levels for LAI antipsychotics (Supplementary Fig. 1).

3.5. Sensitivity analysis 2: focus on patients with schizophrenia spectrum disorders

When including only patients with schizophrenia spectrum disorders we observed similar results to the main analysis (Supplementary Tables 2–4). Responders tended to be younger (51.5 vs 55.6 years, p = 0.007), while the unadjusted prevalence of LAI monotherapy in responders was not significant anymore (64.6 % vs 47.1 %, p = 0.1), but the association remained after adjustment in the Model 2 (aOR 2.41, 95 % CI 1.04–5.58, p = 0.04; Supplementary Table 5). Differences between TRR categories were not significant when exclusively considering patients with schizophrenia spectrum disorders, although in the univariate analysis, supratherapeutic levels tended to be frequently reported in non-responders, but in none of the responders (p = 0.08 and p = 0.07, respectively). Likewise, in multivariate analysis having supratherapeutic concentrations was no longer negatively associated with the response (p = 0.08).

4. Discussion

Our study provides evidence of steady-state trough level pharmacokinetic patterns underlying clinical response to LAI antipsychotics in a real-world setting. Several key patterns with essential clinical implications emerged from our analysis.

Except for patients treated with olanzapine pamoate, responders treated with other LAIs had plasma concentrations that were predominantly within the TRRs recommended for oral antipsychotics (Hiemke et al., 2018). In a previous review we have highlighted the gap regarding TRR between patients treated with oral vs. LAI olanzapine (Schoretsanitis et al., 2021a). The observation made in this retrospective

analysis that IQRs of LAI plasma concentrations were in the low range of TRRs of oral antipsychotics (Supplementary Fig. 1) indicates that these ranges may be considered as target concentrations for LAI antipsychotics guided by TDM. IQRs of plasma concentrations in responders to antipsychotic or antidepressant drugs have been shown to reflect therapeutic reference ranges (Hart et al., 2025; Hiemke, 2019). Likewise, in our sample IQRs of antipsychotic levels essentially overlapped with therapeutic reference ranges (Hart et al., 2025).

While prescribed LAI doses were similar between responders and non-responders, we reported lower response rates in patients with higher concentrations. This pattern was particularly evident in our unadjusted analysis, as there were no responders with supratherapeutic concentrations. This finding highlights the notion of the point of futility regarding antipsychotic plasma concentrations when it comes to reaching response (Meyer and Stahl, 2021). This notion has been supported by findings in patients receiving oral antipsychotics but has been underinvestigated in LAI-treated patients. Indeed, in patients treated with clozapine (Lopez and Kane, 2013) and risperidone (Paulzen et al., 2017; Riedel et al., 2005; Spina et al., 2001), a curvilinear relationship between plasma concentrations and clinical response was suggested (Leucht et al., 2020): specifically, treatment outcomes may improve up to a certain threshold of concentrations but do not further improve or may even decline with further concentration increases. Moreover, dose escalation may lead to a higher ADR risk without essential clinical improvement, as previously reported in patients receiving long-term treatment with oral risperidone and olanzapine (Meyer, 2002; Sakurai et al., 2016). In other words, TDM may help identify non-responders due to insufficient antipsychotic exposure, i.e. subtherapeutic drug concentrations, vs. non-responders with sufficient antipsychotic exposure (concentrations within or above the therapeutic range) due to pharmacodynamic reasons. Disentangling these two groups of non-responders has essential consequences for the clinical decision-making process: in non-responders with subtherapeutic concentrations clinicians may increase the LAI dose to reach therapeutic concentrations, whereas in non-responders with sufficient antipsychotic exposure switching or augmenting may be a reasonable next step. Moreover, in our cohort responders were significantly more often treated with LAI monotherapy, which also was found to be predictive for response in the multivariate analysis. The relationship between higher LAI antipsychotic concentrations, multiple co-medications, and poorer response likely reflects an underlying treatment resistance rather than a direct causative effect of the antipsychotic concentration (Kuzo et al., 2022).

In our cohort, responders were younger than non-responders. Thus, age may serve as a proxy marker for earlier illness stage and reduced cumulative disease burden. Besides, accumulating evidence demonstrates that initiating LAI antipsychotics early on, such as in first-episode schizophrenia patients, may essentially reduce relapse frequency, improve adherence and potentially modify the disease course (Lian et al., 2022). These findings challenge the common practice of reserving LAIs exclusively for patients with established non-adherence or assumed treatment resistance. The relationship between relapse and subsequent antipsychotic responsiveness provides additional support for this hypothesis. Specifically, clinical evidence suggest that psychotic relapses are associated with diminished responsiveness to subsequent antipsychotic interventions (Perkins et al., 2005), thereby strengthening the therapeutic rationale for earlier LAI implementation.

A particularly interesting finding was the role of smoking as a moderate negative predictor of treatment response only in concentration-based models, remaining non-significant in dose-based analysis. So, when LAI plasma concentrations or C/D ratios were replaced with LAI daily doses in the GLMM model, the pathway by which smoking exerted its influence on the treatment response may have not been captured. This change suggests that its impact on the treatment response might have been mediated primarily through its effect on plasma concentrations. Of note, all studied antipsychotics share metabolic pathways involving the cytochrome P450 (CYP) enzyme isoforms CYP2D6 and CYP3A4 (Hiemke et al., 2018), apart from olanzapine pamoate, where CYP1A2 has a major role (Hiemke et al., 2018). While the impact of smoking on CYP1A2 is well-established (Faber et al., 2005)., it is less clear how smoking may impact pharmacokinetics catalyzed by other CYP450 isoenzymes. Previous naturalistic evidence may suggest some role for induction of CYP3A4 as well (Schoretsanitis et al., 2017). Moreover, the renal effects of smoking also need to be considered (Cooper, 2006). Regardless of the exact underlying mechanism, this finding underscores the importance of TDM in capturing variation when considering individual patient characteristics, such as smoking status.

Several important limitations must be considered when interpreting our findings. The retrospective design introduced inherent constraints, as data extraction may be less reliable compared to prospective data collection. This design also limited our ability to assess causal relationships between pharmacokinetic parameters and treatment response. TDM was not performed routinely and was dependent on clinical indications. This non-random sampling may reflect more complex cases and, thus, may limit external validity. Patients on LAIs without TDM were excluded and cannot be characterized here. Thus, generalizability to all LAI-treated patients may be limited because individuals without TDM were not included. The timing of blood sampling relative to clinical response assessment could not be precisely determined, and there might be a short lag between clinical changes and their documentation, although we did not assume any relevant short-term changes in a cohort of clinically stable patients. The use of CGI-I as the primary outcome measure, while clinically relevant, provides a less specific assessment of clinical outcomes. Additionally, our use of single time point measurements rather than repeated plasma level assessments may not fully capture the dynamic nature of drug exposure and response patterns. Besides, in the group of patients with supratherapeutic levels there were only nine patients, which may constrain precision and stability of effect estimates. Furthermore, some LAI antipsychotic subgroups were relatively small, particularly the groups consisting of olanzapine pamoate and zuclopenthixol decanoate, potentially limiting statistical power for these agents. In our analysis based on TRR-interpretation (Model 1a), the low number of patients with supratherapeutic concentrations may have reduced the analysis power and have led to imprecise estimations; however, the analysis based on LAI concentrations (Model 1c) interpretation was consistent with the results of the Model 1a for most of antipsychotics. Limited power might have also resulted in some different findings in the sensitivity analysis including only schizophrenia patients. Furthermore, data for potentially crucial parameters, such as injection site, comorbidities, duration of illness, and renal function (which might have affected the clearance of some LAI antipsychotics), were not available. Additionally, the naturalistic setting introduced considerable heterogeneity in treatment patterns and patient characteristics. Finally, the absence of pharmacogenetic data restricted our ability to identify genetic factors that might influence individual response to LAI treatments.

In conclusion, plasma concentrations of LAI antipsychotics appear to be more informative than LAI doses in predicting clinical outcomes. Patients with supratherapeutic concentrations are unlikely to respond to LAIs and alternative treatment strategies should be considered except for LAI dose increase. In other words, we assume that patients may have not responded to regular LAI doses and their psychiatrists may have continued to increase the dose resulting in higher plasma levels in more symptomatic patients as described previously (Tugg et al., 1997). Further response predictors may include LAI monotherapy and younger age, thus offering clinically valuable guidance independently of pharmacokinetic correlates. This real-world evidence indicates that modern TDM approaches should move beyond simple concentration thresholds towards more comprehensive assessments incorporating pharmacological and clinical parameters. This real-world evidence indicates that modern TDM approaches should move beyond simple concentration thresholds towards more comprehensive assessment incorporating both

pharmacological and clinical parameters.

CRediT authorship contribution statement

Nazar Kuzo: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Davide Gaspari:** Writing – review & editing, Data curation, Conceptualization. **Fabio Carpi:** Writing – review & editing, Data curation, Conceptualization. **Christoph Hiemke:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Michael Paulzen:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Andreas Conca:** Writing – review & editing, Project administration, Formal analysis, Conceptualization. **Georgios Schoretsanitis:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Formal analysis, Conceptualization.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Microsoft 365 Co-Pilot integrated in Microsoft Word to improve the readability and language of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

Declaration of competing interest

Nazar Kuzo has received educational grants from Lundbeck. Michael Paulzen has received speaker's fees from Janssen, ROVI, Neuraxpharm, Idorsia, Lundbeck and Otsuka. He has served as a consultant for Novartis, Otsuka, Idorsia and ROVI. He is editor of an internet-based drug–drug interaction program ("http://www.psiac.de"). Georgios Schoretsanitis has served as a consultant for Dexcel, HLS Therapeutics, and Thermo Fisher and has received speaker's fees from HLS Therapeutics, Lundbeck and Saladax. Other co-authors have no conflicts of interest to declare. All co-authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2025.12.012.

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