The trajectory of sedative adverse events caused by antipsychotics: a meta-analysis of individual participant data from randomised, placebo-controlled, clinical trials in acute phase schizophrenia

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Summary

Background Sedative adverse events are common in patients with schizophrenia undergoing antipsychotic treatment, which affects treatment adherence and the patients' quality of life. Although tolerance to sedation is believed to develop, robust evidence documenting the timing of sedation onset and resolution remains elusive. To address this gap, we aimed to assess the dynamics of onset and resolution of sedation across various antipsychotics in patients with schizophrenia.

Methods In this meta-analysis, we included placebo-controlled, randomised controlled trials (RCTs) of antipsychotic monotherapy for the acute phase of schizophrenia and schizoaffective disorder. We searched PubMed for RCTs from inception until May 6, 2021 and obtained individual participant data of included trials through the Yale University Open Data Access project. We created Kaplan–Meier curves to assess the probability of onset of sedation and resolution from the incidence of sedation across time after treatment initiation. People with lived experience were not involved in this study. This study is registered with PROSPERO, CRD42022351647.

Findings We included a total of 6791 participants (4549 [67·0%] men and 2242 [33·0%] women, with a mean age of 38·0 years [SD 12·4, range 13–81], 1172 [17·3%] were Asian, 1626 [23·9%] were Black, 3654 [53·8%] were White, and 339 [5·0%] were other ethnicities) from 19 RCTs. Sedative adverse events were observed in 582 (8·6%) of 6791 participants and typically occurred shortly after treatment initiation. Among participants receiving antipsychotics, 418 (83%) of 505 sedation events occurred within the first 2 weeks of treatment. Following the onset of sedation, 50% of symptoms were resolved within 1 week. After 4 weeks of treatment, 24% (95% CI 19·7–29·3) continued to have sedation with oral agents and 22·3% (15·3–32·3) with long-acting injectables.

Interpretation The high incidence of sedation within the first 2 weeks of treatment with antipsychotics emphasises the importance of early monitoring. Half of the sedation resolved within 1 week and 75% within 1 month, suggesting that tolerance to sedation is acquired quickly. If sedation is sustained, contributing factors should be evaluated.

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Introduction

Schizophrenia is a common disease with a prevalence of 1% of the global population. Antipsychotics are the primary pharmacological treatment for patients with schizophrenia and are often needed for managing symptoms and preventing relapse.[1] Continued use of antipsychotics is associated with a lower mortality rate.[2] However, antipsychotics cause various side-effects, including sedation, metabolic and cardiovascular disturbances, hyperprolactinaemia, and sexual dysfunction.[3] These side-effects can reduce the user's quality of life, decrease adherence,[4] and ultimately increase the risk of relapse.[5]

Sedative adverse events, such as sedation, somnolence, drowsiness, and fatigue, are some of the most common burdens of antipsychotic treatment, substantially affecting daily activity.[6,7] Hynes and colleagues reported that 75% of inpatients with schizophrenia reported daily drowsiness as a side-effect of antipsychotics.[7] Despite its high prevalence and substantial effect on patient wellbeing, there is no clear evidence for when sedation usually begins and ends after the start of antipsychotic treatment. Although patients might develop tolerance over time, the temporal dynamics of this process remain uncertain.[8–10] This uncertainty complicates clinical decisions, especially when considering treatment changes owing to sedation or further diagnostic evaluations for less common causes of persistent sedation.

Antipsychotic medications, characterised by diverse receptor profiles, are associated with varying risks of sedative adverse events.[11] A comprehensive meta-analysis revealed that the risk of sedation varies from antipsychotic to antipsychotic.[3] Histamine H_1 receptor affinity of

Research in context

Evidence before this study

Sedative adverse events, such as sedation, somnolence, and fatigue, are frequent in patients receiving antipsychotic treatment for schizophrenia, and negatively affect quality of life and treatment adherence. However, there is little understanding of the temporal trajectory of these events, including their onset and resolution, across different antipsychotic drugs. On Aug 10, 2024, we searched PubMed from inception to the search date using the terms ("antipsychotic*" OR "neuroleptic*") AND ("sedation" OR "somnolence" OR "drowsiness" OR "fatigue") AND ("onset" OR "resolution" OR "time to onset" OR "time to resolution" OR "trajectory" OR "time course"), without language restrictions. Our search identified 244 studies. Although many studies reported the incidence of sedation as a common adverse event, very few provided detailed analyses of its time course. The available studies often focused on just two timepoints: the start and end of the observation period, limiting insights into the dynamic changes in sedation over time. One study pooled data from seven randomised controlled trials focusing on asenapine in patients with acute schizophrenia and addressed the time course of sedation. However, these findings were limited by the focus on specific drugs and the relatively small sample. Additionally, it did not explore the effect of important covariates such as sex, age, and weight in a comprehensive manner. No individual participant data meta-analyses on sedation trajectories induced by antipsychotics were identified. Our study aims to fill this gap by offering an analysis of the onset and resolution of sedation across antipsychotics, by use of individual participant data from randomised placebo-controlled trials to assess the effect of patient characteristics and drug-specific factors, informing clinical decision making.

Added value of this study

This study represents the first meta-analysis based on individual participant data to investigate the temporal trajectory of sedative adverse events associated with antipsychotic treatment in patients with schizophrenia and schizoaffective disorder. Our study found that sedation typically begins within the first few days of treatment, with about 80% of events occurring within the first 2 weeks. Sedation resolved in 50% of cases within 1 week, but in approximately 25% of patients, it persisted beyond 4 weeks. By systematically evaluating the time to onset and resolution of sedation across various antipsychotics, this study provides crucial insights into the dynamics of sedative effects and highlights the role of factors such as drug formulation, receptor profiles, and patient demographics. These findings equip clinicians with evidence-based data to anticipate and manage sedative adverse events more effectively.

Implications of all the available evidence

The findings from this meta-analysis have important implications for the management of sedation in schizophrenia treatment. By identifying the temporal patterns of sedative adverse events, this study helps to guide clinical decision making regarding treatment adjustments and the need for further diagnostic evaluations when persistent sedation is observed. With most sedative events occurring in the first 2 weeks and resolving in half of the patients within 1 week, clinicians can inform patients about the probable course of sedation and better manage expectations, potentially improving adherence and reducing early discontinuation. The persistence of sedation in about 25% of patients beyond 4 weeks signals the need for careful monitoring and possible treatment adjustments. Additionally, the study can provide guidance on how patient characteristics such as sex, age, and weight, as well as the specific antipsychotic drug used, influence sedation risk. The insights gained from this research can be applied to future clinical trials, to optimise treatment strategies and enhance the quality of life for patients undergoing antipsychotic therapy.

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antipsychotics is one of the main factors of sedation.[12] However, some studies have reported associations between sedation and muscarinic M1 and M4 receptors,[13] as well as the adrenergic α_1 receptor, indicating that the effects of antipsychotics on various receptors are complex. In addition, sex differences have been reported with regard to tolerability of antipsychotic drugs, including tiredness.[6] Age, weight, and drug formulations (eg, oral and long-acting injectable [LAI]) are associated with differences in pharmacokinetics,[14] and might influence the probability of the occurrence of side-effects. LAIs might generally have fewer side-effects than oral agents.[15] This meta-analysis made use of individual participant data (IPD) to determine the temporal trajectory of sedative adverse events induced by antipsychotic treatment in patients with schizophrenia and schizoaffective disorder, including time to onset and resolution of sedation.

Methods

Search strategy and selection criteria

The PRISMA guidelines for individual participant data (PRISMA-IPD)[16] were used for this IPD meta-analysis (appendix pp 4–7). We included placebo-controlled, randomised controlled trials (RCTs) from the Yale University Open Data Access (YODA) project database. Only studies with available IPD were included. We included patients in the acute phase of schizophrenia or schizoaffective disorder who were diagnosed by operationalised criteria, such as DSM. We included studies that used monotherapy with antipsychotics in any formulation. If antipsychotic monotherapy was switched to polytherapy during the study, only the monotherapy phase was included. Studies switching from polytherapy to monotherapy were excluded. There were no restrictions based on sex, age, or ethnicity. Studies focusing on diagnoses other than schizophrenia or schizoaffective

See **Online** for appendix

For the **YODA project database** see https://yoda.yale.edu/2022

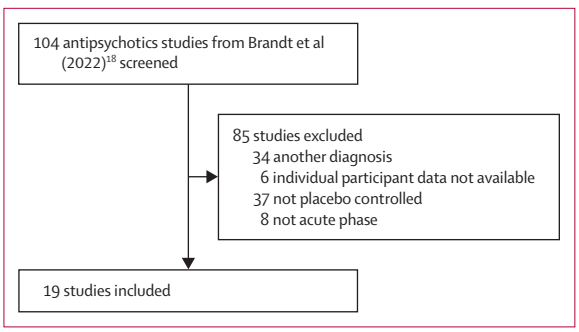

Figure 1: **Study selection**

disorder were excluded. Studies in the maintenance phase and studies focusing on relapse prevention were excluded. Additionally, IPDs with clear indications of non-compliance with the study protocol, such as cases in which the administered medication was uncertain due to allocation errors, were excluded, as this study was specifically designed to investigate drug-induced adverse events rather than the therapeutic effects of the drugs. We identified eligible studies and data through the screening results of a previous systematic review[17,18] from our group, which also used antipsychotic placebo-controlled RCTs with IPD from YODA (figure 1) from database inception until May 6, 2021. This study is registered with PROSPERO, CRD42022351647 (see appendix pp 12–17).

Outcomes

The main aim of the study was to investigate the trajectory of sedation caused by antipsychotics by focusing on two crucial timepoints: from treatment initiation to sedation onset, and from sedation onset to its resolution. The time of onset and resolution of sedation were extracted for all randomly assigned participants in the double-blind phase. Demographic characteristics such as age, sex, and ethnicity, as well as type and formulation (oral or LAI) of antipsychotics, were also extracted. Sedative adverse events were defined by use of MedDRA's preferred terms: sedation, somnolence, and fatigue. These three preferred terms include several lowest level terms, such as sleepiness and tiredness (appendix p 10). When multiple preferred term events overlapped temporally, we treated them as a single event, with the first event marking the onset date, and the last event resolution marking the end date. We only included the first sedation event during the double-blind phase, regardless of the severity or whether the events were associated with the interventions done in each study. The dataset was created with day 1 as the start date of the intervention.

Data analysis

First, we calculated the cumulative incidence (risk) of sedation for both the entire treatment period and the shortest observed treatment duration across interventions, as well as the median time to onset of sedation and the IQR, among patients who had sedation for each antipsychotic and placebo separately. The cumulative incidence was calculated by dividing the number of sedation events during each period by the total number of participants who received the intervention. The patients who dropped out of a study without an event were assumed not to have had sedation. Survival analyses were done on the time to onset and resolution of sedation by use of the Kaplan–Meier estimate to account for varying observation periods across included studies and patient dropout. Weekly cumulative sedation risk was estimated by Kaplan–Meier analysis, and the number needed to harm was calculated as the inverse of the risk difference derived from these weekly risks. Events unresolved by the end of the double-blind phase were censored at the last observation point. Patients who dropped out during the double-blind phase were censored at the dropout time.

Next, we did a one-stage meta-analysis by use of a Cox model, aiming to assess the effect of oral and LAI antipsychotics compared with placebo on the hazard of sedation onset and time to sedation resolution (after occurrence of sedation). Random effects were incorporated to model study-specific heterogeneity, with age, sex, weight, and type of antipsychotic intervention as fixed effect covariates, acknowledging these as key factors that might influence outcomes. Adjusted hazard ratios (aHRs), 95% CIs, and two-tailed p values were estimated. We calculated 95% predictive intervals (PIs) for the treatment effect.[19] The proportional hazards assumption was assessed through a Schoenfeld residuals plot, and we provided a p value for the corresponding test. To evaluate goodness-of-fit and the linearity assumption for the continuous, we calculated Martingale residuals and Cox–Snell residuals. Of note, for this analysis, we used a fixed-effects Cox model, as residuals could not be calculated for the random-effects model.

We analysed the combined data of all oral antipsychotics with oral placebos and all LAI antipsychotics with LAI placebos, grouping drugs by formulation regardless of the specific molecule. Subsequently, we did separate analyses to compare oral and LAI formulations separately with placebo. Then, we did a subgroup analysis by use of only data from individual antipsychotics and placebo to check the robustness of the main results.

We also did a two-stage meta-analysis, calculating study-specific aHRs, which were then pooled by use of a random-effects model and summarised in a forest plot. As a further sensitivity analysis, aiming to incorporate possible heterogeneity of the effects of the covariates across studies, we used a one-stage model with covariate-by-study interaction terms.

As a post-hoc analysis, the main one-stage model was extended to include the baseline Positive and Negative Syndrome Scale (PANSS) score, antipsychotic dose, sedation severity, and concomitant sedative drug use as

additional covariates. Details of this analysis are provided in the appendix (pp 148–56). Additionally, we did a sensitivity analysis including only the terms somnolence and sedation to account for the potential differences from fatigue.[20]

For descriptive and Cox regression analyses, patients with missing baseline characteristics data were excluded, representing 0·4% of all cases (appendix p 11), and those who dropped out during the observation period were right censored at the time of dropout, whereas those who had the event before dropping out were included in the analysis.

Analysis was done with R (version 4.3.2/1), by use of survival for Kaplan–Meier analysis,[21] coxme for random-effects Cox regression analysis,[22] and meta for two-stage IPD meta-analysis.[23] The risk of bias for included studies was assessed by the Cochrane risk of bias tool for randomised trials (RoB1). The quality of evidence was evaluated by the GRADE approach.[24]

The project received approval from the Technical University of Munich ethics committee (number 2024-132-S-SB).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, or data interpretation, in the writing of the report, or in the decision to submit this paper for publication.

	n=6791
Men	4549 (67·0%)
Women	2242 (33·0%)
Age, years	38 (12·4; range 13–81)
Weight, kg	76·9 (20·3)
Positive and Negative Syndrome Scale total*	76·7 (33·3)
Brief Psychiatric Rating Scale total†	47·3 (13·8)
Diagnosis	
Schizophrenia	6125 (90·2%)
Schizoaffective disorder	666 (9·8%)
Intervention	
Paliperidone—oral–LAI	1894 (27·9%)–1390 (20·5%)
Risperidone—oral–LAI	670 (9·9%)–345 (5·1%)
Olanzapine—oral	366 (5·4%)
Quetiapine—oral	159 (2·3%)
Haloperidol—oral	140 (2·1%)
Placebo—oral–LAI	1059 (15·6%)–768 (11·3%)
Ethnicity	
Asian	1172 (17·3%)
Black	1626 (23·9%)
White	3654 (53·8%)
Other	339 (5·0%)

Data are n (%) or mean (SD). LAI=long-acting injectable. *Positive and Negative Syndrome Scale data were obtained from studies other than RIS-USA1.[28] †Brief Psychiatric Rating Scale data were obtained from RIS-USA1.

Table 1: **Baseline characteristics of subjects in the total study**

Results

104 studies of antipsychotic treatment were screened for eligibility. A total of 19 placebo-controlled RCTs were included, six of which tested LAIs and 13 oral antipsychotics (figure 1). Most of the included studies were on a fixed-dose schedule and only four of the 13 tested oral antipsychotic studies used a flexible dose. The characteristics of the included studies are shown in the appendix (pp 18–19). Details of the excluded studies are given in the appendix (pp 20–28). After excluding 112 patients from three studies[25–27] owing to protocol deviations or allocation errors (appendix p 29), the study included 6791 patients. 4549 (67%) were male and 2242 (33·0%) were female. Most patients were diagnosed with schizophrenia (6125 [90·2%]), and 666 (9·8%) were diagnosed with schizoaffective disorder. The mean (SD) of the baseline total PANSS score was 76·7 (33·3) across 18 studies, excluding one that used the Brief Psychiatric Rating Scale.[28] Other participants' characteristics, such as age, weight, and ethnicity, are shown in table 1. We obtained data for oral forms of risperidone, paliperidone, olanzapine, quetiapine, haloperidol, and placebo, and for LAI of risperidone, paliperidone, and placebo. The duration of treatment in the data varied by intervention. Paliperidone LAI provided the longest treatment data, with a median of 85 days (range 1–125), whereas quetiapine provided the shortest, with a median of 14 days (range 2–16; table 2).

According to the overall risk of bias rating by use of the RoB1 tool, two studies (11%) were rated as high risk, one (5%) as moderate, and the remaining 16 (84%) as low risk (appendix p 30).

During the double-blind period, 582 (8·6%) of 6791 participants had sedation events, regardless of study completion status. Among these events, 419 were mild, 155 were moderate, and eight were severe. Figure 2 illustrates the daily distribution of sedation events relative to the total observed during treatment with all

	n events in 2 weeks/total (%)	Incidence in 2 weeks (%)	Incidence in the whole period (%)	Treatment duration median (range), days
Oral*				
Paliperidone (1894)	168/192 (88%)	8·9%	10·1%	42 (1–78)
Risperidone (670)	70/83 (84%)	10·4%	12·4%	38 (1–65)
Olanzapine (366)	58/69 (84%)	15·8%	18·9%	42 (1–61)
Quetiapine (159)	37/37 (100%)	23·3%	23·3%	14 (2–16)
Haloperidol (140)	7/8 (88%)	5·0%	5·7%	33·5 (2–59)
Placebo (1059)	53/57 (93%)	5·0%	5·4%	28 (1–66)
Long-acting injectable				
Paliperidone (1390)	61/79 (77%)	4·4%	5·7%	85 (1–125)
Risperidone (345)	17/37 (46%)	4·9%	10·7%	74 (1–113)
Placebo (768)	18/20 (90%)	2·3%	2·6%	51 (2–115)

*Number in parentheses is the number of participants in each drug group.

Table 2: **The incidence of sedation on each antipsychotic in 2 weeks and the whole double-blind phase**

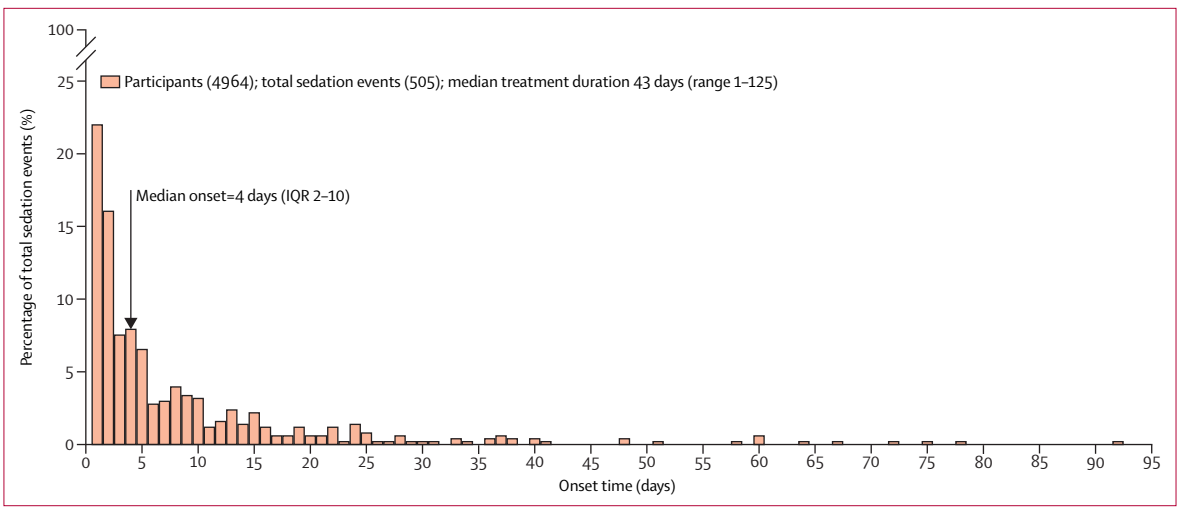

Figure 2: **Distribution of sedation onset for all antipsychotics**

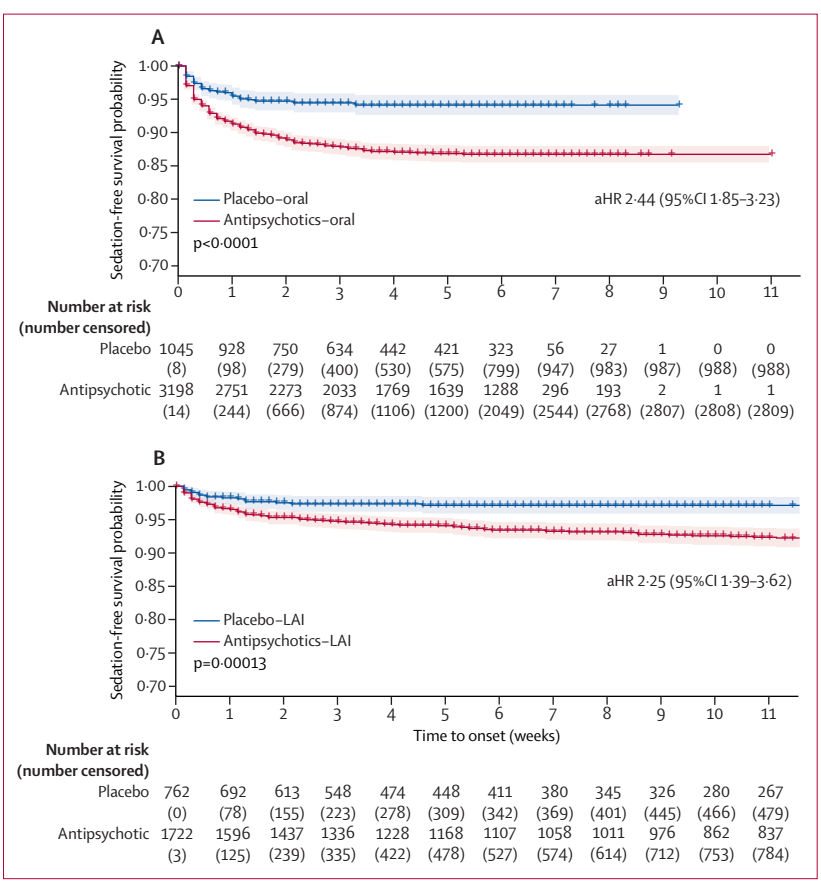

Figure 3: **Kaplan–Meier curves for the time to onset of sedation for oral and LAI antipsychotics and placebo**
(A) Oral antipsychotics and oral placebo. (B) LAI antipsychotics and LAI placebo. The shaded area represents 95% CIs. p value from log-rank test is shown. aHR=adjusted hazard ratios. LAI=long-acting injectable.

antipsychotics, excluding those individuals who received a placebo. Sedation onset peaked on the first two days following treatment initiation, with 418 (83%) of 505 sedation events occurring within the first 2 weeks. The median day of sedation onset was 4 days. The distribution of sedation onset for each individual drug is detailed in the appendix (p 31). The distribution, with peaks in the first few days and concentrated in the initial 2 weeks, was similar for most antipsychotics and placebo. However, haloperidol and LAI risperidone showed later median onset at 9 days and 16 days, respectively. The distribution of sedation duration is detailed in the appendix (pp 32–33).

During the entire observation period, the cumulative incidence of sedation was 10·2% (505 events per 4964 participants) in the antipsychotic group, 26·5% of which was unresolved by the end of the observation period. In the placebo group, the cumulative incidence of sedation was 4·2% (77 events per 1827 participants).

Within the first 2 weeks from the initiation of the intervention, sedation risk was highest for oral quetiapine at 23·3%, followed by olanzapine and oral risperidone both at 15·8%, and oral paliperidone at 8·9%. Haloperidol and oral placebo had the lowest risk, each at 5·0%. For LAIs, the risk tended to be lower than for oral formulations of the same drugs, 4·9% for risperidone, 4·4% for paliperidone, and 2·3% for placebo. Data for other interventions and the risk for the entire observation period are described in table 2.

Number needed to harm was highest in the first week for both oral antipsychotics (23·8, 95% CI 17·3–38·3) and LAIs (57·6, 33·4–211·4), and plateaued after the third week, as detailed in the appendix (p 37).

Figure 3 presents the Kaplan–Meier curves for the time to onset of sedation for all oral and LAI antipsychotics and placebo. The results from the Cox analysis, with all oral and LAI drugs combined by formulation, show an aHR for sedation onset of 2·44 (95% CI 1·85–3·23, 95% PI 0·58–10·20) for oral and 2·25 (95% CI 1·39–3·62, 95% PI 0·56–8·94) for LAI.

According to the GRADE criteria, the evidence supporting these findings is of moderate strength (appendix pp 35–36). The wide prediction intervals for the results reflect heterogeneity, which is probably driven by the different types of antipsychotic medications, as supported by the τ^2 values from individual antipsychotic analyses, which were smaller than those in the combined model: for oral antipsychotics, age had an aHR of 0·99 (95% CI 0·98–0·99) per year, and weight an aHR of 1·01 (1·01–1·02) per kg; for LAI, age had an aHR of 0·99 (95% CI 0·98–1·02) per year and weight an aHR of 1·01 (0·99–1·01) per kg. The aHR for male versus female patients was 0·86 (95% CI 0·71–1·06) for oral versus placebo, and 1·26 (0·86–1·84) for LAI versus placebo, showing weak evidence of an effect of sex. The test for proportional hazards did not provide strong evidence against the null hypothesis (appendix p 38).

The appendix (pp 43–51) illustrates the Kaplan–Meier curves for the time to onset of sedation for each antipsychotic and placebo separately, along with 95% CI. The aHR for sedation onset from Cox analysis, drug versus placebo, by use of all oral or LAI data, was highest for oral quetiapine (aHR 4·36, 95% CI 2·46–7·73), and lowest for oral paliperidone (aHR 1·83, 95% CI 1·34–2·51). The aHRs for oral and LAI formulations were similar across drugs, with risperidone showing aHR of 3·45 (95% CI 2·05–5·81) for oral and 3·74 (1·70–8·20) for LAI, and paliperidone showing 1·83 (1·34–2·51) for oral and 1·97 (1·19–3·27) for LAI (appendix p 52). The test for the proportional hazard suggested potential violations of the proportional hazard

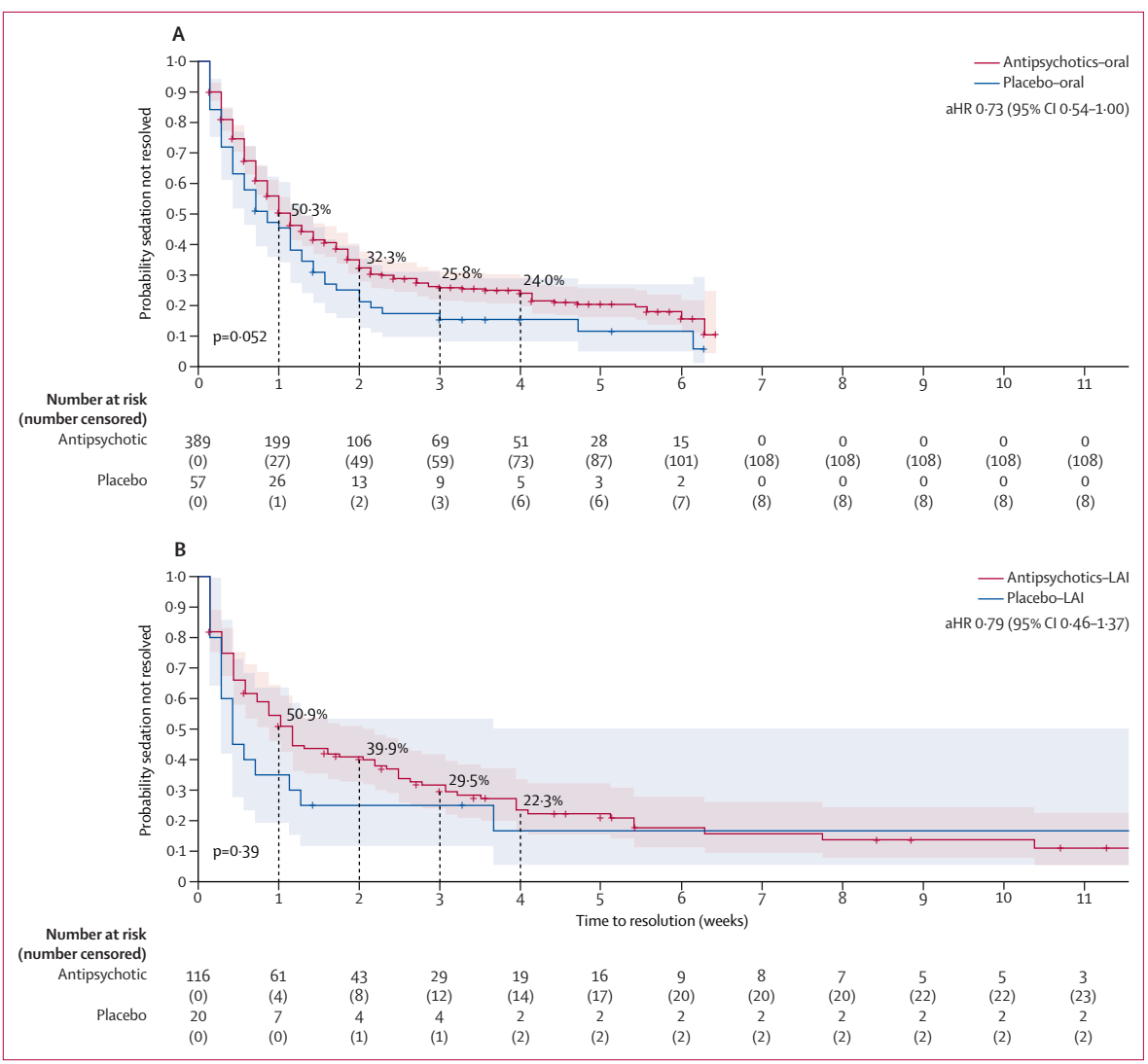

Figure 4: **Kaplan–Meier curves for the time to resolution of sedation for oral and LAI antipsychotics and placebo**
(A) Oral antipsychotics and oral placebo. (B) LAI antipsychotics and LAI placebo. The shaded area represents 95% CIs. p value from log-rank test is shown. The x-axis represents the time taken from the onset of sedation to resolution. aHR=adjusted hazard ratios. LAI=long-acting injectable.

assumption (p=0·0091 for oral, p=0·015 for LAI; appendix pp 53–54).

The results were similar when analysing data from only one antipsychotic and placebo in each Cox regression analysis. However, for the models for haloperidol, risperidone (oral and LAI), and quetiapine there was some evidence against the proportional hazards assumption for the antipsychotic covariates, indicating that their effects on sedation onset might vary over time. Further details are provided in the appendix (pp 55–60).

Figure 4 presents the Kaplan–Meier curves for the time to resolution of sedation for all oral and LAI antipsychotics and placebo. Approximately half of the sedation resolved within the first week after onset for both oral and LAI antipsychotics. However, at 4 weeks, sedation persisted in 24·0% (95% CI 19·7–29·3) of cases caused by oral antipsychotics and 22·3% (15·3–32·3) of cases caused by LAI antipsychotics. Kaplan–Meier curves and detailed data for individual antipsychotics and placebo are available in the appendix (pp 61–70). Among individual antipsychotics, LAI risperidone exhibited the longest duration of sedation, with persistence in 72·4% (59·2–88·5) at 1 week and 29·2% (16·8–50·5) at 4 weeks after onset of sedation.

The Cox analysis, in which oral and LAI antipsychotics were analysed as combined groups, showed an aHR of less than 1 for both forms. Oral antipsychotics (aHR 0·73, 95% CI 0·54–1·00, 95% PI 0·42–1·27) and LAI antipsychotics (aHR 0·79, 95% CI 0·46–1·37, 95% PI 0·21–2·96) both showed slower recovery compared with placebo, albeit with increased uncertainty for the latter. Other results including covariates, proportional hazards tests, and residual analyses are presented in the appendix (pp 71–76).

In the Cox regression analysis of individual oral and LAI antipsychotics, all antipsychotics except oral risperidone (aHR 1·03, 95% CI 0·70–1·51) showed evidence of slower recovery compared with placebo (aHR<1). However, apart from oral paliperidone (aHR 0·64, 95% CI 0·46–0·89), the evidence for all drugs was weak or very weak (appendix pp 77–79). The results were similar, even when analysing data from only one antipsychotic and placebo in each Cox analysis (appendix pp 80–85).

The results of the two-stage meta-analysis were consistent with those from the one-stage model. However, heterogeneity was observed for certain covariates (appendix pp 86–101). After accounting for study-specific heterogeneity by use of interaction terms, the aHR for antipsychotic effects remained consistent with the main analysis. Although some variability was observed for sex, weight, and age, these changes were within the bounds of statistical uncertainty (appendix pp 141–47).

In a post-hoc analysis that included additional covariates, for oral antipsychotics, concomitant sedative drug was associated with faster sedation resolution (aHR 1·34, 95% CI 1·02–1·76), whereas no clear effect was observed for sedation onset. For LAI antipsychotics, no clear effects were found for the additional covariates in either outcome (appendix pp 148–56).

The findings of the sensitivity analysis excluding fatigue were consistent with those of the main analysis, as detailed in the appendix (pp 157–66).

Discussion

To the best of our knowledge, this is the first IPD meta-analysis to comprehensively examine the trajectory of sedative adverse events associated with antipsychotics and placebo in patients with schizophrenia and schizoaffective disorder. We analysed 19 placebo-controlled RCTs, including 6791 participants, and assessed the dynamics of sedation. We found that the onset of sedation peaked in the first few days of treatment initiation, with about 80% of occurrences happening in the first 2 weeks after treatment initiation. About half of the sedation events resolved within a week after onset, and about 75% resolved after at most 1 month. Our present study indicates rapid onset and quick development of tolerance to sedative adverse events during antipsychotic treatment.

Previous meta-analyses have identified variations in sedation risk among antipsychotics compared with placebo. Specifically, in studies evaluating oral antipsychotics, quetiapine was associated with the highest risk whereas paliperidone had the lowest.[3] In studies involving LAI, which targeted acute schizophrenia, results suggested that risperidone might carry a higher sedation risk compared with paliperidone, although these results were not conclusive.[15] Our current analysis confirms these patterns. Quetiapine showed the highest aHR for sedation (aHR 4·36, 95% CI 2·46–7·73), whereas oral paliperidone had the lowest (aHR 1·83, 1·34–2·51). These findings are consistent with previous meta-analyses.[3,15] However, our study, which evaluates sedation events over time rather than just using aggregated data as is done in typical meta-analyses, provides important insights into the temporal dynamics of sedation risks associated with these drugs.

Our results show the peak of sedation onset on the first or second day, followed by a decrease in the occurrence of sedation. Similar findings were reported in a pooled analysis of asenapine trials, showing the early onset and relatively rapid resolution of sedation.[29] This rapid onset might relate to histamine H_1 blockade and subsequent tolerance acquisition. Histamine H_1 receptor binding is known to play a key role in sedation.[30] Previous studies have shown that sedation caused by histamine H_1 blockers appears immediately after administration, with tolerance to sedation confirmed the following day.[31,32] Similarly, antipsychotic-induced sedation, derived from histamine H_1 receptor blockade, might quickly trigger tolerance.

The effect of histamine H_1 receptors on sedation is consistent with the unique results for haloperidol.

Haloperidol, which has the lowest affinity for histamine H_1 receptors among the drugs included in this study,[27] showed a lower overall incidence of sedation except for LAI intervention. The incidence was 5·0% in the first 2 weeks, as it was for placebo. As reported previously,[3] haloperidol might have little sedative effect at recommended doses of up to 20 mg/day. Although haloperidol had an elevated aHR of 3·68 (95% CI 1·47–9·19) for sedation onset compared with placebo, this result violated the proportional hazards assumption. The high aHR might have been overestimated owing to the small event count and temporal clustering within the first 2 weeks.

Although sedation's rapid onset and resolution strongly implicate the histamine H_1 receptor, multiple receptors are believed to be involved in the sedative effects of antipsychotics.[33] The affinity of antipsychotics for the adrenergic α_1 receptor has been associated with sedation.[34] Tolerance to α_1 receptor blockade, such as with terazosin, develops after 1 month,[35] contrasting with the rapid development of tolerance to histamine H_1 receptor antagonists, which typically occurs within a few days. This might explain the prolonged sedation seen with LAI antipsychotics, especially LAI risperidone, which has a high α_1 receptor affinity.[36] In LAI formulations, cumulative incidence was lower, sedation onset was slower, and resolution took longer compared with oral formulations. Participants in the included LAI trials were pretested with the corresponding oral antipsychotic or had a treatment history, during which early histaminergic sedation and rapid tolerance development probably occurred. As a result, the sedation events observed in the double-blind phase might have been more reflective of α_1 receptor-derived sedation and delayed recovery. Sedation is probably also influenced by serotonin and dopamine.[37] Further research is needed to clarify how the receptor diversity of antipsychotics contributes to sedation.

In our study, approximately 24% of sedation continued 1 month after onset. Post-hoc analyses revealed that patients who used sedative medications at least once during the double-blind phase showed faster resolution of sedation. Tthis finding might reflect the discontinuation of sedative drugs in cases of sedative adverse events. Further research is warranted to explore factors contributing to prolonged sedation, including the details of concomitant sedative medications such as drug type, dose, and duration, as well as potential circadian rhythm disturbances and specific symptoms related to sedation such as insomnia,[38] baseline anxiety, and depressive states.[29]

Our study had several limitations that should be noted. First, there was evidence against the proportional hazards in some Cox models comparing the onset of sedation over time, indicating possible time-varying effects of these drugs, with rapid tolerability acquisition being a potential factor. Second, although we did post-hoc analyses including sedative concomitant medications, such as benzodiazepines,[39] we did not account for the large variability in drug type and dose regimen. Most studies discussed here are based on fixed doses; adjusting the dose for side-effects might alter the time until sedation disappears. Third, for certain antipsychotics, such as haloperidol, the small number of sedation events might have reduced the robustness of the analysis. Major drugs such as aripiprazole and clozapine were not included, and haloperidol was the only first-generation antipsychotic studied, despite reports suggesting that first-generation drugs are generally more sedating.[40] Therefore, our findings might not fully represent all antipsychotics. For the analysis of resolution time we used the subgroup of patients who had previously experienced sedation; this means that randomisation was not preserved, and thus relative effects of drugs versus placebo might have been affected by confounding. The study also did not involve individuals with lived experience, which might limit the applicability and relevance of its findings. Although we believe publication bias is unlikely to significantly affect our results, given that the primary outcomes of the included studies differ from our focus and the presence or absence of sedation probably did not influence study publication, the exclusion of studies not available in the YODA database might introduce bias. As our data was derived from RCTs, the findings might not be generalisable to real-world settings. Future studies should consider these factors to better understand the interactions and effects of concomitant medication use on treatment outcomes.

Our study provides clinically important insights into the dynamics of sedation associated with antipsychotics. Sedation typically occurs early in antipsychotic treatment, with over 80% of sedation events concentrated in the first 2 weeks, and tolerance for sedation developing quickly. Regardless of the administration method (oral or LAI), 50% of sedation episodes are resolved within 1 week, although sedation persisted in 24% after 4 weeks. Our results emphasise the need for careful monitoring of patients during the early treatment phase and suggest that additional factors, beyond the antipsychotic itself, should be considered if sedation persists for more than 1 month. Our study offers valuable guidance for managing sedative adverse events during antipsychotic treatment, potentially improving patient care and potentially reducing early treatment discontinuation due to sedation.

Contributors

NN, HT, SL, SS, and JS-T contributed to the conception and design of the study. NN, SL, SS, JS-T, LB, JPa, and OE, contributed to the acquisition and analysis of data. NN, HT, SS, JMD, JS-T, LB, JPr, OE, and SL contributed to drafting the manuscript. NN and SL had access to the raw data used in this study. NN, SL, and SS verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests
NN has received manuscript fees from Sumitomo Pharma and has been awarded a young researcher position grant from the German Center for Mental Health. SL has in the last 3 years received honoraria for advising or consulting, or for lectures or educational material from Angelini, Boehringer Ingelheim, Eisai, Ekademia, GedeonRichter, Janssen, Karuna, Kynexis, Lundbeck, Medichem, Medscape, Mitsubishi, Otsuka, Novo Nordisk, Recordati, Rovi, and Teva. HT has received grants from Daiichi Sankyo and Novartis Pharma; speaker fees from EA Pharma, Kyowa, Janssen, Lundbeck, Meiji Seika Pharma, Mochida, Otsuka, Sumitomo Pharma, Takeda, and Yoshitomiyakuhin; and advisory board fees from Janssen, Mitsubishi Tanabe Pharma, and Sumitomo Pharma. JPr is a member of the trial steering committee of the SINAPPS2 study and is principal investigator at the German Center for Mental Health and the German Center for Neurodegenerative Diseases, group leader at the UK Dementia Research Institute, committee chair at the German Association for Psychiatry, Psychotherapy, and Psychosomatics, committee chair at the German Society of Biological Psychiatry. All other authors declare no competing interests.

Data sharing
For access to any summary data not included in this Article or the appendix, please contact the corresponding author. All individual participant data used in this study can be requested via the Yale Open Data Access (YODA) project. Detailed information regarding the data request and review process can be found on the YODA project's website.

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This study, carried out under YODA Project 2022-4992, used data obtained from the Yale University Open Data Access Project, which has an agreement with Janssen Research & Development. The interpretation and reporting of research on the basis of these data are solely the responsibility of the authors and do not necessarily represent the official views of the YODA Project or Janssen Research & Development. During the preparation of this work the authors used ChatGPT4o–OpenAI in order to improve language and readability. After using this ChatGPT4o–OpenAI, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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