Patients With Early-Phase Schizophrenia Will Accept Treatment With Sustained-Release Medication (Long-Acting Injectable Antipsychotics): Results From the Recruitment Phase of the PRELAPSE Trial

John M. Kane, MD[a,b,c,*]; Nina R. Schooler, PhD[d]; Patricia Marcy, BSN[e]; Eric D. Achtyes, MD[f,g]; Christoph U. Correll, MD[a,b,c,h]; and Delbert G. Robinson, MD[a,b,c]

ABSTRACT

Objective: To document the acceptability of treatment with long-acting injectable (LAI) antipsychotic medication to early-phase schizophrenia patients as demonstrated by enrollment in a cluster-randomized LAI clinical trial.

Methods: Eligible patients aged 18–35 years with a *DSM-5* diagnosis of schizophrenia and less than 5 years of lifetime antipsychotic use were recruited between December 2014 and December 2016. Training for LAI antipsychotic site staff included education regarding the role of nonadherence in relapse/hospitalization and the rationale for LAI antipsychotic use with early-psychosis patients, training in shared decision-making and communication strategies, review of frequently asked questions about LAI antipsychotics, and role-playing to develop skills and solutions to overcoming LAI antipsychotic logistical barriers. Study prescribers also received training on prescribing guidelines.

Results: At the 19 US outpatient clinics randomized to provide LAI antipsychotic treatment, 576 potential participants were identified who met inclusion criteria based on a screening interview. Of these, 83 (14.4%) declined participation because they would not consider LAI antipsychotic treatment and 165 (28.6%) declined for other reasons, resulting in 328 providing written study consent. The first post-consent visit included detailed evaluations to confirm inclusion/exclusion criteria. Thirty-nine participants who consented did not complete this evaluation and 55 were found to not meet criteria, resulting in a final sample of 234 participants. Two hundred thirteen (91.0%) accepted at least one LAI antipsychotic injection during their first 3 months of study participation.

Conclusions: Large numbers of early-phase patients with schizophrenia were willing to participate in an LAI antipsychotic trial and by inference in non-study LAI antipsychotic treatment. LAI antipsychotic–focused staff training has the potential to substantially enhance the use of LAI antipsychotics.

Trial Registration: ClinicalTrials.gov identifier: NCT02360319

J Clin Psychiatry 2019;80(3):18m12546

To cite: Kane JM, Schooler NR, Marcy P, et al. Patients with early-phase schizophrenia will accept treatment with sustained-release medication (long-acting injectable antipsychotics): results from the recruitment phase of the PRELAPSE trial. *J Clin Psychiatry.* 2019;80(3):18m12546.

To share: https://doi.org/10.4088/JCP.18m12546

[a]Departments of Psychiatry and of Molecular Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York

[b]Center for Psychiatric Neuroscience, Feinstein Institute for Medical Research, Manhasset, New York

[c]The Zucker Hillside Hospital, Glen Oaks, New York

[d]Department of Psychiatry, SUNY Downstate Medical Center, Brooklyn, New York

[e]Vanguard Research Group, Glen Oaks, New York

[f]Cherry Health, Grand Rapids, Michigan

[g]Michigan State University College of Human Medicine, Grand Rapids, Michigan

[h]Charité Universitätsmedizin, Department of Child and Adolescent Psychiatry, Berlin, Germany

**Corresponding author:* John M. Kane, MD, The Zucker Hillside Hospital, 75-59 263rd St, Glen Oaks, NY 11004 (jkane2@northwell.edu).

Preventing relapse and hospitalization is an important goal in the treatment of first-episode and early-phase schizophrenia. Associated undesirable outcomes range from disruption of psychosocial and vocational functioning to personal suffering, family burden, and high health care expenditures. Multiple relapses may lead to a diminution or delay in subsequent treatment response[1] and increase the risk for neuroanatomical changes.[2] Hospitalization rates during extended treatment remain high even with coordinated specialty care (CSC) treatment models that are effective for other aspects of early-phase illness.[3–9] For example, the Recovery After an Initial Schizophrenia Episode-Early Treatment Program (RAISE-ETP) trial[9] included 404 first-episode psychosis patients and compared CSC to community care. Over 2 years, 34% of patients at CSC sites and 37% at community care sites (adjusted for length of exposure) had ≥ 1 psychiatric hospitalization.

The ambivalence that many early-phase patients have about taking medication combined with the natural risk for nonadherence constitutes one potentially modifiable contributing variable.[10–14] Long-acting injectable (LAI) antipsychotics are theoretically a very powerful tool to assure adherence and identify nonadherence. In a meta-analysis by Kirson et al,[15] 13 relevant studies (5 randomized controlled trials [RCTs], 4 prospective, 4 retrospective) included information on 19 comparisons of LAI versus oral medications. The adjusted end points resulted in a risk ratio (RR) of 0.89 ($P = .416$) for RCTs. In contrast, there was a significant advantage for LAI formulations in both prospective (RR = 0.62, $P < .001$) and retrospective (RR = 0.56, $P < .001$) studies, implying conversion factors of 1.43 and 1.59 between RCTs and prospective and retrospective designs, respectively. In tightly controlled RCTs, the benefits of LAI antipsychotics were not significantly superior to those of oral formulations. This may be because RCTs enroll

Clinical Points

- Anosognosia and nonadherence remain significant barriers to sustained remission in patients with first-episode and early-phase schizophrenia.
- Little is known about whether first-episode and early-phase patients would be willing to try a long-acting injectable antipsychotic medication (LAI) if offered.
- The authors found that 91.0% (213 of 234) of first-episode and early-phase patients were willing to try at least one dose of an LAI when the option was presented in a supportive manner.

more adherent patients and because subjects benefit from the extra care being given in an RCT setting. In contrast, as study design shifts toward prospective and retrospective studies in real-world clinical settings, LAI formulations display significant advantage.

We selected aripiprazole to study in this population because of its relatively benign side effect profile[16] and its promising effectiveness in first-episode psychosis patients.[17,18] Data support the potential impact of utilization of LAI antipsychotics specifically in early-phase patients. Despite a promising open-label study,[19] 2 studies[20,21] in first-episode patients utilizing risperidone microspheres (RLAI) versus oral antipsychotics showed only trends toward initial clinical improvement or better adherence for RLAI. However, Subotnik et al[22] and Schreiner et al[23] have shown dramatically lower rates of relapse and hospitalization in early-phase patients randomly assigned to LAIs in comparison to oral medications. The Subotnik et al study also revealed a significantly greater increase in cortical myelination in the patients treated with LAIs compared to those treated with the same medication in oral formulation.[24]

The greatest challenge in taking advantage of this evidence is in dissemination and implementation. Most clinicians do not consider LAI medications for this patient population and, if they do, often assume that the patients are unlikely to accept them. LAI medication utilization rates in the United States are currently low—13% of those with schizophrenia spectrum disorders in a large Medicaid database between January 2013 and June 2014 (A. Hartry, PhD; personal written communication, November 2018). In RAISE-ETP, patients assigned to CSC received LAI medications 18% of their total treatment time and CC patients 13% of their treatment time.[25] Current data from OnTrack New York sites delivering CSC to first-episode patients indicate that only 12% of patients were receiving a long-acting injectable medication at the time of admission to the program between November 2016 and November 2018 (L. Dixon, MD; personal written communication, November 2018). This low utilization is despite the fact that 50%–75% of patients will have clinically significant problems with medication taking over the course of a 2-year follow up and nonadherence is the major cause of relapse and hospitalization.[10] Tiihonen et al[26] reported that 35.7% of patients admitted for their first hospitalization for schizophrenia or schizoaffective disorder stopped their antipsychotic within 30 days of discharge and 54.3% discontinued antipsychotic within 60 days of discharge. This Finnish study included 5,221 person-years of follow-up and of these the total time of LAI medication monotherapy was only 298 person-years. Kahn et al[27] found that 42% of first-episode patients discontinue oral antipsychotic medications within the first year of treatment, and Robinson et al[28] reported that first-episode patients who discontinue antipsychotic medications are 5 times more likely to relapse than those who continue to take such medication. A rationale for considering use of LAI medications in early-phase schizophrenia has been summarized by Heres et al.[29]

Prescribers are one central factor[30,31] contributing to the underutilization of LAI antipsychotics. In a survey[32] of patients without LAI antipsychotic experience, 79% of patients reported that they had never been informed about the option by their psychiatrist. In that same survey, although 75% of psychiatrists reported that they informed the patient about LAI antipsychotics, only 33% of those patients felt informed. A recent study[33] of communication patterns in the offer of LAI antipsychotics at 10 community mental health clinics found that psychiatrists generally presented LAI antipsychotic therapy in a negative light, resulting in the acceptance by patients of only 11 (33%) of 33 LAI antipsychotic treatment recommendations. During a post-visit interview in which LAI antipsychotics were presented in a more positive light and with more information, 27 (96%) of 28 patients who seemed to decline the initial recommendation changed their mind, stating that they actually would be willing to try LAI antipsychotic treatment.

On the basis of such data, we concluded that a multistep process is necessary to facilitate use of LAI antipsychotics in early-phase patients. Initiating a therapeutic trial of LAI antipsychotics is the first step, but facilitating sustained utilization is also critical in achieving long-term goals. We are currently conducting an investigator-initiated cluster randomized RCT named *PRELAPSE* that enrolls first-episode and early-phase patients into a large simple trial of LAI antipsychotics and compares them with a group receiving clinician's choice of treatment. The key to the success of this project is a sufficiently high utilization rate of LAI antipsychotics by the "experimental" sites to allow for a meaningful, statistically powered comparison to usual care in which some proportion of patients might receive LAI antipsychotics. This article describes the design of the study and enrollment of consenting and eligible subjects into 2 clusters: one that only ensures appropriate subject inclusion and limited assessment and a second that also offers and encourages use of an LAI antipsychotic.

METHODS

Overview

Thirty-nine outpatient clinics located in 19 US states were selected and agreed to participate. All sites were community ("real world") mental health clinics that are very

representative of where most patients receive ambulatory services. Twenty-eight had no academic affiliations and 11 had some academic affiliations. Thirty had no first-episode specialty treatment programs. Clinics were paired based on having similar site and patient population factors (urban vs rural, academic vs community, presence of first-episode psychosis treatment vs no specialized first-episode psychosis treatment) and then randomly assigned to one of the treatment conditions based on a predetermined computer-generated randomization list. Nineteen sites were randomized to provide LAI treatment with long-acting aripiprazole monohydrate (the Aripiprazole Once Monthly [AOM] condition) and 20 sites to treatment as usual (the Clinician's Choice [CC] condition). Study enrollment was between December 2014 and December 2016. The primary study hypothesis was that the opportunity for treatment with a once-monthly injectable antipsychotic (in this case, AOM) would significantly delay time to first hospitalization in patients with early-phase schizophrenia.

Signed, informed consent was obtained prior to initiating any study procedures. All study procedures were performed in concordance with the Declaration of Helsinki and good clinical practice. The study was overseen by the Feinstein Institute for Medical Research Northwell Health institutional review board (IRB) and local IRBs as required by individual sites. The study was registered at ClinicalTrials.gov (identifier: NCT02360319).

Participants

To enhance the generalizability of findings to the population of patients with early-phase schizophrenia, inclusion and exclusion criteria were kept to the minimum needed to address the trial questions. Inclusion criteria were (1) schizophrenia diagnosis confirmed by the Structured Clinical Interview for *DSM-5*, Research Version (SCID-5-RV)[34]; (2) less than 5 years of antipsychotic lifetime use; (3) age of 18–35 years; and (4) ability to provide informed consent. Exclusion criteria were (1) primary *DSM-5* diagnosis other than schizophrenia, (2) being pregnant or lactating (for women), (3) unstable medical condition making trial participation unwise, (4) prior clozapine use, and (5) history of intolerance to aripiprazole (AOM sites only).

At study entry, participants were classified as having either (1) less than 1 year of prescribed treatment with antipsychotic medication and only 1 lifetime episode of psychosis (the "first-episode" cohort) or (2) 1 to 5 years of antipsychotic treatment and/or more than 1 episode of psychosis (the "early-phase" cohort). Our goal was to recruit approximately equal numbers of subjects in each cohort to facilitate subgroup analyses.

Treatment

The CC sites offered clinicians' choice of medication (including possible LAI) and other available services to their participants. The AOM sites offered AOM to their participants in addition to other available services. AOM prescribers were required to prescribe AOM within the US Food and Drug Administration (FDA)–approved guidelines for AOM treatment but were not otherwise restricted in their medication prescriptions.

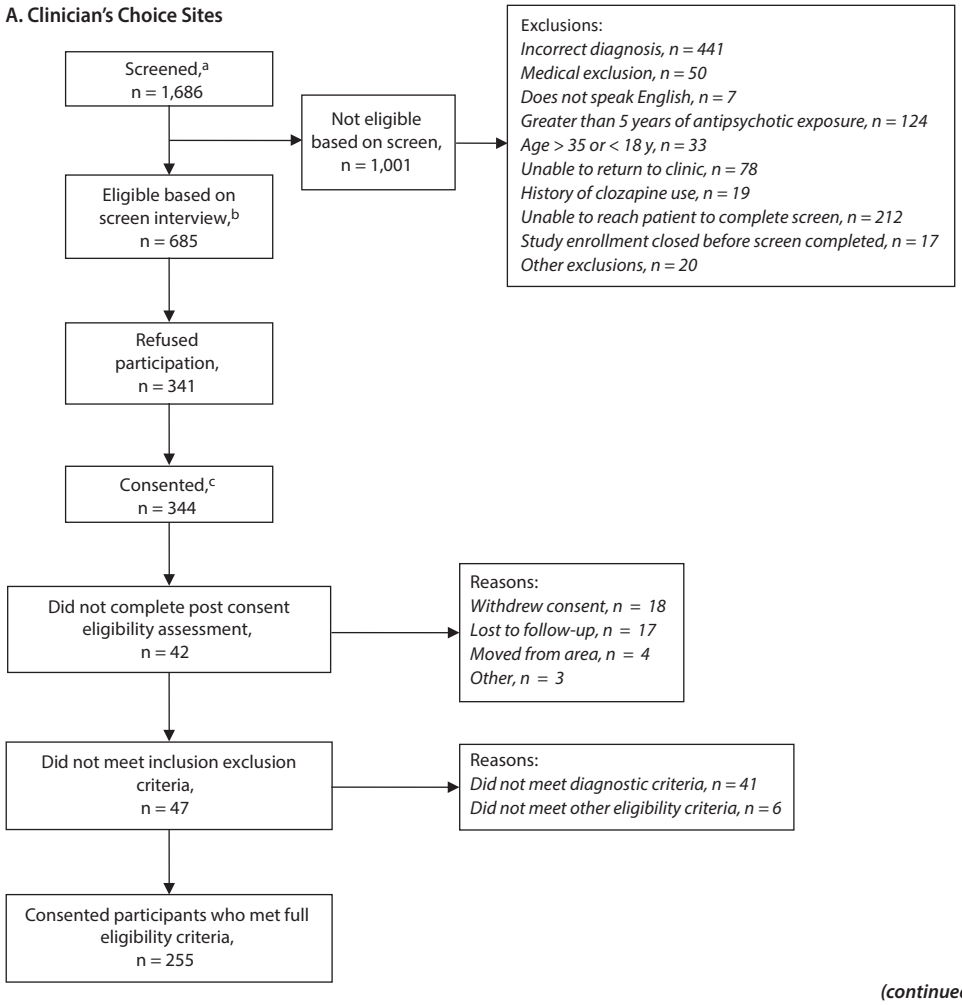
Assessments

Participants were followed for a 2-year period. Subjects remained in the 2-year follow-up regardless of their decisions about treatment (eg, subjects at AOM sites who refused or stopped AOM continued in the follow-up assessments). Masked assessments conducted via live, 2-way video by central assessors included the SCID-5-RV at baseline only and the Brief Psychiatric Rating Scale (BPRS),[35] the Clinical Global Impression Scale (CGI-S),[36] the Columbia Suicide Severity Rating Scale (C-SSRS),[37] and the Heinrichs-Carpenter Quality of Life Scale (QLS)[38] at baseline and at 1 and 2 years. The Repeatable Battery for Assessment of Neuropsychological Status (RBANS)[39] was administered by site personnel at baseline and at 1 and 2 years. Safety assessments and laboratory tests were obtained at baseline and at 6, 12, 18, and 24 months. Participants were interviewed via phone every other month for data on hospitalizations and emergency department use and every 4 months for completion of the Service Use and Resource Form (SURF).[40] In comparison with most RCTs, this assessment schedule minimizes contact with participants outside of routine clinical care. Magnetic resonance imaging (MRI) was performed at 10 centers (5 in each treatment arm) at baseline and at 12 and 24 months for participants consenting to this extra assessment (data on MRI consent will be presented in a separate report). Patients at MRI sites could still participate in the clinical trial that is the focus of this report even if they refused or were not eligible for the MRI component.

Staff Training

All site teams attended 3 in-person investigator meetings over the 2-year enrollment period to provide general education about the protocol and procedures and to strategize about challenges encountered during subject recruitment. The initial training lasted 2 days for AOM sites and 1 day for CC sites. Training topics for all sites included study rationale and overview, characteristics of early psychosis patients, recruitment and retention strategies, good clinical practice, data management, and adverse event querying and reporting. AOM-specific training included information on the role of nonadherence in relapse and hospitalization and the effectiveness of LAI antipsychotics in this context, the rationale for LAI antipsychotic use and for selection of aripiprazole with early psychosis patients, shared decision-making principles,[41] discussion of LAI antipsychotics with patients and families; discussion of optimal ways to transition to LAI medication,[42] and specific prescribing guidelines consistent with the package insert for LAI aripiprazole. Training included providing suggested "scripts," discussing frequently asked questions, and role-playing as well as suggestions for overcoming potential logistical barriers to the use of LAI antipsychotics across different health care settings.

Figure 1. Recruitment Flow



(continued)

At 2 subsequent in-person meetings (1 day for both AOM and CC sites), we reviewed recruitment successes and challenges as well as retention strategies. Sites were consistently reminded that the design of a "large, simple" trial is to have a "light touch" on patients, meeting only as needed for study visits, thereby decreasing the effects of the enhanced patient-staff contact often part of studies, which may drive some of the lack of benefit seen in RCTs studying adherence and LAI antipsychotics.[43,44] Role-playing exercises for AOM sites addressed common challenges to prescribing LAI antipsychotics. AOM site training suggestions included presenting subjects the option to try one injection to see if they liked it better than taking oral medications daily as there is evidence that once patients try an LAI antipsychotic, the majority prefer it to oral formulations.[45]

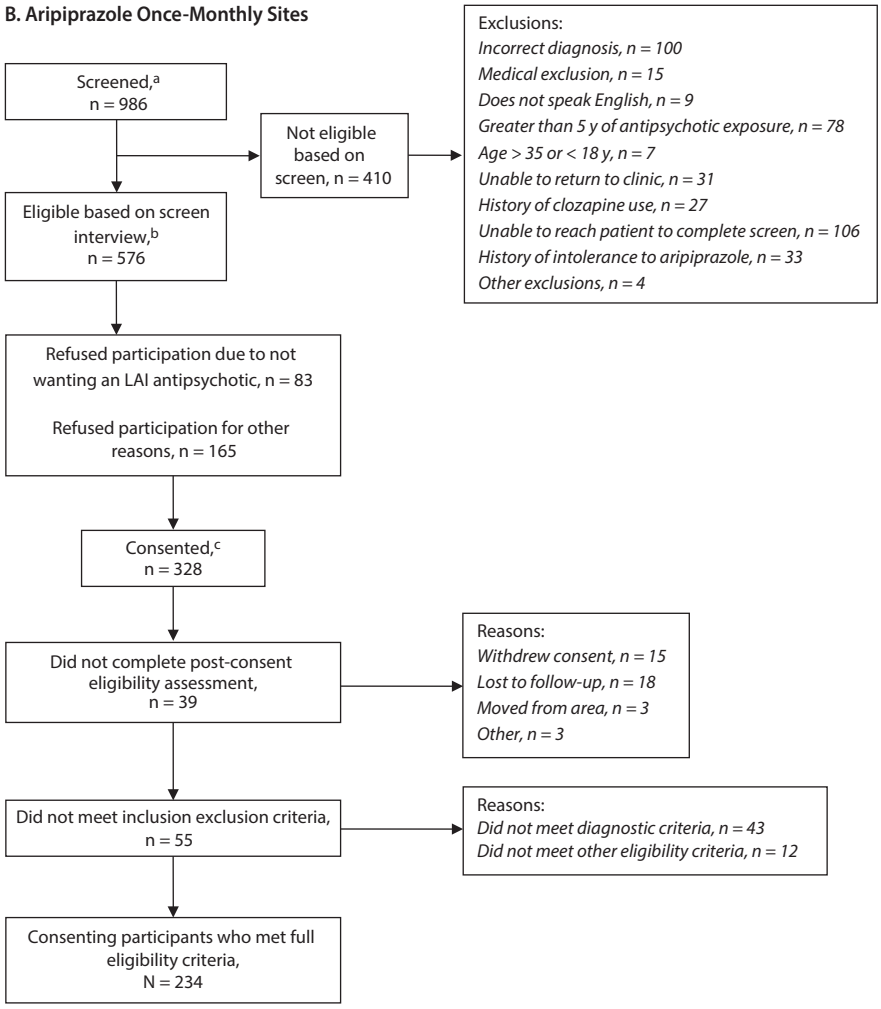
We provided group web-based tutorials followed by monthly 1-hour teleconsultation with members of the central team for the purpose of troubleshooting problems with recruitment, retention, adverse event reporting, and handling data queries and to share successes and challenges across sites. Separate tutorials and teleconsultation were provided for CC and AOM sites. Scheduled teleconferences continued throughout the trial. Site personnel could also directly ask central team members questions about protocol requirements. For AOM prescribers, these questions could include information about protocol medication options (ie, if a prescription did or did not conform to FDA labeling for AOM). Central team members did not provide specific medication recommendations for participants, only information on what was allowed by the protocol (eg, the minimum time between AOM injections as per FDA labeling).

RESULTS

Participant Recruitment

Figure 1 presents the participant flow. At AOM sites, 576 potential participants were identified who met inclusion/exclusion criteria based on a screening interview. Of these, 83 (14.4%) declined participation because they would not consider LAI antipsychotic treatment and 165 (28.6%) declined for other reasons. Combined, 248 (43%) declined,

Figure 1 (continued).



[a]Potential research subjects contacted by research staff.
[b]Potential subjects meeting brief (pre-consent) checklist.
[c]Potential subjects who signed informed consent form and agreed to participate in study if eligibility criteria were met.
Abbreviation: LAI = long-acting injectable.

resulting in 328 providing written study consent. The first post-consent visit included detailed evaluations to confirm inclusion/exclusion criteria. Thirty-nine participants who consented (11.9%) did not complete this evaluation, and 55 (16.8%) were found to not meet criteria, resulting in a final sample of 234 participants. At CC sites, 685 potentially eligible participants were identified, and 341 (49.8%) of these declined study participation, resulting in 344 providing written consent. Forty-two patients (12.2%) who provided consent did not complete the post-consent eligibility assessment, and 47 (13.7%) did not meet criteria on this assessment, resulting in a final sample of 255 participants.

Patients receiving LAI antipsychotics at the time of consent were not excluded from study participation. Sites were told that recruitment should be from representative samples of their patient populations; eg, recruitment of patients already taking LAI antipsychotics was allowed but should be at rates comparable to the rate of LAI antipsychotic use in their clinical services. One hundred sixty-six (70.9%) of the 234 participants were not receiving an LAI antipsychotic at the time of consent, and 68 (29.1%) were receiving either AOM (n = 36 [15.4%]) or another LAI antipsychotic (n = 32 [13.7%]).

Participant Demographic Characteristics

The population in this study was typical of participants in early-phase schizophrenia trials. Participants were young (mean [SD] age = 25.2 [4.2] years) and mostly male (75.3%). The most frequent racial background was African American (43.6%) followed by white (35.0%). Most had experienced inpatient hospitalization for psychiatric illness prior to study entry; 12.5% had never been hospitalized, 26.6% had 1 hospitalization, 16.2% had 2, 43.4% had 3 or more, and 1.4% provided no data on prior hospitalization. A total of 46.0% of participants had 1 year or less of lifetime antipsychotic exposure.

Acceptance of LAI Antipsychotic Within the First 3 Months of the Trial

PRELAPSE enrollment has now been completed. Two hundred thirteen (91.0%) of the 234 subjects at AOM sites received at least 1 AOM study injection during the first 3 months. Of the 21 participants who did not receive an AOM injection within that period, only 4 refused the injection. Other reasons for not receiving an injection were being ineligible for an injection due to not tolerating an oral aripiprazole challenge (n = 2), dropping out (n = 12), and having other reasons (n = 3). Of the 213 participants who received an AOM injection within the first 3 months, 145 were not receiving an LAI antipsychotic at the time of consent.

DISCUSSION

To our knowledge, PRELAPSE is the largest study evaluating the effectiveness of LAI antipsychotics with first-episode and early-phase patients. Our ability to receive consent from 234 participants for the AOM condition and for 213 of these to receive a study AOM injection within 3 months of entry demonstrates the feasibility of performing LAI antipsychotic studies with this patient group. Notably, the number of AOM potential participants who refused to provide informed consent due to not wanting an LAI antipsychotic (n = 83) was approximately half the number who refused for other reasons. These data provide evidence that early-phase schizophrenia patients will consent to participate in a study that involves administration of an LAI antipsychotic and that they will confirm that consent by actually receiving at least one LAI antipsychotic injection.

One potential concern for investigators contemplating LAI antipsychotic studies with first-episode and early-phase patients is whether recruitment would be difficult enough to require numbers of sites or recruitment durations that would not be feasible. RAISE-ETP recruited first-episode patients for a comparison of coordinated specialty care (that did not require LAI antipsychotic treatment) with usual care.[9] Examining recruitment for the experimental intervention with both studies, site numbers (17 for RAISE-ETP and 19 for PRELAPSE) were similar as were the final sample sizes (223 for RAISE-ETP and 234 for PRELAPSE). Recruitment for both studies lasted 2 years. Both used site/cluster randomization that required participants to consent to study participation but not to randomization to alternative treatments. Although the inclusion criteria for the studies differed (eg, less antipsychotic treatment was allowed in RAISE-ETP but diagnostic criteria were broader), the overall similar recruitment outcomes suggest that LAI antipsychotic studies with first-episode and recent-onset patients are feasible with the range of resources usually needed for large early-phase trials.

Some limitations to this approach warrant consideration. PRELAPSE site participation requirements included the capability to provide AOM treatment and agreement to provide that treatment if required by the randomization. Thus, our sites were probably more interested in and had more infrastructure for LAI antipsychotic treatment than typical treatment sites. The finding that 68 participants were taking LAI antipsychotics at consent suggests this as sites already had a number of first-episode and recent-onset patients receiving LAI antipsychotics. In addition, clinicians in the AOM arm were trained in methods for discussing the earlier use of LAI antipsychotics with patients. Thus, they were equipped to offer this treatment and address concerns of patients and family members. This kind of specialized training may not currently be available at most community treatment sites, limiting the generalizability of this approach.

Table 1. Factors Associated With Infrequent Use of Long-Acting Injectable (LAI) Antipsychotics

- Clinician overestimation of patients' degree of adherence
- Bias against injections as being invasive, punitive, or overly painful
- Perception that including LAI antipsychotics in the discussion about treatment options would take inordinate time
- Belief that offering LAI antipsychotics means that the clinician does not trust the patient and therefore LAIs will disrupt the therapeutic alliance
- Difficulties in interpreting the mixed results of research studies assessing the benefits of LAI antipsychotics over oral antipsychotics in chronic patients
- Lack of appreciation of the advantages of LAI antipsychotic treatment for patients, families, and health care providers in the context of guidelines that relegate LAI antipsychotics to a last-resort approach
- Lack of training in the use of LAI antipsychotics, including the best approaches for switching to an LAI antipsychotic, administration, dose adjustments, and managing adverse effects
- Insufficient involvement of family members and peer counselors
- Inadequate training in effective shared decision-making approaches and anticipating/answering frequently asked questions
- Inadequate discussion or implementation of LAI antipsychotics by referring inpatient units
- Belief that LAI antipsychotics are inappropriate for early-phase schizophrenia patients who have not clearly demonstrated patterns of nonadherence leading to relapse

The majority (70.9%) of AOM consented participants were not taking LAI antipsychotics at consent. Our success in recruiting these participants was informed by our understanding of the reasons for the low use of LAI antipsychotics in patients with schizophrenia generally and especially in those early in the course of illness. We believe that these reasons, summarized in Table 1, can be successfully addressed in the broader treatment community.

We believe that even in early-phase patients, a much higher rate of LAI antipsychotic use can be achieved in community mental health centers than is currently the case in the United States. Although PRELAPSE trial results are not yet available, we believe that a very strong case can currently be made for more frequent consideration and discussion of LAI antipsychotic use early in the course of schizophrenia treatment.

Submitted: August 27, 2018; accepted November 29, 2018.

Published online: April 23, 2019.

Potential conflicts of interest: **Dr Kane** has been a consultant for or received honoraria from Alkermes, Eli Lilly, EnVivo (Forum), Forest (Allergan), Genentech, H. Lundbeck, Intracellular Therapies, Janssen, Johnson & Johnson,

Merck, Neurocrine, Otsuka, Pierre Fabre, Reviva, Roche, Sunovion, Takeda, and Teva; has received grant support from Otsuka, Lundbeck, and Janssen; and is a shareholder in Vanguard Research Group and LB Pharmaceuticals. **Dr Schooler** has received grant support from Otsuka and has provided consultation or participated in advisory boards for Allergan, Alkermes, and Roche. **Ms Marcy** is Executive Director for Vanguard Research Group and a stockholder of Pfizer. **Dr Achtyes** has received research support from Alkermes, AssurEx, Astellas, Avanir, Boehringer Ingelheim, Janssen, Neurocrine Biosciences, Novartis, Otsuka, Pfizer, Pine Rest Foundation, Priority Health, Network180, and Vanguard Research Group and has served on advisory panels for Roche, Janssen, Neurocrine Biosciences, and the Vanguard Research Group. **Dr Correll** has been a consultant and/or advisor to or has received honoraria from Alkermes, Allergan, Angelini, Gerson Lehrman Group, IntraCellular Therapies, Janssen/Johnson & Johnson, LB Pharma, Lundbeck, Medavante, Medscape, Merck, Neurocrine, Otsuka, Pfizer, ROVI, Servier, Sunovion, Takeda, and Teva; has provided expert testimony for Bristol-Myers Squibb, Janssen, and Otsuka; has served on Data Safety Monitoring Boards for Lundbeck, Rovi, and Teva; has received royalties from UpToDate and grant support from Janssen and Takeda; and is also a shareholder of LB Pharma. **Dr Robinson** has been a consultant to Costello Medical Consulting, Innovative Science Solutions, Janssen, Neurocrine, Otsuka, and US WorldMeds.

Funding/support: The study is supported by an investigator-initiated award to Dr Kane from Otsuka and Lundbeck.

Role of the sponsor: Otsuka and Lundbeck participated in formulating the study protocol but had no role in conducting the study, analyzing or interpreting the study data, or drafting the manuscript. Staff of Otsuka and Lundbeck provided no input into the final manuscript prior to submission.

Previous presentation: International Society for CNS Clinical Trials and Methodology meeting; August 31–September 2, 2017; Paris, France ▪ Schizophrenia International Research Society meeting; April 4–8, 2018; Florence, Italy.

Acknowledgments: We wish to acknowledge the invaluable contributions of our study participants. We also wish to acknowledge the contributions of the staff at our study sites: Apalachee Center, Tallahassee, Florida; Carey Counseling Center Inc, Huntingdon, Tennessee; The Center for Health Care Services, San Antonio, Texas; The Central Community Health Board of Hamilton County, Cincinnati, Ohio; Cherry Health, Grand Rapids, Michigan; Chestnut Health System, Granite City, Illinois; Community Healthcore, Longview, Texas; Community Mental Health for Central Michigan, Mount Pleasant, Michigan; Corrigan, Fall River, Massachusetts; The Counseling Center of Wayne and Holmes Counties, Wooster, Ohio; Creighton University, Omaha, Nebraska; Emory University, Atlanta, Georgia; ETCH, East Lansing, Michigan; Friends Research, Granada Hills, California; Georgia Regents Research Institute, Augusta, Georgia; Healthwest, Muskegon, Michigan; Healthy Perspectives, Nashua, New Hampshire; Henderson Behavioral Health, Fort Lauderdale, Florida; Jerome Golden, West Palm Beach, Florida; Lifestream Behavioral Health, Leesburg, Florida; The Mental Health Center for Greater Manchester, Manchester, New Hampshire; Meridian Behavioral Health, Gainesville, Florida; New Bridge, Paramus, New Jersey; Northwestern University, Chicago, Illinois; PeaceHealth, Eugene, Oregon; Psychiatric and Behavioral Health Solutions, Salt Lake City, Utah; Psychcare Consultants, St. Louis, Missouri; Spindletop Center, Beaumont, Texas; St. Louis University, St. Louis, Missouri; Stanford Medical Center, Palo Alto, California; Suncoast Center, St. Petersburg, Florida; Synapse Clinical Research and Consulting, Durham, North Carolina; University of Florida of Jacksonville, Jacksonville, Florida; University of Michigan, Ann Arbor, Michigan; University of Texas at Houston, Houston, Texas; University of Massachusetts, Worcester, Massachusetts; University of Iowa, Iowa City, Iowa; Western Michigan University, Kalamazoo, Michigan.

REFERENCES

1. Wiersma D, Nienhuis FJ, Slooff CJ, et al. Natural course of schizophrenic disorders: a 15-year followup of a Dutch incidence cohort. *Schizophr Bull*. 1998;24(1):75–85.
2. Andreasen NC, Liu D, Ziebell S, et al. Relapse duration, treatment intensity, and brain tissue loss in schizophrenia: a prospective longitudinal MRI study. *Am J Psychiatry*. 2013;170(6):609–615.
3. Craig TKJ, Garety P, Power P, et al. The Lambeth Early Onset (LEO) Team: randomised controlled trial of the effectiveness of specialised care for early psychosis. *BMJ*. 2004;329(7474):1067.
4. Gafoor R, Nitsch D, McCrone P, et al. Effect of early intervention on 5-year outcome in non-affective psychosis. *Br J Psychiatry*. 2010;196(5):372–376.
5. Petersen L, Jeppesen P, Thorup A, et al. A randomised multicentre trial of integrated versus standard treatment for patients with a first episode of psychotic illness. *BMJ*. 2005;331(7517):602.
6. Bertelsen M, Jeppesen P, Petersen L, et al. Five-year follow-up of a randomized multicenter trial of intensive early intervention vs standard treatment for patients with a first episode of psychotic illness: the OPUS trial. *Arch Gen Psychiatry*. 2008;65(7):762–771.
7. Srihari VH, Tek C, Kucukgoncu S, et al. First-episode services for psychotic disorders in the US public sector: a pragmatic randomized controlled trial. *Psychiatr Serv*. 2015;66(7):705–712.
8. Ruggeri M, Bonetto C, Lasalvia A, et al; GET UP Group. Feasibility and effectiveness of a multi-element psychosocial intervention for first-episode psychosis: results from the cluster-randomized controlled GET UP PIANO trial in a catchment area of 10 million inhabitants. *Schizophr Bull*. 2015;41(5):1192–1203.
9. Kane JM, Robinson DG, Schooler NR, et al. comprehensive versus usual community care for first-episode psychosis: 2-year outcomes from the NIMH RAISE early treatment program. *Am J Psychiatry*. 2016;173(4):362–372.
10. Kane JM, Kishimoto T, Correll CU. Non-adherence to medication in patients with psychotic disorders: epidemiology, contributing factors and management strategies. *World Psychiatry*. 2013;12(3):216–226.
11. Zipursky RB, Menezes NM, Streiner DL. Risk of symptom recurrence with medication discontinuation in first-episode psychosis: a systematic review. *Schizophr Res*. 2014;152(2–3):408–414.
12. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353(5):487–497.
13. Peterson AM, Takiya L, Finley R. Meta-analysis of trials of interventions to improve medication adherence. *Am J Health Syst Pharm*. 2003;60(7):657–665.
14. DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. *Med Care*. 2004;42(3):200–209.
15. Kirson NY, Weiden PJ, Yermakov S, et al. Efficacy and effectiveness of depot versus oral antipsychotics in schizophrenia: synthesizing results across different research designs. *J Clin Psychiatry*. 2013;74(6):568–575.
16. Stroup TS, Lieberman JA, Marder SA. Pharmacotherapies. In: Lieberman JA, Stroup TS, Perkins DO, eds. *Essentials of Schizophrenia*. Washington, DC: American Psychiatric Publishing; 2011:173–206.
17. Crespo-Facorro B, de la Foz VO, Mata I, et al. Treatment of first-episode non-affective psychosis: a randomized comparison of aripiprazole, quetiapine and ziprasidone over 1 year. *Psychopharmacology (Berl)*. 2014;231(2):357–366.
18. Robinson DG, Gallego JA, John M, et al. A randomized comparison of aripiprazole and risperidone for the acute treatment of first-episode schizophrenia and related disorders: 3-month outcomes. *Schizophr Bull*. 2015;41(6):1227–1236.
19. Emsley R, Medori R, Koen L, et al. Long-acting injectable risperidone in the treatment of subjects with recent-onset psychosis: a preliminary study. *J Clin Psychopharmacol*. 2008;28(2):210–213.
20. Weiden PJ, Schooler NR, Weedon JC, et al. Maintenance treatment with long-acting injectable risperidone in first-episode schizophrenia: a randomized effectiveness study. *J Clin Psychiatry*. 2012;73(9):1224–1233.
21. Malla A, Chue P, Jordan G, et al. An exploratory, open-label, randomized trial comparing risperidone long-acting injectable with oral antipsychotic medication in the treatment of early psychosis. *Clin Schizophr Relat Psychoses*. 2016;9(4):198–208.
22. Subotnik KL, Casaus LR, Ventura J, et al. Long-acting injectable risperidone for relapse prevention and control of breakthrough symptoms after a recent first episode of schizophrenia: a randomized clinical trial. *JAMA Psychiatry*. 2015;72(8):822–829.
23. Schreiner A, Aadamsoo K, Altamura AC, et al. Paliperidone palmitate versus oral antipsychotics in recently diagnosed schizophrenia. *Schizophr Res*. 2015;169(1–3):393–399.
24. Bartzokis G, Lu PH, Raven EP, et al. Impact on intracortical myelination trajectory of long acting injection versus oral risperidone in first-episode schizophrenia. *Schizophr Res*. 2012;140(1-3):122–128.
25. Robinson DG, Schooler NR, Correll CU, et al. Psychopharmacological treatment in the RAISE-ETP study: outcomes of a manual and computer decision support system based intervention. *Am J Psychiatry*. 2018;175(2):169–179.
26. Tiihonen J, Haukka J, Taylor M, et al. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. *Am J Psychiatry*. 2011;168(6):603–609.
27. Kahn RS, Fleischhacker WW, Boter H, et al; EUFEST study group. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet*. 2008;371(9618):1085–1097.
28. Robinson D, Woerner MG, Alvir JMJ, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry*. 1999;56(3):241–247.
29. Heres S, Lambert M, Vauth R. Treatment of early episode in patients with schizophrenia: the role of long acting antipsychotics. *Eur Psychiatry*. 2014;29(suppl 2):1409–1413.
30. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice

guidelines? a framework for improvement. *JAMA*. 1999;282(15):1458–1465.
31. Kim S-W, Lee Y-H, Jang J-E, et al. Comparison of attitudes toward long-acting injectable antipsychotics among psychiatrists and patients. *Int Clin Psychopharmacol*. 2013;28(2):80–86.
32. Jaeger M, Rossler W. Attitudes towards long-acting depot antipsychotics: a survey of patients, relatives and psychiatrists. *Psychiatry Res*. 2010;175(1–2):58–62.
33. Weiden PJ, Roma RS, Velligan DI, et al. The challenge of offering long-acting antipsychotic therapies: a preliminary discourse analysis of psychiatrist recommendations for injectable therapy to patients with schizophrenia. *J Clin Psychiatry*. 2015;76(6):684–690.
34. First MB, Williams JBW, Karg RS, et al. *Structured Clinical Interview for DSM-5, Research Version (SCID-5-RV)*. Arlington, VA: American Psychiatric Association; 2015.
35. Woerner MG, Mannuzza S, Kane JM. Anchoring the BPRS: an aid to improved reliability. *Psychopharmacol Bull*. 1988;24(1):112–117.
36. Guy W. *ECDEU Assessment Manual for Psychopharmacology*. Revised Edition. Washington, DC: US Department of Health, Education, and Welfare; 1976.
37. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. 2011;168(12):1266–1277.
38. Heinrichs DW, Hanlon TE, Carpenter WT Jr. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. *Schizophr Bull*. 1984;10(3):388–398.
39. Randolph C, Tierney MC, Mohr E, et al. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. *J Clin Exp Neuropsychol*. 1998;20(3):310–319.
40. Rosenheck RA, Leslie DL, Sindelar J, et al; CATIE Study Investigators. Cost-effectiveness of second-generation antipsychotics and perphenazine in a randomized trial of treatment for chronic schizophrenia. *Am J Psychiatry*. 2006;163(12):2080–2089.
41. Adams JR, Drake RE. Shared decision-making and evidence-based practice. *Community Ment Health J*. 2006;42(1):87–105.
42. Correll CU. Real-life switching strategies with second-generation antipsychotics. *J Clin Psychiatry*. 2006;67(1):160–161.
43. Rosenheck RA, Krystal JH, Lew R, et al; CSP555 Research Group. Long-acting risperidone and oral antipsychotics in unstable schizophrenia. *N Engl J Med*. 2011;364(9):842–851.
44. Alphs L, Schooler N, Lauriello J. How study designs influence comparative effectiveness outcomes: the case of oral versus long-acting injectable antipsychotic treatments for schizophrenia. *Schizophr Res*. 2014;156(2–3):228–232.
45. Caroli F, Raymondet P, Izard I, et al. Opinions of French patients with schizophrenia regarding injectable medication. *Patient Prefer Adherence*. 2011;5:165–171.