CNS Drugs
https://doi.org/10.1007/s40263-025-01225-0

ORIGINAL RESEARCH ARTICLE

Impact of Long-Acting Injectable Versus Oral Antipsychotic Treatment on All-Cause Discontinuation Risk in People with Early Phase Schizophrenia and Comorbid Substance Use Disorder: A Secondary Analysis of the EULAST Randomized Trial

Matin Mortazavi[1,2] · Zahra Aminifarsani[1,2] · Inge Winter-van Rossum[3,4] · René S. Kahn[4] · W. Wolfgang Fleischhacker[5,13] · Michael Davidson[6,14] · Mark Weiser[7,8] · Dan Siskind[9,10] · Stefan Leucht[11] · EULAST Study Group · Alkomiet Hasan[2,12] · Elias Wagner[1,2]

Received: 16 May 2025 / Accepted: 26 August 2025

Abstract

Background Individuals with schizophrenia and comorbid substance use disorder (SUD) often experience poor treatment adherence, leading to worse clinical outcomes. However, high-quality evidence from randomized trials on the preferred mode of antipsychotic treatment in this population remains limited.

Aims The aim was to examine whether long-acting injectable (LAI) antipsychotic treatment reduces the risk of all-cause discontinuation (ACD) compared with oral antipsychotics in individuals with early phase schizophrenia and comorbid SUD.

Methods This study was a secondary analysis of the European Long-Acting Antipsychotics in Schizophrenia Trial (EULAST), a multisite, randomized, open-label trial conducted across multiple European healthcare settings. A total of 471 individuals with early phase schizophrenia were included in this secondary analysis, stratified by presence ($n = 143$) or absence ($n = 328$) of comorbid SUD. The observation period lasted 18 months. Participants were randomly assigned to second-generation LAI or oral second-generation antipsychotic treatment. The primary outcome was ACD, an indirect measure of treatment efficacy, defined as discontinuation of the initially assigned treatment for any reason. Hazard ratios (HRs) were estimated using Cox proportional hazards regression models, adjusted for relevant covariates.

Results Among 143 individuals with schizophrenia and SUD, LAI treatment was associated with a 36% lower risk of ACD compared with oral antipsychotics (adjusted HR = 0.641; 95% CI, 0.438–0.938; $P = 0.022$). Kaplan–Meier curves showed longer median time to ACD for LAI treatment (158 days) versus oral antipsychotics (97 days). By contrast, among the 328 individuals without SUD, LAI treatment did not significantly reduce ACD risk ($P = 0.282$). Crude HRs were also assessed, replicating the adjusted hazard findings.

Conclusions LAI antipsychotics significantly delayed treatment discontinuation compared with oral antipsychotics in participants with early phase schizophrenia and comorbid SUD but not in those without SUD. While these findings provide robust evidence supporting the use of LAIs in people with schizophrenia and comorbid SUD, future studies are needed to more precisely quantify the potential clinical benefits and tolerability of LAIs in this high-risk population. EULAST was registered at ClinicalTrials.gov (NCT02146547).

1 Introduction

Schizophrenia is a serious mental disorder with a lifetime prevalence of about 0.5–1% and accounts for a substantial healthcare burden [1]. There is a large body of evidence on the association between schizophrenia and unhealthy lifestyle, including sedentary behavior, unhealthy diet, smoking, and substance abuse, which contribute to increased risk of cardiovascular disease, and related death [2]. Schizophrenia is often associated with comorbid substance use disorders

Matin Mortazavi and Zahra Aminifarsani have shared first authorship.

Alkomiet Hasan and Elias Wagner have shared last authorship.

Members of EULAST Study Group are listed in the acknowledgements section.

Extended author information available on the last page of the article

Published online: 11 September 2025

Key Points

In participants with early phase schizophrenia and comorbid substance use disorder, long-acting injectable (LAI) antipsychotics significantly reduced the risk of treatment discontinuation by 36% compared with oral antipsychotic medication.

This therapeutic advantage was not observed in participants with early phase schizophrenia who did not have a comorbid substance use disorder, highlighting the specificity of the finding.

Our findings represent the first evidence from a pragmatic randomized controlled trial demonstrating the superior effectiveness of LAI antipsychotics in this high-risk dual disorder population. Results may help guide clinical decision-making and inform treatment guidelines.

(SUD) with a prevalence of dual disorders ranging from 26 to 31% [3]. This disease-comorbidity association is bidirectional, since both disorders are presumed to share common genetic and socioeconomic factors [4–7]. Notably, cannabis use, particularly of high-potency formulations, is recognized as a significant etiological risk factor that could trigger or exacerbate psychosis, thereby contributing to the high rates of comorbidity in this population [8].

Evidence from Scandinavian registries notes that multiple drug use and alcohol use disorders are the most prevalent SUD, followed by cannabis [3]. The presence of any SUD comorbidity, notably multiple drug use and alcohol use, was associated with a 50–100% increase in hospitalization and mortality compared with individuals without SUD [3]. The drivers of elevated mortality risk were suicides and other external causes [3].

Treatment of individuals with schizophrenia and comorbid SUD can be challenging, with reduced compliance and medication adherence [3]. Available real-world evidence shows a significant association with unfavorable disease course in individuals with dual disorder [3, 9, 10]. Two independent national cohorts consistently showed that risk of relapse (psychiatric hospital admission and SUD-related hospital admission) were lowest for clozapine, antipsychotic polytherapy and long-acting injectables (LAI) [3]. The Treatment Response and Resistance in Psychosis (TRRIP) working group noted that the optimal definition of treatment resistance would include at least one failed trial with a long-acting injectable antipsychotic (LAI) [11]. This inclusion of a trial of an LAI is notable, since adherence is challenging in difficult-to-treat-schizophrenia with or without SUD, where about a third of individuals are presumed to be nonadherent rather than treatment-resistant [12]. The improved real-world outcomes for individuals with schizophrenia and comorbid SUD during LAI treatment suggests that this high-risk group represents a difficult-to-treat or nonadherent population that benefits from the additional adherence associated with LAI treatment. Nevertheless, this population, despite its high prevalence in real-world settings, remains underinvestigated in randomized controlled trials (RCTs) among people with schizophrenia. This was highlighted when eligibility criteria typically used in RCTs, i.e., serious somatic comorbidities, concomitant use of mood stabilizers or antidepressants, and history of substance use and risk of suicide, were applied in two national cohorts [13].

To date, the European First Episode Schizophrenia Trial (EUFEST) [14], the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) [15] and the Optimization of Treatment and Management of Schizophrenia in Europe (OPTiMiSE) Trial [16] have examined differences in treatment response among individuals with schizophrenia and comorbid SUD. Overall, findings have been inconsistent, with EUFEST reporting no significant association between SUD and treatment outcomes and CATIE finding that individuals with moderate substance use exhibited a poorer antipsychotic response. In OPTiMiSE, no significant differences regarding symptomatic remission emerged between individuals with comorbid suicidality and/or SUD and noncomorbid individuals [16].

A recent meta-analysis of the efficacy of antipsychotics in subjects with schizophrenia and comorbid substance use highlighted the paucity of robust evidence from high-quality RCTs to inform clinical guidelines [17]. Therefore, we investigated an indirect effectiveness measure, all-cause discontinuation, in the large-scale multicenter European Long-Acting Antipsychotics in Schizophrenia Trial (EULAST) trial, among people with early phase schizophrenia with or without SUD receiving second-generation oral or LAI antipsychotic treatment.

2 Methods

2.1 Subjects

The present investigation is a secondary analysis of the data from the European Long-Acting Antipsychotics in Schizophrenia Trial (EULAST). EULAST is a randomized open-label trial carried out across 50 general hospitals and psychiatric clinics in 15 European countries and Israel. The relevant regulatory bodies and ethics committees in each participating country approved the study and its adherence to local regulations and the Declaration of Helsinki. The trial was overseen by the University Medical Center Utrecht in the Netherlands, following the guidelines

of Good Clinical Practice and the International Conference on Harmonization. An independent Data Safety Monitoring Board conducted annual safety assessments for the study [18].

Details regarding the recruitment procedures, inclusion/exclusion criteria, and demographic and clinical screenings performed in EULAST can be found in the publication of the primary endpoint [18]. In short, participants in the EULAST were inpatients and outpatients, recruited at the collaborating healthcare institutions and fulfilling the following criteria: age (18 years or older), diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) as verified by the Mini International Neuropsychiatric Interview 5 Plus (MINI). Additionally, participants were required to have experienced their illness for a minimum of 6 months and a maximum of 7 years, defining a rather early disease course. A randomization table including allocation sequence was generated by Data Management Department of Julius Center (University Medical Center Utrecht) using SAS syntax. The participants were randomly assigned using block randomization (1:1:1:1) to one of four groups: long acting injectable (LAI) paliperidone or aripiprazole or the respective oral formulations of these antipsychotics. Participants were then followed up for up to 18 months. The randomization process was stratified by country and duration of illness. All participants followed a standardized, fixed-flexible dosing schedule as prespecified in the parent trial protocol (for details see section L, appendix of the primary endpoint publication [18]). Schizophrenia symptom severity was evaluated using the Positive and Negative Syndrome Scale (PANSS). Written informed consent was provided by all subjects prior to study inclusion.

The subjects employed in our analysis represent a subset of the EULAST cohort. From the original intention-to-treat (ITT) population utilized in the initial investigation ($n = 511$), subjects without consent forms for secondary data analysis were excluded ($N = 16$). To pursue the aim of this study, information regarding current and lifetime substance abuse and dependence (including alcohol) was retrieved using a seven-item scale according to the relevant diagnostic modules of the MINI; those individuals lacking such details were excluded ($N = 3$). The seven-item scale characterized current/lifetime substance dependence or abuse (see Supplementary Material) and was employed to categorize the remaining 492 subjects into two distinct groups: "any substance use disorder (SUD)" and "no substance use disorder (no SUD)." A subject was classified as SUD if they fulfilled the following diagnostic criteria in the MINI: substance dependence or abuse current and/or lifetime (alcohol or nonalcohol); if a subject had missing information in one or more of the items but fulfilled criteria for any of the remaining, they were subsequently classified as SUD. The "no SUD" category consisted of subjects who did not fulfill any of the aforementioned items. In instances where a subject had responded "no" to several items and had no responses to the remaining items, meaning a lack of a "yes" response to any of the items, their substance use status was classified as unknown, and they were excluded from the pool of subjects ($N = 21$). The final sample consisted of 471 participants, including 143 SUD individuals (LAI antipsychotic groups combined $N = 74$; oral antipsychotics groups combined $N = 69$) and 328 no SUD individuals (LAI antipsychotic groups combined $N = 174$; oral antipsychotic groups combined $N = 154$). Figure 1 presents an inclusion/exclusion profile for our study.

2.2 Data Analysis

The main outcome in this study was, in accordance with the primary endpoint publication [18], time to all-cause discontinuation (days), compared using survival analysis between oral antipsychotic treatment (oral aripiprazole and paliperidone) and the combined LAI treatment group (LAI aripiprazole and LAI paliperidone) during 19 months of treatment. This was performed separately in the "SUD" and "no SUD" groups, and then their results were compared. The criteria and types of all-cause discontinuation are thoroughly outlined in the original manuscript [18]. To summarize, discontinuation was classified as being due to either lack of treatment efficacy, concerns regarding safety (including side effects), or other reasons (e.g., study participant missed visits, stopped the treatment, or withdrew consent from the study). The time to all-cause discontinuation was calculated by counting the days from the date of randomization (visit 2 of 21 possible visits) to the date on which the study participant met all-cause discontinuation criteria. For participants who completed all 21 visits without meeting the all-cause discontinuation criteria, a truncated survival time of 540 days, representing the entire possible follow-up period of 18 months, was considered as the time to all-cause discontinuation.

R 4.3.2 [19] and R-Studio [20] were used to perform statistical analysis. The survival analyses were executed using R-packages Survival (version 3.6-4). Cox proportional regression models were calculated with time to all-cause discontinuation (in days) as the outcome (continuous variable) and the mode of antipsychotic treatment as the predictor (LAI versus oral, dichotomous categorical variable). Age (continuous variable) and sex (categorical variable) were added to the model as covariates. This model was run separately for SUD (N events = 109) and no SUD (N events = 208). Additionally, a complementary analysis was performed examining a crude hazard ratio of all-cause discontinuation

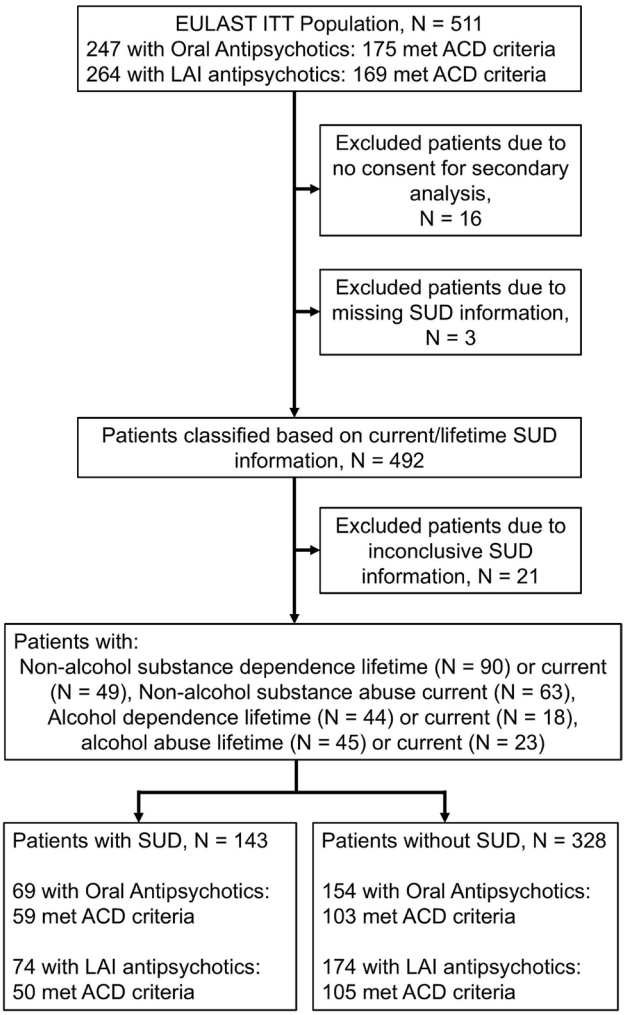

Fig. 1 Inclusion/exclusion profile of this secondary analysis of the European Long-Acting Antipsychotics in Schizophrenia Trial (EULAST). Note: the numbers for specific SUD categories are not mutually exclusive, as an individual could meet criteria for multiple categories. The total "any SUD" group (n = 143) represents the unique count of individuals meeting criteria for at least one SUD category. The "lifetime nonalcohol substance abuse" category was not available in the provided dataset, likely to maintain focus on the most clinically significant diagnoses of dependence and current abuse. ITT, intention-to-treat; SUD, substance use disorder; ACD, all-cause discontinuation; LAI, long-acting injectable

only in those individuals of the SUD sample who had a current drug/alcohol use/dependence (N = 99). The analysis was stratified by SUD status and conducted separately for each subgroup (SUD and no-SUD). This approach was chosen to provide a clear and direct estimation of the treatment effect within each clinically distinct population, which was the primary goal of this secondary analysis. The status of subjects without all-cause discontinuation was set as censored. The impact of each factor in the model on the hazard of all-cause discontinuation was estimated using hazard ratios (HRs) and 95% confidence intervals (CIs). These models calculated the adjusted HRs, while crude HRs were assessed using similar regression models without controlling for the covariates sex and age. The fit of the models and the statistical significance were assessed using both the likelihood ratio test and the Wald test. The mean concordance of the model was reported along with its standard error. Survival curves were plotted using the Kaplan–Meier method as implemented in the Survminer (version 0.5.0) package in R.

The proportional hazards assumption for the Cox regression models was tested by examining the scaled Schoenfeld residuals in our dataset. A formal test revealed no evidence of a time-dependent effect for the variables ($P > 0.05$), confirming that the assumption was met. Comparisons between groups regarding clinical and demographic variables were performed using t-tests, Mann–Whitney U tests, or chi-squared tests, depending on the outcome variable and test assumptions. Descriptive statistics are shown as mean ± standard deviation of the mean. For all analyses, the threshold for statistical significance was set at a P value < 0.05. This secondary analysis is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement where applicable.

3 Results

3.1 Demographics and Clinical Characteristics of the Whole Cohort (with and without SUD)

The combined with SUD and without SUD sample consisted of 471 participants, including 143 people with SUD (83.2% males, 28.86 ± 9.13 years old; illness duration 2.87 ± 1.74 years; PANSS total score at baseline = 72.20 ± 19.44; combined LAI antipsychotic arm N = 74, combined oral antipsychotics arm N = 69) and 328 without SUD (59.5% males, 31.42 ± 9.86 years old; illness duration 3.09 ± 1.91 years; PANSS total at baseline = 75.69 ± 18.17; combined LAI antipsychotic arm N = 174, combined oral antipsychotics arm N = 154). Table 1 provides additional details on the clinical and demographic characteristics of the whole cohort.

Independent t-tests showed no difference between the two groups regarding PANSS total at baseline (t = 1.78, degrees of freedom (df) = *454,* P = 0.08, 95% confidence intervals CI −0.37 to 7.34) and illness duration (t = 1.19, df = 469, P = 0.23, 95% CI −0.14 to 0.57). Moreover, the SUD sample was to be marginally younger than the without SUD sample (28.86 ± 9.13 years old versus 31.42 ± 9.86 years old, respectively; t = 2.73, df = 469, P = 0.007, 95% CI 0.72–4.41). The chi-squared test of independence showed a significantly higher male/female proportion in substance users than in not substance users (χ^2 = 24.25, df = 1, P < 0.001).

Table 1 Demographics and clinical characteristics of individuals included in this secondary analysis of the European Long-Acting Antipsychotics in Schizophrenia Trial (EULAST)

Variable		With SUD ($N = 143$)	Without SUD ($N = 328$)
Age (years), mean (SD)		28.86 (9.13)	31.42 (9.86)*
Duration of illness (months), mean (SD)		44.55 (116.91)	45.94 (109.66)
Gender, *N* (%)	Female	24 (16.8%)	133 (40.5%)*
	Male	119 (83.2%)	195 (59.5%)*
Treatment, *N* (%) (medications)	Aripiprazole	73 (51.0%)	158 (48.2%)
	Paliperidone	70 (49.0%)	170 (51.8%)
Race, *N* (%)	Asian	9 (6.2%)	7 (2.1%)
	Black	17 (12.0%)	17 (5.2%)
	White	103 (72.0%)	279 (85.1%)
	Other	14 (9.8%)	25 (7.6%)
Years of education, Mean (SD)		11.58 (2.55)	12.01 (2.91)
Living independently, *N* (%)		47 (32.9%)	59 (18.3%)
Major depressive disorder (current), *N* (%)		5 (3.5%)	6 (1.8%)
Suicidality (current), *N* (%)		56 (39.2%)	54 (16.5%)
PANSS positive, mean (SD)		17.48 (6.24)	17.37 (5.91)
PANSS negative, mean (SD)		18.27 (6.75)	20.69 (6.34)
PANSS general, mean (SD)		36.45 (10.35)	37.63 (9.45)
PANSS total, mean (SD)		72.20 (19.44)	75.69 (18.17)
CGI severity, mean (SD)		4.35 (1.0)	4.38 (0.99)

PANSS Positive and Negative Syndrome Scale for Schizophrenia, *CGI* Clinical Global Impression, *SD* standard deviation of the mean, *SUD* substance use disorder

*Participants with SUD are significantly different (*P*-value < 0.05) when compared with participants without SUD using *t*-test/chi-squared test of independence

3.2 Demographics and Clinical Characteristics of SUD (oral versus LAI)

The mean age of the SUD population was 28.86 ± 9.13 years, and 16.8% were female. The mean duration of illness was 2.87 ± 1.74 years. Among the participants with SUD, $N = 73/143$ (51%) received aripiprazole and 70/143 (49%) received paliperidone. In the oral versus LAI groups there were no significant differences regarding any clinical parameter including age ($Z = -1.081$, $P = 0.280$), duration of illness ($Z = -0.503$, $P = 0.615$), sex ($\chi^2 = 0.404$, $P = 0.525$), aripiprazole versus paliperidone ($\chi^2 = 0.168$, $P = 0.682$), and PANSS total scores at baseline ($Z = -0.882$, $P = 0.378$). Table 2 provides additional details on the clinical and demographical characteristics of the SUD cohort.

3.3 Demographics and Clinical Characteristics of without SUD (oral versus LAI)

The mean age of the without SUD population was 31.42 ± 9.86 years, and 40.5% were female. The mean duration of illness was 3.09 ± 1.91 years. $N = 158/328$ (48.2%) received aripiprazole, and 170/328 (51.8%) received paliperidone. In the oral versus LAI groups, there were no significant differences regarding any clinical parameter including age ($Z = -0.388$, $P = 0.698$), duration of illness ($Z = -0.915$, $P = 0.360$), sex ($\chi^2 = 2.815$, $P = 0.093$), aripiprazole versus paliperidone ($\chi^2 = 0.389$, $P = 0.533$), and PANSS total scores at baseline ($Z = -0.88$, $P = 0.38$). Supplementary Table 1 provides additional details on the clinical and demographical characteristics of the without SUD cohort.

3.4 Lower Hazard Ratios for LAIs than Oral Antipsychotics in SUD

The Cox proportional hazard regression model in SUD demonstrated moderate concordance of 0.595 (standard error, SE = 0.028), with a statistically significant fit as supported by the likelihood ratio test (χ^2 (3) = 11.88, $P = 0.008$) and Wald test (χ^2 (3) = 11.43, $P = 0.01$).

The model indicated a significant effect for mode of antipsychotic treatment (LAI versus oral) on adjusted hazard ratios (HRs) of all-cause discontinuation in SUD (adjusted HR = 0.641, 95% CI 0.438–0.938, $P = 0.022$). Kaplan–Meier curves (Fig. 2a) demonstrated favorable

Table 2. Demographics and clinical characteristics of individuals with substance use disorder (SUD)

Variable		Oral antipsychotics medication ($N = 69$)	LAI antipsychotics medication ($N = 74$)
Age (years), mean (SD)		29.48 (9.25)	28.28 (9.04)
Duration of illness (month), mean (SD)		53.35 (166.84, $n = 69$)	36.35 (22.77, $n = 74$)
Gender, *N* (%)	Female	13 (18.8%)	11 (14.9%)
	Male	56 (81.2%)	63 (85.1%)
Treatment, *N* (%) (medications)	Aripiprazole	34 (49.3%)	39 (52.7%)
	Paliperidone	35 (50.7%)	35 (47.3%)
Race, *N* (%)	Asian	4 (5.8%)	5 (6.8%)
	Black	8 (11.6%)	9 (12.2%)
	White	48 (69.6%)	55 (74.3%)
	Other	9 (13.0%)	5 (6.8%)
Years of education, mean (SD)		11.53 (2.69)	11.62 (2.43)
Living independently, *N* (%)		25 (36.2%)	22 (29.7%)
Major depressive disorder (current), *N* (%)		1 (1.45%)	4 (5.4%)
Suicidality (current), *N* (%)		24 (34.8%)	32 (43.2%)
Alcohol abuse, *N* (%)		35 (54.7%)	42 (60.9%)
Substance abuse, *N* (%)		57 (83.8%)	60 (81.1%)
PANSS positive, mean (SD)		17.79 (6.68)	17.21 (5.86)
PANSS negative, mean (SD)		18.25 (7.29)	18.28 (6.29)
PANSS general, mean (SD)		36.06 (10.75)	36.79 (10.05)
PANSS total, mean (SD)		72.11 (20.73)	72.28 (18.38)
CGI severity, mean (SD)		4.3 (1.1, $n = 63$)	4.39 (0.91, $n = 72$)

PANSS Positive and Negative Syndrome Scale for Schizophrenia, *CGI* Clinical Global Impression, *SD* standard deviation of the mean

survival trajectories for LAI antipsychotics (median time to all-cause discontinuation = 158 days, events = 50, censored = 24) than oral antipsychotics (median time to all-cause discontinuation days = 97, events = 59, censored = 10). Moreover, older age in participants was significantly associated with lower hazard ratios of all-cause discontinuation (adjusted HR = 0.973, 95% CI 0.952–0.995, $P = 0.015$). An interaction factor between age and mode of antipsychotic treatment was incorporated in the model to examine the modulatory impact of these two significant factors on each other. The interaction term did not yield a significant effect on the hazard ratio ($P > 0.1$), yet the likelihood ratio and Wald test continued to demonstrate statistical significance for the model following the introduction of the interaction term. This suggests a similar modulation of hazard ratios by age in LAI and oral antipsychotic treatments. The model revealed no significant impact for sex on the hazard ratios (HR = 0.755, 95% CI 0.463–1.231, $P = 0.260$).

The model examining the crude hazard ratio of all-cause discontinuation in SUD sample revealed similar findings, showing a significant effect for mode of antipsychotic treatment (LAI versus oral; crude HR = 0.659, 95% CI 0.451–0.962, $P = 0.031$) with favorable survival rates for LAI antipsychotics, with a statistical significance for the overall model according to likelihood ratio (χ^2 (1) = 4.7, $P = 0.03$) and Wald test (χ^2 (1) = 4.74, $P = 0.03$).

3.5 Lower Hazard Ratios for LAIs than Oral Antipsychotics in Current SUD

The Cox proportional hazard regression model including subjects with current SUD had an overall model fit similar to that of the extended SUD sample, with a moderate concordance of 0.54 (SE = 0.031) and a chi-squared coefficient of 3.51 ($df = 3$) and 3.48 ($df = 3$) in the likelihood ratio and Wald test, respectively. Both tests showed, however, a marginally significant fit ($P = 0.06$), most probably due to a low statistical power of the subsample and a resulting higher type II error. The model showed lower crude-hazard ratios of all-cause discontinuation for LAI compared with oral antipsychotics for current substance users (crude HR = 0.65, 95% CI 0.42–1.02 $P = 0.062$), which were statistically marginally significant. These results replicate the statistically significant lower crude and adjusted HRs of all-cause discontinuation observed in the extended SUD sample.

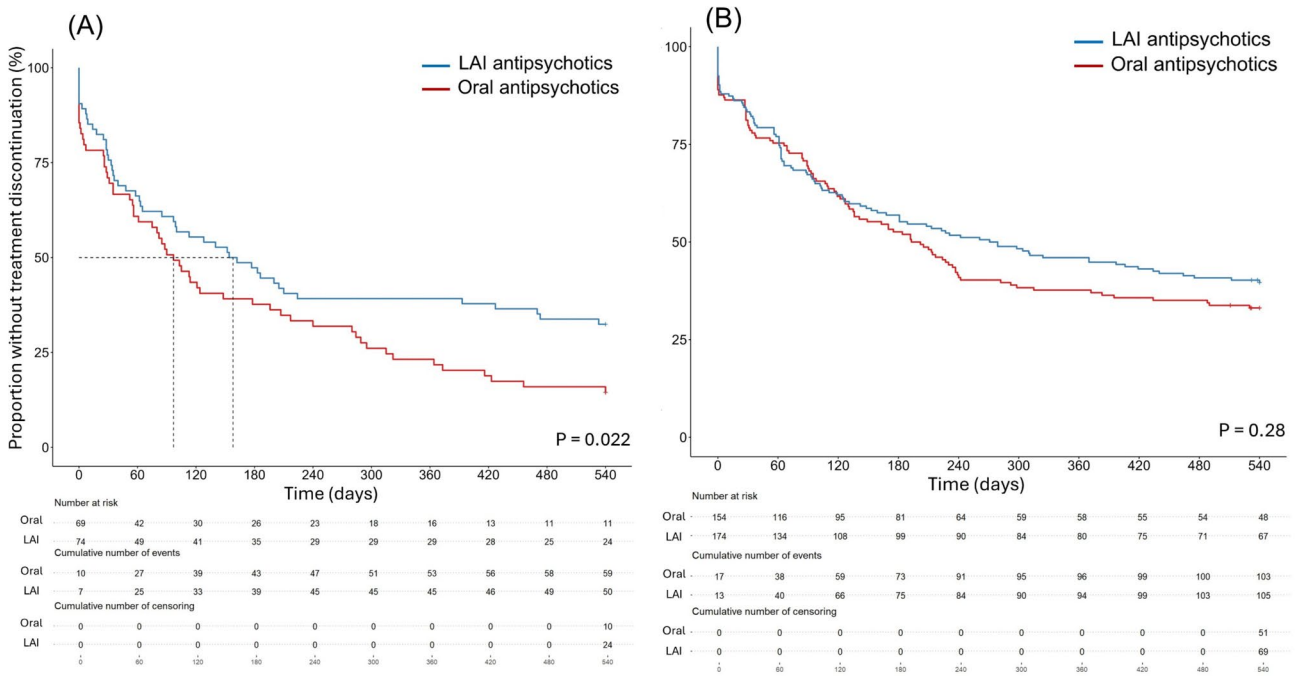

Fig. 2 Treatment discontinuation of LAI and oral antipsychotic treatments because of any cause in participants (**A**) with comorbid SUD and in (**B**) without comorbid SUD. Dashed lines indicate median time without treatment discontinuation under treatment. *P* values for the effect of mode of antipsychotic treatment (oral versus LAI) on the adjusted HR of all-cause discontinuation are shown in each plot. *LAI* long-acting injectable

3.6 Comparable Hazard Ratios for LAIs and Oral Antipsychotics in Non-SUD

The Cox proportional hazard regression model in non-SUD demonstrated a poor discriminative performance with a concordance index comparable to chance (0.52, SE = 0.021). The likelihood test (χ^2 (3) = 2.38, $P = 0.5$) and Wald test (χ^2 (3) = 2.37, $P = 0.5$) revealed that the model is not a statistically significant predictor of hazard ratios of all-cause discontinuation. Consequently, none of the factors within the model were found to be significantly associated with hazard ratios of all-cause discontinuation. This included mode of antipsychotic treatment (LAI versus oral; $P = 0.282$), age ($P = 0.69$), and sex ($P = 0.4$). Kaplan–Meier curves (Fig. 2b) demonstrated comparable survival trajectories for LAI antipsychotics and oral antipsychotics in non-SUD.

Similar findings were found by the model examining the crude hazard ratio for all-cause discontinuation in the non-SUD sample. The overall model was not statistically significant as per likelihood ratio test (χ^2 (1) = 1.27, $P = 0.3$) and Wald test (χ^2 (1) = 1.28, $P = 0.3$), with a nonsignificant effect for mode of antipsychotic treatment (LAI versus oral; crude hazard ratio = 0.855, 95% CI 0.651–1.122, $P = 0.259$).

4 Discussion

To our knowledge, this is the first analysis of an effectiveness measure, such as all-cause discontinuation, in a pragmatic clinical trial among people with early course schizophrenia and comorbid SUD. The risk for all-cause discontinuation during the observation period of 19 months was 36% lower for LAI antipsychotic treatment compared with oral antipsychotic treatment in the population with SUD ($P = 0.022$), whereas there was no significant association between mode of treatment (LAI versus oral) in the population without SUD ($P = 0.282$). This finding was robust, holding true even when the analysis was restricted to the subgroup of individuals with a current SUD.

Our analysis complements existing evidence from other secondary analyses of large-scale schizophrenia trials such as EUFEST, OPTiMiSE, and CATIE, where symptom severity in people with comorbid SUD was investigated. In the secondary analyses of the EUFEST trial, people with first-episode schizophrenia with SUD versus without SUD showed similar psychopathology and neuropsychological performances at baseline and during the first 6 months of antipsychotic treatment, but here, only oral antipsychotics were investigated [14]. In CATIE, significantly poorer outcomes were observed in the domains of psychosis, symptoms of depression, and quality of life for moderate

and severe drug users; however, here, only oral agents were under investigation. In OptiMiSe, suicidality and comorbid SUD were mixed without showing significant associations to worse symptomatic remission outcomes [16].

To the best of our knowledge, randomized controlled trials examining the use of LAI antipsychotics in people with dual disorder remain scarce [21–23]. In the open-label randomized controlled study from Rubio et al., people randomized to LAI risperidone ($n = 57$) showed less symptom severity than people with LAI zuclopenthixol ($n = 58$) after 6 months [21]. In the randomized trial from Green et al., $n = 95$ participants with DSM-IV-text revision (TR) diagnoses of schizophrenia and alcohol use disorder were randomized to 6 months of oral or LAI risperidone [22]. Here, the LAI group showed lower average drinking days per week [22]. In another randomized trial in people with psychosis (including bipolar disorder) and comorbid SUD, LAI (namely aripiprazole and paliperidone) treatment was beneficial in terms of symptom severity and quality of life during a 1-year follow-up period [23]. Overall, the most convincing evidence regarding the association of LAI versus oral in dual disorders is derived from representative within-individual analyses from Finnish and Swedish registers, where the superiority of LAI was shown in terms of hospitalization risk [10]. Thus, we provide here the first large-scale randomized controlled trial addressing the clinically relevant question of whether people with schizophrenia and SUD may profit from LAI-treatment. Our work can help to answer the clinically relevant question of whether LAI treatment has advantages over oral antipsychotic treatment—so far, guidelines are not conclusive regarding this question and do not recommend LAIs as a specific treatment for psychosis and coexisting substance misuse [11, 24–26]. The reason is that meta-analyses comparing oral versus LAI treatment in schizophrenia did not show a clear advantage for LAIs based on methodological issues that may overestimate the efficacy of oral antipsychotics in those designs [27, 28]. This stands in contrast not only to real-world registry data [10] but also to several key randomized trials in early phase schizophrenia that have demonstrated a clear advantage for LAIs in preventing relapse, a more definitive clinical endpoint than all-cause discontinuation [29, 30]. However, most guidelines use only meta-analyses of RCTs or large-scale RCTs as main source of evidence, and thus, our studies will give further support to recommend LAIs, especially in those individuals with schizophrenia and comorbid SUD. This assertion is further substantiated by recent systematic reviews that have begun to emphasize the potential for LAIs as a first-line treatment strategy in people with dual disorder, thereby underscoring the growing recognition of their importance in clinical practice [31].

Our approach has several strengths. First, it has to be mentioned that EULAST was a negative study regarding ACD as primary outcome [18], and the superiority of LAI versus oral was only shown in our secondary analysis among people with comorbid SUD, underlying the need to define subgroups when analyzing clinical trials. Second, the assessment of treatment adherence or patient preferences regarding LAI versus oral did not play a role in randomization processes, and thus, participants preferring oral medication might have been randomized to the LAI group, which further strengthens the clinical relevance of our findings. Third, given that the study's design encompassed diverse European healthcare systems and settings, it can be reasonably assumed that the findings are indeed applicable to a broader population. Finally, the most frequently used second-generation LAIs were used in our trial, making the setting comparable to clinical reality.

As limitations, it should be mentioned that we did not control for active drug use during the trial, since this information at every quarterly visit was incomplete, which may hamper meaningful interpretation in the EULAST dataset. Furthermore, we were not able to dissect our findings by specific SUDs (e.g., alcohol versus cannabis versus opioids) or by polysubstance use, as this level of detail was not available for analysis from the original trial. This is an important limitation, as the type of substance can have differential effects on treatment adherence and clinical outcomes. The large Scandinavian registry studies in similar populations have identified alcohol use disorders, cannabis use disorders, and polysubstance use as single comorbidity or together as the most prevalent comorbidities in schizophrenia [3], but we cannot confirm if this distribution applies to our specific EULAST subsample. Methodologically, our analysis was stratified by SUD status rather than employing a single model with a formal interaction term. While our approach directly addresses the clinical question of treatment effectiveness within each subgroup, we acknowledge that future prospective studies designed specifically to compare these effects could benefit from a design that supports a formal interaction analysis with adequately powered and matched groups. In addition, future studies should include a larger population of people diagnosed with a current or lifetime SUD, to attain adequate statistical power to differentiate between the advantages of LAI across these two distinct subgroups. Finally, our preliminary evidence suggests that LAIs may offer a benefit in terms of delaying treatment discontinuation in individuals with psychosis and comorbid SUD. Further research is necessary to accurately quantify the potential clinical benefits and tolerability of LAIs in this specific population.

5 Conclusions

This secondary analysis of the multisite randomized open-label EULAST trial provides high-quality evidence for the significant superiority of second-generation LAI versus oral second-generation treatment strategies in people with early phase schizophrenia and comorbid SUD. We wish to conclude that LAI treatment in people with schizophrenia and SUD has the potential to enhance the likelihood for a relapse free disease course with less hospitalizations. However, whether this finding translates to higher quality of life remains elusive. Our findings will inform clinicians and clinical guidelines for schizophrenia and comorbid SUD.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40263-025-01225-0.

Acknowledgements The original study was overseen by a Data Safety Monitoring Board (DSMB), an independent board of experts responsible for protecting participant safety and data quality. We are grateful for the involvement and contribution of the DSMB, consisting of the following members: Pál Czobor, Robin Emsley, and Stephen Marder. M.M. and E.W. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

EULAST Study Group: René Sylvain Kahn, Walter Wolfgang Fleischhacker, Michael Davidson, Inge Winter-van Rossum, Mark Weiser, Jurjen Luykx, Alkomiet Hasan, Monica Mosescu, Silvana Galderisi, Marina Kupchik, Nikos Stefanis, Alexander Teitelbaum, Paola Rocca, Georg Psota, George Umoh, Istvan Bitter, Lucho Hranov, Alex Hofer, Joachim Cordes, Ramin Nilforooshan, Julio Bobes, Solveig Klebo Reitan, Manuel Morrens, Aurel Nirestean, John Geddes, Benedicto Crespo Faccorro, Marcin Olajossy, Alessandro Rossi, Erik Johnsen, Csekey László, Adela Ciobanu, Peter Haddad, Igor Oife, Miquel Bernardo, Rodicutza Stan, Marek Jarema, Dan Rujescu, Libor Ustohal, Neil Mayfield, Paola Dazzan, Avi Valeversuski, Jan Libiger, Richard Köhler, Pavel Mohr, Sofia Pappa, Petros Drosos, Thomas Barnes, Esther DeClercq, Elias Wagner, Paola Bucci, Armida Mucci, Yaacov Rabinowitz, Adam Adamopoulous, Benjamin Draiman, Cristiana Montemagni, Manfred Greslechner, Hannah Herlihy, Csilla Bolyos, Christian Kraepelin-Schmidt, Jessica True, Leticia Alvarez Garcia, Berit Walla, Bernhard Sabbe, Lucaks Emese, Sarah Mather, Nikodem Skoczen, Serena Parnanzone, Jill Bjarke, Krisztina Karácsonyi, Steve Lankshear, Marina Garriga, Adam Wichniak, Heidi Baumbach, Timo Schurr, Leonie Willebrands, Lyliana Nasib, Cynthia Okhuijsen-Pfeifer, and Elianne Huijsman.

Funding Open Access funding enabled and organized by Projekt DEAL. This work was also supported by the clinical trials infrastructure of the DZPG [German Center for Mental Health, Munich, Augsburg] (FKZ: 01EE2303C to Alkomiet Hasan). As outlined in the primary endpoint publication, we thank Lundbeck and Otsuka, who provided financial support and study medication. Neither company had an influence on study conduction, data analysis and writing of the manuscript. The article processing fees were covered by the open access agreement between Springer Nature and the Augsburg University through the German DEAL Consortium.

Declarations

Conflicts of interest The authors declare that there are no conflicts of interest in relation to the subject of this study. General declaration of potential conflict of interests: E.W. was invited to advisory boards from Recordati, Teva, and Boehringer Ingelheim. A.H. was and is a member of advisory boards and received paid speakership by Boehringer-Ingelheim, Lundbeck, Otsuka, Rovi, Teva (no speakership), AbbVie, Recordati, and Advanz. He is editor of the AWMF German guidelines for schizophrenia. W.W.F. has received grants from Otsuka and Lundbeck and speaker's fees from Sumitomo Pharma. M.D. is an employee of Minerva Neurosciences, a biotech developing central nervous system drugs. In the past 3 years, S.L. has received honoraria as a consultant, adviser, or lecturer from Alkermes, Angelini, Eisai, Gedeon Richter, Janssen, Lundbeck, Lundbeck Institute, Merck Sharpp and Dome, Otsuka, Recordati, Rovi, Sanofi Aventis, TEVA, Medichem, and Mitsubishi. D.S. has no conflicts to declare. All other authors declare no competing interests.

Consent to participate All study participants provided informed written consent for secondary data analysis.

Consent for publication All study participants provided informed written consent.

Ethics approval Relevant regulatory bodies and ethics committees in each participating country approved the study and its adherence to local regulations and the Declaration of Helsinki. The trial was overseen by the University Medical Center Utrecht in the Netherlands, following the guidelines of Good Clinical Practice and the International Conference on Harmonization.

Availability of data and material 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.

Code availability A request for receipt of the codes (R scripts and SPSS Syntax) can be submitted for review and approval by the study management group.

Author contributions M.M., E.W., and A.H. designed the secondary analysis. M.M. and Z.A. conducted the statistical analysis. M.M., A.H., and E.W. interpreted the data and wrote the initial draft of the manuscript. A.H., E.W., and I.W.-v.R. conceptualized the study, provided supervision, and critically revised the manuscript for important intellectual content. I.W.-v.R., R.S.K., W.W.F., M.D., M.W., S.L., and the EULAST Study Group were responsible for the design and conduct of the original EULAST trial and the acquisition of the data. D.S. provided critical intellectual contributions and revisions. All authors reviewed and approved the final manuscript. M.M. and Z.A. share the first authorship; A.H. and E.W. share the last authorship.

References

1. Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. PLoS Med. 2005;2(5):e141. https://doi.org/10.1371/journal.pmed.0020141.
2. Solmi M, Seitidis G, Mavridis D, et al. Incidence, prevalence, and global burden of schizophrenia—data, with critical appraisal, from the Global Burden of Disease (GBD) 2019. Mol Psychiatry. 2023;28(12):5319–27. https://doi.org/10.1038/s41380-023-02138-4.
3. Lähteenvuo M, Batalla A, Luykx JJ, et al. Morbidity and mortality in schizophrenia with comorbid substance use disorders. Acta Psychiatr Scand. 2021;144(1):42–9. https://doi.org/10.1111/acps.13291.
4. Mallard TT, Harden KP, Fromme K. Genetic risk for schizophrenia is associated with substance use in emerging adulthood: an event-level polygenic prediction model. Psychol Med. 2019;49(12):2027–35. https://doi.org/10.1017/s0033291718002817.
5. Ward HB, Nemeroff CB, Carpenter L, et al. Substance use disorders in schizophrenia: prevalence, etiology, biomarkers, and treatment. Pers Med Psychiatry. 2023;39–40:100106. https://doi.org/10.1016/j.pmip.2023.100106.
6. Guloksuz S, Pries LK, Delespaul P, et al. Examining the independent and joint effects of molecular genetic liability and environmental exposures in schizophrenia: results from the EUGEI study. World Psychiatry. 2019;18(2):173–82. https://doi.org/10.1002/wps.20629.
7. Khokhar JY, Dwiel LL, Henricks AM, Doucette WT, Green AI. The link between schizophrenia and substance use disorder: a unifying hypothesis. Schizophr Res. 2018;194:78–85. https://doi.org/10.1016/j.schres.2017.04.016.
8. Solmi M, De Toffol M, Kim JY, Choi MJ, Stubbs B, Thompson T, Dragioti E. Balancing risks and benefits of cannabis use: umbrella review of meta-analyses of randomised controlled trials and observational studies. BMJ. 2023;382.
9. Schmidt LM, Hesse M, Lykke J. The impact of substance use disorders on the course of schizophrenia—a 15-year follow-up study: dual diagnosis over 15 years. Schizophr Res. 2011;130(1–3):228–33. https://doi.org/10.1016/j.schres.2011.04.011.
10. Lähteenvuo M, Luykx JJ, Taipale H, et al. Associations between antipsychotic use, substance use and relapse risk in patients with schizophrenia: real-world evidence from two national cohorts. Br J Psychiatry. 2022;221(6):758–65. https://doi.org/10.1192/bjp.2022.117.
11. Howes OD, McCutcheon R, Agid O, et al. Treatment-resistant schizophrenia: treatment response and resistance in psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. Am J Psychiatry. 2017;174(3):216–29. https://doi.org/10.1176/appi.ajp.2016.16050503.
12. McCutcheon R, Beck K, D'Ambrosio E, et al. Antipsychotic plasma levels in the assessment of poor treatment response in schizophrenia. Acta Psychiatr Scand. 2018;137(1):39–46. https://doi.org/10.1111/acps.12825.
13. Taipale H, Schneider-Thoma J, Pinzón-Espinosa J, et al. Representation and outcomes of individuals with schizophrenia seen in everyday practice who are ineligible for randomized clinical trials. JAMA Psychiat. 2022;79(3):210–8. https://doi.org/10.1001/jamapsychiatry.2021.3990.
14. Wobrock T, Falkai P, Schneider-Axmann T, et al. Comorbid substance abuse in first-episode schizophrenia: effects on cognition and psychopathology in the EUFEST study. Schizophr Res. 2013;147(1):132–9. https://doi.org/10.1016/j.schres.2013.03.001.
15. Kerfoot KE, Rosenheck RA, Petrakis IL, et al. Substance use and schizophrenia: adverse correlates in the CATIE study sample. Schizophr Res. 2011;132(2–3):177–82. https://doi.org/10.1016/j.schres.2011.07.032.
16. Nasib LG, Winter-van Rossum I, Zuithoff NPA, Boudewijns Z, Leucht S, Kahn RS. Generalizability of the results of efficacy trials in first-episode schizophrenia: comparing outcome and study discontinuation of groups of participants in the optimization of treatment and management of schizophrenia in Europe (OPTiMiSE) Trial. J Clin Psychiatry. 2023. https://doi.org/10.4088/JCP.22m14531.
17. Krause M, Huhn M, Schneider-Thoma J, Bighelli I, Gutsmiedl K, Leucht S. Efficacy, acceptability and tolerability of antipsychotics in patients with schizophrenia and comorbid substance use. A systematic review and meta-analysis. Eur Neuropsychopharmacol. 2019;29(1):32–45. https://doi.org/10.1016/j.euroneuro.2018.11.1105.
18. Winter-van Rossum I, Weiser M, Galderisi S, et al. Efficacy of oral versus long-acting antipsychotic treatment in patients with early-phase schizophrenia in Europe and Israel: a large-scale, open-label, randomised trial (EULAST). Lancet Psychiatry. 2023;10(3):197–208. https://doi.org/10.1016/s2215-0366(23)00005-6.
19. R Core Team. _R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2024. https://www.R-project.org/.
20. RStudio Team. RStudio: integrated development for R. Boston: RStudio, PBC; 2020. http://www.rstudio.com/.
21. Rubio G, Martínez I, Ponce G, Jiménez-Arriero MA, López-Muñoz F, Alamo C. Long-acting injectable risperidone compared with zuclopenthixol in the treatment of schizophrenia with substance abuse comorbidity. Can J Psychiatry. 2006;51(8):531–9. https://doi.org/10.1177/070674370605100808.
22. Green AI, Brunette MF, Dawson R, et al. Long-acting injectable vs oral risperidone for schizophrenia and co-occurring alcohol use disorder. J Clin Psychiatry. 2015;76(10):1359–65. https://doi.org/10.4088/JCP.13m08838.
23. Cuomo I, Kotzalidis GD, de Persis S, et al. Head-to-head comparison of 1-year aripiprazole long-acting injectable (LAI) versus paliperidone LAI in comorbid psychosis and substance use disorder: impact on clinical status, substance craving, and quality of life. Neuropsychiatr Dis Treat. 2018;14:1645–56. https://doi.org/10.2147/ndt.S171002.
24. NICE. Clinical guideline [CG120]: Coexisting severe mental illness (psychosis) and substance misuse: assessment and management in healthcare settings. 2011.
25. Buchanan RW, Kreyenbuhl J, Kelly DL, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophr Bull. 2010;36(1):71–93. https://doi.org/10.1093/schbul/sbp116.
26. Keepers GA, Fochtmann LJ, Anzia JM, et al. The American Psychiatric association practice guideline for the treatment of patients with schizophrenia. Am J Psychiatry. 2020;177(9):868–72. https://doi.org/10.1176/appi.ajp.2020.177901.
27. Leucht C, Heres S, Kane JM, Kissling W, Davis JM, Leucht S. Oral versus depot antipsychotic drugs for schizophrenia–a critical systematic review and meta-analysis of randomised long-term trials. Schizophr Res. 2011;127(1–3):83–92. https://doi.org/10.1016/j.schres.2010.11.020.
28. Ostuzzi G, Bertolini F, Tedeschi F, et al. Oral and long-acting antipsychotics for relapse prevention in schizophrenia-spectrum

disorders: a network meta-analysis of 92 randomized trials including 22,645 participants. World Psychiatry. 2022;21(2):295–307. https://doi.org/10.1002/wps.20972.
29. Subotnik KL, Casaus LR, Ventura J, Luo JS, Hellemann GS, Gretchen-Doorly D, et al. Long-acting injectable risperidone for relapse prevention and control of breakthrough symptoms after a recent first episode of schizophrenia: a randomized clinical trial. JAMA Psychiat. 2015;72(8):822–9.
30. Kane JM, Schooler NR, Marcy P, Correll CU, Achtyes ED, Gibbons RD, et al. Effect of long-acting injectable antipsychotics versus usual care on time to first hospitalization in early-phase schizophrenia: a randomized clinical trial. JAMA Psychiatr. 2020;77(12):1217–24.
31. Martinotti G, Chiappini S, Mosca A, Miuli A, Santovito MC, Pettorruso M, et al. Atypical antipsychotic drugs in dual disorders: current evidence for clinical practice. Curr Pharm Des. 2022;28(27):2241–59.

Authors and Affiliations

Matin Mortazavi[1,2] · Zahra Aminifarsani[1,2] · Inge Winter-van Rossum[3,4] · René S. Kahn[4] · W. Wolfgang Fleischhacker[5,13] · Michael Davidson[6,14] · Mark Weiser[7,8] · Dan Siskind[9,10] · Stefan Leucht[11] · EULAST Study Group · Alkomiet Hasan[2,12] · Elias Wagner[1,2]

✉ Matin Mortazavi
matinmortazavi3@gmail.com

1 Evidence-based Psychiatry and Psychotherapy, Faculty of Medicine, University of Augsburg, Augsburg, Germany

2 Department of Psychiatry, Psychotherapy and Psychosomatics, Medical Faculty, University of Augsburg, BKH Augsburg, Augsburg, Germany

3 Department of Psychiatry, UMC Utrecht Brain Centre, University Medical Centre Utrecht, Utrecht University, Utrecht, Netherlands

4 Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA

5 Department of Psychiatry, Psychotherapy and Psychosomatic Medicine, Medical University of Innsbruck, Innsbruck, Austria

6 Department of Basic and Clinical Sciences, Psychiatry, University of Nicosia Medical School, 2414 Nicosia, Cyprus

7 Pinchas and Drora Division of Psychiatry, Sheba Medical Center, Tel HaShomer, Israel

8 Department of Psychiatry, Tel Aviv University School of Medicine, Ramat Aviv, Israel

9 Addiction and Mental Health Service, Metro South Health, Brisbane, Australia

10 Faculty of Health, Medicine And Behavioural Sciences, University of Queensland, Brisbane, Australia

11 Department of Psychiatry and Psychotherapy, School of Medicine and Health, Technical University of Munich, 81675 Munich, Germany

12 DZPG (German Center for Mental Health), Partner site München/Augsburg, Augsburg, Germany

13 Weill Cornell Medicine, New York, NY, USA

14 Minerva Neurosciences, 1500 District Avenue, Burlington, MA 01803, USA