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)

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Introduction

Given the potentially far-reaching consequences of a relapse of psychotic symptoms in schizophrenia,[1] relapse prevention is crucial. Maintenance treatment with antipsychotic medication reduces this risk considerably, and medication discontinuation is by far the most important reason for relapse.[2] As almost half of patients take less than 70% of their oral medication,[3] switching patients from oral antipsychotics to long-acting injectable (LAI; also known as depot) antipsychotics seems theoretically to be a way to enhance medication continuation, and thereby reduce the risk for relapse.[4] LAIs are administered by health-care professionals on a regular basis, enabling a rapid response to non-adherence

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See Online for appendix

Research in context

Evidence before this study

Research on the reduction of risk of psychotic relapse in schizophrenia is crucial, given the personal, social, and financial impacts of relapse. Discontinuation of antipsychotic medication is the most important reason for relapse, and switching patients from oral antipsychotics to long-acting injections (LAI) seems intuitively to be a way to monitor medication adherence and reduce risk for relapse. If LAI were associated with less medication discontinuation, this could translate into fewer relapses, which might reduce the associated costs. LAIs are injections administered by a health-care professional every few weeks. We searched PubMed from database inception until March 1, 2022, for randomised trials and cohort studies in which patients with schizophrenia, schizophreniform, or schizoaffective disorder (any diagnostic criteria) had been treated with an antipsychotic drug, and in which oral antipsychotics and LAI were compared. Search terms included synonyms of (1) antipsychotics; (2) schizophrenia and related disorders; (3) randomised or cohort studies; and (4) depot (long-acting) injections (full list of search terms is available in the appendix). A further selection criterion was early phase of illness, defined as less than 7 years. No restriction was placed on language. 16 reports fit these search criteria, including seven randomised controlled trials, one cluster randomised trial, seven observational studies, and one post-hoc analysis. These studies used diverse outcomes and methodologies, and they reported conflicting results. No large-scale pragmatic study in patients with early-phase schizophrenia has compared time to all-cause discontinuation in oral versus long-acting antipsychotic treatments.

Added value of this study

We found no significant difference in the time to all-cause discontinuation between patients taking oral paliperidone or aripiprazole and those taking LAI paliperidone or aripiprazole over a 19-month treatment period. These findings suggest that there is no benefit to using long-acting antipsychotic medication over oral antipsychotics in early-phase schizophrenia in terms of time to discontinuation. The current study contributes in a unique way to the ongoing debate on the potential benefits of LAI over oral antipsychotics medication, because the intention of the pragmatic design was to study a more representative patient population compared with previous randomised controlled trials and to provide data that should be generalisable to daily clinical practice. In addition, the focus of the study is on patients in the early phase of schizophrenia, whereas most studies have been conducted in individuals who are chronically ill.

Implications of all the available evidence

Overall, there is no consistent evidence supporting the use of LAI over oral antipsychotics in patients in an early phase of schizophrenia. The use of LAI should be carefully considered on an individual benefit–risk basis.

(ie, when patients do not show up for their visit), while removing the need for patients to remember to take their medication on a daily basis. Research so far has provided conflicting results on this topic. The 2021 meta-analyses on randomised controlled trials (RCTs), observational studies, and pre–post studies by Kishimoto and colleagues[5] showed a benefit of LAIs over oral antipsychotics in preventing hospitalisation and relapse across a range of research designs. However, a 2022 meta-analysis limited to RCTs did not show differences between the two formulations of antipsychotics.[6] This inconsistency could be explained by the research settings included in the meta-analyses: patients agreeing to participate in RCTs might be more adherent, and the frequent study visits, trial procedures, and retainment activities in RCT participants might improve adherence as well, masking the potential benefits of LAIs.[6]

LAIs are commonly studied in patients with chronic schizophrenia, in the context of poor adherence or multiple relapses.[7] Although studies in these patients are important, relapses during the first few years of illness are particularly impactful as these are crucial years of acquiring social, academic, and vocational skills.[8] Studies in the early phase of the illness, using diverse research methods, have reported conflicting results. In 2022, the first meta-analysis of the early stages of psychosis (defined as illness duration of ≤5 years) by Lian and colleagues[9] examined seven RCTs and seven observational studies including 10 584 patients. Among various outcome measures, time to all-cause discontinuation was assessed; this outcome is considered to reflect the overall efficacy and practical usefulness of antipsychotics and is presumed to integrate both patients' and physicians' attitudes towards the drug in a single measurement, taking into account both efficacy (reduction of symptoms) and tolerability (severity of side effects). This measure includes the patient's preference: they will discontinue medication that they find unhelpful or if they view the negatives to outweigh the benefits. In the study by Lian and colleagues,[9] no benefits were found for LAI over oral antipsychotics in relapse rates or time to all-cause discontinuation. However, time to discontinuation due to inefficacy and non-adherence was found to be longer for LAIs than for oral antipsychotics. Hospitalisation rates were lower with LAIs in the RCTs only; this differential effect was not found in naturalistic studies.[9] A systematic review was published in 2022 by the same research group, including eight RCTs, four post-hoc analyses, two case reports, and 19 naturalistic studies in patients with schizophrenia with a treatment duration of 5 years or less.[10] The authors concluded that most reports show reduced relapse risk for LAIs in this early phase of the illness. In addition, patients

with a more recent diagnosis of schizophrenia responded better to treatment than did patients with a longer duration of illness.[10] A trial by Kane and colleagues,[11] which randomly allocated participating hospitals instead of individual patients, provided either LAI or oral antipsychotic treatment to patients with schizophrenia with fewer than 5 years of antipsychotic use. They reported a significant delay in time to first hospitalisation for LAIs compared with oral antipsychotics, but hospitalisation rates did not differ. Overall, no firm conclusion can be drawn on the benefits of LAI over oral antipsychotics in early-phase schizophrenia in terms of relapse rates or time to discontinuation.

We therefore conducted a large-scale, international randomised clinical trial, employing methodology closely reflective of everyday clinical practice and comparing LAI and oral formulations of aripiprazole and paliperidone in terms of time to all-cause discontinuation.

Methods

Study design and participants

The European Long-acting Antipsychotics in Schizophrenia Trial (EULAST) is a pragmatic, open-label, randomised study conducted at 50 general hospitals and psychiatric specialty clinics located in 15 European countries and Israel. The study was approved in each country by the respective regulatory authorities and ethics committees according to the local regulations and consistent with the Declaration of Helsinki. The University Medical Center Utrecht (Utrecht, the Netherlands) monitored the trial according to the Good Clinical Practice and International Conference on Harmonisation guidelines.[12] The safety of the study was annually monitored by an independent Data Safety Monitoring Board.

Inpatients and outpatients were recruited at the participating health-care facilities. Eligible participants were aged 18 years or older and met the criteria of the DSM-IV for schizophrenia as confirmed by the Mini International Neuropsychiatric Interview 5 plus.[13] Patients had to have been ill for at least 6 months and no more than 7 years. In the absence of clear guidance in the available literature on the definition of early-phase schizophrenia, the 7-year cutoff was found to be a reasonable compromise as 5 years was found to be too short and 10 years too long. The implementation of stratification by illness duration helps to clarify a potential effect of length of illness. Start of illness was defined by the first contact with a health-care professional in relation to psychotic symptoms. If patients were using antipsychotics, a medication switch was to be under consideration by the treating physician. Exclusion criteria were as follows: having intolerance or hypersensitivity to both study drugs; being pregnant or lactating; currently using clozapine; not fully comprehending the study purpose or not being competent to make a rational decision regarding participation; having documented history of treatment non-response to both study drugs (or risperidone, of which paliperidone is the chief active metabolite) administered for 6 weeks or longer within the registered dose range; being forensic patients; having been treated with an investigational drug within 30 days before screening; simultaneously participating in another intervention study (including medication or psychosocial interventions); or having severe hepatic illness (based on all summaries of product characteristics, SmPC). All study participants provided written informed consent.

Randomisation and masking

Patients were randomly allocated to one of four treatment arms: aripiprazole LAI, paliperidone LAI, oral aripiprazole, or oral paliperidone. These two antipsychotics were selected because their administration regimens are reasonably similar and their efficacy and safety profiles are well established and documented.[14] In addition, aripiprazole and paliperidone are among the most commonly selected antipsychotics for the maintenance treatment of schizophrenia, being two of the more effective treatments with good evidence for relapse prevention.[14] A randomisation table, using block randomisation (1:1:1:1) and including the allocation sequence, was generated by the Data Management Department of Julius Center (University Medical Center Utrecht) using SAS syntax. Randomisation, stratified by country and duration of illness (6 months to 3 years *vs* 4–7 years), was completed online by a randomisation module built into the Electronic Data Capture system (TrialMaster, built by OmniComm, Bonn, Germany), which provided the allocated treatment. Randomisation was performed by the local study team. None of the study team members (local or central) were masked to treatment allocation. Patients who received pre-study treatment with aripiprazole or paliperidone (or risperidone) could not continue on the same compound; however, they could be assigned to either LAI or oral antipsychotics of the other study medication.

Procedures

A complete overview of the study procedures is provided in the appendix (pp 11–12). Within 10 days after the screening visit, the baseline visit was conducted (visit 2, week 0) and patients were randomly allocated. The next 4 weeks were used to cross-taper between pre-study antipsychotic and the oral form of the study medication up to the optimal dose; patients randomly allocated to LAIs were initiated on oral medication first. 4 weeks after baseline (visit 3, month 1), the pre-study antipsychotic was discontinued and patients who were randomly allocated to LAIs received their first injection according to the respective SmPC, administered by experienced health-care professionals and provided on a monthly basis. Assuming a steady state for all treatment groups at 8 weeks after baseline (visit 4), a longer visit with extensive

measurements occurred at this point, which was repeated every 3 to 4 months. At each monthly visit between these longer visits, study assessments were kept to a minimum. To measure adherence, study drug concentration was assessed at baseline and at every longer visit. Concomitant medications, including psychotropic drugs, were allowed as long as they were prescribed according to the local SmPC. Augmentation with another antipsychotic beyond visit 4 was allowed up to a prespecified threshold, after which all-cause discontinuation criteria were met. The medications in the four treatment groups were dosed according to their respective SmPC; the medication dose was flexible throughout the trial and according to the clinician's discretion. Withdrawal criteria are presented in the appendix (p 18).

Outcomes

The primary outcome measure was time to all-cause discontinuation in the combined oral antipsychotics treatment group (oral aripiprazole and paliperidone) versus the combined LAI treatment group (LAI aripiprazole and LAI paliperidone) during 19 months of treatment. Various international, large-scale trials on schizophrenia have applied this simple but comprehensive measure as a primary outcome.[15,16] All-cause discontinuation criteria were defined as follows: (1) the allocated treatment is stopped or used at doses outside the allowed range; (2) medication is switched to or augmented with another antipsychotic after visit 4 (week 8) for more than 1 month (30 days) continuously or for more than 3 months (90 days) cumulatively; (3) the patient misses a monthly visit and does not show up after being reminded; (4) the patient withdraws consent for the study; (5) the clinician decides to withdraw the patient from the study; or (6) discontinuation due to any other reason, such as the patient being lost to follow-up or no longer wanting any treatment for schizophrenia symptoms, or the patient's death. Based on the reason for discontinuation, supported by narrative information, reasons were coded into three main criteria: discontinuation due to no efficacy, safety concerns (including side effects), or other reasons.

Originally, the treatment period was set to 18 months. The first LAI injections were provided at visit 3, and starting at this point, patients were treated for 18 months. However, to align with current statistical practices, the starting point of the analyses was pulled forward to the time of randomisation (visit 2), resulting in a 19-month treatment period in our analyses.

Secondary outcomes were changes in different dimensions of psychopathological symptoms, global psychosocial functioning, hospitalisations, and side effects in the combined LAI and oral antipsychotics groups.

Statistical analysis

For the power analysis we used a two-sided α level of 0·05 and a type-two error of 0·2, giving a power of 0·8. Sample size determination was based on a meta-analysis by Leucht and colleagues[17] comparing LAI and oral antipsychotic medication, which reported an overall risk ratio of 0·53, favouring LAI to oral application in open-label trials. For this trial, we used a value of 0·61 to determine the smallest detectable, statistically significant hazard ratio (HR) for LAI versus oral medication. The HR of 0·61 can be converted to a Cohen's d of 0·39, which is a small to medium effect size.[18] Based on a sample size formula provided by Weaver,[19] involving the HR and the expected treatment discontinuation rate, a total of 520 patients was required for the intention-to-treat (ITT) analysis. The original power analysis in the protocol deviates from this description. The protocol was based on per protocol analysis, but after the protocol had been completed, there was a change of the responsible statistician, and the new statistician strongly proposed to use an ITT approach for the analysis, as this is the gold standard for clinical trials.[20] The original power analysis in the protocol had led to a HR of 0·55, but as the HR of 0·61 is closer to 1 and hence represents a smaller effect size, the change in the analysis approach from per protocol to ITT resulted in a small gain in power.

Statistical analyses of primary and secondary outcomes were conducted with SPSS (version 27.0) and R (version 4.1.2). Kaplan-Meier curves were generated using the Survminer (version 0.4.9) R package. Analysis of the primary outcome was performed by ITT using survival analysis, including all randomly allocated participants. For patients who met all-cause discontinuation criteria, the time from randomisation to all-cause discontinuation was used as survival time. Given the ITT methodology combined with the primary objective, the concept of drop out was not applicable; all randomly allocated participants were included in the current analyses, and participants dropping out during the study were defined as meeting all-cause discontinuation criteria instead of being regarded as drop out. For patients who completed the study (ie, completed visit 21 without having met all-cause discontinuation criteria), the exact time from randomisation to the final visit 21 (approximately 19 months after randomisation) differed; this was mainly due to the visit windows, defined as 1 month (SD 4 days) relative to the previous visit. It was therefore decided to truncate the survival time at a time shortly before visit 21, namely at day 540 or 18 months after randomisation. The reason for this was to avoid favouring (or disadvantaging) patients whose final visit took place a little earlier or later than the scheduled day according to the protocol. The status of the patients in this group was coded as censored, to reflect the fact that no all-cause discontinuation had occurred until visit 21. A log-rank test was used to analyse differences of discontinuation probabilities between the combined oral antipsychotics and combined LAI antipsychotics groups. The Kaplan-Meier method was applied to estimate the probability of survival until meeting discontinuation

criteria. Cox proportional hazard regression analysis was employed for the estimation of HRs, together with 95% CIs.

Methods for the secondary analyses are described in detail in the appendix (p 1), as well as extensive additional analyses including a survival analysis per protocol, an analysis of efficacy data over time, and analyses concerning safety and tolerability. Post-hoc, a Cox regression analyses was conducted for the effect of illness duration (6 months to 3 years *vs* 4–7 years) on time to all-cause discontinuation.

This trial is registered with ClinicalTrials.gov, NCT02146547, and is complete.

Role of the funding source

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

Results

Participants were recruited between Feb 24, 2015, and Dec 15, 2018, and the final study visit took place on Aug 26, 2020. A total of 533 patients signed the informed consent and were assessed for eligibility; ten patients were excluded before randomisation, and after randomisation, the data of a further 12 patients could not be included in the analyses for various reasons, including inability to confirm the diagnosis of schizophrenia (eligibility rejection, figure 1). These patients did not differ significantly from the ITT sample with regards to important baseline variables (age, sex, education, Positive and Negative Syndrome Scale [PANSS] score, Clinical Global Impression [CGI] severity scale score, and Personal and Social Performance scale [PSP] scale score; appendix p 10). 511 patients met diagnostic criteria, including 171 (33%) women and 340 men (67%), with a mean age of 30·5 (SD 9·6) years; 410 (80%) of the study sample were White, 35 (7%) were Black, 20 (4%) were Asian, and 46 (9%) were other ethnicity. Baseline characteristics of this ITT sample of 511 patients in the combined oral and combined LAI antipsychotics treatment groups are shown in table 1. Of the 511 patients, 167 (33%) completed the 19-month treatment.

In the combined oral antipsychotics treatment group, 72 (29%) of 247 patients completed the study and 175 (71%) met all-cause discontinuation criteria. In the combined LAI antipsychotics treatment group, 95 (36%) of 264 patients completed the study and 169 (64%) met all-cause discontinuation criteria. The Cox regression analysis (HR 1·16, 95% CI 0·94–1·43, p=0·18) showed that treatment discontinuation for any cause did not differ between the two combined treatment groups. The Kaplan-Meier survival curve for the time to all-cause discontinuation (log rank test χ^2=1·87 [df 1]; p=0·17)

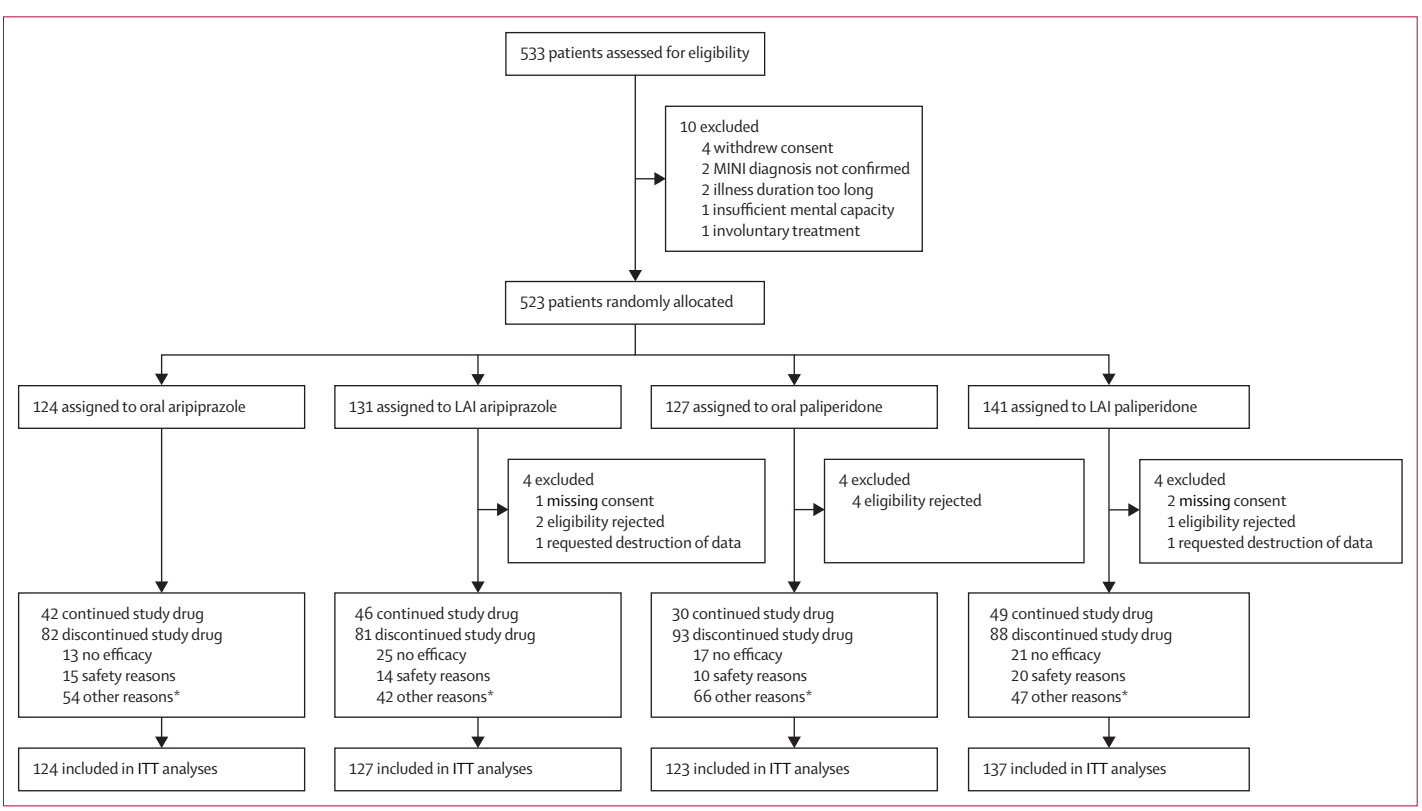

Figure 1: **Trial profile**
MINI=Mini-International Neuropsychiatric Interview. LAI=long-acting injectable. *Full list of other reasons is given in the appendix (pp 1–2).

	Combined oral antipsychotics group (n=247)	Combined LAI antipsychotics group (n=264)	Test statistic*	p value
Demographic and clinical characteristics				
Age, years (mean [SD], range)	30·8 (10·0), 18–66	30·3 (9·3), 18–63	Z=0·20	0·98
Sex assigned at birth				
Male	75 (30%)	96 (36%)	χ^2=2·06	0·15
Female	172 (70%)	168 (64%)	..	..
Race				
White	195 (79%)	215 (81%)	χ^2=0·50	0·48
Asian	13	7	..	..
Black	14	21	..	..
Other	25	21	..	..
Years of education†	11·7 (2·9)	12·2 (2·7)	Z=–2·32	0·020‡
Living independently	66 (27%)	55 (21%)	χ^2=1·15	0·28
Employed or student	81 (33%)	103 (39%)	χ^2=2·14	0·14
Duration of illness, years				
Mean (SD)	2·92 (1·89, n=246)	3·05 (1·84, n=246)	Z=–1·00	0·32
Median (IQR)	2·55 (1·35–4·23, n=246)	2·69 (1·46–4·39, n=246)	..	..
Major depressive disorder (current)§	13 (6%, n=234)	19 (8%, n=245)	χ^2=0·93	0·33
Suicidality (current)§	26 (11%)	29 (11%)	χ^2=0·03	0·87
Substance misuse or dependence in past 12 months§	47 (19%)	40 (15%)	χ^2=1·36	0·24
Inpatient status	130 (53%)	131 (50%, n=263)	χ^2=0·41	0·52
PANSS total score¶	74·7 (19·0)	74·1 (17·9)	Z=0·28	0·78
PANSS positive subscale¶	17·5 (6·1)	17·3 (5·8)	Z=0·12	0·90
PANSS negative subscale¶	20·0 (6·5)	19·8 (6·5)	Z=0·26	0·79
PANSS general subscale¶	37·2 (9·9)	37·0 (9·5)	Z=0·13	0·89
CGI severity‖	4·3 (1·0)	4·4 (1·0)	Z=–1·51	0·13
Overall functioning (PSP)**	50·9 (16·9)	52·7 (15·6)	Z=–1·16	0·25
Physical characteristics per combined treatment arm at baseline				
Prolactin, mean (SD)	155·7 (437·0)	159·3 (378·0)	Z=–0·87	0·38
Prolactin exceeding prespecified range††	129 (57%, n=225)	148 (64%, n=232)	χ^2=2·00	0·16
Cholesterol, mean (SD)	146·7 (75·5)	144·5 (79·5)	Z=0·44	0·66
Cholesterol outside prespecified range††	57 (24%, n=234)	57 (23%, n=252)	χ^2=0·20	0·65
HDL, mean (SD)	40·7 (24·6)	40·5 (23·7)	Z=0·09	0·93
HDL outside prespecified range††	75 (33%, n=229)	112 (46%, n=246)	χ^2=8·11	0·0044‡‡
LDL, mean (SD)	86·4 (50·2)	87·7 (53·0)	Z=–0·19	0·85
LDL outside prespecified range††	72 (33%, n=216)	69 (30%, n=228)	χ^2=0·48	0·49
Akathisia§§	26 (15%, n=174)	24 (12%, n=197)	χ^2=0·60	0·42
Dystonia§§	3 (2%, n=174)	7 (4%, n=197)	χ^2=1·18	0·28
Parkinsonism§§	26 (15%, n=174)	37 (19%, n=198)	χ^2=0·92	0·34
Dyskinesia§§	8 (5%, n=174)	7 (4%, n=197)	χ^2=0·26	0·61
Tardive dyskinesia, mean (SD)¶¶	0·24 (0·66)	0·19 (0·54)	Z=0·70	0·49
Overweight (visit 1)‖‖				
Overweight	80 (33%, n=240)	87 (34%, n=258)	χ^2=0·01	0·93
Obese	46 (19%, n=240)	43 (17%, n=258)	χ^2=0·53	0·47
BMI, mean (SD)	26·0 (5·1)	25·7 (5·1)	Z=0·78	0·43

Data are n/N (%) or mean (SD) or median (IQR). Denominators change where indicated due to incomplete data. LAI=long-acting injectable. PANSS=Positive and Negative Syndrome Scale. CGI=Clinical Global Impression. PSP=Personal and Social Performance scale. *χ^2 test or Mann-Whitney U test (Z score). †Years in school from age 6 years onwards. ‡Not significant after Bonferroni correction (p=16×0·0201=0·3216). §According to the Mini-International Neuropsychiatric Interview 5 plus. Suicidality includes medium to high suicide risk. ¶Theoretical scores range from 30 to 210 (total scale), 7 to 49 (positive scale), 7 to 49 (negative scale), and 16 to 112 (general psychopathology scale); higher scores indicate more severe psychopathology. ‖Theoretical scores range from 1 to 7; higher scores indicate greater severity of illness. **Theoretical scores range from 1 to 100; higher scores indicate better functioning. ††Pre-specified range: upper limit of normal value, as determined by the laboratory reference ranges at each individual centre. ‡‡Not significant after Bonferroni correction (p=16×0·0044=0·0704). §§As determined through St Hans scale. ¶¶As determined through Abnormal Involuntary Movement Scale eighth item (severity of abnormal movements overall as indicated by clinician; score range 0–4). ‖‖Overweight defined as BMI 25 to <30, obese defined as BMI ≥30; measurements taken at visit 1.

Table 1: **Demographic, clinical, and physical characteristics per combined treatment groups at baseline**

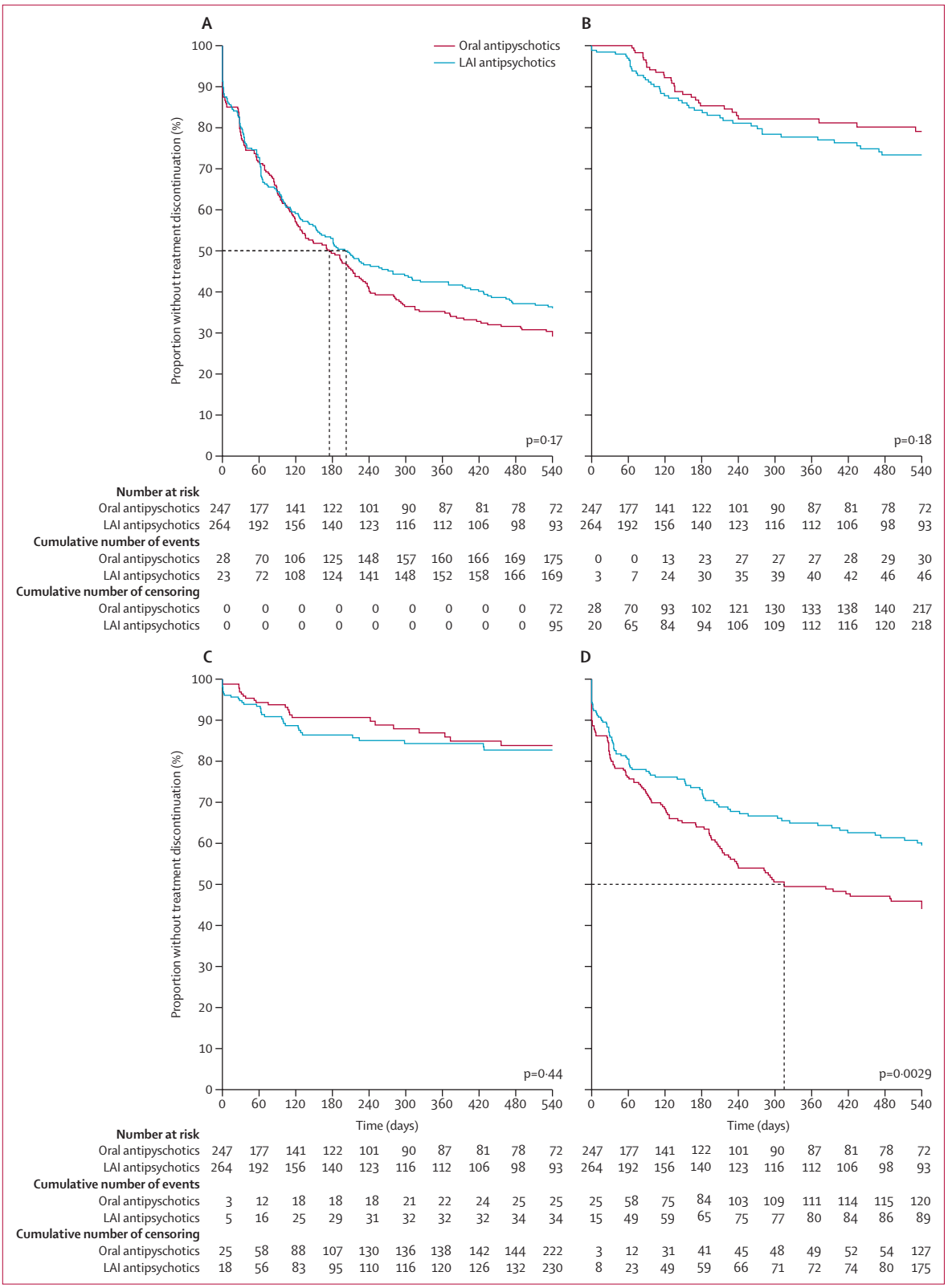

***Figure 2*: Treatment discontinuation of oral and LAI antipsychotics because of any cause (A), efficacy (B), safety (C), or other reasons (D)**
Dashed lines indicate median time without treatment discontinuation under treatment; median follow-up due to any cause was 186 days (IQR 40–540).
LAI=long-acting injectable.

indicated that the time to all-cause discontinuation also did not differ between the combined oral and LAI antipsychotics treatment groups (median 175 days [95% CI 122–228] *vs* 200 days [131–269]; figure 2A).

The reasons for all-cause discontinuation were grouped into three major categories: discontinuation due to efficacy, safety issues or concerns, or other reasons. These other reasons included loss to follow-up, patients not showing up at their study visits after one reminder, treatment refusal, withdrawal due to the time investment, patients preferring another or no medication, manic episode, suicide attempt, and death; a full list of the other reasons is in the appendix (pp 1–2).

	Oral aripiprazole (mean [SE])	LAI aripiprazole (mean [SE])	Oral paliperidone (mean [SE])	LAI paliperidone (mean [SE])	Statistics *† (*F* [df])	p value
PANSS total score						
Baseline*	73·7 (1·68)	73·6 (1·67)	75·7 (1·83)	74·5 (1·48)	0·32 (3)	0·8082
Visit 21	54·4 (1·13)	54·4 (1·22)	55·6 (1·19)	54·7 (1·09)	0·27 (3)	0·8467
Change	–19·3‡ (1·13)	–19·2‡ (1·12)	–20·1‡ (1·19)	–19·8‡ (1·09)	..	..
PANSS negative symptoms						
Baseline	19·2 (0·63)	19·6 (0·63)	19·8 (0·61)	19·2 (0·59)	0·26 (3)	0·8580
Visit 21	14·4 (0·42)	15·0 (0·41)	14·8 (0·43)	14·8 (0·40)	0·74 (3)	0·5304
Change	–4·8‡ (0·42)	–4·6‡ (0·41)	–5·0‡ (0·43)	–4·4‡ (0·40)	..	..
PANSS positive symptoms						
Baseline	21·3 (0·65)	20·9 (0·60)	21·8 (0·66)	21·8 (0·54)	0·53 (3)	0·6617
Visit 21	14·6 (0·41)	13·8 (0·41)	14·5 (0·43)	14·6 (0·40)	0·99 (3)	0·3982
Change	–6·7‡ (0·41)	–7·1‡ (0·41)	–7·3‡ (0·43)	–7·2‡ (0·40)	..	..
PANSS disorganised thought						
Baseline	15·8 (0·45)	16·5 (0·49)	16·5 (0·52)	16·2 (0·40)	0·42 (3)	0·7365
Visit 21	11·7 (0·30)	12·6 (0·30)	12·6 (0·31)	12·0 (0·29)	0·59 (3)	0·6219
Change	–4·1‡ (0·30)	–3·9‡ (0·30)	–3·9 (0·31)	–4·2‡ (0·29)	..	..
PANSS uncontrolled hostility or excitement						
Baseline	7·3 (0·31)	6·7 (0·25)	7·4 (0·29)	7·4 (0·27)	1·46 (3)	0·2243
Visit 21	5·7 (0·18)	5·1 (0·18)	5·8 (0·19)	5·6 (0·17)	0·57 (3)	0·6380
Change	–1·6‡ (0·18)	–1·6‡ (0·18)	–1·6‡ (0·19)	–1·8‡ (0·17)	..	..
PANSS anxiety or depression						
Baseline	10·1 (0·33)	10·0 (0·35)	10·1 (0·34)	9·9 (0·32)	0·10 (3)	0·9595
Visit 21	7·7 (0·24)	7·7 (0·23)	7·6 (0·25)	7·6 (0·23)	0·29 (3)	0·8355
Change	–2·4‡ (0·24)	–2·3‡ (0·23)	–2·5‡ (0·25)	–2·3‡ (0·23)	..	..
CGI severity§						
Baseline	4·24 (0·09)	4·50 (0·09)	4·38 (0·09)	4·37 (0·08)	1·52 (3)	0·2076
Visit 21	2·96 (0·09)	3·11 (0·09)	3·06 (0·09)	3·06 (0·09)	0·49 (3)	0·6861
Change	–1·30‡ (0·09)	–1·39‡ (0·09)	–1·32‡ (0·09)	–1·31‡ (0·09)	..	..
PSP total score¶						
Baseline	50·6 (1·60)	53·3 (1·43)	51·0 (1·54)	52·1 (1·31)	0·65 (3)	0·5864
Visit 21	66·3 (1·24)	68·1 (1·23)	62·9 (1·30)	68·2 (1·20)	0·49 (3)	0·6925
Change	15·7‡ (1·24)	14·8‡ (1·23)	15·9‡ (1·30)	16·1‡ (1·20)	..	..

Simple mean values are shown for baseline data, whereas estimated mean values derived from the linear mixed model are shown for visit 21 data and for changes from baseline to visit 21. The PANSS scale includes five factors: negative symptoms (seven items), positive symptoms (eight items), disorganised thought (seven items), uncontrolled hostility or excitement (four items), and anxiety or depression (four items); 495 patients had a valid PANSS baseline, 442 of these had a valid last PANSS observation, and 53 had baseline values only. LAI=long-acting injectable. PANSS=Positive and Negative Syndrome Scale. CGI=Clinical Global Impression. PSP=Personal and Social Performance scale. *Analysis of baseline data by general linear model. †Analysis in the course of time by linear mixed models with AR(1) covariance structure, model: group plus visit plus baseline of dependent variable (for adjustment). Test statistics and p values refer to the group effect. ‡p<0·0001 for test of the null hypothesis "change=0" within groups in the linear mixed model, always t>5. §494 patients had a valid CGI severity baseline, 442 of whom had a valid last CGI severity observation and 52 had baseline CGI values only. ¶493 patients had a valid PSP baseline, 442 of whom had a valid last PSP observation and 51 had baseline PSP values only.

Table 2: **Outcomes of efficacy and functioning**

In the combined oral antipsychotics group, 30 (12%) of 247 patients discontinued because of efficacy, compared with 46 (17%) of 264 patients in the combined LAI antipsychotics group. Cox regression analyses showed these were not significantly different (HR 0·73, 95% CI 0·46–1·16; p=0·19). The Kaplan-Meier curve showing time to discontinuation due to efficacy also did not differ between the combined treatment groups (log rank test χ^2=1·77 [df 1]; p=0·18; figure 2B).

Safety concerns were the main reason for discontinuation in 25 (10%) of 247 patients in the combined oral antipsychotics group, compared with 34 (13%) of 264 patients in the combined LAI antipsychotics group. Cox regression analyses showed that this difference was not significant (HR 0·82, 95% CI 0·49–1·37; p=0·44), and the difference in time to discontinuation due to safety was also not significant (log rank test χ^2=0·60 [df 1]; p=0·44; figure 2C).

120 (49%) of 247 patients in the combined oral antipsychotics group discontinued due to other reasons, compared with 89 (34%) of 264 patients in the combined LAI antipsychotics group. Cox regression analyses showed that this difference reached significance (HR 1·51, 95% CI 1·15–1·98; p=0·0034). In this group, a log rank (Mantel-Cox) test showed significantly longer continued use of medication for patients treated with LAIs compared with oral antipsychotics (log rank test χ^2=8·84 [df 1]; p=0·0029; figure 2D). This difference remained significant after a Bonferroni correction. A survival analysis of the three most frequently occurring other reasons, namely "Patient did not want to continue", "Patient did not show up after one reminder", and "Clinician decision due to non-compliance to the protocol", showed that there were no significant differences between the oral and LAI antipsychotics groups after a Bonferroni correction for multiple testing (always χ^2 <3·95 [df 1]; p corrected >0·14).

A Cox regression analysis revealed that illness duration (6 months to 3 years *vs* 4–7 years) had a significant effect on time to all-cause discontinuation. Patients with longer illness duration showed a poorer response than those with shorter duration (HR 1·26, 95% CI 1·01–1·56; p=0·038). However, a stratification by illness duration yielded no significant difference between oral antipsychotics and LAIs in either of the two subgroups (6 months to 3 years: χ^2=1·30 [df 1]; p=0·25; 4–7 years: χ^2=0·90 [df 1]; p=0·34).

The analyses according to protocol are included in the appendix (pp 6–7). As an additional post-hoc outcome measure of interest, the four individual treatment groups were compared on time to all-cause discontinuation (appendix pp 2–4). Driven by recent scientific publications, a post-hoc survival analysis was conducted

for two age strata (≤25 years and >25 years; appendix pp 4–6); no statistically significant results were found.

Table 2 shows the mean scores for the total scores for psychopathology (assessed by PANSS) as well as the PANSS subscales and Marder factors (appendix p 11) for each of the allocated treatments, the severity of illness (assessed by CGI severity scale), and the personal and social functioning scores (assessed by PSP) per allocated treatment group during the 19-months follow-up. No significant treatment effects for any of the efficacy variables were detected for the four treatment groups or for oral versus LAI formulations. Applying imputation for missing data in PANSS did not change the results (appendix pp 8–10). Note that within the individual treatment groups all efficacy outcome measures improved significantly and substantially.

Table 3 shows the outcomes of safety and tolerability per allocated treatment. For prolactin, the highest value during follow-up was used; favourable post-hoc pair-wise comparisons were found for both forms of aripiprazole. For cholesterol, LDL and HDL, values outside the prespecified range in both directions (too high and too low) were used. Two patients died during the follow-up period; one patient assigned to LAI aripiprazole died, and possible relationships with the study medication cannot be ruled out as the cause of death was never shared with the local study team; one patient assigned to LAI paliperidone died following an occlusion of a cerebral artery after a stroke, and according to the clinician, there was no relationship with the study medication.

During the study, 121 psychiatric hospitalisations occurred in 103 patients. No significant differences were found in the number of patients hospitalised for psychiatric reasons or the actual number of hospitalisations between the treatment groups (appendix pp 12–13).

Discussion

To our knowledge, this is the first large, pragmatic, open-label randomised clinical trial comparing long-acting injectable antipsychotics with their oral equivalents in

	Oral aripiprazole	LAI aripiprazole	Oral paliperidone	LAI paliperidone	Test statistic (df)	p value
Prolactin						
Mean (SD)	56·5 (241·9)	45·4 (113·9)	395·2 (734·8)	203·5 (346·4)	H=152·03 (3)	<0·0001*
Exceeding prespecified range†	19/94 (20%)	15/90 (17%)	79/82 (96%)	96/100 (96%)	χ^2=225·61 (3)	<0·0001‡
Cholesterol						
Mean (SD)	152·2 (67·7)	132·5 (72·2)	149·1 (78·5)	154·7 (77·6)	H=7·26 (3)	0·064
Outside prespecified range†	34/94 (36%)	32/91 (35%)	32/84 (38%)	36/101 (36%)	χ^2=0·19 (3)	0·98
HDL						
Mean (SD)	43·1 (21·0)	38·6 (22·9)	39·7 (21·6)	41·0 (21·7)	H=1·21 (3)	0·75
Outside prespecified range†	47/92 (51%)	54/91 (59%)	39/84 (46%)	56/99 (57%)	χ^2=3·53 (3)	0·32
LDL						
Mean (SD)	91·1 (44·6)	77·8 (46·9)	90·5 (52·5)	95·5 (51·8)	H=7·68 (3)	0·053
Outside prespecified range†	43/87(49%)	32/88 (36%)	29/83 (35%)	44/97 (45%)	χ^2=5·26 (3)	0·15
Akathisia§	24/90 (27%)	20/83 (24%)	17/80 (21%)	25/97 (26%)	χ^2=0·78 (3)	0·86
Dystonia§	3/90 (3%)	2/83 (3%)	6/80 (8%)	3/97 (3%)	χ^2=3·51 (3)	0·32
Parkinsonism§	14/90 (16%)	14/83 (17%)	19/80 (24%)	23/97 (24%)	χ^2=3·16 (3)	0·37
Dyskinesia§	5/90 (6%)	4/83 (5%)	5/80 (6%)	5/97 (5%)	χ^2=0·18 (3)	0·98
Tardive dyskinesia¶	0·16 (0·43)	0·10 (0·28)	0·17 (0·38)	0·17 (0·43)	H=2·53 (3)	0·47
Overweight‖						
Overweight	49/123 (40%)	46/124 (37%)	43/121 (36%)	56/135 (42%)	χ^2=1·15 (3)	0·77
Obese	26/123 (21%)	30/124 (24%)	36/121 (30%)	32/135 (24%)	χ^2=2·59 (3)	0·46
Maximum BMI, mean (SD)**	26·5 (4·8)	27·3 (6·1)	27·7 (5·5)	27·3 (5·3)	H=2·64 (3)	0·45
Maximum weight gain ≥7% ††	28/123 (23%)	41/124 (33%)	34/121 (28%)	49/135 (36%)	χ^2=6·34 (3)	0·096

Data are mean (SD) or n/N (%). χ^2 test is conducted on the patient level, the Kruskal-Wallis test is conducted on the number of serious adverse events. LAI=long-acting injectable. *Post-hoc pairwise comparisons by Mann-Whitney U test (oral aripiprazole *vs* oral paliperidone [Z=–8·80], oral aripiprazole *vs* LAI paliperidone [Z=–9·16], LAI aripiprazole *vs* oral paliperidone [Z=–8·04], LAI aripiprazole *vs* LAI paliperidone [Z=–8·35]; no other significant differences; p<0·0001). †Prespecified range: upper limit of normal value, as determined by the laboratory reference ranges at each individual centre. ‡Post-hoc pairwise comparisons by χ^2 test (oral aripiprazole *vs* oral paliperidone [χ^2=102·9], oral aripiprazole *vs* LAI paliperidone [χ^2=115·3], LAI aripiprazole *vs* oral paliperidone [χ^2= 109·9], LAI aripiprazole *vs* LAI paliperidone [χ^2=122·7]; no other significant differences; p<0·0001). §As determined through St Hans scale. ¶As determined through Abnormal Involuntary Movement Scale eighth item (severity of abnormal movements overall as indicated by clinician; score range 0–4); oral aripiprazole n=95; LAI aripiprazole n=90; oral paliperidone n=87; LAI paliperidone n=106. ‖Overweight defined as BMI 25 to <30 kg/m^2; obese defined as BMI ≥30 kg/m^2. **Linear mixed model analysis within groups showed a significant linear increase in BMI over time in all four groups, always t>3. Mean weight gain per month (oral aripiprazole β=0·054 [SE 0·016; p=0·0009], LAI aripiprazole β=0·135 [0·016; p<0·0001], oral paliperidone β=0·079 [0·020; p=0·0001], LAI paliperidone β=0·112 [0·017; p<0·0001]). ††p<0·05 for oral *vs* LAI with higher prevalence of adverse events and ≥7% weight gain in patients in LAI group (35%) than in those in oral group (25%); χ^2=5·33; p=0·0209; significance not retained after Bonferroni correction (p=14*0·0209–0·292).

Table 3: **Outcomes of safety and tolerability**

patients with schizophrenia in the early phase of their illness (defined as less than 7 years since first contact with a health-care provider in relation to psychotic symptoms), using all-cause time to discontinuation of medication as the main outcome measure. For the primary analysis, the two LAI treatment groups were combined, as were the two oral treatment arms. We did not find a difference in time to all-cause discontinuation between the combined oral and combined LAI groups. After separating the reasons for discontinuation into no efficacy, safety reasons, and other reasons, we only found a significant difference in favour of LAI for the other reasons category; although the number of patients discontinuing medication for this reason over the follow-up period did not differ, patients on LAI continued treatment for a longer time. There was no differential effect on PANSS symptoms or personal and social functioning, or number of hospitalisations. Our findings are largely in line with the results from the meta-analysis conducted by Lian and colleagues,[9] which found no evidence for a difference in time to all-cause discontinuation and time to discontinuation due to safety concerns in patients in the early phase of schizophrenia (defined as first episode psychosis, recent-onset psychosis, or early psychosis) between LAIs and oral antipsychotics.

In a meta-analysis of 15 antipsychotics in the treatment of schizophrenia, Leucht and colleagues[21] concluded that there are significant differences in efficacy across antipsychotics, which was paralleled in their meta-analyses on time to discontinuation;[21] the most effective drugs also had the longest time to discontinuation. Head-to-head comparisons, using the same molecules in the LAI and oral antipsychotics groups, as in the current study, provide the opportunity to directly compare the effect of the two formulations without confounding by potential differences in efficacy between specific antipsychotics. Only two studies in patients with early -phase schizophrenia report on such head-to-head comparisons, both using risperidone LAI and risperidone oral antipsychotics. The naturalistic study by Kim and colleagues[22] (n=50) showed a reduced relapse rate over a 2-year follow-up period for LAI risperidone, compared with oral risperidone. These results were mirrored in the 1-year RCT (n=83) by Subotnik and colleagues,[23] using the same outcome measure. The apparent contrast with our results can be explained by the use of a broader and different outcome measure, namely time to all-cause discontinuation, in our study.

In the current study, a larger number of patients on oral antipsychotics discontinued their study medication due to other reasons, compared with patients on LAIs, and the time to discontinuation was also significantly shorter for the oral antipsychotics treatment arms. These results are difficult to interpret given the wide variety of reasons for discontinuation captured in this category, including patients being lost to follow-up, not showing up at their visit after a reminder, not wanting to be part of the study or wanting any treatment, or making a suicide attempt (full list in appendix pp 1–2). The wide variety in reasons for discontinuation prevented an informative subgroup analysis.

After 19 months of treatment, symptom severity decreased substantially from a mean PANSS total score ranging between 73·6 and 75·7, to a range between 54·4 and 55·6, meaning being approximately moderately ill,[24] regardless of the allocated treatment. Mean severity of illness decreased from moderately to mildly ill according to the CGI score, and personal and social functioning improved by 12–13% as measured with the PSP. These changes did not differ across the combined treatment groups. We did not find lower rates of hospitalisation for patients assigned to LAIs. This is in line with a 2020 report by Kane and colleagues[11] on a similar patient population randomly allocated to 2-year LAI aripiprazole versus treatment as usual, which found no difference in hospitalisation rate (although they did report superiority regarding time to hospitalisation for the LAI). Our finding conflicts with those of Subotnik and colleagues,[23] who reported lower hospitalisation rates for risperidone versus oral risperidone in a 1-year RCT in 83 patients with first-episode schizophrenia-spectrum disorder. That single-site study consisted mostly of clinically stable patients, excluding participants with alcohol use or drug use disorders, at study entry, who were assigned either oral or LAI risperidone after having completed a lead-in period of at least 3 weeks of monotherapy oral risperidone treatment.

When interpreting these findings, limitations need to be considered. The current study was an open-label trial, as any attempt to blind the trial would create constraints that would have made this trial less reflective of routine clinical management. In addition, a blinded design could negatively affect acceptance to participate, which might have masked a possible benefit of LAI medication. To address this potential effect, the attitudes of the Principal Investigators towards the different types and brands of medication were assessed. Overall, an attitude bias in favour of LAIs was most pronounced (appendix pp 10–11), hence it is unlikely that the study design had an effect on the study results. Another limitation concerns the interpretation of secondary outcome measures, specifically the side effects: for patients who used one of the study treatment options as pre-study medications, assignment to this compound was blocked. In addition, although drug serum concentrations were assessed as a proxy measure for adherence, these results provide insufficient detail to address in a valid manner (appendix p 13); however, we suspect that the decreased plasma concentrations in the oral antipsychotics group reflect adherence issues. A further limitation is that we based our sample size estimation on differences in relapse rates rather than all-cause discontinuation. However, with 511 participants, our sample size had

sufficient power to detect small to medium effect sizes in the survival analysis comparing oral and LAI medication. Finally, even though the design of the study was relatively pragmatic, random allocation to treatment options and implementation of a protocol-driven visit schedule, including an extensive assessment every 3 months, might have moved our patient sample to some extent away from the general population of patients with schizophrenia.

In conclusion, the findings from this pragmatic study do not support a clear advantage for the use of LAI antipsychotics over oral antipsychotics in a large, representative patient population with early-phase schizophrenia, if the goal is to prevent discontinuation of antipsychotic medication.

Contributors

RSK, WWF, MD, SG, SL, IB, BG, MW, and IWvR designed the study. RSK, WWF, and MD obtained funding. RSK, WWF, MD, and IWvR supervised the study. GK, TS, and IWvR had access to and have verified the underlying data. GK and TS analysed the data. RSK, WWF, MD, IWvR, GK, and TS interpreted the data. IWvR, RSK, WWF, and MD drafted the report. MW, JL, AH, MM, SG, MK, NS, AT, PR, GP, IB, CL, MBH, SL, and BG participated in the collection of data. All authors had full access to all the data in the study, participated in the critical revision of the report, and approved the final report. RSK, WWF, and IWvR were responsible for the decision to submit the manuscript.

Declaration of interests

SG reports consulting fees from Angelini, Janssen Pharmaceuticals, Gedeon-Richter, Recordati, and Innova Pharma; and honoraria and expenses from Angelini, Gedeon-Richter, Recordati, Janssen Pharmaceuticals, Janssen-Cilag, Lundbeck, Lundbeck Italia, and Sunovion. SL reports payments to the institution from European Group for Research In Schizophrenia for the conduct of the trial; consulting fees from Alkermes, Angelini, Lundbeck, Lundbeck Foundation, Otsuka, Recordati, Rovi, and Teva; and honoraria for lectures from Angelini, Eisai, Gedeon, Lundbeck, Medichem, Merck, Mitsubishi, Otsuka, Recordati, and Sanofi-Aventis. IB reports grants from the EU to the Semmelweise University; royalties from Oxford University for a published book (editor); consulting fees from Gedeon Richter, Janssen, Janssen Cilag; speaker fees from Hikma Janssen, Janssen Cilag, Gedeon Richter, Medichem Pharmaceuticals by Unilab, and Mitsubishi Tanabe Pharma Signapure; and leadership or fiduciary roles with European College of Neuropsychopharmacology, the European Psychiatry Association, and Clincal Pharmacological Ethics Committee and Medical Research Council (Hungary). BG has been the leader of a Lundbeck Foundation Centre of Excellence for Clinical Intervention and Neuropsychiatric Schizophrenia Research (January, 2009–December, 2021), which was partially financed by an independent grant from the Lundbeck Foundation based on international review and partially financed by the Mental Health Services in the Capital Region of Denmark, the University of Copenhagen, and other foundations; all grants are the property of the Mental Health Services in the Capital Region of Denmark and administrated by them. AH reports speaker fees from Lundbeck, Otsuka, Janssen, Recordati, and Rovi; was member of advisory boards for Lundbeck, Otsuka, Janssen, Recordati, and Rovi; and is an Editor of the German Association of Scientific Medical Societies in Germany and World Federation of Societies of Biological Psychiatry schizophrenia guidelines. GP reports honoraria from Lundbeck, Janssen, Schwabe Austria; support for attending meetings from Schwabe Austria; being president at the Austrian Society for Social Psychiatry and Gerontopsychiatry; and stock with Janssen. PR reports an advisory board role for Angelini. NS reports honoraria for lectures from Recordati Hellas, BGP Pharmaceuticals, Lundbeck Hellas, and Vianex. MD is an employee of Minerva Neurosciences with stock options. RSK reports consulting fees from Alkermes, Sunovion, Gedeon-Richter, and Otsuka. WWF reports consultant fees from Angelini, Richter, Recordati, Lundbeck, Otsuka, Teva, Boehringer-Ingelheim, Pierre Fabre, Janssen, Sunovion, Dainippon-Sumitomo, Takeda, and Pfizer; speaker fees from Janssen, Lundbeck, Otsuka, Richter, and Recordati; and grants from Janssen, Lundbeck, and Otsuka. All other authors declare no competing interests.

Data sharing

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

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