

Effect of Long-Acting Injectable Antipsychotics vs Usual Care on Time to First Hospitalization in Early-Phase Schizophrenia

A Randomized Clinical Trial

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IMPORTANCE Long-acting injectable antipsychotics (LAIs) can potentially reduce hospitalization risk by enhancing medication adherence but are rarely considered for early-phase schizophrenia treatment.

OBJECTIVE To determine whether encouraging use of a LAI compared with usual care delays the time to first hospitalization with patients with early-phase illness.

DESIGN, SETTING, AND PARTICIPANTS The Prevention of Relapse in Schizophrenia (PRELAPSE) trial was cluster randomized with a follow-up duration of 2 years. The study began in December 2014, was completed in March 2019, and was conducted in 39 mental health centers in 19 US states. Site randomization assigned 19 clinics to encourage treatment with long-acting aripiprazole monohydrate (aripiprazole once monthly [AOM] condition) and 20 to provide treatment as usual (clinician's choice [CC] condition). Participant eligibility criteria included (1) schizophrenia diagnosis confirmed by a structured clinical interview, (2) fewer than 5 years of lifetime antipsychotic use, and (3) age 18 to 35 years. The AOM sites identified 576 potentially eligible participants, of whom 234 (40.6%) enrolled; CC sites identified 685 potentially eligible participants, of whom 255 (37.2%) enrolled.

INTERVENTIONS There were no restrictions on treatment at CC sites (including using LAIs) or at AOM sites with the exception that aripiprazole monohydrate had to be prescribed within US Food and Drug Administration–approved guidelines.

MAIN OUTCOMES AND MEASURES The primary outcome was time to first psychiatric hospitalization based on participant interviews every 2 months, the service use resource form administered every 4 months, and other sources (eg, health records) as available. Potential events were adjudicated by an independent committee masked to treatment assignment.

RESULTS The 489 participants (368 men [75.3%]) had a mean (SD) age of 25.2 (4.2) years and 225 (46.0%) had 1 year or less lifetime antipsychotic use. Fifty-two AOM (22%) and 91 CC participants (36%) had at least 1 hospitalization. The mean survival time until first hospitalization was 613.7 days (95% CI, 582.3-645.1 days) for AOM participants and 530.6 days (95% CI, 497.3-563.9 days) for CC participants. For time to first hospitalization, the hazard ratio was 0.56 (95% CI, 0.34- 0.92; $P = .02$), favoring AOM. Survival probabilities were 0.73 (95% CI, 0.65-0.83) for AOM participants and 0.58 (95% CI, 0.50-0.67) for CC participants. The number needed to treat to prevent 1 additional hospitalization was 7 participants treated with AOM compared with CC.

CONCLUSIONS AND RELEVANCE Long-acting injectable antipsychotic use by patients with early-phase schizophrenia can significantly delay time to hospitalization, a personally and economically important outcome. Clinicians should more broadly consider LAI treatment for patients with early-phase illness.

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The prevention of relapse and hospitalization in schizophrenia is a major public health challenge. Antipsychotic medications reduce the relapse risk compared with placebo with a number to treat (NNT) of 3,¹ and epidemiological studies find substantial reductions in all-cause mortality compared with no use.² Long-acting injectable antipsychotics (LAIs) are superior to oral counterparts in this regard.³⁻⁵

The consequences of relapse can be substantial for patients at all illness stages.⁶ For patients with early-phase illness, an additional consequence is that prospective studies⁷ report that second episodes of psychosis in the same individual respond less well to the same treatment than the first episode. Despite these risks, Tiihonen et al⁸ reported that 35.7% of patients admitted for their first hospitalization with schizophrenia stopped taking their antipsychotic within 30 days of discharge and 54.3% discontinued taking antipsychotics within 60 days of discharge. Adherence enhancement interventions are needed for patients with early-phase illness.⁹ Long-acting injectable antipsychotics can enhance adherence,¹⁰ but surveys of physician attitudes about LAIs show that they consider LAIs primarily for patients who have already had repeated hospitalizations and relapses.¹¹

For patients with first-episode and early-phase schizophrenia, some randomized clinical trials (RCTs)^{12,13} and naturalistic/cohort studies⁸ have shown substantial superiority for LAIs, whereas others have not.^{14,15} Although RCTs can provide the highest level of evidence, this design may selectively recruit participants who are more adherent to treatment than general patient populations.¹⁶ For studies that focus on nonadherence and its consequences, this may diminish the possibility of detecting differences between alternative treatment approaches. A partial solution to this challenge is large simple trials.¹⁷ Such trials are less likely to affect adherence as they are embedded in the delivery of care, demand little extra effort from physicians and patients, and involve 1 or 2 objective outcome measures.

This study was designed with this intent, focusing on patients in the early phase of schizophrenia illness before a long-term pattern of frequent hospitalizations has been established. The primary outcome measure, time to first psychiatric hospitalization, is one that can be verified objectively. The primary objective was to determine on an individual level the time to first psychiatric hospitalization with the LAI aripiprazole monohydrate compared with antipsychotic treatment as usual over a 2-year period.

Using cluster randomization at the clinic level enabled us to train the clinical staff at clinics randomized to provide LAI treatment with long-acting aripiprazole monohydrate (aripiprazole once monthly [AOM] condition) without affecting the care at clinics providing antipsychotic medication treatment as usual (clinician's choice [CC] condition). In addition, participants were not required to consent to individual treatment randomization, but only to consent to the treatment assigned to their clinic site.

Methods

The Prevention of Relapse in Schizophrenia (PRELAPSE) study was an investigator-initiated, multicenter, cluster-

Key Points

Question Compared with usual care, does the use of a long-acting formulation of antipsychotic medication reduce the risk of hospitalization in early-phase schizophrenia?

Findings In this cluster randomized trial of 489 participants, use of long-acting injectable aripiprazole monohydrate was associated with a significant delay in time to first hospitalization, with the number needed to treat to prevent 1 hospitalization of 7.

Meaning Long-acting formulations are infrequently used in early-phase treatment, and the association between their use and decreased hospitalization risk can have implications for individual treatment decisions and public health efforts.

randomized clinical trial. The trial design, education strategies for informing potential participants about the trial, and baseline participant characteristics have been published previously.¹⁸ The trial protocol ([Supplement 1](#)) was approved by the Feinstein Institute for Medical Research Northwell Health institutional review board and local institutional review boards as required by individual sites. The study used an independent data and safety monitoring board to evaluate participant safety, the adequacy and integrity of accumulating data, and the study's ability to test the hypotheses. Written informed participant consent was obtained before initiating any participant study procedures. Enrollment began in December 2014 and the last assessment occurred in March 2019.

Sites and Randomization

Clinics were eligible to participate if they had adequate populations of patients with early-phase illness, the capacity to offer LAI medication, and the willingness to be randomized. Clinics were paired based on having similar site and patient population factors (eg, urban vs rural, academic vs community, and presence of first-episode treatment vs no specialized treatment) and randomly assigned to treatment condition based on a predetermined computer-generated randomization list. No clinic withdrew after learning of their randomization. Forty-one clinics were randomized; 1 in each condition did not recruit any participants and were terminated, leaving 39 active clinical sites in 19 states. Nineteen (48.7%) of these were randomized to provide LAI treatment with long-acting aripiprazole monohydrate (AOM condition) and 20 (51.3%) to provide antipsychotic medication treatment as usual (CC condition).

Participants

Patients receiving treatment at participating clinics were approached about their willingness to engage in the study and screened to determine eligibility. Inclusion and exclusion criteria were kept to the minimum needed to address the trial questions. Participant inclusion criteria included: (1) schizophrenia diagnosis confirmed by the Structured Clinical Interview for *DSM-5*, Research Version (SCID-5),¹⁹ (2) less than 5 years of lifetime antipsychotic use, (3) age of 18 to 35 years,

and (4) ability to provide informed consent. Exclusion criteria included (1) primary *DSM-5* diagnosis other than schizophrenia, (2) pregnant or lactating women, (3) unstable medical condition making trial participation unwise, (4) prior clozapine use, and (5) history of intolerance to aripiprazole (AOM sites only). Consent was obtained from individual participants after the cluster randomization of the sites took place (AOM staff training about presenting the AOM condition is described in the eAppendix in [Supplement 2](#)).

Treatment

The CC sites offered CC (including possible LAI) medication and other available services to their participants. The AOM sites offered AOM without charge to their participants in addition to other available services. The AOM prescribers were required to prescribe AOM within its US Food and Drug Administration-approved guidelines, which included oral aripiprazole use before LAI AOM initiation and adherence to the approved injection interval, but were not otherwise restricted in their treatment. Participants at AOM sites who did not tolerate aripiprazole, had inadequate response to aripiprazole, or wished to stop AOM for other reasons received alternative treatment as clinically determined at their site and continued with the study outcome assessment.

Outcomes

Outcomes were assessed at the individual participant level only. Participants were assessed for 2 years regardless of the treatment being received.

Primary Outcome

Participants were interviewed via telephone every other month to obtain data on hospitalizations and emergency department and crisis unit use and every 4 months via completion of the service use resource form.^{20,21} Hospitalizations were verified from other sources (eg, medical records) as available. Potential events were adjudicated by an independent committee masked to treatment assignment. Included in the definition of psychiatric hospitalization were 2 related events: overnight stays in crisis stabilization units and overnight stays in psychiatric emergency departments for treatment of psychiatric symptoms. Inpatient admissions solely for substance detoxification were not counted as psychiatric hospitalizations (additional information is available in the eAppendix in [Supplement 2](#)).

Other Outcomes

Assessments conducted via live, 2-way video by central, masked assessors included a SCID-5 interview¹⁹ (baseline only), the Brief Psychiatric Rating Scale (BPRS),²² the Clinical Global Impressions Scale,²³ the Columbia Suicide Severity Rating Scale,²⁴ and the Heinrichs-Carpenter Quality of Life Scale (QLS)²⁵ at baseline, 12 months, and 24 months. The Repeatable Battery for Assessment of Neuropsychological Status²⁶ was obtained by site personnel at baseline, 12 months, and 24 months. Adverse event assessments using unstructured inquiries and laboratory tests were obtained at baseline, 6, 12, 18, and 24 months. Compared with most RCTs, this limited

assessment schedule was designed to minimize contact with participants outside of routine clinical care.

Sample Size

Sample size calculations were performed using the formula developed by Latouche et al²⁷ for proportional hazards modeling of Cox regression. The proportion of failures of interest (ie, first hospitalization) was set at 60% for the treatment as usual (CC) arm. For the sample size calculation, we hypothesized the corresponding proportion in the LAI arm to be 30%. The minimum detectable subdistribution hazard ratio (HR) at 80% power and a 5% significance level with 398 participants equally allocated in the 2 treatment arms was 1.48. Accounting for a 20% dropout rate from the hospitalization analyses, the corresponding sample was 498, or 249 per treatment group. With 400 participants who completed the study (ie, 200 per group), the cause-specific HR was estimated at 80% power and 5% significance level was 1.38.

Statistical Analyses

The intention-to-treat analyses included all participants who provided informed consent and met eligibility criteria that were comprehensively assessed at the first postconsent visit. The primary analysis involved a Cox regression model with a robust sandwich covariance matrix estimate to account for intracluster dependence.²⁸ As a sensitivity analysis, we conducted a discrete-time mixed-effects survival analysis^{29,30} for the primary end point. In terms of secondary end points, a mixed-effects Poisson regression model³¹ was used to examine overall rates of hospitalizations. Three-level linear mixed-effects regression models³¹ were used to study differences between treated and control participants in terms of QLS and BPRS changes from baseline at months 12 and 24 adjusted for clustering of participants nested within study sites and repeated observations nested within participants. Results of secondary analyses were reported as point estimates of treatment-related effects and 95% confidence intervals. A Kaplan-Meier survival plot was used to illustrate the overall marginal effect for time to first hospitalization. Analyses were conducted using SAS, version 9.4 (SAS Institute).

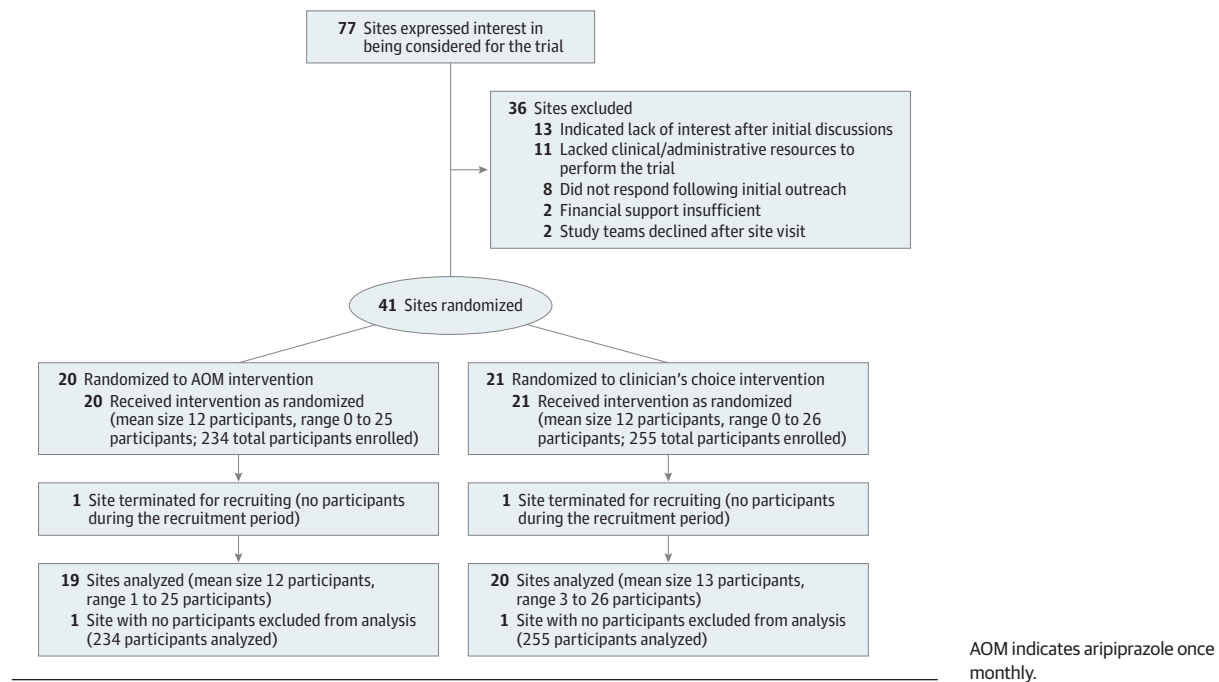
Results

Figure 1 presents the site participant flow. There were 489 participants overall, with 234 AOM (47.9%) and 255 CC patients (52.1%). A detailed individual participant flow chart has been published previously.¹⁸ At AOM sites, 576 potential participants were identified who met inclusion/exclusion criteria based on a screening interview. Of these, as previously reported,¹⁸ 83 (14.4%) declined participation because they would not consider LAI treatment and 165 (28.6%) declined for other reasons.

Patient Characteristics

Patients were mostly men (368 [75.3%]) (**Table 1**). The mean (SD) age of CC participants was 24.7 (4.1) years and for AOM 25.7 (4.3) years. The mean (SD) number of prior hospitaliza-

Figure 1. Site Participant Flow



tions was 3 (2.5) and 3.4 (2.9) for AOM and CC, respectively; 97 AOM (41.5%) and 94 CC patients (36.9%) had 0 or only 1 prior hospitalizations. The mean (SD) duration of antipsychotic treatment was 612.1 (547.4) days for CC and 646.6 (554.4) for AOM; importantly, 102 participants in AOM (43.6%) and 123 in CC (48.2%) had 1 year or less of lifetime antipsychotic treatment.

LAI Usage

Seventy-two of the 234 AOM patients (30.8%) patients were receiving either AOM (36 [15.4%]) or another LAI (36 [15.4%]) at the time of consent. In comparison, 70 of the 255 CC patients (27.4%) were receiving either AOM (10 [3.9%]) or another LAI (60 [23.5%]).

Two hundred fourteen of the 234 participants at AOM sites (91.0%) received at least 1 AOM study injection during the study. Of the 20 participants who did not receive an AOM injection, only 1 refused the injection. Other reasons for not receiving an injection were because 2 were not eligible for an injection because of not tolerating an oral aripiprazole challenge, 16 dropped out before receiving an injection, and 1 relocated out of the area. Of the 214 participants who received an AOM injection during the study, 142 (66.4%) were not receiving an LAI at the time of consent. In the CC group, 130 participants (51%) were prescribed an LAI at some point during the study; of these, 23 were prescribed an LAI only after a first hospitalization.

Outcomes and Hospitalizations

The mean (SD) number of total days followed up was 594.3 (250.7) for the AOM group and 573.5 (253.9) for the CC group. The total number of psychiatric hospitalizations was 341 (133 [39.0%]) among the 234 AOM participants and 208 [61.0%] among the CC participants). The primary causes of

hospitalizations were psychotic symptoms (264 hospitalizations [77.4%]), other than psychotic symptoms (72 hospitalizations [21.1%]), and unclear (5 hospitalizations [1.5%]).

Primary Outcome

Fifty-two AOM participants (22.2%) met criteria for a first hospitalization and 91 of the CC group (36.0%). Of these, 40 of the AOM group were receiving aripiprazole monohydrate at the time of first hospitalization and 22 of the CC group any LAI. The mean survival time until first hospitalization was 613.7 days (95% CI, 582.3-645.1 days) for AOM participants and 530.6 days (95% CI, 497.3-563.9 days) for CC participants.

Under the proportional hazards assumption, the HR for time to first hospitalization was 0.56 (95% CI, 0.34-0.92; $P = .02$), favoring AOM. A sensitivity analysis using a discrete-time survival model with random site-effect produced identical results (odds ratio [OR], 0.56; 95% CI, 0.34-0.91; $P = .02$). The Kaplan-Meier curves are displayed in **Figure 2**. The mean survival time until first hospitalization was 613.7 days (95% CI, 582.3-645.1 days) for AOM participants and 530.6 days (95% CI, 497.3-563.9 days) for CC participants. The estimated survival probabilities from the Cox model were 0.73 (95% CI, 0.65-0.83) for AOM participants and 0.58 (95% CI, 0.50-0.67) for CC participants. This translates to an NNT for prevention of 1 additional hospitalization of 6.67 participants treated with AOM relative to CC. The mean (SD) time to first hospitalization for those hospitalized was 275.1 (234.6) days with AOM and 261.1 (188.9) days for CC.

Secondary Outcomes

The AOM option was associated with a 36% decrease in rate for total hospitalizations but the difference was not statisti-

Table 1. Participant Characteristics at Study Entry

Characteristic	No. (%)	
	AOM (n = 234)	CC (n = 255)
Age, mean (SD), y	25.7 (4.3)	24.7 (4.1)
Age at first antipsychotic treatment, mean (SD), y	21.9 (4.4)	21.3 (4.2)
Men	172 (73.5)	196 (76.9)
Race		
White	80 (34.2)	91 (35.7)
Black	109 (46.6)	104 (40.8)
Other	45 (19.2)	58 (22.7)
Unknown	0 (0.0)	2 (0.8)
Marital status		
Married	13 (5.6)	9 (3.5)
Divorced	7 (3.0)	8 (3.1)
Single	212 (90.6)	238 (93.3)
Unknown	2 (0.9)	0 (0.0)
Current residence		
Living alone	32 (13.7)	33 (12.9)
Supported living environment	10 (4.3)	5 (2.0)
Structured environment	8 (3.4)	12 (4.7)
Family of origin	154 (65.8)	174 (68.2)
Family of orientation	17 (7.3)	13 (5.1)
Other	13 (5.6)	18 (7.1)
Duration of antipsychotic treatment, mean (SD), d	646.6 (554.4)	612.1 (547.4)
Log (duration of antipsychotic treatment +1) (SD)	5.86 (1.41)	5.83 (1.32)
Had <1 y or less of antipsychotic treatment	102 (43.6)	123 (48.2)
No. of hospitalizations for psychiatric illness		
0	29 (12.4)	32 (12.5)
1	68 (29.1)	62 (24.3)
2	38 (16.2)	41 (16.1)
3	31 (13.2)	37 (14.5)
4	26 (11.1)	24 (9.4)
≥5	40 (17.1)	54 (21.2)
No. of hospitalizations for psychiatric illness (treated as continuous variable), mean (SD)	3 (2.5)	3.4 (2.9)

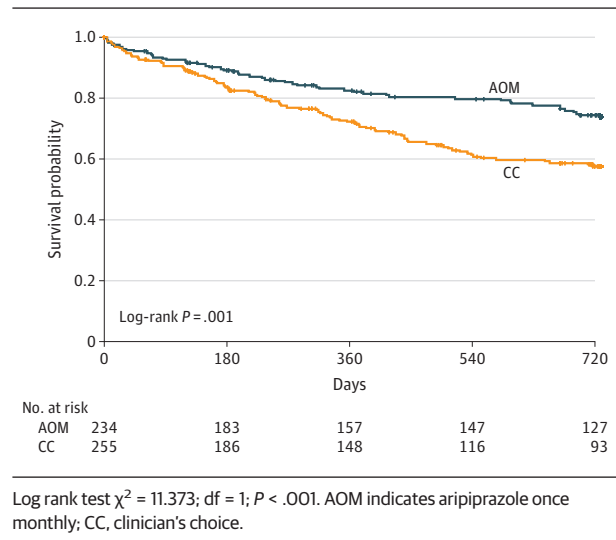
Abbreviations: AOM, aripiprazole once monthly; CC, clinician's choice.

cally significant (relative risk, 0.64; 95% CI, 0.33-1.26; $P = .20$). The estimated change from baseline to month 12 or month 24 did not differ between the conditions for either QLS or BPRS total scores or the respective subfactor scores (Table 2 and eFigures 1-3 in Supplement 2).

Harms

Two deaths occurred; 1 CC participant died by suicide and 1 CC participant died of unknown causes. Four participants in each condition made suicide attempts (completed suicide excluded). Table 3 presents adverse events occurring after the baseline visit in 5% or more of either AOM or CC participants.

Figure 2. Time Remaining Without Having a First Hospitalization



Discussion

To our knowledge, this is the first large-scale, multisite LAI study for patients with early-phase schizophrenia conducted in the US. The use of an LAI in this population produced a significant 44% reduction in the incidence rate of first hospitalization for the AOM group compared with the CC group and an NNT of 7 for the prevention of hospitalization. In the secondary measure of total number of hospitalizations, a 36% decrease was found, but that difference was not statistically significant. These reductions are notable given that 2 aspects of the design may have decreased the ability to find differences. First, the usual care condition allowed the use of LAIs. Clinics had to have clinical and administrative support to participate in an LAI study; therefore, not surprisingly, the study's CC clinics had higher rates of LAI use at baseline and during the trial than US statistics would suggest. Second, psychiatric hospitalizations included those for all psychiatric symptoms. Although most of the study hospitalizations were because of psychotic symptoms, some were because of other psychiatric symptoms.

The QLS and BPRS scores did not differ. One possible factor is that the long duration between assessments limited the ability to capture the trajectories of these domains.

Two previous RCTs have reported the superiority of LAIs over oral antipsychotics in first-episode or patients with early-phase schizophrenia. Schreiner et al¹² reported on 715 participants within 1 to 5 years of a schizophrenia diagnosis who were randomly assigned to receive LAI paliperidone vs an array of oral medications at 141 centers in 26 countries. The time to relapse was substantially longer in the LAI group. Schreiner et al¹² used the Csernansky criteria for relapse,³² which allow for a broad interpretation of worsening. Our study required hospitalization, which generally assures a more severe level of exacerbation and provides a strong health economic rationale. The Schreiner et al¹² study sample was considerably older (age 33 years) than our group (age 25 years). Their inclusion

Table 2. Change in Heinrich Carpenter Quality of Life and Brief Psychiatric Rating Scale Total Scores Between AOM and CC Conditions From Baseline to 12 Months and 24 Months^a

Score	Estimate (95% CI)	
	Change to mo 12	Change to mo 24
Heinrich Carpenter quality of life		
Total score	1.068 (−2.911 to 5.047)	−2.014 (−6.252 to 2.225)
Subscale scores		
Interpersonal relations ^b	0.166 (−1.703 to 2.034)	0.247 (−1.737 to 2.231)
Instrumental role ^c	1.079 (−0.575 to 2.732)	−1.095 (−2.856 to 0.666)
Intrapsychic foundations ^d	0.137 (−1.285 to 1.559)	−1.015 (−2.535 to 0.504)
Common objects and activities ^e	−0.055 (−0.459 to 0.349)	−0.104 (−0.535 to 0.328)
BPRS scores		
Total score	0.960 (−1.105 to 3.025)	0.334 (−1.993 to 2.661)
Factor scores		
Anxiety/depression ^f	0.080 (−0.126 to 0.286)	0.016 (−0.204 to 0.237)
Anergia ^g	0.150 (−0.049 to 0.350)	0.136 (−0.090 to 0.362)
Thought disturbance ^h	0.035 (−0.185 to 0.254)	−0.141 (−0.376 to 0.095)
Activation ⁱ	−0.021 (−0.129 to 0.087)	−0.017 (−0.138 to 0.105)
Hostile suspiciousness ^j	0.062 (−0.128 to 0.252)	−0.014 (−0.219 to 0.191)

Abbreviations: AOM, aripiprazole once monthly; BPRS, Brief Psychiatric Rating Scale; CC, clinician's choice.

^a The 3-level model of outcome included treatment, time, treatment by time, and age.

^b Sum of quality of life items 1 to 8.

^c Sum of quality of life items 9 to 12.

^d Sum of quality of life items 13 to 17, 20, and 21.

^e Sum of quality of life items 18 to 19.

^f Mean of BPRS items 1, 2, 5, and 9.

^g Mean of BPRS items 3, 13, and 16.

^h Mean of BPRS items 4, 8, 11, 12, and 15.

ⁱ Mean of BPRS items 6, 7, and 17.

^j Mean of BPRS items 10, 11, and 14.

criteria required 2 inpatient admissions within the past 2 years, whereas approximately 40% of our study's sample had a lifetime history of fewer than 2 hospitalizations. Thus, our study's sample was earlier in the illness course and at a stage when clinicians traditionally are less likely to consider LAIs. In addition, our study was conducted exclusively in the US as compared with 26 different countries. Subotnick et al,¹³ in a small study conducted at a single academic site, randomly assigned 86 patients with first-episode illness to receive oral or

Table 3. Adverse Events Occurring After Baseline Visit in 5% or More of Either AOM or CC Participants

Adverse event	Participants experiencing adverse event, No. (%)	
	AOM ^a	CC ^b
Worsening of psychotic symptoms	51 (23)	97 (40.2)
Weight gain	32 (14.4)	47 (19.5)
Suicidal ideation without suicide attempt ^c	19 (8.6)	23 (9.5)
Depression	23 (10.4)	20 (8.3)
Anxiety	27 (12.2)	15 (6.2)
Hyperprolactemia	9 (4.1)	31 (12.9)
Elevated cholesterol levels	15 (6.8)	24 (10.0)
Hepatic enzyme abnormalities	15 (6.8)	22 (9.1)
Insomnia	19 (8.6)	17 (7.1)
Hypertension	12 (5.4)	18 (7.5)
Somnolence	16 (7.2)	11 (4.6)
Hostility/aggression	16 (7.2)	7 (2.9)
Tachycardia	7 (3.2)	12 (5.0)
Restlessness	14 (6.3)	2 (0.8)

Abbreviations: AOM, aripiprazole once monthly; CC, clinician's choice.

^a Two hundred twenty-two AOM participants had a visit after the baseline visit.

^b Two hundred forty-one CC participants had a visit after the baseline visit.

^c Does not include the one CC participant who died by suicide. Participants who made suicide attempts concurrent with recorded suicidal ideation are not included; participants who made suicide attempts but also had suicidal ideation not concurrent with an attempt are included.

LAI risperidone and found substantially different respective relapse rates of 33% vs 5%. Our study extends these findings. To our knowledge, it is the only large-scale trial conducted in the US with first-episode and patients with early-phase schizophrenia conducted primarily in community mental health centers in addition to academic settings with a more pragmatic than explanatory design.³³

Many attribute the low rate of LAI use in clinical practice to patient refusal. However, PRELAPSE demonstrates that, with proper training, practitioners are able to communicate potential advantages of LAIs, even in early illness stages, and engage patients in shared decision-making resulting in high acceptance rates. Antipsychotics should be reserved for those for whom there is a clear indication for ongoing treatment.³⁴ Once that decision is made, the question becomes with which formulation is the patient most likely to derive the benefits intended. The use of LAIs does not deprive patients of autonomy or choice. The choice is made each time an injection is administered. As part of any such discussion with patients, the phenomenon of nonadherence needs to be normalized and destigmatized. It is human nature to have difficulty taking medication on a long-term basis, regardless of the illness and medication type.³⁵⁻³⁷ The recommendation of LAIs should not be construed as a pejorative or punitive stance, which can undermine the therapeutic alliance. Additionally, it should be recognized/acknowledged that even with guaranteed antipsychotic medication, some patients with schizophrenia will require hospitalization because of symptoms other than psychosis or from a relapse of psychotic symptoms, a phenomenon that requires additional research.³⁸

Limitations

Our study's 2 participant groups had very similar baseline characteristics (eg, baseline use of LAIs, hospitalization, and antipsychotic treatment history). Nevertheless, selection effects may have occurred with our cluster randomization design. Our results might have underestimated the effects of LAIs on hospitalization because of the relatively high LAI use rates for patients with first-episode/early-phase illness in the CC condition. The nature of the patients and clinical sites in the overall trial suggests good generalizability, but training of the AOM sites was an important element in the success of patient enrollment and strategies should be implemented to ensure that clinics gener-

ally have access to such training. This study involved only 1 long-acting injectable formulation; however, to our knowledge, there are no data suggesting differences in efficacy among the second-generation LAIs regarding prevention of hospitalization.

Conclusions

The use of LAIs for individuals with early-phase schizophrenia produced a significant and clinically meaningful 44% reduction in the incidence rate of first hospitalization and an NNT of 7 for the prevention of hospitalization.

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