Treatment Journey From Diagnosis to the Successful Implementation of a Long-Acting Injectable Antipsychotic Agent in Young Adults With Schizophrenia

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ABSTRACT

Objective: Long-acting injectable antipsychotic agents (LAIs) are effective in schizophrenia relapse prevention but are often underutilized. This study aims to understand treatment patterns leading to a successful LAI implementation following schizophrenia diagnosis in a large dataset that included commercially insured patients in the United States.

Methods: Patients aged 18–40 years with a first schizophrenia diagnosis (per *ICD-9* or *ICD-10* criteria), successful second-generation LAI implementation (defined a priori as ≥ 90 consecutive days of use), and ≥ 1 second-generation oral antipsychotic agent (OA) were identified from IBM® MarketScan® Commercial and Medicare Supplemental databases from January 1, 2012, to December 31, 2019. Outcomes were measured descriptively.

Results: Of 41,391 patients with newly diagnosed schizophrenia, 1,836 (4%) received ≥ 1 LAI; 202 (< 1%) met eligibility criteria of successful LAI implementation following ≥ 1 second-generation OA. Median (range) time between diagnosis and first LAI was 289.5 (0–2,171) days, time between LAI initiation and successful implementation was 90.0 (90–1,061) days, and time to LAI discontinuation after successful implementation was 166.5 (91–799) days. Before LAI initiation, 58% received ≥ 2 OAs. For 86% with successful LAI implementation, the implementation was accomplished with the first LAI.

Conclusions: In this dataset of mainly commercially insured patients, LAI use in early-phase schizophrenia was very low (4%). For the majority for whom a LAI was successfully implemented per a priori definition, the implementation was accomplished with the first LAI and in a short period of time (90 days). However, even when LAIs were used in early-phase schizophrenia, they were generally not the first therapy, as most patients had several prior OA treatments.

J Clin Psychiatry 2023;84(3):22m14544

To cite: Kane JM, Mychaskiw MA, Lim S, et al. Treatment journey from diagnosis to the successful implementation of a long-acting injectable antipsychotic agent in young adults with schizophrenia. *J Clin Psychiatry.* 2023;84(3):22m14544.

To share: https://doi.org/10.4088/JCP.22m14544

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Schizophrenia is often a progressive and severely debilitating mental disorder that is characterized by positive (eg, hallucinations, delusions, disorganized speech or behavior), negative (eg, lack of motivation or emotional expressivity), and cognitive (eg, working memory, attention) symptoms.[1] Although the lifetime global prevalence of schizophrenia is approximately 1%,[2] the early age at typical disease onset, great degree of disability, and premature mortality rate associated with the illness underscore its substantial personal, social, and economic burden.[3–5]

Antipsychotic agents are an important part of treatment for many patients with schizophrenia.[6] Since the initial development of these agents during the 1950s, the efficacy of antipsychotic agents, regardless of route of administration, has been thoroughly established[7] and includes reductions in psychopathology, rates of relapse, rates of hospitalization, and mortality rates.[8,9] Although early antipsychotic agents (ie, first-generation antipsychotic agents) demonstrated efficacy, they also were known to cause neurologic side effects, some of which could be very disabling. Newer antipsychotic agents (ie, second-generation antipsychotic agents) introduced in the 1990s generally have a higher degree of occupancy of the serotonergic 5-HT_{2A} receptors.[10] Given their pharmacodynamic properties, second-generation antipsychotic agents are generally tolerated better than first-generation drugs, particularly in early-phase psychosis.[11] As a result, second-generation antipsychotic agents are the most commonly used type of antipsychotic agent.[12]

The benefits of antipsychotic agents may be more pronounced in patients receiving treatment with long-acting injectable antipsychotic agents (LAIs) compared with patients receiving oral antipsychotic agents (OAs).[13–17] LAIs have demonstrated improvement in adherence rates and continuity of treatment among patients with schizophrenia compared with OAs.[15,17,18] This may be particularly true for individuals in the early phase of the illness, when treatment interruption and nonadherence is most likely.[18,19] Despite increasing data supporting the effectiveness of LAIs compared with OAs,[14,20] LAIs are underutilized, with fewer than 14% of Medicaid beneficiaries with schizophrenia receiving LAIs.[17] The degree to which LAIs are used

Clinical Points

- A real-world dataset of mainly commercially insured patients with schizophrenia was analyzed to evaluate treatment utilization patterns among young adults with first-episode schizophrenia who were treated with second-generation long-acting injectable antipsychotic agents (LAIs).
- These data indicate that despite the overwhelming evidence in favor of LAIs over oral antipsychotic agents for relapse prevention and the evidence that indicated LAI treatment during the early phase of schizophrenia is most effective, LAIs are markedly underutilized among patients with early-phase schizophrenia.
- These data support previous findings about the acceptability of LAIs in younger individuals with schizophrenia, highlighting a disconnect between treatment utilization and acceptability that should be addressed in future research and clinical practice.

in individuals with early-phase schizophrenia is not well understood, since previous epidemiologic studies typically captured individuals who were chronically ill and excluded patients with early-phase schizophrenia who are more likely to have private insurance.

Although continuous long-term antipsychotic therapy is most often required, poor treatment adherence represents a major obstacle in the management of schizophrenia.[21,22] This is particularly true for individuals in the early phase, when treatment nonadherence/discontinuation is most common.

Treatment adherence among patients with schizophrenia hospitalized for first-episode psychosis is particularly poor, with 54.3% of these patients in one large cohort stopping their antipsychotic agent within 30 days of being discharged.[19] Indeed, it is known that interruptions of antipsychotic treatment tend to be the greatest earlier in the illness, decreasing over time.[18] Inadequate treatment, relapse, and prolonged periods of untreated psychosis, especially during the early stages of schizophrenia, are particularly concerning because of their association with the risk of developing treatment-resistant disease.[23–27]

Schizophrenia most often begins in late adolescence or early adulthood,[28] and young adults with this illness are more likely to have commercial insurance (often through their parents until the age of 26 years) than those who have been ill for longer periods of time.[29] Therefore, it is thought that many patients with first-episode psychosis and early-phase schizophrenia are not reflected in public insurance datasets in the US. However, most LAI utilization studies have been conducted using Medicaid/Medicare databases, which are more likely to include older patients[29] with presumably more established disease.[30] This study contributes to the advancement of knowledge by investigating trends in the use of LAIs in the initial phase of the illness, when the use of LAIs is particularly relevant yet data are most often unavailable in the existing literature.

In this analysis, a US-based, real-world dataset of mainly commercially insured patients with schizophrenia was analyzed to descriptively evaluate treatment utilization patterns among young adults (ie, aged 18–40 years) with first-episode schizophrenia who were treated with second-generation LAIs. Patient data were analyzed from schizophrenia diagnosis to the first LAI administration and from first LAI administration to successful implementation (defined as continuous LAI use for ≥ 90 days, allowing 7-day gaps between each fill) to understand the early use of LAIs and barriers to successful implementation for patients and clinicians.

METHODS

Data Sources

The IBM® MarketScan® Commercial and Medicare Supplemental databases were used to analyze patient claims data from January 1, 2012, to December 31, 2019. The IBM MarketScan Commercial Database contains data regarding medical and pharmacy claims for individuals enrolled in fee-for-service, partially capitated, and fully capitated commercial health plans.[31,32] The IBM MarketScan Medicare Supplemental Database captures medical and pharmacy claims data for individuals enrolled in Medicare Supplemental health plans.[31,32] This study was exempt from review by an institutional review board because the database was compliant with the Health Insurance Portability and Accountability Act of 1996 and because the data do not include any identifiable patient information.

Patient Population and Cohorts

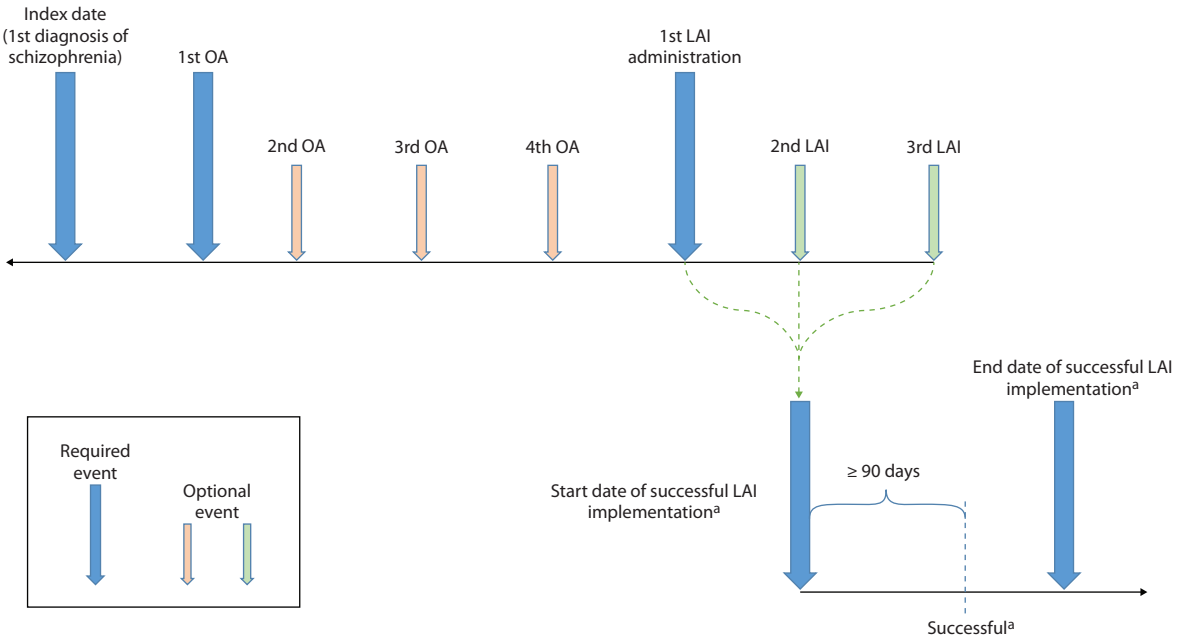
Patients with schizophrenia who were identified in the IBM MarketScan Commercial and Medicare Supplemental databases were eligible for inclusion in this analysis. Additional

Table 1. Selection of Study Population

Patient Group	n
Patients with schizophrenia diagnosis between January 1, 2013, and September 30, 2019	76,147
Patients without schizophrenia diagnosis or OA/LAI claim within 12 months prior to index date	41,391
Patients with ≥ 1 claim for a second-generation LAI	1,836
Patients with continuous LAI treatment for ≥ 90 days (with ≤ 7-day gaps)	680
Patients with continuous enrollment in pharmacy benefit (≤ 30-day gaps allowed) from 12 months prior to the index date to the end of continuous LAI treatment between January 1, 2012, and December 31, 2019	345
Patients aged 18–40 years at index date	249
Patients with ≥ 1 claim for a second-generation OA prior to first LAI administration	202

Abbreviations: LAI = long-acting injectable antipsychotic agent, OA = oral antipsychotic agent.

Figure 1. Study Design



[a]Successful implementation of LAI is treatment with a LAI for minimum 90 consecutive days, allowing 7 days' gap in treatment. Not all patients received > 1 OA and/or LAI.
Abbreviations: LAI = long-acting injectable antipsychotic agent, OA = oral antipsychotic agent.

inclusion criteria (Table 1) were a diagnosis of schizophrenia (according to *International Classification of Diseases*, 9th Revision [*ICD-9*] or 10th Revision [*ICD-10*], codes for schizophrenia) between January 1, 2013, and September 30, 2019 (index date); no schizophrenia diagnosis or OA/LAI claims during 12-month pre-index period; pharmacy claim for a second-generation LAI (aripiprazole, olanzapine, paliperidone, or risperidone) and continuous use (≥ 90 consecutive days, allowing 7-day gaps between each fill); continuous enrollment in commercial or Medicare supplemental medical and pharmacy benefits from ≥ 12 months before the index date to the end of continuous LAI treatment; aged 18–40 years at index date; and ≥ 1 OA claim (aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, or ziprasidone) prior to first LAI administration. The index date range of January 1, 2013, to September 30, 2019, was selected to allow a ≥ 12-month pre-index period during which no diagnosis of schizophrenia or administration of antipsychotic therapy was permitted and a ≥ 90-day post-index period to discern possible successful implementation of LAI therapy. These constraints were put in place to identify individuals with a recent onset of schizophrenia, as opposed to chronic illness.

Patients included in this analysis were grouped according to the LAI used for the successful LAI implementation (defined a priori as continuous LAI use for ≥ 90 days, allowing 7-day gaps between each fill). Because the recommended dose frequencies of LAIs available at the time of this research ranged up to once every 3 months, the threshold set for successful LAI implementation was 90 consecutive days to increase the likelihood of capturing at least 2 administrations of a LAI. Although comparison

Table 2. Patient Demographics[a]

Variable	Overall LAIs[b] (N = 202)	Risperidone[b] (n = 17)	Paliperidone[b] (n = 122)	Aripiprazole[b] (n = 63)
Male	168 (83.2)	14 (82.4)	107 (87.7)	47 (74.6)
Age, mean (SD), y	23.8 (4.8)	23.2 (5.7)	23.4 (4.5)	24.8 (5.0)
Age group, y				
18–23	130 (64.4)	12 (70.6)	87 (71.3)	31 (49.2)
24–29	40 (19.8)	3 (17.6)	16 (13.1)	21 (33.3)
30–35	26 (12.9)	1 (5.9)	16 (13.1)	9 (14.3)
36–40	6 (3.0)	1 (5.9)	3 (2.5)	2 (3.2)
Insurance type				
PPO	119 (58.9)	10 (58.8)	73 (59.8)	36 (57.1)
HMO	25 (12.4)	0	15 (12.3)	10 (15.9)
CDHP	18 (8.9)	1 (5.9)	12 (9.8)	5 (7.9)
POS	14 (6.9)	0	11 (9.0)	3 (4.8)
Comprehensive	10 (5.0)	3 (17.6)	4 (3.3)	3 (4.8)
HDHP	9 (4.5)	1 (5.9)	5 (4.1)	3 (4.8)
POS with capitation	1 (0.5)	1 (5.9)	0	0
Missing	6 (3.0)	1 (5.9)	2 (1.6)	3 (4.8)
Region				
South	82 (40.6)	7 (41.2)	48 (39.3)	27 (42.9)
North Central	63 (31.2)	5 (29.4)	42 (34.4)	16 (25.4)
Northeast	37 (18.3)	4 (23.5)	20 (16.4)	13 (20.6)
West	17 (8.4)	1 (5.9)	10 (8.2)	6 (9.5)
Unknown	3 (1.5)	0	2 (1.6)	1 (1.6)

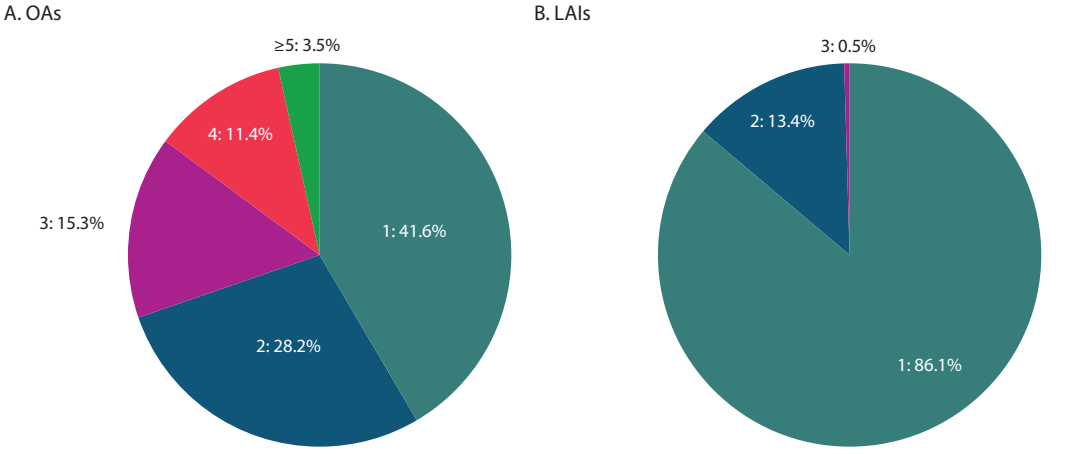
[a]Values are shown as n (%) unless otherwise noted.
[b]LAI with which successful implementation was achieved.
Abbreviations: CDHP = consumer directed health plan, HDHP = high-deductible health plan, HMO = health maintenance organization, LAI = long-acting injectable antipsychotic agent, POS = point of service, PPO = preferred provider organization.

Table 3. Time to First Treatment Administration and Duration of LAI Treatment[a]

Variable	Overall LAIs[b] (N = 202) Mean (SD)	Overall LAIs[b] (N = 202) Median (Range)	Risperidone[b] (n = 17) Mean (SD)	Risperidone[b] (n = 17) Median (Range)	Paliperidone[b] (n = 122) Mean (SD)	Paliperidone[b] (n = 122) Median (Range)	Aripiprazole[b] (n = 63) Mean (SD)	Aripiprazole[b] (n = 63) Median (Range)
Time between schizophrenia diagnosis and first LAI administration	414.8 (427.3)	289.5 (0–2,171)	333.2 (336.3)	192.0 (11–1,043)	389.9 (415.8)	264.5 (0–2,171)	484.9 (466.2)	313.0 (13–1,843)
Time between first LAI administration and successful implementation	186.4 (166.6)	90.0 (90–1,061)	207.8 (241.5)	90.0 (90–1,061)	195.3 (169.2)	119.5 (90–840)	163.4 (135.1)	90.0 (90–739)
Duration of LAI treatment (persistence)	194.3 (109.9)	166.5 (91–799)	177.4 (86.4)	152.0 (96–379)	191.7 (101.5)	162.0 (94–720)	203.9 (130.0)	175.0 (91–799)

[a]All mean (SD) and median (range) values denote time in days.
[b]LAI with which successful implementation was achieved.
Abbreviation: LAI = long-acting injectable antipsychotic agent.

Figure 2. Treatment Patterns Prior to Successful LAI Implementation: (A) Number of Different OAs Prior to LAI Initiation and (B) Number of Different LAIs Between LAI Initiation and Successful Implementation of LAI



Abbreviations: LAI = long-acting injectable antipsychotic agent, OA = oral antipsychotic agent.

between LAIs was not in the scope of this analysis, grouping patients according to the LAI used in successful implementation allowed for descriptive examination.

Outcome Measures

Figure 1 describes the sequence of events used for this analysis. Analyzed outcomes included the time between diagnosis of schizophrenia (index date) and first LAI administration; time between first administration and successful implementation of a LAI, per the aforementioned definition; time to LAI discontinuation (ie, > 7-day gaps between injections); number of different OAs received between the index date and first administration of a LAI; number of and overall treatment patterns with different LAIs received between first administration and successful implementation of a LAI; and proportion of patients for whom the initial LAI was successfully implemented.

Statistical Analysis

The distribution of patient demographic characteristics, use of second-generation antipsychotic agents, and time to LAI initiation and successful implementation were descriptively evaluated for each LAI group. Numbers and proportions were calculated for categorical variables, whereas means, standard deviations (SDs), medians, and ranges were calculated for continuous variables.

RESULTS

Analysis Set

Claims data for 98,416,202 individuals were present in the IBM MarketScan commercial and Medicare supplemental databases from January 1, 2012, to December 31, 2019 (index date between January 1, 2013, and September 30, 2019); among these individuals, 76,147 patients with any schizophrenia diagnosis (according to *ICD-9* or *ICD-10* codes for schizophrenia) within the index date range were identified. Of these patients, 41,391 had no schizophrenia diagnosis and no LAI/OA claim during 12 months prior to the index date (ie, newly diagnosed), of whom 1,836 (4%) had ≥ 1 LAI claim after the index date. Among these patients with newly diagnosed schizophrenia, 202 patients with successful LAI implementation met eligibility criteria and composed the analysis set for this study (Table 1).

Patient Demographics and Baseline Characteristics

At the time of first diagnosis (ie, index date), patient demographics and baseline disease characteristics were similar among successful LAI implementation groups (Table 2). Mean (SD) age of included patients was 23.8 (4.8) years with 64.4% of the population aged 18–23 years and 19.8% aged 24–29 years. Most (83.2%) of the patients in this study were male.

Antipsychotic Agent Use and Utilization Outcomes

The median (range) time between the index date and initial treatment with a LAI among all patients in this analysis was 289.5 (0–2,171) days; for patients initially treated with LAI risperidone, LAI paliperidone, or LAI aripiprazole, the time between diagnosis and first LAI use were 192.0 (11–1,043) days, 264.5 (0–2,171) days, and 313.0 (13–1,843) days, respectively (Table 3). The median (range) time between initial treatment with a LAI and successful implementation was 90.0 (90–1,061) days for patients overall, 90.0 (90–1,061) days for those who achieved successful implementation with risperidone, 119.5 (90–840) days with paliperidone, and 90.0 (90–739) days with aripiprazole (Table 3). Overall, the median (range) persistence with a successfully implemented LAI was 166.5 (91–799) days, and 152.0 (96–379) days, 162.0 (94–720) days, and 175.0 (91–799) days for patients who achieved successful implementation with risperidone, paliperidone, and aripiprazole, respectively (Table 3).

Prior to LAI initiation, risperidone (34.7%, n = 70) was the most frequently used first-line OA among patients who would later have a successful LAI implementation, followed by aripiprazole (16.3%, n = 33), olanzapine (14.9%, n = 30), paliperidone (13.4%, n = 27), and quetiapine (10.9%, n = 22). As second-line therapy, aripiprazole (22.9%, n = 27/118) and paliperidone (22.0%, n = 26/118) were the most utilized OA agents. Before initiating a LAI, more than half (58.4%) of patients received ≥ 2 distinct OAs; most patients received treatment with either 1 (41.6%), 2 (28.2%), or 3 (15.3%) distinct OAs before initiating treatment with a LAI (Figure 2).

Among patients who had a successful LAI implementation, paliperidone was most frequently used as first-line and second-line LAI treatment (57.9% [n = 117] and 50.0% [n = 14/28], respectively), followed by aripiprazole (27.7% [n = 56], 28.6% [n = 8/28], respectively) and risperidone (12.9% [n = 26], 21.4% [n = 6/28], respectively). The LAIs with which patients achieved successful implementation were paliperidone (60.4%, n = 122), aripiprazole (31.2%, n = 63), and risperidone (8.4%, n = 17); none of the individuals achieved successful LAI implementation with olanzapine. Most patients (86.1%, n = 174) who achieved a successful LAI implementation achieved it with their first LAI (Figure 2).

DISCUSSION

Although several clinical studies have previously described LAI treatment patterns in individuals with first-episode schizophrenia,[33–35] this study marks the first time, to the best of our knowledge, that the utilization patterns of LAIs in a national cohort of individuals were analyzed. Our main finding was that LAI utilization among patients early in the course of illness is very low. For the majority of those for whom a LAI was utilized, a LAI was initiated relatively soon after diagnosis (median = 290 days), although the sustained use of the LAI after first administration was limited (median = 167 days).

The rates of LAI acceptability among those prescribed LAIs aligns with a previous report from a clinical trial focused on the patients with early-phase illness.[36] In that study, the vast majority of those to whom a LAI was offered agreed to use it at least once,[36] indicating that younger patients may be accepting of an alternative to taking oral medication daily. In this study, the majority (84%) of the population were aged 18–29 years, making the onset congruent with the early onset of disease described previously.[28,37] In addition, it seems that patients with early-phase schizophrenia would be among those who would benefit the most from LAI formulations, as they are the most likely to interrupt treatment.[18,19] This population also may not respond to reintroduced treatments as well as they responded to the initial implementation.[26] There is a growing body of evidence suggesting that LAIs are acceptable and advantageous for a variety of outcomes in early-phase schizophrenia.[38] Early treatment with LAIs also aligns with recently revised treatment guidelines, which are increasingly supportive of the use of LAIs among younger individuals with early-phase disease.[39]

However, one of the other main findings was that only 4% of patients newly diagnosed with schizophrenia were treated with a LAI medication. This finding emphasizes the relevance of studying specific patterns of LAI utilization among patients with first-episode psychosis, as rates of antipsychotic agent use may be substantially different from those in public insurance databases reflective of individuals further along in the course of illness. For instance, a recent evaluation of Medicaid data reported that the LAI (both first- and second-generation) utilization rate in the US ranges between 4% and 22% depending on the state,[40] which, although lower than recommended, is a higher rate than observed in our study. This finding may indicate that there is still a prioritization of LAIs for older individuals, who may have already experienced several relapses and who may not benefit as much from relapse prevention as younger individuals would. The disconnect between the data on acceptability and utilization of LAIs among patients with early-phase schizophrenia is striking and suggests that LAIs are not yet offered often enough to younger individuals by clinicians and that their use is mostly reactive (ie, following several relapses after treatment discontinuation) rather than proactive (ie, earlier on before relapses have occurred). Although data describing patients declining a LAI were not captured, utilization by clinicians along with data on the acceptance of LAIs by patients suggest the need to provide training and treatment systems to health care providers so younger individuals are offered LAI formulations as an alternative to OA medication. In

addition to misperceptions of LAIs by clinicians, barriers to the utilization of LAIs may also include payers' requiring prior authorization or a preference over a first-generation LAI (ie, haloperidol decanoate). Also, these data suggest that, even when LAIs were used proactively in patients with early-phase schizophrenia, they were generally not the first therapy used, as most individuals in this study had several prior treatment episodes with OAs. This finding indicates that LAIs are often not administered as a standard-of-care by clinicians, even among patients who will eventually accept them. Thus, there is more work needed to update treatment practices so that the utilization of LAIs in individuals in the early phase of the illness is more proactive. In addition, LAIs were in general used for only about 1 year following initiation. This finding aligns with the literature on treatment discontinuation in patients with early-phase schizophrenia. We did not compare time to treatment discontinuation between LAIs and OAs, since it was out of the scope of this analysis; however, it is well documented that LAIs are used for longer periods of time than their oral counterparts.[17,18] Nonetheless, further work is necessary to reduce the risk of unjustified LAI discontinuation.

Among patients with newly diagnosed schizophrenia who received at least 1 LAI, approximately 11% (202 of 1,836 patients) achieved successful LAI implementation per the a priori definition of continuous use for ≥ 90 days, allowing 7-day gaps. The low proportion of patients who used LAIs longer than 90 days could be attributed to suboptimal efficacy or tolerability; however, it is also possible that the study failed to capture patients who continued to receive LAI treatment after successful implementation but had a gap longer than 7 days between dosing periods. In addition, the low rate of successful LAI implementation lasting longer than 90 days supports recent findings on treatment discontinuation[18]; although time to treatment discontinuation may be short, it is still a long period for maintenance treatment for schizophrenia in general. It is also possible that the low rate could have been affected by patients who either switched insurance quickly after successful LAI implementation, missed follow-up office visits, or encountered financial and/or accessibility issues related to subsequent administrations. Regardless of the reason, patients with newly diagnosed schizophrenia could benefit from initiatives that encourage continued treatment, including patient assistance programs, reminders of scheduled office visits, and other mitigation strategies that can lessen the impact of limited accessibility.

Some additional limitations need to be considered when interpreting these data. First, our data are not reflective of the use of first-generation LAIs. However, the market share of first-generation LAIs is very small and consists largely of patients who initiated LAI treatment before second-generation LAIs came to market and have continued such treatment. Thus, we do not believe that exclusion of first-generation LAIs had a major impact on these results, since our focus was patients with early-phase schizophrenia. Second, these data were generated from insurance claims and are subject to the common limitations of these datasets, such as the exclusion of patients for whom there was interrupted coverage. Third, our follow-up period did not cover the entire initial 5 years of treatment for each individual, which is considered by many specialty programs as the period of early-phase schizophrenia. Because the objective of this analysis was to examine patients from diagnosis (ie, index date) to successful implementation, some patients may have had less than 5 years between their index date and the end of the study period. Therefore, it is possible that there is a more comprehensive pattern of LAI utilization in the early phases of illness that was not captured by these data. Lastly, although the MarketScan databases capture comprehensive commercial medical and pharmacy claims data, the databases consist of convenience samples that use nonrandom methods to select patients and might not be representative of the national population of patients with early-phase schizophrenia. However, because many patients are still on their parent's or guardian's insurance (ie, commercially available) at the time of diagnosis, the MarketScan databases are more likely to capture younger patients with early-phase schizophrenia compared with traditional analyses that use public insurance (ie, Medicaid/Medicare) databases.

In conclusion, these data indicate that despite the overwhelming evidence in favor of LAIs over OAs for relapse prevention[41] and the evidence that indicated LAI treatment during the early phase of schizophrenia is most effective,[18,19,39] LAIs are markedly underutilized among patients with early-phase schizophrenia. Our data support previous findings about the acceptability of LAIs in younger individuals with schizophrenia, highlighting a disconnect between treatment utilization and acceptability that should be addressed in future research and clinical practice.

Submitted: May 25, 2022; accepted November 17, 2022.

Published online: April 19, 2023.

Relevant financial relationships: **Dr Kane** has been a consultant for or received honoraria from Alkermes, EnVivo Pharmaceuticals (Forum), Forest (Allergan), Genentech, Intra-Cellular Therapies, Janssen, Johnson & Johnson, Karuna Therapeutics, LB Pharmaceuticals, Lilly, Lundbeck, Lyndra Therapeutics, Merck, Neurocrine Biosciences, Otsuka, Pierre Fabre, Reviva Pharmaceuticals, Roche, Saladax Biomedical, Sunovion, Takeda, and Teva Pharmaceuticals; has received grant support from Janssen, Lundbeck, and Otsuka; and is a shareholder of LB Pharmaceuticals and Vanguard Research Group. **Drs Mychaskiw, Suett**, and **Tian** are employees and stockholders of Teva Pharmaceuticals. **Mr Lim** is an employee of Teva Pharmaceuticals. **Dr Rubio** has been a consultant for and has received support for attending meetings/travel from Teva Pharmaceuticals; has received honoraria from Lundbeck; has received grants from Alkermes and the National Institute of Mental Health (NIMH); has received royalties/licensing fees from UpToDate; and owns stock/stock options in Doximity.

Funding/support: This study was supported by Teva Branded Pharmaceutical Products R&D, Inc.

Role of the sponsor: The sponsor participated in the design and conduct of the study and in the collection, management, analysis, and interpretation of the data and funded the preparation of the manuscript. All authors, including those affiliated with the sponsor, fulfilled all authorship criteria and participated in the review and approval of the manuscript and in the decision to submit the manuscript for publication.

Previous presentations: Presented at the European College of Neuropsychopharmacology Congress; Lisbon, Portugal; October 2–5 2021 ▪ Annual

Psych Congress; San Antonio, Texas; October 29–November 1, 2021 • American College of Neuropsychopharmacology Annual Meeting; San Juan, Puerto Rico; December 5–8, 2021.

Acknowledgments: The authors would like to thank Seojin Park, PharmD, of Teva Branded Pharmaceutical Products R&D, Inc., at the time of this research, for contributions to the conduct of the study. Medical writing support was provided by Mark Skopin, PhD, CMPP, and Jennifer C. Jaworski, MS, BCMAS, CMPP, and editorial support by Kelsey Hogan, MS, of Ashfield MedComms, an Inizio company, and was funded by Teva Branded Pharmaceutical Products R&D, Inc. The individuals acknowledged received indirect compensation from Teva Branded Pharmaceutical Products R&D, Inc., for their roles in the conduct of the study and development of this manuscript.

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