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The Use of Long-Acting Injectable Antipsychotics in Schizophrenia: Evaluating the Evidence

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Overview

This CME activity evaluates the efficacy, safety, and tolerability of long-acting injectable antipsychotics (LAIs) versus placebo, versus oral antipsychotics, and among LAIs; reviews the effect of LAI treatment on effectiveness, patient-centered service delivery, and health care cost outcomes; and provides guidance on when to consider LAI treatment as well as best clinical practices that can maximize acceptability and experience for all stakeholders.

CME Objectives

After completing this educational initiative, you should be able to:

- Evaluate and interpret efficacy, safety, and outcomes data for LAIs for schizophrenia
- Select the most appropriate patients for LAI intervention
- Institute collaborative discussions with patients that include incorporating LAIs as a potential management option

Statement of Need and Purpose

Schizophrenia treatment has come a long way with the initial development of antipsychotics and then atypical antipsychotics.[1,2] However, effective symptom management still remains a problem in a large number of patients with schizophrenia.[3] Relapse is a common occurrence, often due to lapses in medication adherence.[4] Patient education regarding the need for consistent medication is critical, and improved relationships with physicians can greatly facilitate patients' understanding of the necessity to consistently take schizophrenia medication.[5]

The risk of hospitalization has been significantly correlated with adherence and gaps in antipsychotic medication use.[6] Looking at the effect of medication gaps reveals that even missing 1 to 10 days of medication leads to nearly twice the odds of hospitalization compared with a person who has no medication gaps.[7] The risk of relapse increases with more time spent off an antipsychotic.[8] There is also an increase in suicide attempt rate when atypical antipsychotic therapy is interrupted.[9] Injectable medications can increase adherence, due to less frequent dosing schedules.[10,11] Their use can improve schizophrenia outcomes, including symptom reduction[12] and reduction in relapses[13] and hospitalizations,[12] and reduce risk of hospitalization compared with oral antipsychotics.[14] However, stigma and misunderstanding of LAIs have limited the use of this approach.[15] LAI use can also be limited because clinicians are unfamiliar with LAI antipsychotics and lack training in using them.

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Target Audience

This activity is designed to educate psychiatrists and other mental health care professionals who manage patients with schizophrenia.

Accreditation Statement

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The Use of Long-Acting Injectable Antipsychotics in Schizophrenia: Evaluating the Evidence

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Long-acting injectable antipsychotics (LAIs) are among the most effective treatments in psychiatry, yet they remain underutilized in clinical practice. Although LAIs are typically used to maintain treatment adherence in patients with chronic schizophrenia, recent research has suggested that they may also provide an effective treatment strategy for patients with early-phase or first-episode disease. In October 2015, a group of 8 experts on the management of schizophrenia and LAIs met to evaluate the evidence surrounding the efficacy, safety, and cost-effectiveness of LAIs and to develop practical recommendations regarding the clinical use, education, and unmet needs related to LAIs. Participants were also asked to rate the importance of several patient characteristics when choosing an LAI versus an oral antipsychotic, from the perspectives of 4 different stakeholder groups: patients, health care professionals, families, and payers. The evidence review demonstrated that LAIs are superior to placebo for acute and maintenance treatment of schizophrenia and, in general, appear to be similar to one another in terms of schizophrenia relapse prevention. Study design impacts the demonstrated efficacy of LAIs versus oral antipsychotics, but recent database and randomized controlled studies favor the use of LAIs in early-phase schizophrenia patients. LAIs vary considerably in their propensity to cause certain adverse effects, including weight gain, metabolic effects, extrapyramidal symptoms, and prolactin elevation, and these differences can be used to help guide LAI selection. Some studies, but not all, have demonstrated significant reductions in health care utilization or overall costs with LAIs. The expert panel identified several barriers to LAI use in current practice, including clinician lack of knowledge, negative attitudes about LAIs, and resource and cost issues. The participants also identified a number of additional factors that should be considered when weighing the use of LAI therapy, including medication adherence, relapse risk and severity, cognitive impairment, ease of use, substance misuse, access and cost, stigma, social support, patient autonomy, control over medication dosing, fear of needles, and the potential for patient harm due to relapses and associated loss of functioning. This evidence review, discussion, and summary recommendations may help clinicians, patients, families, payers, and other stakeholders to better characterize the role of LAIs in the treatment of schizophrenia.
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Given the high frequency of suboptimal adherence to oral antipsychotics and the strong link between nonadherence and relapse, long-acting injectable antipsychotics (LAIs) are among the most effective treatments in psychiatry, yet they remain underutilized in clinical practice.[1–4] LAIs have traditionally been used in patients with chronic schizophrenia who have frequent relapses accompanied by marked social and occupational disabilities. However, it is likely that LAIs may benefit patients beyond the population of those with a history of poor treatment adherence. Recent research has focused in particular on the efficacy of LAIs in early-phase or first-episode schizophrenia. Although patients with a first episode of psychosis often respond very well to initial antipsychotic therapy, few are able to attain long-lasting symptom remission or functional recovery.[5] LAIs may provide an important treatment option for helping patients remain on therapy and reduce relapse risk and disease progression. As this supplement will demonstrate, LAIs may be underused for many reasons, including lack of familiarity among many physicians, inaccurate perceptions about safety and efficacy, cost and access to treatment, and negative perceptions of injectable therapy among patients, families, and providers.

This supplement was developed from a consensus roundtable that was held October 31, 2015. The goal of this roundtable was to examine current evidence regarding the role of LAIs in the treatment of schizophrenia in order to develop specific, practical recommendations for their use in clinical practice. The panel also identified areas in which additional research is needed to better understand LAI use for schizophrenia as well as health care policy and education goals to improve appropriate implementation of LAIs.

METHODS

A group of 8 experts on the management of schizophrenia and LAIs met to evaluate the evidence and to develop a set of recommendations regarding the clinical use, education, and unmet research needs related to LAIs. Attendees included representatives from academic and community psychiatry settings, the National Alliance on Mental Illness, and a commercial insurance company. Six attendees provided brief presentations related to LAIs, including efficacy, safety, considerations in clinical trial design, value and cost-effectiveness, patient selection, and optimizing LAI use. Participants discussed the information presented and used the information to develop recommendations for treatment, research, and policy.

Participants were also asked to rate the importance of several patient characteristics when choosing an LAI versus an oral antipsychotic. They rated the importance of each characteristic from the perspectives of 4 different stakeholder groups: patients, health care professionals, families, and payers. The importance of each characteristic and stakeholder group was

evaluated using a 10-point scale, in which 10 = an extremely important characteristic or a characteristic that trumps all other aspects when deciding to use an LAI and 1 = an extremely inappropriate characteristic or a characteristic that trumps all other aspects when deciding *against* using an LAI. The consensus opinion on the value of LAIs for each scenario and stakeholder group was presented with mean and standard deviation of the pooled ratings.

The first portion of this supplement reviews the efficacy and safety of LAIs, while the second part examines practical issues in LAI use. A series of recommendations is provided regarding treatment and patient selection, education about LAIs for patients and providers, and additional topics for research. Finally, the supplement concludes with recommendations for identifying patients who should be considered for LAI therapy.

PART 1: EFFICACY AND SAFETY OF LAIS

Efficacy of LAIs Versus Placebo, Versus Oral Antipsychotics, and Among LAIs

LAIs versus placebo. Although LAIs are typically advocated for relapse prevention in patients with chronic schizophrenia,[6] data from placebo-controlled, randomized controlled trials (RCTs) show that these agents also reduce symptoms when administered as first-line therapy in acutely ill patients.[7–9]

Placebo-controlled RCTs have also demonstrated reduction in relapses with long-acting formulations of second-generation antipsychotics (SGAs) administered at intervals of biweekly to once every 3 months, including paliperidone palmitate (39–156 mg every 4 weeks or 273–819 mg every 3 months), olanzapine pamoate (150 or 300 mg every 2 weeks or 405 mg every 4 weeks), aripiprazole monohydrate (400 mg every 4 weeks), and aripiprazole lauroxil (441, 662, or 882 every 4 weeks or 881 mg every 6 weeks).[10,11] RCTs that have compared LAI antipsychotics with placebo in patients with schizophrenia are summarized in Table 1.[7–9,11–17]

Notably, newer studies of SGA LAIs were sometimes discontinued prematurely on the basis of interim analyses demonstrating efficacy.[11,17] This early discontinuation may underestimate the true magnitude of improvement that would have been observed had all patients been followed for a longer period of time (eg, 1 year), as was more typical with older studies of first-generation antipsychotics (FGAs).

LAIs versus oral antipsychotics. Many trials and several meta-analyses have compared the efficacy of LAI versus oral antipsychotics for the treatment of patients with schizophrenia. A meta-analysis of 21 RCTs (N = 5,176) found similar rates of relapse and all-cause discontinuation for patients treated with LAIs versus oral antipsychotics.[18] Although the results of this analysis suggest that treatment outcomes appeared similar for LAIs and oral therapy, it should be recognized that the meta-analysis was associated with certain limitations. The studies varied in patient enrollment criteria and the ways in which relapse was defined. Most RCTs enrolled chronically ill patients with schizophrenia who had received antipsychotics for months or years. Most importantly, patients willing to be randomized to blinded treatment were likely less severely ill than those receiving LAIs in clinical care, and they also were more likely to be adherent to oral antipsychotics.[18,19] It is also likely that trial participation itself had an impact on adherence to oral therapy, given enhanced attention as compared to usual practice. The results of studies that compared LAIs to oral antipsychotic agents are summarized in Table 2.[20–46]

Strong evidence for the superiority of LAIs over oral antipsychotics is demonstrated by mirror-image studies, in which patients receive LAIs after an initial treatment with oral antipsychotics, with each patient serving as his or her own control. A meta-analysis of 25 mirror-image studies (N = 4,066) found that LAIs were superior to oral antipsychotics for preventing psychiatric hospitalization.[47] The results of mirror-image studies that compared outcomes before and after switching to LAIs can be found in references 48 through 72 (see also Supplementary eTable 1 at PSYCHIATRIST.COM). Although mirror-image studies assess more representative patients than RCTs, they have methodological drawbacks, which are discussed later (see Implications of Study Design).[73]

LAIs may be especially useful in early-phase or first-episode patients, a population that is characterized by frequent nonadherence. Two recently published RCTs provided evidence for efficacy of LAIs in early-phase schizophrenia. In a 12-month study of 86 first-episode patients, relapse and/or exacerbation of psychosis was noted for 5% of patients randomized to an LAI antipsychotic versus 33% with oral risperidone (relative risk reduction, 84.7%; $P < .001$).[43] In another study, recently diagnosed (≥ 1–5 years) patients with schizophrenia were randomized to up to 2 years of open-label, rater-blinded treatment with paliperidone palmitate (n = 352) versus investigator's choice of oral antipsychotic (aripiprazole, olanzapine, quetiapine, paliperidone extended-release, risperidone, or haloperidol; n = 363).[74] Time to relapse was significantly longer for patients randomized to paliperidone palmitate than to oral antipsychotics ($P = .0191$); relapse rates were also lower (14.8% vs 20.9%; $P = .032$). In a prospective, nationwide cohort study conducted in Finland (N = 2,588), depot antipsychotics (risperidone depot, zuclopenthixol decanoate, haloperidol decanoate, or perphenazine decanoate) were associated with a significantly reduced risk of rehospitalization compared with the same antipsychotics in oral form (hazard ratio, 0.36; $P = .007$).[75] A very recent randomized open-label study showed no advantage for LAIs over oral antispsychotics (see Table 2).[39]

LAIs versus LAIs. There is little evidence for superior efficacy of one LAI versus another. The results of studies that compared one LAI versus another are summarized in Table 3.[76–80] Although symptom improvement and relapse rates are generally similar with different LAIs, differences

Table 1. Long-Acting Injectable Antipsychotics vs Placebo: Randomized Controlled Trials

Study/ Country	N	Study Design	Duration (wk)	Inclusion Criteria	Definition of Relapse-Related Outcome	Mean Age, y	% Male	% Hp at BL	Chronicity	Drug Tx	n	Dosing	Efficacy	Safety
Kane et al[12] 2003/USA	554	DB, PC	12	SCZ	Change in PANSS total score	38	75	About 50	76% Dx paranoid SCZ	RIS LAI	400	25, 50, or 75 mg/ 2 wk	Clinical improvement 47%, 48%, and 39%, respectively vs PBO	AEs similar in all groups
Lauriello et al[13] 2008/Int.	466	DB, PC	8	SCZ w/PANSS-derived BPRS score ≥ 30	Mean change in PANSS total score	40	72	100	74% concomitant BZD use	OLA LAI	404	210 or 300 mg/ 2 wk or 405 mg/4 wk	Mean decreases in PANSS total scores significantly greater for all 3 OLA LAI vs PBO	Sedation, increased appetite more frequent w/300 mg/2 wk vs PBO
Hough et al[14] 2010/Int.	951	DB, PC, OL	63	SCZ w/PANSS total score < 120	(1) Hp, (2) increase in PANSS total score, (3) deliberate self-injury, aggressive behavior, suicidal/homicidal ideation	39	53	NR	Mean no. of Hps = 3	PP	410	IM PP (50 mg eq) weekly; then 25, 50, or 100 mg eq, flexibly dosed, once monthly	Time-to-relapse favored PP ($P < .0001$, log rank test) at interim and final analysis	No new safety signals
Kramer et al[15] 2010/Int.	266	DB, PC	9	SCZ w/PANSS total score 70–120, BMI 15–35 kg/m^2	Mean change in PANSS total score	38	41	100	67% had ≥ 3 Hps	PP	247	50 or 100 mg eq fixed doses on days 1, 8, and 36	Mean PANSS total scores improved for 50 and 100 mg eq groups vs PBO	More parkinsonism-related disorders in LAI vs PBO
Nasrallah et al[16] 2010/Int.	620	DB, PC	13	SCZ w/PANSS total score 70–120, BMI > 15.0 kg/m^2	Change in PANSS total score	41	67	100	45% had ≥ 4 Hps	PP	518	IM fixed doses (25, 50, or 100 mg eq) on days 1 and 8, then days 36 and 64	PANSS total scores improved for all dose groups	Locally and systemically tolerated
Pandina et al[7] 2010/Int.	855	DB, PC	13	Acutely exacerbated SCZ	Definition not given	39	67	100	NR	PP	652	50, 100, or 150 mg IM on day 1, day 8, and then monthly	PANSS total scores improved ($P \leq .034$) in all PP dose groups vs PBO	AEs w/PP injection-site pain, dizziness, sedation, pain in the extremity, and myalgia
Kane et al[17] 2012/Int.	843	DB, PC	52	SCZ, history of relapse without Tx	CGI-C and PANSS total score increases, Hp, risk of suicide, violent behavior	LAI 40.1; PBO 41.7 (range, 18–60)	LAI 60.2; PBO 79	NR	NR	ARI IM-depot	843	300 and 400 mg monthly	Relapse delayed and improvements in CGI-C and PANSS total scores w/Tx vs PBO	Insomnia, tremor, and headache
Meltzer et al[9] 2015/Int.	848	DB, PC	12	SCZ w/acute exacerbation	Defined by changes in PANSS total score	39	68	NR	NR	ARI lauroxil	623	441 or 882 mg monthly	Significant ($P \leq .004$) improvements in both active Tx groups	Most common AEs: insomnia, akathisia, headache, and anxiety
Kane et al[8] 2014/Int.	506	DB, PC	12	SCZ w/acute psychotic episode	Defined by PANSS total score	IM 42, PBO 43	79	NR	Mean age at Dx was 24 y	ARI IM	340	400 mg monthly	Improvement in PANSS total score at all time points w/ARI vs PBO	AEs vs PBO: increased weight (16.8% vs 7.0%), headache (14.4% vs 16.3%), and akathisia (11.4% vs 3.5%)
Berwaerts et al[11] 2015/Int.	620	DB, PC	60	SCZ w/PANSS total score lower than 120	Hp, increase PANSS total score, deliberate self-injury or violent behavior, suicidal/ homicidal ideation	38	75	0	92% had at least 1 prior Hp	PP	305	175, 263, 350, or 525 mg eq or PBO once every 3 mo	Time-to-first-relapse significantly higher in PP group	Most frequent AEs vs PBO: headache (9% vs 4%), weight increased (9% vs 3%), nasopharyngitis (6% vs 1%), and akathisia (4% vs 1%)

Abbreviations: AE = adverse event, ARI = aripiprazole, BL = baseline, BMI = body mass index, BPRS = Brief Psychiatric Rating Scale, BZD = benzodiazepine, CGI-C = Clinical Global Impressions-Change score, DB = double-blind, Dx = diagnosis, eq = equivalent, Hp = hospitalization, IM = intramuscular, Int. = international, LAI = long-acting injectable antipsychotic, N = study population, n = randomized number, NR = not reported, OL = open label, OLA = olanzapine, PANSS = Positive and Negative Syndrome Scale, PBO = placebo, PC = placebo-controlled, PP = paliperidone palmitate, RIS = risperidone, SCZ = schizophrenia, Tx = treatment, USA = United States of America, w/ = with.

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Table 2. Long-Acting Injectable vs Oral Antipsychotics: Randomized Controlled Trials

Study/ Country	N	Study Design	Duration (wk)	Inclusion Criteria	Definition of Relapse-Related Outcome	Mean Age, y (Range)	% Male	% Hp at BL	Chronicity	Medication	n	Mean Dose (Range)	Efficacy	Safety
First-Generation Long-Acting Injectables														
Fluphenazine Depot														
Crawford and Forrest[20] 1974/UK	31	DBDD	40	Stable and cooperative OPs w/SCZ, adherent to medication, attending clinic	Withdrawal: termination due to significant Sx that warranted unblinding Tx	NR (20–65)	29	0	NR	FPZ decanoate	14	Same dose as before the trial	Discontinuation rate favored FPZ decanoate but did not reach statistical significance	NR
										Trifluoperazine	17	10 mg/d (fixed)		
del Giudice et al[21] 1975/USA	88	DBDD/ RM[a]	69	IPs w/SCZ, responded to oral FPZ, were discharged	Re-Hp	NR (20–50)	100	0	48.8% had 5–10 Hps in the past	FPZ enanthate	27	25 mg/2 wk (fixed)	Median time to re-Hp: 420 d w/depot injection vs 100 d w/oral FPZ ($P<.001$)	AEs were uncommon w/both Txs
										FPZ	61	21.7 mg (5–80 mg)		
Rifkin et al[22] 1977/USA	73[b]	DBDD	52	Stable OPs[c] on FPZ depot or oral for 4 wk, no or minor AEs, cooperative and compliant	Relapse: clinical deterioration w/marked social impairment	23.7 (17–38)	67	0	Mean no. of Hps in the past: 1.79	FPZ decanoate	23	NR (0.5–2 mL/2 wk)	No difference in relapse rates between the 2 medications	35% of Pts receiving FPZ decanoate developed severe akinesia
										FPZ	28	NR (5–20 mg)		
Falloon et al[23] 1978/UK	53	DBDD	52	SCZ Pts returning to the community following Hp for an acute episode	Relapse: SCZ features that led to withdrawal from the trial, regardless of re-Hp	39 (17–60)	45	0	81% had ≥ 2 Hps in the past	FPZ decanoate	NR	25 mg/2 wk[d] (flexible)	Relapse/ deterioration: 40% FPZ vs 23% w/pimozide (not statistically significant)	AEs were similar between the 2 drugs
										Pimozide	NR	8 mg/d[d] (flexible)[e]		
Hogarty et al[24] 1979/USA	105	DBDD	104	Pts w/SCZ received major neuroleptic Tx during the Hp; discharged	Relapse: unequivocal clinical deterioration of such magnitude that Hp appeared imminent; or suicide	34.2 (18–55)	46	0	88% had ≥ 1 Hp in the past	FPZ decanoate	55	34 mg/2 wk (12.5–125 mg/ 2 wk)	Similar relapse rates w/FPZ decanoate and oral FPZ	NR
										FPZ	50	9.9 mg/d (2.5–40 mg/d)		
Schooler et al[25] 1980/USA	290	DBDD	52	Pts w/SCZ discharged after acute-phase Tx in community	Relapse: deterioration that could not be managed after adjustment of dosage	29 (18–55)	59	100/0[f]	100% new Hps	FPZ decanoate	143	34.2 mg/3 wk (12.5–100 mg/ 3 wk)	No differences between the 2 Txs	NR
										FPZ	147	24.8 mg/d (2.5–60 mg/d)		
Barnes et al[26] 1983/UK	36	DBDD	52	OPs w/SCZ regularly receiving depot FPZ for ≥ 6 mo	Relapse: marked exacerbation of psychotic features requiring increased medication and re-Hp	49.5 (NR)	50	0	≥ 77.8% have social performance limitations	FPZ decanoate	19	Same dose as before the trial	Similar rates of relapse, withdrawal, and study completion between groups	NR
										Pimozide	17	Dose equivalent before the trial		
Kaneno et al[27] 1991/Japan	263	DBDD	24	Chronic SCZ needing long-term Tx	Discontinuation due to worsening of psychiatric Sx	90% of Pts were 30–59 years old	65	NR	81% had duration of illness ≥ 10 y	FPZ decanoate	130	12.6–50 mg/ 4 wk[d] (up to 75 mg/4 wk)	FPZ superior to HAL on Hp rate, measures of global improvement	No significant between-group differences in AEs
										HAL	133	3.1–12.0 mg/d[d] (up to 18 mg/d)		

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Table 2 (continued). Long-Acting Injectable vs Oral Antipsychotics: Randomized Controlled Trials

Study/ Country	N	Study Design	Duration (wk)	Inclusion Criteria	Definition of Relapse-Related Outcome	Mean Age, y (Range)	% Male	% Hp at BL	Chronicity	Medication	n	Mean Dose (Range)	Efficacy	Safety
Haloperidol Depot														
Glick and Marder[28] 2005/USA	35	OL	48	OPs w/SCZ or SzAD needing long-term Tx	No longer exacerbation-free	42.3 (NR)	80	0	Mean duration of illness: 16.5 y	HAL decanoate	14	170 mg/4 wk (Target dose: 200 mg/4 wk)	No between-group differences in Pts remaining exacerbation-free; QUE more effective for negative Sx ($P<.05$)	EPS rates low in both groups; QUE associated w/less rigidity, akathisia
										QUE	21	493 mg/d (Target dose: 500 mg/d)		
Zuclopenthixol Depot														
Arango et al[29] 2006/Spain	46	RM	52	Pts w/SCZ, violent episode in previous year, score ≥3 on physical aggression subscale of OAS	Hp	34 (NR)	83	0	NR	Zuclopenthixol depot	26	233 mg/ 2 wk (NR)[e]	Lower incidence of violent acts in depot group	NR
										Zuclopenthixol	20	35 mg/d (NR)[e]		
Second-Generation Long-Acting Injectables														
Olanzapine LAI														
Kane et al[30] 2010/Int.	1,065[g]	DBDD	24	Clinically stable Pts w/SCZ, OP status for ≥4 wk, BPRS-P ≤4 on the following items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content	Psychotic exacerbation: increased BPRS-P, Hp as the result of worsening of positive psychotic Sx	38.9 (18–75)	65	0	Mean duration of illness: 13.3 y	OLA LAI	599	150 mg/2 wk, 405 mg/4 wk, 300 mg/2 wk (fixed)	24-wk exacerbation-free rate was 93% w/oral OLA and 95%, 90%, and 84% w/high, medium, and low LAI doses, respectively	No clinically important differences in safety parameters
									36.9% had ≥2 psychotic episodes or exacerbations in last 24 mo	OLA	322	14.3 mg/d (10, 15, 20 mg/d)		
Detke et al[31] 2011/Int.	524	OL	104	OPs w/SCZ, no acute Hp in 8 wk prior, PANSS total score <70, CGI-S score ≤4 at visits 1 and 2, ≥2 episodes of clinical worsening in the past 2 y	Relapse: Hp, increase in PANSS total score or CGI-S, deliberate injury to self or others, discontinuation due to worsening Sx	40.9 (18–65)	67	0	Mean duration of illness: 14.7 y	OLA LAI	264	386.6 mg/4 wk (15–405 mg/ 4 wk)	No differences in discontinuation or relapse rate; mean duration of Hp significantly longer for oral than LAI, 1.80 vs 0.43 d, ($P=.02$)	No clinically significant group differences in AEs
									Mean psychotic episodes in last 24 mo: 2.7	OLA	260	12.7 mg/d (5–20 mg/d)		
Risperidone LAI														
Chue et al[32] 2005/Int.	779	DBDD	12	SCZ w/PANSS total score ≥50	PANSS total score change from DB baseline	40	64	NR	Mean no. of Hps in past: about 5	RIS LAI	319	25–75 mg	Both Txs showed comparable efficacy in PANSS total scores	Most AEs were rated mild/moderate: insomnia, anxiety, headache, psychosis
										Oral RIS	321	2–6 mg		

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Table 2 (continued). Long-Acting Injectable vs Oral Antipsychotics: Randomized Controlled Trials

Study/ Country	N	Study Design	Duration (wk)	Inclusion Criteria	Definition of Relapse-Related Outcome	Mean Age, y (Range)	% Male	% Hp at BL	Chronicity	Medication	n	Mean Dose (Range)	Efficacy	Safety
Keks et al[33] 2007/Int.	629	OL	53	IPs/OPs w/SCZ or SzAD[h] who had acute exacerbation in the past 2 mo, additional acute exacerbation in the past 2 y, PANSS total score ≥ 50, BMI ≤ 40	Significant deterioration: 1. Hp for Sx exacerbation 2. need for an increased level of care and ≥ 2-point increase in CGI-S 3. self-injury, suicidal/ homicidal ideation or violent behavior	35.2 (≥ 18)	57	44	Mean duration of illness: 8.6 y	RIS LAI	253	40.7 mg/2 wk (25, 50 mg/2 wk)	RIS LAI was not inferior to oral OLA	Discontinuation due to AEs: 3% w/RIS LAI, 4% w/OLA
										OLA	310	14.6 mg/d (5–20 mg/d)		
Bai et al[34] 2007/Taiwan	50	RM	48	Stable SCZ on oral RIS for ≥ 3 mo, PANSS total score < 80, PANSS conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content < 4, CGI-I screening visit and baseline were same	Relapse: definition not given	46.4 (18–65)	50	100	Mean duration of Hp stay: 127.9 mo	RIS LAI	25	Equivalent to oral 5.0 mg/d (25, 37.5, 50 mg/2 wk)[i]	No significant differences in PANSS total scores between the 2 Txs	RIS LAI group had lower scores on rating scales of side effects ($P = .048$), motor Sx ($P = .028$), prolactin levels ($P = .046$)
										RIS	25	4.0 mg/d (same dose as before the trial)		
Potapov et al[35] 2008/Russia	41	OL	52	OPs w/SCZ (*ICD-10*), PANSS total score ≥ 60	Relapse: ≥ 5-point increase in CGI-S and ≥ 20% in PANSS total score compared to previous	34.9 (18–65)	58	0	NR	RIS LAI	20	41.7 mg/2 wk (NR)	PANSS total score decreased in both groups from baseline but did not differ significantly from one another	EPS rate: 40% w/RIS LAI, 35% w/OLA
										OLA	21	15.9 mg/d (NR)		
Kamijima et al[36] 2009/Japan	205	OL	24	IPs/OPs w/SCZ, taking RIS ≤ 6 mg/d, PANSS total score ≥ 60 to < 120	Tx discontinuation due to worsening of psychiatric Sx	42.7 (≥ 20)	62	28	Mean duration of illness: 14.9 y	RIS LAI	153	32.3 mg/2 wk (25, 37.5, 50 mg/2 wk)	RIS LAI was not inferior to RIS tablets on several outcomes, including PANSS and CGI-C from baseline	Rates of AEs and discontinuations due to AEs were similar for the 2 Txs
										RIS	52	3.4 mg/d (2–6 mg/d)		

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Table 2 (continued). Long-Acting Injectable vs Oral Antipsychotics: Randomized Controlled Trials

Study/ Country	N	Study Design	Duration (wk)	Inclusion Criteria	Definition of Relapse-Related Outcome	Mean Age, y (Range)	% Male	% Hp at BL	Chronicity	Medication	n	Mean Dose (Range)	Efficacy	Safety
Gaebel et al[37] 2010/Int.	710[j]	OL	104	Stable IPs and OPs w/ SCZ or SzAD[k]; stable dose of RIS, OLA, or FGA; living in the same residence for > 30 d; candidates for switching Tx	Relapse: 1. psychiatric Hp 2. increase in level of care and PANSS total score 3. deliberate self-injury 4. clinically significant suicidal/homicidal ideation 5. violent behavior resulting in significant injury to another person or property 6. CGI-C ≥ 6 7. exceeding registered drug dose	41.6 (≥ 18)	58	NR	Mean duration of illness: 10.0 y; mean no. of Hps in the past: 5.3	RIS LAI	355	33.6 mg/2 wk (up to 50 mg/ 2 wk)	Time-to-relapse significantly longer w/RIS LAI than QUE ($P < .0001$); relapse occurred in 16.5% of Pts w/RIS LAI and 31.3% w/QUE	Both agents well tolerated; hyperprolactinemia was reported in 13.1% w/RIS LAI and 1.5% w/QUE; somnolence in 2% of Pts w/RIS LAI and 11% w/QUE
										QUE, ARI	401	QUE: 413.4 mg/d (up to 750 mg/d) ARI: 15.1 mg/d (10–30 mg/d)		
Macfadden et al[38] 2010/Int.	355	RM	104	SCZ, ≥ 2 psychotic relapses in the past 2 y, stabilized for ≥ 2 mo	Relapse: 1. worsening of psychiatric Sx 2. increased PANSS total score 3. deliberate self-injury, clinically significant suicidal/homicidal ideation, or violent behavior 4. drug discontinuation or addition of another AP for > 1 wk because of lack of efficacy 5. dosage beyond recommended dosage	37.9 (≥ 18)	60	0	Mean duration of illness: 9.9 y	RIS LAI	179	41.8 mg/2 wk (25–50 mg/2 wk)	No significant differences between RIS LAI and ARI groups in time-to-relapse or time-in-remission. Relapse rates 45.8% and 43.6% for RIS LAI and ARI, respectively	The study was discontinued before completing 2 y by about 29% of Pts in each group
										ARI	176	19.9 mg/d (10–30 mg/d)		
Malla et al[39] 2016/Canada	85	OL	104	IPs/OPs; early-onset SCZ, SzAD, or schizophreniform disorder,[l] PANSS total scores ≥ 60 and ≤ 120, currently on monotherapy atypical AP or Tx naïve; Pts stable within 18 wk entered the maintenance phase	Relapse: 1. psychiatric Hp 2. increased PANSS total score and psychiatric care 3. self-injury, suicidal/ homicidal ideation, or violence 4. CGI-C ≥ 6	22.7 (18–30)	84	NR	Mean duration of illness: 2.1 y	RIS LAI	44	NR (25–50 mg/2 wk)	Similar improvements in PANSS total score and CGI-S for both Tx groups	RIS LAI and oral agents had similar safety profiles
										Oral SGA except CLO	41	NR (flexible dose)		

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Table 2 (continued). Long-Acting Injectable vs Oral Antipsychotics: Randomized Controlled Trials

Study/ Country	N	Study Design	Duration (wk)	Inclusion Criteria	Definition of Relapse-Related Outcome	Mean Age, y (Range)	% Male	% Hp at BL	Chronicity	Medication	n	Mean Dose (Range)	Efficacy	Safety
Rosenheck et al[40] 2011/USA	382	RM	104	SCZ or SzAD, at risk of Hp	Hp	51 (≥ 18)	91	40	Mean duration of illness: 23.4 y	RIS LAI	190	40.9 mg/1.5 wk (25, 37.5, 50 mg/2 wk)	Hp rate was similar for RIS LAI (39%) and oral APs (45%)	RIS LAI was associated w/more injection-site reactions and EPS
										Any oral AP except CLO	192	NR (flexible)		
Buckley et al[41] 2015/USA	305	RM	74–130[m]	OPs w/SCZ or SzAD (32%), exacerbation within 12 mo, CGI ≥ 4, in community ≥ 4 wk, ≥ 1 mo since the most recent exacerbation	Relapse: masked committee, Hp for psychosis, increases in level of care, substantial clinical deterioration (BPRS), and deliberate self-injury or violent behavior	38.2 (18–65)	71	NR	Mean duration of illness: 15.9 y; mean no. of Hps in the past: 11.0	RIS microsphere	153	33.6 mg/2 wk (12.5–75 mg/ 2 wk)	Psychotic Sx and BPRS improved more in the RIS group, but relapse and Hp rates were similar	Anorexia significantly lower in oral than RIS arm; other AEs similar between Txs
										Oral SGA	152	NR (flexible)		
Green et al[42] 2015/USA	95	Proof of concept	24	SCZ or SzAD and current alcohol use disorder, at community mental health and VA clinics	Heavy drinking (≥ 5 drinks/d), intensity of drinking (no. of drinks/wk)	42	77	NR	Mean lifetime Hps: 7.5	RIS LAI	49	≤ 50 mg every 2 wk	Heavy drinking in the oral group worsened over time (P = .024)	79% had AEs; most common were pain, upper respiratory tract infection, drooling, nausea or stomach discomfort, diarrhea, vomiting, other digestive, or hepatic problems
										Oral RIS	46	6 mg/d		
Subotnik et al[43] 2015/USA	266	RCT	52	Recent onset SCZ, SczAD depressed type, or schizophreniform disorder	Increases in the BPRS items unusual thought content, hallucinations, or conceptual disorganization	22	78	NR	First major psychotic episode within the past 2 y	Oral RIS	43	2 mg/d	Psychotic exacerbation, relapse rate, hallucinations/ delusions lower w/RIS LAI vs oral	Oral RIS Pts more frequently prescribed AE medication
										RIS LAI	43	25 mg/2 wk		
Paliperidone Palmitate LAI														
Schreiner et al[44] 2015/Int.	775	OL	24	SCZ, PANSS total score of 70–120	Hp; increase in PANSS total score, deliberate self-injury, suicidal/ homicidal ideation, violent behavior, clinical deterioration (CGI-S)	33	58	32.4	Dx within 1–5 y; ≥ 2 Hps in the preceding 24 mo	PP LAI	376	150 mg eq on day 1, 100 mg eq on day 8, 75 mg eq on day 38, then monthly w/ flexible dosing 25–150 mg eq	Time-to-relapse was significantly longer in the PP group than oral AP group (P = .0191)	Injection-site pain, nasopharyngitis, increase in weight, headache, tremor, anxiety, insomnia, SCZ, suicidal ideation
										ARI, QUE, OLA, paliperidone extended-release, RIS, or HAL	388	Varied		

(continued)

Table 2 (continued). Long-Acting Injectable vs Oral Antipsychotics: Randomized Controlled Trials

Study/ Country	N	Study Design	Duration (wk)	Inclusion Criteria	Definition of Relapse-Related Outcome	Mean Age, y (Range)	% Male	% Hp at BL	Chronicity	Medication	n	Mean Dose (Range)	Efficacy	Safety
Alphs et al[45] 2015/USA and PR	693	OL	60	SCZ with a history of incarceration	Arrest/incarceration, Hp, suicide, Tx discontinuation or supplementation, increased psychiatric services	38	86	0	Mean no. of Hps > 5	PP LAI	230	234 mg on day 1 and 156 mg on day 8 (± 4 d), then monthly 50–150 mg eq started on day 38	PP delayed time to first Tx failure vs oral AP (P = .011)	Common AEs for PP: injection site pain, insomnia, weight increased, akathisia, anxiety
										Oral AP (ARI, HAL, OLA, paliperidone, perphenazine, QUE, RIS)	220	Dosage determined by package insert		
Aripiprazole LAI														
Fleischhacker et al[46] 2014/Int.	1,118	DB	38	SCZ	Increased CGI-S or PANSS total score; Hp; violent behavior resulting in clinically relevant self-injury, injury to self or another person, or property damage	42	60.4%	NR	≥ 3 y	ARI LAI	265	400 mg/mo	Impending relapse rates at week 26 were 7.12% for ARI once monthly 400 mg and 7.76% for oral ARI; ARI once monthly was not inferior to oral ARI	ARI once monthly: insomnia, akathisia, headache, and weight decrease/ increase reported by 9%–12% of Pts
						41	63.2%	NR		ARI oral	266	10–30 mg/d		
						40	59.5%	NR		ARI LAI	131	50 mg/mo		
						41	60.0%			PP LAI	147	50–150 mg/mo [EU and Canada] or 78–234 mg/mo [USA]		

[a]Raters were masked for 3 arms, but DBDD were applied to 2 arms. [b]Patients allocated to placebo arm are not included in the analysis. [c]100% schizophrenia by clinical diagnosis but included 15% nonschizophrenia when assessed by research psychiatrists. [d]Most common dosing. [e]Accurate safety/efficacy evaluation information not found. [f]100% during intensive treatment phase; 0% in maintenance phase. [g]Very low dose (OLA LAI 45 mg/4 wks) group is not included in the analysis. [h]SzAD = 17.3%. [i]Depot dose based on prior oral dose. [j]Including exploratory arm (ARI), randomized: n = 45, efficacy: n = 44. [k]SzAD = 17.7%. [l]SzAD = 6.5%, schizophreniform = 3.9%. [m]Full study period ranged between 17–30 months depending on enrollment date.

Abbreviations: AE = adverse event, AP = antipsychotic, ARI = aripiprazole, BL = baseline, BMI = body mass index, BPRS = Brief Psychiatric Rating Scale, BPRS-P = Brief Psychiatric Rating Scale-Positive, CGI-C = Clinical Global Impressions-Change score, CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, CLO = clozapine, DB = double-blind, DBDD = double-blind double-dummy, Dx = diagnosis, EPS = extrapyramidal side effects, eq = equivalent, EU = European Union, FGA = first-generation antipsychotic, FPZ = fluphenazine, HAL = haloperidol, Hp = hospital/hospitalization, *ICD = International Classification of Diseases*, Int. = International, IP = inpatient, LAI = long-acting injectable antipsychotic, N = study population, n = randomized number, NR = not reported, OAS = Overt Aggression Scale, OL = open label, OLA = olanzapine, OP = outpatient, PANSS = Positive and Negative Syndrome Scale, PP = paliperidone palmitate, PR = Puerto Rico, Pt = patient, QUE = quetiapine, RCT = randomized controlled trial, RIS = risperidone, RM = rater masked, *SCZ* = schizophrenia, *SGA* = second-generation antipsychotic, Sx = symptom(s), *SzAD* = schizoaffective disorder, Tx = treatment, UK = United Kingdom, USA = United States of America, VA = US Department of Veterans Affairs, w/ = with.

between LAIs have been reported for some other efficacy measures. For example, a recently published study (N = 295) compared aripiprazole once monthly 400 mg with paliperidone palmitate once monthly on a rating scale of quality of life and functioning in patients with schizophrenia.[80] At the end of the 28-week study, the mean change from baseline on quality of life total score was significantly higher for patients treated with once monthly aripiprazole than paliperidone palmitate (P = .036), and the effect was driven by differences in younger patients (≤ 35 years).

Characteristics of LAIs. Characteristics of selected FGA and SGA LAIs are summarized in Table 4.[10,81–88] FGA LAIs (fluphenazine decanoate, haloperidol decanoate) are supplied in oil-based formulations, which may be more painful to inject than water-based formulations of SGA LAIs. Injection intervals vary from once every 2 to 4 weeks (or monthly) with most agents, to 6 weeks with aripiprazole lauroxil 882 mg, and once every 3 months with paliperidone palmitate LAI. Oral supplementation is required during the first few weeks of treatment with some medications, including risperidone LAI (3 weeks), aripiprazole LAI (2 weeks), and aripiprazole lauroxil (3 weeks). Time to reach steady-state plasma concentration varies considerably among the different agents. Olanzapine pamoate requires a 3-hour postinjection observation period due to potential postinjection delirium and sedation.[89]

Summary and conclusions. LAIs are superior to placebo for acute and maintenance treatment of schizophrenia. Superiority of LAIs over oral antipsychotics is most pronounced in mirror-image studies that arguably are more representative of usual care patients and practices. In general, LAIs appear to be similar to one another in terms of relapse prevention, although differences in other domains have been reported.

Safety and Tolerability of LAIs Versus Placebo, Versus Oral Antipsychotics, and Among LAIs

Side effect liability is an important consideration when selecting antipsychotics. Antipsychotics differ in their propensity to cause a wide range of

Table 3. Long-Acting Injectable vs Long-Acting Injectable: Randomized Controlled Trials

Study/ Country	N	Study Design	Duration (wk)	Inclusion Criteria	Definition of Relapse-Related Outcome	Mean Age, y	% Male	% Hp at BL	Chronicity	Medication	n	Dosing	Efficacy	Safety
Pandina et al[76] 2011/ Int.	1,220	DBDD	13	SCZ, PANSS total score 60–120, BMI ≥ 17.0 kg/m^2 and <40 kg/m^2	Defined by a change in the PANSS total score	39	58	NR	NR	PP LAI + PBO	607	150 mg eq on day 1, 100 mg eq on day 8, and monthly flexible dosing on days 36 and 64; oral PBO (days 1–28)	PP was not inferior to RIS LAI (primary analysis)	The tolerability and safety of PP was generally similar to RIS LAI w/no new safety or tolerability findings
										RIS LAI + oral RIS	613	Days 8 and 22 (25 mg), days 36 and 50 (25 or 37.5 mg), and days 64 and 78 (25, 37.5 or 50 mg); oral RIS supplementation 1–6 mg/d (days 1–28)		
Li et al[77] 2011/ China	452	OL, rater blinded	13	SCZ, acute Sx, PANSS total score 60–120, BMI ≥ 17.0 kg/m^2	Determined by changes in PANSS total scores	32	38	NR	NR	PP LAI	229	50–150 mg eq, flexibly dosed, without oral paliperidone supplementation	PP was not inferior to RIS LAI	Most common AEs were akathisia, tremor, and insomnia
						32	42			RIS LAI	223	25–50 mg, flexibly dosed, w/oral RIS supplementation		
McEvoy et al[78] 2014/ USA	311	DB	52–104	SCZ or SzAD, at risk of efficacy failure (history of medication noncompliance and/or significant substance abuse)	Efficacy failure: psychiatric Hp, crisis stabilization, increased outpatient visits, inability to discontinue oral APs, discontinuation of LAI due to insufficient benefit of AP	43	73.1	16.6		PP LAI	145	325 mg mean dose on days 1 and 8; 129–169 mg/mo thereafter	No statistically significant difference in the rate of efficacy failure for PP compared to HAL	68.0% PP Pts vs 59.9% HAL reported at least 1 moderate/ severe AE; 1 death from unknown causes
						45	75.9	19.3		HAL LAI	145	94 mg mean dose on days 1 and 8; 67–83 mg/mo thereafter		
Nielsen et al[79] 2015/ Denmark	4,532	Retrospective cohort	260	SCZ, filling ≥ 1 outpatient LAI prescription	Hp	39	56	7	Mean years Dx = 9	FGA LAIs[a]	2,454	Varied	RIS LAI was similar to FGA LAIs re time to hospitalization and time to all-cause discontinuation	NR
						36	60	6		RIS LAI	2,078	NR		
Naber et al[80] 2015/ Int.	295	OL	28	SCZ; stable, not acutely psychotic; inadequate response, poor tolerability, or lack of adherence w/current oral AP	QLS scores	43	69	NR	NR	ARI LAI	148	400 mg/mo	QLS total score confirmed noninferiority and established superiority of ARI once monthly	AEs were more frequent w/PP; most common were increased weight, psychotic disorder, and insomnia
						41	60			PP LAI	147	50–150 mg/mo [EU and Canada] *or* 78–234 mg [USA]		

[a]Zuclopenthixol decanoate, haloperidol decanoate, perphenazine decanoate, fluphenazine decanoate, and flupenthixol decanoate.

Abbreviations: AE = adverse event, AP = antipsychotic, ARI = aripiprazole, BL = baseline, BMI = body mass index, DB = double-blind, DBDD = double-blind double-dummy, Dx = diagnosis, eq = equivalent, EU = European Union, FGA = first-generation antipsychotic, HAL = haloperidol, Hp = hospitalization, Int. = international, LAI = long-acting injectable antipsychotic, N = study population, n = randomized number, NR = not reported, OL = open label, PANSS = Positive and Negative Syndrome Scale, PBO = placebo, PP = paliperidone palmitate, Pt = patient, QLS = Quality of Life Scale, re = regarding, RIS = risperidone, SCZ = schizophrenia, SzAD = schizoaffective disorder, Sx = symptom(s), USA = United States of America, w/ = with.

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Table 4. Characteristics of Selected First-Generation and Second-Generation Long-Acting Injectable Antipsychotics (LAI) in the United States of America[a]

Antipsychotic	Base	Dose Interval	Dosage Strengths/Forms	Starting Dose	Maintenance Dose	Oral Supplementation	Time to Peak	Steady State	Postinjection Observation
Fluphenazine decanoate[81]	Oil	Varies	25 and 100 mg/mL ampoules/vials/syringes	Varies, 12.5 mg	Varies, 12.5–100 mg	No	2–4 d	2–3 mo	No
Haloperidol decanoate[82] (Haldol and others)	Oil	4 wk	50 and 100 mg/mL ampoules	Varies, 50 mg	Varies, 300 mg	No	6–7 d	2–3 mo	No
Risperidone microspheres[83] (Risperdal Consta)	Water	2 wk	25, 37.5, 50 mg vial kits	25 mg	25 mg (25–50 mg)	3 wk	4–6 wk	1.5–2 mo	No
Olanzapine pamoate[84] (Zyprexa Relprevv)	Water	2 or 4 wk	210, 300, 405 mg vial kits	Varies, up to 300 mg/ 2 wk	Varies, up to 300 mg/ 2 wk	No	4 d	3 mo	At least 3 hours
Paliperidone palmitate LAI[85] (Invega Sustenna)	Water	Monthly	78, 117, 156, 234 mg prefilled syringes	150 mg (day 1) + 100 mg (day 8)	75 mg (25–150 mg)	No	13 d	7–11 mo	No
Paliperidone palmitate LAI[86] (Invega Trinza)	Water	Once every 3 mo	273, 410, 546, 819 mg prefilled syringes	Depending on once-monthly dose	Varies, 273–819 mg	No	30–33 d	Continues steady state at equivalent dose	No
Aripiprazole monohydrate[87] (Abilify Maintena)	Water	Monthly	300, 400 mg vial kits and dual-chamber syringe	400 mg	400 mg (300–400 mg)	2 wk	5–7 d	400: 4–8 mo; 300: 3–4 mo	No
Aripiprazole lauroxil[88] (Aristada)	Water	Monthly (or 6 weekly: 882 mg)	441, 662, 882 mg prefilled syringes	Varies, 441–882 mg	Varies, 441–882 mg	3 wk	4 d	4–6 mo	No

[a]Data from package inserts of each antipsychotic and Citrome.[10]

side effects including sedation, extrapyramidal symptoms (EPSs), weight gain, metabolic disturbance, and prolactin elevation.[90] However, a simple division of FGAs and SGAs in terms of side effect profiles is today generally seen as simplistic and misleading, although in the past it was advocated. Adverse events (AEs) may contribute to poor treatment adherence and increased long-term morbidity, and they may limit the maximal level of functional recovery that patients can achieve.[91,92] Importantly, patients and physicians may differ in their perceptions of the importance of AEs. The roundtable participants felt that patients are more likely to respond to the subjective distress produced by side effects, whereas clinicians typically focus more on the objective severity of the AE and how this affects patient safety and risk. All of these issues should be addressed through shared decision-making and psychoeducational approach.[93]

Comparison of adverse events associated with antipsychotic drugs. AEs associated with LAIs generally follow the known AE profiles of the oral molecule. In a large meta-analysis of 15 antipsychotics in schizophrenia, antipsychotics were ranked by 5 different AE domains (sedation, EPSs, weight gain, prolactin elevation, and QTc elevation). Results indicated small to large differences in adverse events among antipsychotics[90] that should be taken into consideration also when choosing among LAIs. A more recent meta-analysis of 16 RCTs (n = 4,902) showed that of 119 reported adverse events, LAIs and oral antipsychotics did not differ significantly, aside from akinesia, low-density lipoprotein cholesterol change, anxiety (higher with LAIs), and prolactin change (lower with LAIs).[93a]

Differences in AE rates between antipsychotic drugs may be quantified using number needed to harm (NNH). NNH answers the question "How many patients would you need to treat with Intervention A instead of Intervention B before you would expect to encounter one additional outcome of interest that you would like to avoid?" In general, NNH values < 10 for medication versus placebo denote potentially common AEs that can be expected to be seen frequently in day-to-day clinical practice.[94–96] As shown in Supplementary eTable 2, NNH versus placebo can help to determine how often we can expect to encounter important adverse outcomes such as weight gain ≥ 7%, somnolence, or akathisia with different atypical antipsychotics.[97,98]

Overall, treatment discontinuation rates have generally been similar for patients treated with LAI antipsychotics versus the same oral agent.[99] The most common AEs with LAIs are summarized in Supplementary eTable 3.[82–88]

Considerations in choosing an LAI. Practical issues that can help in selecting among LAIs are summarized in Table 5.[97]

Summary and conclusions. Information about adverse event differences among LAIs comes largely from indirect comparisons and spontaneously reported AEs. The available data suggest that LAIs vary considerably in their propensity to cause certain adverse effects, including weight gain, EPSs, and prolactin elevation. This information can be used to help guide the selection of LAIs.

Implications of Study Design

LAIs have been examined using several study design strategies—RCTs, mirror-image studies, and cohort studies—each of which has strengths and limitations.[18,73,77]

Table 5. Considerations in Selection of a Long-Acting Injectable Antipsychotic

Consideration	Selecting a Long-Acting Injectable Antipsychotic (LAI)
Is the patient demonstrating adequate efficacy and tolerability on oral fluphenazine, haloperidol, risperidone, paliperidone, olanzapine, or aripiprazole?	• Switching to the corresponding LAI formulation is relatively simple • For patients receiving oral risperidone, paliperidone palmitate may be considered for convenience • For patients receiving oral fluphenazine or haloperidol, potential disadvantages should be weighted for using concomitant oral anticholinergic agents for the management of motor adverse effects, which adds complexity to the regimen and may interfere with memory and other cognitive functions
Is the patient being treated acutely, and is the patient averse to using oral medications?	• Consider LAI antipsychotics that do not require oral supplementation, where the clinical trials have demonstrated acute efficacy (either paliperidone palmitate or olanzapine pamoate)
Are weight gain and metabolic adverse effects a concern for this individual patient?	• Consider aripiprazole LAI, paliperidone palmitate, or risperidone microspheres among the second-generation antipsychotics, in that order • A first-generation LAI antipsychotic may also be considered in this case
Is prolactin elevation a clinical concern for this individual patient?	• Consider aripiprazole LAI • Avoid paliperidone palmitate, risperidone microspheres, or first-generation LAI antipsychotics
Is cost the primary concern?	• First-generation LAI antipsychotics may be the only option
Are any of the following people or entities not enrolled in the Olanzapine Pamoate Patient Care Program: patient, prescriber, health care facility, pharmacy?	• Olanzapine pamoate cannot be used

RCTs are usually considered the "gold standard" for comparing the efficacy and safety of different treatments. However, explanatory RCTs are most likely not the optimal study design for the comparison of LAIs with oral antipsychotics. Strengths of RCTs include objective rating of patient outcomes and the elimination of biases on the part of investigators, including expectations about the different treatments. However, this approach may not be the best way to study interventions with potential adherence benefits, as patients enrolled in RCTs may differ from the general patient population in important ways, including higher levels of motivation or willingness to comply with instructions. RCT patients may also have less severe disease than many of those seen in typical practice. In addition, the trial itself, with reminders for appointments, more comprehensive assessments, payments for participation, free medication, and so on, can impact adherence rates.

Mirror-image studies examine patients who are switched from one medication to another, comparing pretreatment with posttreatment study periods. This design is more reflective of actual clinical practice than an RCT. Expectation bias is inherent in the design of a mirror-image study and may affect the main outcome. In mirror-image studies of LAIs, patients have been switched from oral antipsychotics to LAIs, but no studies have examined reversing this switching sequence. This design is also subject to potential time or cohort effects (eg, changing hospitalization practices over time).

In cohort studies, patient selection bias is reduced compared with other study types. However, the selection of medication in open studies may introduce bias by improving adherence. More importantly, patients selected for treatment with LAIs in cohort studies may be categorically different than those treated with oral antipsychotics, including having greater severity of illness and less illness insight or psychosocial support. Therefore, it is important to identify and adjust for confounding factors. One analysis of outcomes from LAI studies found that as study designs shift toward real-world patient populations, LAIs are associated with a larger magnitude of improvement on outcomes, such as relapses, hospitalizations, and all-cause discontinuation.[100]

Summary and conclusions. LAIs have been studied in RCTs, mirror-image studies, and cohort studies, each of which has its own strengths and limitations. Therefore, different methodological issues must be considered in the design and interpretation of clinical studies examining the effects of LAIs, creating a full picture only when viewed from these different angles.

Effect of LAIs on Adherence and Costs

Medication nonadherence in schizophrenia. Studies have demonstrated that approximately one-third of patients with schizophrenia are poorly adherent to oral medications at any time, whether this is evaluated using reports from patients, family members, other caregivers, or clinicians.[101–104] More importantly, nonadherence is even higher when patients are followed over time. For example, in a study[105] of more than 34,000 patients with schizophrenia in the Veterans Health Administration, approximately one-third were nonadherent in any one year, but more than 60% of patients were nonadherent at some point during the 4-year study, where nonadherence was defined as an entire year with a medication possession ratio < 0.8. Consistent nonadherence across all 4 years of the study was noted for 18% of the patients. This suggests that medication adherence is suboptimal but also varies over the long-term treatment course. Detection of nonadherence in clinical practice is often challenging, and adherence assessed by patient self-report or physician judgment may be markedly lower than adherence measured using quantitative techniques, such as pill counting, pharmacy records, or blood antipsychotic level tests.[106] Potential clinical consequences of undetected medication nonadherence include unnecessary antipsychotic medication or dosage changes, addition of concomitant medications, and labeling

of patients as "treatment resistant."[106,107] A 3-year, prospective study[108] that examined functional outcomes associated with treatment adherence in patients with schizophrenia found that nonadherent patients had higher rates of several adverse outcomes, including psychiatric hospitalization (26.8% vs 14.1% for nonadherent vs adherent patients, respectively), emergency care (10% vs 6%), arrest (8.4% vs 3.5%), violent behaviors (10.8% vs 4.8%), being the victim of a crime (15.1% vs 7.8%), and substance misuse (31.1% vs 21.5%).[108]

Poor treatment adherence is usually considered the primary clinical indication for LAI use, yet studies have reported that fewer than 20% of patients with schizophrenia receive LAIs, even when there is evidence of recent poor treatment adherence.[40,109]

Health care costs. Studies have examined how the use of LAIs affects overall health care cost of patients with schizophrenia. One study[110] compared treatment costs for patients with schizophrenia or schizoaffective disorder who were randomized to either risperidone LAI (n = 187) or the physician's choice of an oral antipsychotic (n = 182). Overall, mean quarterly outpatient medication costs were higher for patients randomized to LAI ($3,028) than oral medication ($1,913; $P = .003$), although total treatment costs did not differ significantly between the two treatments ($14,916 vs $13,980; $P = .73$). Health care utilization and costs have also been compared among propensity score–matched adults with schizophrenia in the Veterans Health Administration system who initiated use of either LAI or oral antipsychotics. During the 12-month follow-up period, patients treated with LAI compared to oral antipsychotics had significantly lower average inpatient costs, higher average pharmacy costs, and similar total health care costs.[111]

A recent Medicaid health care utilization study[112] in the United States compared health care utilization and treatment costs for hospitalized patients with schizophrenia who had been on short-duration LAI treatment (defined as 30–79 days; n = 2,856) versus longer-term LAI treatment (≥ 180 days; n = 2,838). The longer-term LAI patients had significantly lower levels of some health care utilization measures, including mean number of hospitalizations and mean length of hospital stay. Mean total hospital payments were 26% lower for patients in the long-term LAI group than those in the short-term LAI group, suggesting that the economic benefit of LAI therapy may increase over time. Lin and colleagues[113] compared real-world health care costs and medication adherence between patients with schizophrenia who initiated LAI (n = 394) versus oral antipsychotics (n = 2,610) using medical claims data from commercially insured patients. Schizophrenia-related hospital costs decreased by a mean of $5,981 in the LAI group and increased by a mean of $758 for patients who received oral antipsychotics ($P < .001$). Mean outpatient cost increased by $134 versus $568 for the LAI and oral antipsychotic groups, respectively ($P = .023$). The mean drug cost was $4,132 with LAIs versus $2,562 with oral agents ($P < .001$). Similar outcomes were observed in patients with Medicare coverage.

The impact of LAI use on health care costs has also been examined in several international studies. A mirror-image study conducted in Taiwan[48] examined treatment costs from medical claims data during 1 year before and after initiating LAI therapy. After a switch from oral to LAI antipsychotics, mean costs decreased for some outcomes (eg, inpatient services, other nonmedication services) but increased for others (eg, outpatient psychiatry, medication costs). A mirror-image study performed with patients treated in public hospitals in Hong Kong[114] found that switching from oral to LAI therapy was associated with significantly lower total medical costs driven largely by lower hospitalization costs, although outpatient department and pharmacy costs significantly increased during the LAI treatment period. By contrast, a mirror-image study conducted in the United Kingdom,[115] which included predominantly patients with schizophrenia, reported that in the year following LAI therapy initiation, total health care costs significantly increased along with inpatient bed days, although the number of inpatient admissions declined. These unexpected results may be partially explained by the high level of illness severity reflected in the large proportion of study patients who started LAI therapy as inpatients. In a study conducted in Sweden,[116] investigators modeled per-patient costs associated with several sequences of LAI or oral antipsychotics, including total costs associated with medical care, institutional care, and indirect costs. Treatment strategies that used LAIs had lower total 1-year treatment costs than strategies that included oral antipsychotic therapy. A strategy of paliperidone palmitate LAI followed by olanzapine LAI for patients with relapses was considered not only cost-effective but also cost-saving for the health care system as a whole, compared with other antipsychotic strategies.

A prospective observational study[117] that recruited and followed adults with schizophrenia from 10 European countries provides additional support for health care savings related to LAI therapy. Among outpatients who were previously medication nonadherent, those who initiated FGA LAIs were significantly more likely to be medication adherent (55%) than those who initiated FGA oral agents (39%) during the 18-month follow-up period. The total schizophrenia-related treatment costs of the patients treated with LAIs were only one-half of those incurred by the patients treated with oral antipsychotics. Finally, a study conducted in Canada[118] compared health care resource use during 1 year before and after initiation of LAI treatment in 1,992 patients with schizophrenia or schizoaffective disorder. Overall 1-year costs associated with health care utilization were significantly lower after a switch to LAI therapy ($27,234 vs $16,987 for the preinitiation vs the postinitiation year; $P < .001$).

Summary and conclusions. Nonadherence in patients with schizophrenia is common and difficult to detect. Although LAIs may provide one method to help improve treatment adherence, only a minority of medication nonadherent patients receive them. Significant reductions in health care utilization or costs associated with schizophrenia have been demonstrated in some studies of LAI antipsychotics, although other studies have not demonstrated these effects and showed cost-neutrality or even greater cost.

PART 2: PRACTICAL CONSIDERATIONS AND RECOMMENDATIONS REGARDING LAI USE

When to Consider LAI Treatment: Patient Eligibility and Selection

Guidelines for LAI use. Several schizophrenia management guidelines, including those by the American Psychiatric Association, recognize LAIs as a treatment option but usually only when nonadherence to oral medication has resulted in repeated schizophrenia relapses or when LAI is preferred by the patient.[119–122] However, even when guidelines recommend LAIs as an option if preferred by the patient, many patients may not be aware that LAIs are available.

Patient and mental health provider perceptions of LAIs. The use of LAIs in clinical practice may depend to a large degree on provider and patient attitudes, which are closely related to previous and current experiences. In a survey of attitudes about LAIs among patients with schizophrenia shortly before hospital discharge, acceptance of LAI therapy was 73% among patients who were current users of LAIs (n = 60), 45% among past users of LAIs (n = 95), and 23% among LAI-naive patients (n = 145).[123] These data show that patients are more likely to favor their current treatment. Similar findings were reported in a study of outpatients with schizophrenia or schizoaffective disorder in the United Kingdom.[124] Perceptions about LAI use may also differ among health care providers. In a survey in the United Kingdom,[125] most psychiatrists (91%) felt that LAIs were as efficacious as oral medications and improve patient adherence (81%) and prevent relapse (94%); however, despite this, 48% felt that depot medications are stigmatizing, and 69% believed LAI antipsychotics are less acceptable to patients. However, psychiatrists' knowledge about LAIs was positively associated with more favorable attitudes ($r = 0.39$, $P < .001$). When these data were compared to data from a survey of nurses in the United Kingdom, the nurses were significantly more likely than the psychiatrists to characterize LAIs as coercive, compromising of patient autonomy, or more bothersome to prescribe and monitor than oral medication.[126]

Why are psychiatrists reluctant to use LAIs? Despite the high rate of nonadherence and the consequences of poor adherence among patients with schizophrenia, many psychiatrists remain reluctant to use LAI antipsychotics. Most psychiatrists say that they are interested in using LAI antipsychotics only if they can be clearly shown to be superior to oral agents. For example, in a survey of 106 German psychiatrists, most favored an LAI only if it was associated with an absolute decrease in relapse rate of 10% compared with oral therapy.[127]

In addition, many clinicians lack knowledge about practical issues in the use of LAIs, including dose selection, pharmacokinetics, and what to do when a patient is late for an injection or has persistent symptoms after starting therapy. Younger staff members may have little or no experience with FGA LAIs. Many clinicians mistakenly believe that LAIs are associated with a greater side effect burden than oral agents, among other misconceptions about LAI treatment. Clinician attitudes may also be a barrier to LAI use. Physicians often overestimate the treatment adherence of their own patients, and they may have concerns about suggesting LAIs to their patients because of beliefs about stigmatization or coercion.[125,128]

Although several studies suggested possible benefits of LAIs in first-episode schizophrenia,[43,74,75] surveys of clinicians have shown that many psychiatrists regard LAIs as inappropriate for first-episode patients.[128,129] In a study conducted in the United Kingdom, approximately one-third of psychiatrists thought that LAIs were always inappropriate for first-episode patients, whereas in a German study approximately 70% of psychiatrists thought that LAIs were inappropriate for a first episode.[128,129] In many cases, physician beliefs and perceptions about LAIs may prevent patients from learning that LAIs are a potential option.[130,131] For example, in a study of communication patterns in the offer of LAIs made by psychiatrists to patients with schizophrenia at 10 health clinics, psychiatrists generally presented LAIs in a negative light, resulting in only 11 of 33 LAI recommendations (33%) being accepted by patients.[132] However, during a postvisit interview, during which LAIs were presented in a more positive light and with more information, 27 of the 28 patients (96%) who declined the initial recommendation changed their mind, stating that they actually would be willing to try LAI treatment.

Other obstacles to LAI use include service barriers (eg, lack of community nurses to administer injections, failure to consider partnering with primary care providers to administer maintenance LAI treatment) and financial barriers (eg, higher acquisition costs, payer reluctance to cover LAIs unless there is clear documentation of nonadherence, clinician and payer failure to consider the total costs associated with treating the illness).[123,125]

What patient and illness factors should influence LAI use? Several factors may favor the use of LAI therapy in patients with schizophrenia:

- Willingness by clinicians to consider LAI treatment
- Early-phase or first-episode schizophrenia, as these patients usually have the most to gain by remaining in remission and the most to lose through relapse (eg, in terms of education or employment)
- A history of nonadherence with oral medication
- Risk factors that are associated with increased risk of poor adherence, such as younger age, comorbid substance misuse, or lack of insight
- Factors that suggest a high risk of relapse and that relapse is associated with significant clinical risk, such as a history of psychosis associated with vulnerability, self-harm, or aggression or a history of violence
- Preference of LAI by the patient

Conversely, LAIs may be less suitable for some patients, including those who demonstrate intolerance to or inefficacy

with the parent compound, establish good adherence with oral therapy, have a strong preference for oral therapy, or require chronic anticoagulation therapy. Furthermore, cost considerations may limit access to LAIs in certain states or settings.

What factors should influence LAI selection? As the efficacy of different LAIs is generally similar, side effect profiles are often a key consideration when selecting an LAI. However, few studies have directly compared side effect profiles of different LAIs in the treatment of schizophrenia. Rubio and colleagues[133] compared risperidone LAI and zuclopenthixol decanoate in patients with schizophrenia and substance misuse. Over 6 months of follow-up, risperidone LAI was associated with fewer EPSs as well as more improvement on the Positive and Negative Syndrome Scale and better adherence to a substance use management plan. McEvoy and colleagues[78] compared haloperidol LAI and paliperidone LAI in patients with schizophrenia, reporting greater weight gain and prolactin elevation but less akathisia with paliperidone LAI, although changes in glucose and lipid parameters and in the overall rate of EPS were similar between the two treatment groups. Finally, Naber and colleagues[80] examined use of aripiprazole LAI and paliperidone LAI in patients with schizophrenia, reporting that aripiprazole LAI was associated with numerically fewer adverse events and treatment discontinuations and significantly greater improvement in interviewer-rated quality of life scores.

In the absence of an extensive body of research comparing the safety profiles of different LAIs, it is reasonable to extrapolate from the oral formulation of the same drug. Meta-analysis has quantified the relative risk of a range of side effects using data from RCTs of oral antipsychotics.[90] Cost is often an important consideration in treatment selection, with acquisition costs of SGA LAIs higher than those of FGA LAIs. Finally, the patient's current oral regimen is also an important consideration. If the patient is well stabilized on one oral medication, switching to a different medication in a LAI formulation might be associated with a risk of relapse or new adverse effects. In such cases, there would be an argument for using the same antipsychotic in LAI form, assuming this was available.

Summary and conclusions. Schizophrenia treatment guidelines generally emphasize nonadherence and relapse with oral antipsychotic agents as the most important reasons for LAI use. Barriers to LAI use in current practice include clinicians' lack of knowledge and negative attitudes about LAIs, resource issues, and cost. Those who might benefit from LAIs include first-episode patients and patients early in the course of psychosis as well as patients with known poor adherence, high risk of nonadherence, lack of insight, and the potential for significant consequences associated with relapse.

Best Practices to Maximize LAI Acceptability and Experience for Stakeholders

The appropriate use of antipsychotics is a concern not only for patients and physicians but also for many additional stakeholder groups, including family and friends, employers, court-appointed guardians, law enforcement and the judiciary, and society as a whole. In some cases, stakeholder groups may have differing interests and concerns. For example, in a survey of perceptions about medication use, patients with schizophrenia were less likely to agree that the good things about medication outweigh the bad (61% of patients) than were psychiatrists (81%) or family members (80%).[130] Stakeholder groups may also differ in their attitudes toward other issues, such as medication cost, access to care, and reimbursement.

Patient-centered medicine. The concept of patient-centered medicine provides one approach that can help optimize LAI treatment and find a balance between the concerns and considerations of patients and physicians. Patient-centered medicine seeks to focus attention first on the needs and concerns of the patient, rather than the physician, and to consider social and economic factors.[134] Several steps may help to maximize alignment of treatment goals between patient and provider. The clinician should take a thorough history and listen carefully to the patient's account and beliefs. The patient should be given time to make his or her views known and to ask questions. Consideration of the patient's past positive and negative treatment experiences is critical to developing a successful treatment plan. The clinician should be flexible, adjusting treatment when appropriate to make sure the patient has a voice in his or her care. However, the clinician should not agree to a treatment plan that is not clinically indicated or that could result in patient harm. Patient-centered care relies heavily on collaboration between the provider, the patient, the patient's family members, and other caregivers as well as a broader support network, such as close friends or clergy. Patients should be encouraged to be involved in all aspects of planning, delivery, and evaluation of their health services, with particular emphasis on empowering patients and family members to make effective decisions.[135]

Education. Psychoeducation for patients about schizophrenia and the benefits and risks of its treatment is clearly a critical part of this process and may be especially important in making decisions about the use of LAIs. Psychoeducation should also reinforce the concept that the patient is "an expert" by experience and that the patient should be involved in the development of the treatment plan. Education should also include a plan to improve adherence, crisis management, and prevention of relapses and suicide.

Likewise, education about the potential benefits of LAIs should also be provided to clinicians and the health care team.[136] Health care providers should be able to anticipate and address issues that patients have about LAIs. The first step in this educational process is to acknowledge concerns about using LAIs. An overview of the benefits and limitations of LAIs should be followed by detailed education about LAI therapy and its most appropriate uses. Team members are often the first line of contact to identify patients for whom LAIs may improve outcomes and to educate those patients and their families about this treatment option.

There is also a need to educate clinicians regarding practical issues associated with the dosing and switching of LAIs

and what to do should adverse effects emerge. The LAIs currently available each have specific and unique characteristics. The clinician needs to understand how each LAI should be initiated (eg, test dosing using the oral counterpart, the need for loading doses or necessary oral coverage). Selecting the appropriate dose can be informed by previous experiences with the oral version; dosage may need to be titrated and adjusted based on clinical presentation. There is also some flexibility in dosing intervals, and each LAI has recommendations for what to do if the patient misses his or her injection appointment.

Finally, payers also need to be educated and encouraged to look beyond the short-term financial decisions around drug cost and consider the potential long-term benefits of reduced hospitalizations, relapses, and quality of life. Research recommendations to help make this case as well as financial analyses within health systems will be helpful in this regard. Furthermore, payers and industry should be encouraged to take a "value-based" approach to payment for and pricing of drugs so that access is more broadly assured.

Summary and conclusions. Patient-centered medicine involves aligning the priorities of the patient and the provider to arrive at a shared vision of care. For patients with schizophrenia, this shared vision might include agreement about the goals of therapy, a discussion of whether LAI use is helpful for meeting these goals, and offering an LAI if indicated. Patient and provider should also arrive at a flexible arrangement for administration of the LAI, which might include administration at the physician's office or clinic, in the pharmacy, at a health care home, or possibly even in the patient's own home.

Additional LAI Considerations

Beyond efficacy and safety data for LAIs, the panel discussed a number of additional factors that should be considered when weighing the use of LAI therapy. These factors impact multiple different stakeholders, including patients and their families, providers, and payers.

Nonadherence. Although efficacy of LAIs and oral antipsychotics has been generally similar in RCTs, some studies have demonstrated benefits of LAIs in first-episode patients, a population that is associated with a high rate of nonadherence.[44,75] First-episode patients, or patients early in the course of psychosis, may be especially likely to discontinue treatment because they do not accept the chronic nature of the illness. In addition, nonadherence is frequently unrecognized, and current medication adherence should not preclude the use of LAIs, since an important goal of therapy should be to prevent future nonadherence, which is always a possibility for patients with schizophrenia. Although often used in research studies, the medication possession ratio alone is not a sufficient indicator of treatment adherence. Patients may fill a prescription but then fail to take the medication. Together, these observations suggest that LAIs should not be viewed simply as a treatment for patients with poor adherence.

Currently, patients who are adherent to antipsychotic therapy may not meet criteria for insurance reimbursement of LAIs. The roundtable experts recommended that patients should not have to first prove that they have relapsed on oral medications before becoming eligible for LAIs. Relapses produce detrimental effects at many levels, including societal, individual, biological, and psychosocial. Preventing the likelihood of future relapses should be an important goal of therapy, even for those who do not yet have a history of relapse.

Relapses. Patients may relapse because of lack of drug effectiveness but also because of changes in the use of other drugs, home care, or other environmental factors. In many cases, the reason for a relapse is unknown, and scant research has examined why patients relapse on medication. Clinicians may be unsure of what to do when a patient relapses on an LAI or how to switch from LAI to another antipsychotic (oral or another LAI), and more research is needed to better define the optimal approach to patients with relapsing schizophrenia while on LAI therapy. Blood antipsychotic levels may help in understanding whether relapses occur because patients are not receiving an adequate medication dose, although these levels are not always obtained in routine clinical practice.[137]

One of the most important issues in schizophrenia care in the United States is the gap between in-hospital treatment for an acute episode and the transition to outpatient care after discharge. The observations that LAIs reduce relapse risk in acutely ill patients suggest that these agents provide an important strategy to help bridge this gap and ensure that patients leave the hospital with effective antipsychotic coverage.

Severity of episode or relapse. The patient's type and history of relapse may also be important considerations when weighing the potential benefits of LAI treatment. For example, continuous coverage with LAI treatment may be considered especially desirable when there is a history of relapse associated with violence, self-harm, or self-neglect.

Very little research has focused on the treatment of patients with LAIs beginning in the emergency room, which could provide more data regarding relapse. A clinical trial could investigate randomization at the time of initial contact with the emergency department or as soon as possible afterward to treatment with an LAI versus home or in-hospital treatment with oral antipsychotics. However, accessing the patient's treatment history while the patient is in the emergency department may be difficult at some facilities, and the informed consent process might delay randomization.

Cognitive and memory problems. Patients with cognitive impairment or memory problems may have difficulty remembering to take medication as prescribed, and they may also overestimate their own adherence to treatment when asked. LAIs are a good choice to reduce the impact of forgetting on antipsychotic adherence.

Ease of use. Aside from issues of comparative efficacy or safety of LAI versus oral formulations, LAIs offer many patients the benefit of improved convenience. Some patients may simply prefer to receive a single injection every 2, 4, 6, or even 12 weeks rather than being required to take oral medication every day. LAIs that offer longer intervals between administrations may be even more convenient for patients. Patients and families should understand that longer injection

intervals do not mean that the patient will not be seen by the physician or other mental health team members; they should know that the patient will continue to have regular follow-up visits and that the injection schedule is distinct from the schedule of follow-up appointments.

For providers, there may be differences in ease of use among the available LAIs. For example, risperidone microspheres and paliperidone palmitate require specialized injection needles with a modified internal bore, which is larger than that of a conventional needle. With aripiprazole lauroxil, there is an opportunity to administer the second injection as early as 14 days after the first, according to the product label.[88] This LAI also provides longer coverage against a late injection (up to a month on the 662 mg or 882 mg doses) without needing to restart oral supplementation.

Substance misuse. Substance misuse is one of the most common reasons for poor adherence to antipsychotics,[138] yet patients with substance misuse are often excluded from RCTs. Data from the Paliperidone Palmitate Research in Demonstrating Effectiveness (PRIDE) study, which included patients with substance misuse problems among other patient groups who are often excluded from clinical studies, suggest that these patients are more likely to benefit from an LAI compared to an oral antipsychotic.[45]

Access and cost. Issues of access and cost may be viewed from many perspectives, including those of the patient, the provider, insurers, and the health care system as a whole. In fact, many of these issues will vary by state or geographic region.

An important barrier to LAI access is the fact that many patients have copayments or deductibles. In addition, many regions are underserved by health care professionals, especially those with experience in mental health. It might be possible to improve patient access to care through the use of 2-way video or other telemedicine approaches. There may also be significant differences in access to LAI therapy from state to state.

The cost of LAIs presents a barrier to their use. However, from the health system perspective, although LAI products are associated with higher drug acquisition costs, they may save money across the entire continuum of care due to reduced relapses or hospitalizations. A review of 28 studies that examined health care costs associated with LAIs or oral antipsychotics found that most studies demonstrated lower overall treatment costs with LAIs.[139] In studies in the United States, cost-effectiveness analyses are largely influenced by number of hospital days, and even substantially greater medicine acquisition costs can be offset by small changes in the required days of hospitalization. Potential cost savings were shown on a system-wide basis in Canada[118] and Sweden.[116] There is a clear need for a large-scale cost study in the United States. Although 30-day hospital readmission rate is often used as a measure of care quality, this time period may be too short to adequately evaluate the effects of LAIs on quality and service utilization, and post hoc analyses have demonstrated that the benefits of LAIs are greater for patients who have been on treatment for longer periods of time.[140,141]

Stigma. LAIs are most frequently recommended for patients with schizophrenia who have a history of poor adherence to medication. Patients or families may view the physician's recommendation of LAI therapy as a form of punishment or as a sign that the patient is very ill or has recently worsened.[124] However, it should be recognized that there are many different types of nonadherence. Some patients exhibit what might be referred to as "distracted nonadherence," which results from issues such as cognitive impairment or disorganization. Other patients exhibit insight-based nonadherence (ie, the patient does not believe that he or she has an illness or that the illness requires medication) or accessibility-based nonadherence (eg, lack of insurance coverage). Patients with distracted or insight-based nonadherence may respond favorably to the suggestion of LAI use as a lifestyle benefit that reduces the need to take daily medication. This may be especially true for patients who work night shifts or otherwise experience many daily stressors. In this way, the physician is not recommending an LAI because the patient is at fault for not taking medication, but simply as a way to make the patient's life simpler. This approach may help to reduce some of the stigma associated with nonadherence. When talking to patients, it may also help to note that long-acting treatment strategies are increasingly common in other areas of medicine, such as rheumatoid arthritis or infusion pumps for patients with diabetes. It might also be preferable to present LAIs as a tool that might be used for a period of time rather than as something that the patient will remain on indefinitely. In some regions, patients may receive LAI injections directly from a pharmacist, without needing to come to the physician's office. Because other people in the pharmacy might be receiving injections for any number of other conditions, including standard vaccinations, patients may experience less stigma when obtaining the injection. Laws about pharmacist-administered injections and access to this type of program vary from state to state.

Stigma about the use of LAI antipsychotics is not limited to patients and their families. Many health care professionals also have negative attitudes toward the use of these agents and may be unwilling to inform patients about the availability of this treatment option.[125,126,129] It is critical to the care process that all health care providers are knowledgeable about the use of LAIs, including physicians, nursing staff, pharmacists, social workers, and others who are charged with patient care. Nurses in particular may play an important role in patient attitudes toward LAIs.[120] Nurses spend the most time with patients and family and may have a significant influence on perception of LAI therapy. There is an urgent need for training of mental health professionals, including social workers, nurses, and peer counselors. Moreover, it is critical to identify the key aspects of LAI use that should be communicated to professionals in different disciplines. Exposure to using LAIs in a residency setting may reduce the perceived stigma associated with LAIs and improve confidence among providers regarding their use.

Finally, it is also important to emphasize the need to destigmatize nonadherence. It is sufficiently common across

Table 6. Importance of Characteristics When Choosing or Not Choosing Long-Acting Injectable Antipsychotic (LAI) Treatment

Six of the 8 participants (psychiatrists) were asked to rate on a scale from 1 to 10 their best estimate on the importance of each characteristic when deciding whether to prescribe an LAI medication. Values shown are mean (SD) based on the group responses.
Instructions to participants: PLEASE RATE FOR EACH CELL GIVING YOUR BEST ESTIMATE:
10 = Extremely important: characteristic that trumps all other aspects when deciding on using an LAI.
8–9 = Usually important: among the most important characteristics for the stakeholder to consider.
6–7 = Equivocal for LAI: characteristic the stakeholder would sometimes consider when deciding for an LAI.
4–5 = Equivocal against LAI: characteristic the stakeholder would sometimes consider when deciding against an LAI.
2–3 = Usually inappropriate: among the most important characteristics for the stakeholder not to consider an LAI.
1 = Extremely inappropriate: characteristic that trumps all other aspects when deciding against using an LAI.

Characteristic[a]	Total Mean Scores	Patients, Mean (SD)	Health Care Professionals, Mean (SD)	Family, Mean (SD)	Payers, Mean (SD)
Danger to self or others during relapse(s)	7.9	6.7 (1.5)	8.5 (1.9)	8.5 (2.1)	7.7 (2.2)
Level of nonadherence with oral medications	7.6	6.0 (1.9)	8.7 (1.9)	8.3 (1.0)	7.3 (2.1)
Number of prior relapses	7.6	6.5 (2.0)	8.5 (1.4)	7.8 (1.2)	7.5 (2.2)
Severity of episodes/relapse(s)	7.6	7.2 (1.5)	8.0 (2.0)	7.8 (1.6)	7.3 (1.9)
Recency of last relapse(s)	7.1	6.7 (1.2)	7.2 (1.9)	7.7 (1.6)	6.8 (1.8)
Family conflict over patient's adherence	6.9	6.0 (2.1)	7.5 (1.2)	8.0 (1.1)	6.0 (0.9)
Ease of use of the treatment	6.6	7.0 (1.4)	6.0 (2.1)	7.5 (1.6)	5.9 (2.1)
Potential for loss of function	6.5	5.7 (2.3)	6.8 (1.7)	7.3 (2.0)	6.2 (2.0)
Comorbid substance abuse/dependence	6.4	5.3 (2.2)	7.3 (1.4)	7.2 (1.5)	5.8 (1.5)
Degree of lack of social support	6.2	5.5 (1.0)	6.7 (1.4)	6.5 (1.2)	6.0 (0.9)
Level of cognitive/memory impairment	5.9	5.4 (1.4)	6.4 (1.1)	6.3 (1.1)	5.6 (1.0)
Stigma associated with treatment	4.5	3.9 (1.1)	4.8 (0.9)	4.3 (1.1)	5.1 (0.2)
Wish to be able to adjust dose quickly	4.5	4.3 (0.8)	4.0 (1.1)	4.8 (0.4)	4.8 (0.4)
Injection site pain	4.4	3.2 (1.2)	4.8 (0.4)	4.5 (0.8)	5.1 (0.2)
Patient is on chronic blood-thinning therapy	4.2	4.3 (1.7)	4.1 (1.7)	4.3 (1.7)	4.1 (1.8)
Coercion/diminished patient autonomy	4.2	3.0 (0.9)	4.5 (0.5)	4.3 (0.5)	4.9 (0.8)
Level of nonadherence with LAI medications	4.2	3.8 (2.1)	4.3 (1.5)	4.7 (1.3)	3.8 (0.8)
Access to/cost of treatment	4.2	4.4 (1.0)	4.2 (0.8)	4.3 (0.9)	3.7 (1.6)
Wish to be able to stop treatment abruptly if needed	4.0	3.3 (1.0)	3.7 (1.2)	4.0 (0.9)	5.1 (0.2)
First-episode/early-phase illness	3.8	3.0 (5.7)	4.8 (1.3)	4.1 (1.2)	3.3 (1.3)
Patient is afraid of needles	3.6	2.5 (1.5)	3.8 (1.2)	3.3 (1.5)	4.8 (0.9)
Patient had neuroleptic malignant syndrome on an antipsychotic	3.0	2.8 (1.8)	2.7 (1.6)	2.5 (1.5)	3.8 (2.1)

[a]Characteristics ordered by mean scores across the ratings for patients, health care professionals, family members, and payers.

all of medicine to view nonadherence as an aspect of human nature, not "bad behavior."

Level of social support. Poor adherence affects families as well as patients, and family members often help patients to ensure that they are adherent to medications. Family members, therefore, may have a key role in acting as advocates to help patients to use LAIs when appropriate. In addition, it can be difficult for patients with schizophrenia to advocate for themselves. Including families in the discussion can help to ensure that patients have an advocate who is educated about the role of LAIs in schizophrenia treatment. In addition, family members are often those who suffer the immediate and disturbing consequences of relapse. They are the ones who might find themselves needing to call the police, for example, when a loved one relapses and loses insight.

Conflict over and fear of nonadherence. Medication adherence can become a source of ongoing conflict between patients and providers. One potential advantage of LAIs is the removal of this source of conflict by changing how LAIs are approached and discussed, possibly strengthening the patient-provider relationship.

Autonomy. There is sometimes a concern among patients, family members, and even clinicians that LAIs diminish patient autonomy. Some may perceive an injection of LAI as similar to injecting a sedative for a patient with acute agitation. However, it should be stressed that in the case of LAIs, the patient voluntarily agrees to receive each injection. Agreeing to LAI therapy does not involve a surrender of autonomy on the part of the patient. The goal is to control the illness, not the patient.

Wish to control treatment and dosing. Because LAI treatment is administered only once every few weeks or months, some patients or providers may believe that it is difficult to adjust or control the medication dose. As LAIs are used as a maintenance treatment, there is likely to be less need to adjust the dose than would be the case during acute

Table 7. Concluding Recommendations

Research Recommendations
• Long-acting injectable antipsychotics (LAIs) should be studied in acute and maintenance treatment of schizophrenia, with the goal of helping patients to bridge the gap from early treatment to lifelong care.
• Studies of clinical effectiveness of LAI therapy should examine the effects of the intervention under existing or usual conditions that resemble real-world clinical practice to maximize ecological or external validity, with special attention to moderating and mediating factors (eg, duration of illness).
• Appropriately powered head-to-head randomized controlled trials (RCTs) with specific inquiry into common tolerability issues are needed to more accurately assess differences among LAIs in terms of adverse event frequency.
• Different study designs are associated with divergent findings regarding relative benefits of LAIs vs oral medications; RCTs may not be the appropriate gold standard in this context.
• Pragmatic (large simple) trials are likely to be the most informative and generalizable. A large simple trial that compares offer/no offer of LAI on the course of illness in young adults with schizophrenia who are followed through claims records for antipsychotic adherence and hospital admissions may be the most appropriate method for assessing the impact of LAIs. In contrast with other areas of medicine, there are few very large RCTs in the treatment of schizophrenia. Given the public health considerations and the recent efforts toward health care reform and reducing costs, larger trials should be performed to examine outcomes with different schizophrenia treatment strategies.
• As more attention is given to reducing avoidable hospitalizations and their associated costs, the importance of such studies will increase. A compelling health economics study may be necessary to sway reimbursement in many states, including financial analyses within health systems.
• Greater choices in terms of specific molecules, delivery methods, and injection intervals should be pursued to help drive increased utilization.
• A clinical trial should be considered that compares different strategies (eg, motivational interviewing, family education, peer groups) for introducing LAIs to schizophrenia patients, with the primary outcome of LAI acceptance.
• An observational analysis that compares outcomes of schizophrenia patients across clinics and that uses historical clinic rate of LAI use as an instrumental variable should also be considered.
Education and Training
• All patients should be informed of the option of an LAI and the pros and cons of LAI versus oral medication discussed.
• Tailored education about LAIs should be developed for different groups of professionals who interact with patients, including physicians, nurse practitioners, nurses, physician assistants, pharmacists, social workers, residents, peer counselors, and others.
• Residents (and potentially all providers in training) should be required to be exposed to using LAIs during their training to improve confidence, experience, and familiarity with these agents.
• Even patients on LAIs can become nonadherent, so ongoing education and support is required.
Patient Eligibility and Treatment Selection
• Selection of a specific LAI should consider an individual patient's preferences and prior history of sensitivity to specific tolerability concerns, including extrapyramidal side effects, akathisia, elevations in prolactin, weight gain, and sedation.
• Previous poor adherence and the presence of risk factors for future nonadherence increase the argument for LAI use.
• When relapse is predicted to be associated with high risks or "a lot to lose," the argument for LAI use is stronger.
• When selecting an LAI, the acquisition cost and the effectiveness of the oral antipsychotic used in the acute treatment phase should be considered.
• Clinicians, patients, and family should all be involved in a patient-centered approach in deciding whether an LAI is indicated.
• LAIs should not be viewed as the final choice for patients who are consistently nonadherent.
Guidelines and Policy
• A quality metric should be developed to measure the proportion of adults with schizophrenia in a health plan that have an annual antipsychotic medication possession ratio of < 0.80.
• Information systems should be developed that allow patients to voluntarily permit their treating clinicians to access their pharmacy claims information in "real time."
• Claims-based tools should be developed that permit Medicaid mental health directors and other clinical policy leaders to track LAI use patterns across large systems of care.
• Guidelines should be created for clinicians to assess the potential for LAI use for patients taking oral antipsychotics who are not improving, who are nonadherent, or who are hospitalized repeatedly or within short periods of time.
• Institutional support should be put in place to facilitate the administration of LAIs, which includes injection sites or clinics and the involvement of primary care. Options outside of the medical office, such as at the pharmacy or at home, should be considered.
• Incentives for guideline-consistent behaviors could be provided for clinicians, and reimbursement at the institutional and state levels should be streamlined.
• The long-term benefits and cost savings associated with LAI use and routine health monitoring should be emphasized to patients and insurance providers.
• Payers should be strongly encouraged to look beyond the short-term financial decisions around drug cost and consider the potential long-term benefits of reduced hospitalizations, relapses, and quality-of-life issues.
• As an alternative to current market-based drug pricing approaches, payers may consider working with pharmaceutical companies to identify value-based pricing and payment strategies for LAIs.

treatment. In addition, many LAIs are available in a range of doses, enabling dose adjustment. Finally, if symptoms of relapse occur during LAI treatment, then symptom control can often be most rapidly achieved by coprescribing an oral antipsychotic and simultaneously increasing the dose of the LAI. If the patient's symptoms respond, then the oral supplementation can subsequently be withdrawn once sufficient time has elapsed for the LAI to reach a new steady state. Clinical experience suggests that it is also possible to adjust LAI dosing through the use of calendars and scheduling injection visits at a specific interval to attain higher or lower plasma drug concentrations. For example, if the label recommends injections every 26 to 28 days, an individual patient who is believed by his or her physician to be just below a therapeutic plasma drug concentration may be treated at a somewhat shorter dosing interval (eg, 25 days). Conversely, a patient who is thought to be at a higher-than-optimal plasma drug concentration might be treated once every 29 or 30 days.

Fear of needles and pain. Some patients are especially concerned about the potential for pain or discomfort with LAIs. Clinical experience suggests that the older depot antipsychotics that used oil-based vehicles were associated with more discomfort than the aqueous solution used with newer LAIs, although no head-to-head studies have investigated this. Selecting agents with smaller injection volumes or choosing agents with longer injection intervals may also reduce the discomfort associated with LAIs.

Potential for loss of functioning. LAIs may offer an important option when the potential for loss of normal functioning associated with a relapse could have important consequences for the patient. Examples include college students living away from home who have recently experienced a first psychotic episode and need to take treatment while away from their usual source of care/support, or individuals with employment that could be jeopardized by a relapse of schizophrenia.

Recommending LAI Therapy for Patients With Schizophrenia

Table 6 summarizes the opinions of participants regarding the importance of several clinical factors in the selection of LAIs and how these factors might influence decision-making by patients, health care professionals, family members, and payers.

Concluding Recommendations

Concluding recommendations from the panel are summarized in Table 7.

Drug names: aripiprazole (Abilify), aripiprazole lauroxil (Aristada), aripiprazole monohydrate (Abilify Maintena), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), olanzapine (Zyprexa and others), olanzapine pamoate (Zyprexa Relprevv), paliperidone palmitate (Invega Sustenna, Invega Trinza), pimozide (Orap), quetiapine (Seroquel and others), risperidone (Risperdal and others), risperidone microspheres (Risperdal Consta).

Supplementary material: Available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: The Use of Long-Acting Injectable Antipsychotics in Schizophrenia: Evaluating the Evidence

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Supplementary eTable 1. Summary of Mirror-Image Studies

Study/ Country	N[a]	Data Source	LAI Phase	Follow-Up Duration, mo Oral AP/LAI	Inclusion Criteria	Reported Outcome	Age, y (mean ± SD)	% Male	Chronicity	Medication: LAI (n)[b] / Oral AP (n)[b]	Medication: Dose, mg (mean ± SD)	Key Outcomes
Chang et al[48] 2012/Taiwan	184	Medical claims data, nationwide	Retrospective, dropouts excluded	12/12	SCZ (*ICD-9*), started RLAI, followed ≥ 1 y before and after RLAI initiation, treated regularly with RLAI	# Hps # Outpatient visits # ER visits % Hps[c] # Hp days # Relapse Cost	36–55[d]	50.5	DOI ≥ 6 y in 77.2%	RLAI (184) CLO (7) RIS (80) Other SGA (50) Oral FGA (91)	total 177/3 mo NR	Reduction of 34% and 32% of total inpatient services costs and inpatient nonmedication costs, respectively ($P < .005$) Overall psychiatric service costs increased 26%
Rosa et al[49] 2012/Int.	98	Multinational	Prospective, dropouts excluded	6/6	SCZ/SzAD (*DSM-IV*), nonacute, previously treated with OLA (stable dose) and willing to switch to RLAI, not known as RIS nonresponder	# Experienced Hps # Experienced Hps due to psychotic disease # Experienced relapses # Hp days Psychopathology Social functioning Safety measures	40.2 ± 14.0[e]	77.1[e]	Mean DOI: 13.5 y[e]	RLAI (79) OLA (79)	32.6 ± 7.1/ 2 wk 16.2 ± 5.6	Significant efficacy changes vs baseline were observed for PANSS, CGI-S, and GAF (all $P < .0001$) TEAEs were similar with 1 wk and 3 wk OLA taper (40.0% and 46.5%, respectively) TEAEs were generally mild (34.5%) or moderate (49.0%) in intensity
Crivera et al[50] 2011/USA	435	Multicenter	Prospective, dropouts included	12/1[f]	SCZ (*DSM-IV*), appropriate for RLAI initiation	# Hps # Psychiatric Hps # ER visits % Psychiatric Hps	41.9 ± 12.6	66.7	Mean ± SD DOI: 17.6 ± 12.1 y	RLAI (435, 343) NR (435, 343)	25/2 wk NR	Annual number of Hps (for any reason and psychiatric Hps) and ER visits decreased significantly after initiation of RLAI (all P values <.0001)
Ren et al[51] 2011/USA	924	VA, multicenter	Retrospective, dropouts included	12/12	SCZ (*ICD-9*), started RLAI, and had ≥ 4 RLAI injections	# Psychiatric Hps % Psychiatric Hps % ≥ 2 Psychiatric Hps # Hp days Length of stay	51 ± 11	94	NR	RLAI (924) NR (924)	38.9 ± 13.0/ 2 wk NR	Initiation of RLAI associated with significant reductions in number of psychiatric Hps, % of patients hospitalized, # Hp days, and length of stay
Peng et al[52] 2011/USA	147	Commercial claims data, multicenter	Retrospective, dropouts included	6/6	SCZ (*ICD-9*), started any depot, but without depot injection in the 6 mo before baseline, ≥ 2 outpatient visits or ≥ 1 Hp within 180 d	# Hps % Hps % Psychiatric Hps % Hps for SCZ # Hp days # Psychiatric Hp days # Hp days for SCZ	42.6 ± 14.7	53.7	NR	RLAI (38) HAL (69) FPZ (40) NR (147)	NR NR	Psychiatric Hps decreased from 49.7% before depot initiation to 22.4% after depot initiation Decreases also noted for total Hps, SCZ-related Hps, and total health care costs

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Supplementary eTable 1 (continued). Summary of Mirror-Image Studies

Study/ Country	N[a]	Data Source	LAI Phase	Follow-Up Duration, mo Oral AP/LAI	Inclusion Criteria	Reported Outcome	Age, y (mean ± SD)	% Male	Chronicity	Medication LAI (n)[b] / Oral AP (n)[b]	Medication Dose, mg (mean ± SD)	Key Outcomes
Carswell et al[53] 2010/New Zealand	443	Multicenter (5 centers)	Retrospective, dropouts included	12/12	SCZ (*DSM-IV*), nonadherent to oral AP (or preferred RLAI), intensive treatment in the year prior to switching to RLAI	# Hps # Hp days # Days of compulsory treatment order Cost	35.9 ± 12.4	64.3	Mean ± SD DOI: 11.7 ± 9.9 y	RLAI (427) NR (427)	41.5/2 wk[g] NR	The mean number of Hp admissions was significantly lower post-RLAI than pre-RLAI (1.38 vs 0.61, $P < .001$), although mean length of stay was longer and mean costs were also lower
Girardi et al[54] 2010/Italy	88	Multicenter	Prospective, no dropouts during the 6-month phase	6/6 (24)[f]	SCZ/SzAD (*DSM-IV*), with clinically inadequate response to ≥2 oral APs within 3 mo, BPRS total score ≥ 65	% Hps Response rate Psychopathology Safety	41.2 ± 10.6	64.8	Mean ± SD DOI: 18 ± 5.0 y, Mean ± SD # Hp: 8.26 ± 2.79	RLAI (88) OLA (29) CLO (26) QUE (21) HAL (13) ARI (9) RIS (2)	47.4 ± 10.1/ 2 wk NR	Transition to RLAI was associated with improvement on all outcomes studied, including BPRS scores and hospitalization AEs were reduced by 2.5- to 7.4-fold during 18 mo of follow-up with RLAI
Su et al[55] 2009/Taiwan	108	Medical claims data, nationwide	Retrospective, dropouts excluded	12/12	SCZ (*ICD-9*), regularly treated with RLAI for ≥1 y, ≥1 y data in pre-RLAI periods, had < 90 d Hps	# Hps # ER visits # Hp days # Relapses	42.0 ± 10.4	50	NR	RLAI (108) RIS (17) Other SGA (41) FGA (27) FGA + RIS (10) FGA + other SGA (5) None (8)	175.4 ± 54.5/ 3 mo NR	Switching to RLAI was associated with significant reductions in the total annual numbers of acute hospital admissions (55% reduction, $P = .0003$), Hp days (48% reduction, $P = .0021$), and relapses (54% reduction, $P = .0005$)
Lam et al[56] 2009/15 countries	2,300	Multinational	Prospective, dropouts included	12/12	SCZ who participated in RLAI clinical trials	% Hps All cause discontinuation Psychopathology	38.4	NR	Mean DOI: 10.3 y	RLAI (1,748) OAP (1,748)	NR NR	12-mo Hp rate was 44.5% on oral AP vs 16.4% on RLAI ($P < .001$)
Fuller et al[57] 2009/USA	106	VA (Ohio), multicenter (5 centers)	Retrospective, dropout included	10.2 ± 6.4/ 10.2 ± 6.4 (mean ± SD)	SCZ/SzAD (*ICD-9*) at any time of the study period (1/2003 to 1/2006), with continuous enrolment throughout the study period, ≥4 injections of RLAI	# Psychiatric Hps % Psychiatric Hps % ≥ 2 Psychiatric Hps # Psychiatric Hp days # Psychiatric Hp days/ months # Psychiatric-related outpatient visits Compliance Cost	51.9 ± 10.2	93	NR	RLAI (106) ARI (7) OLA (19) QUE (30) RIS (57) ZIP (8)	35.5/ 2 wk (end) 26.3 ± 4.9 15.1 ± 7.1 423.5 ± 275.5 3.8 ± 1.9 107.7 ± 45.1	Fewer patients had psychiatric Hps after switch to RLAI (75% vs 42%, $P < .001$) Post-switch patients also had significantly lower mean number and duration of Hps

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Supplementary eTable 1 (continued). Summary of Mirror-Image Studies

Study/ Country	N[a]	Data Source	LAI Phase	Follow-Up Duration, mo Oral AP/LAI	Inclusion Criteria	Reported Outcome	Age, y (mean ± SD)	% Male	Chronicity	Medication LAI (n)[b] / Oral AP (n)[b]	Medication Dose, mg (mean ± SD)	Key Outcomes
Beauclair et al[58] 2005/Canada	63	Multicenter	Retrospective, dropouts included	39.4/ 40.3	SCZ who participated in RLAI clinical trials	# Hps % Hps % Experienced ≥ 2 Hps # Hp days All cause discontinuation Concomitant anticholinergic/ anxiolytic/ sedative	NR	NR	NR	RLAI (63) NR (63)	NR NR	Hp rate was lower after initiation of RLAI (52.4% vs 4.8% of patients, $P < .0001$). RLAI was also associated with decreased number of patients with multiple Hps, duration of Hps, and use of concomitant medications (eg, anxiolytics)
Bourin et al[59] 1998/France	48	Single center	Retrospective, dropouts excluded	62.4 ± 33.6/ 69.6 ± 38.4 (mean ± SD)	SCZ (*ICD-10*), hospitalized	# Hps # Hp days	NR	50	NR	FGA (44) OAP (48)	NR NR	Mean number of Hps was higher during depot treatment than during treatment with oral APs (4.8 vs 7.2 Hps), as was the mean number of Hps per year (0.93 vs 1.25)
Svestka et al[60] 1984/Czech	34	Single center	Prospective, dropouts included	10.3/10.3	SCZ, in remission	% Hps	37.4	23.5	Mean DOI: 9.2 y, # Hps in lifetime: 1–12	Clopenthixol decanoate (34) NR	169.5/3.7 wk NR	Lower Hp risk while on LAI than on oral AP (risk ratio = 0.43, $P < .0001$).
Waldmann and Neumann[61] 1984/Germany	65	Single center	Retrospective, dropouts excluded	31.2/31.2	SCZ/SzAD, outpatients and patients in day hospital who were receiving FPZ decanoate	# Hps	NR	27.7	Duration of treatment: 1–9 y	FPZ (65) NR (65)	17.7/3 wk NR	Lower number of Hps while on LAI than on oral AP (rate ratio = 0.0201, $P < .0001$).
Michel et al[62] 1981/Chile	112	Single center	Retrospective, dropouts excluded	12–17/12–17 (range)	SCZ, on depot when study was conducted	# Hp days	25–44[h]	67.9	NR	FPZ NR	NR NR	93% of patients had less medical resource use (eg, nursing consultations, injections, use of concomitant medications) after switching to LAI FPZ, and 96% of patients had fewer consultations after switching

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Study/ Country	N[a]	Data Source	LAI Phase	Follow-Up Duration, mo Oral AP/LAI	Inclusion Criteria	Reported Outcome	Age, y (mean ± SD)	% Male	Chronicity	Medication: LAI (n)[b] Oral AP (n)[b]	Medication: Dose, mg (mean ± SD)	Key Outcomes
Tan et al[63] 1981/Singapore	127	Multicenter (6 centers)	Retrospective, dropouts excluded	24/24	SCZ, DOI ≤ 8 y, ≥ 24 mo treatment before and after the institution of FPZ depot	# Hps # Hp days Compliance	32.5 ± 8.8	61.4	6–8 y	FPZ (127) NR (127)	25/mo NR	Of 127 patients, 105 had reductions in relapses requiring readmission after switching to depot FPZ. Relapses increased in 19 patients and were unchanged in 3.
Arató and Erdós[64] 1979/Hungary	51	Single center	Retrospective, dropouts excluded	44/26	SCZ/SzAD, ≥1 y on depot, ≥2 Hps in the past	# Hps # Patients who experienced Hps	34	100	Mean DOI: 7.2 y	Mixed FGA NR	FPZ (12.5–25 mg/ 4 wk), Flupenthixol (20 mg/3 wk) NR	During LAI treatment, patients had lower incidence of Hp (risk ratio = 0.204, $P < .0001$) and # Hps (rate ratio = 0.106, $P < .0001$)
Devito et al[65] 1978/USA	122	Single center	Retrospective, dropouts excluded	12/12	SCZ spectrum disorders, treated in the same inpatient program and referred for outpatient treatment in the FPZ program	# Hps % Hps Length of stay # Hps per patient	18–39[i]	50.8	NR	FPZ (61) NR (61)	37.5 mg/ 3–4 wk NR	Hp readmission rate was 25% with FPZ vs 44% with oral AP. FPZ group also had shorter mean length of stay (7 vs 20 d)
Polonowita and James[66] 1976/New Zealand	43	Single center	Retrospective, dropouts included	13/13	SCZ (*ICD-8*), started FPZ depot	# Hps # Hp days	NR	67.4	NR	FPZ decanoate (43) NR (43)	NR NR	FPZ associated with significantly fewer Hps (total of 60 vs 22 admissions for oral AP vs FPZ groups, $P < .004$) and a lower mean # Hp days (1,463 vs 327, $P < .00005$)
Lindholm[67] 1975/Sweden	24	Multicenter (2 centers)	Retrospective, dropouts excluded	26.9/26.9	SCZ, administered perphenazine enanthate for > 1 y	# Hps % Hps # Hp days Concomitant antiparkinson medication	44.9	25.0	Mean DOI: 6.8 y	Perphenazine enanthate (24) NR (24)	107 mg NR	Mean # Hps per year decreased from 1.31 during the control period to 0.59 during treatment with perphenazine enanthate ($P < .05$). Perphenazine enthanate was also associated with fewer total Hp days.
Gottfries and Green[68] 1974/Sweden	58	Single center	Retrospective, dropouts excluded	NR	SCZ, discharged, treated with flupenthixol decanoate during observation period	# Relapses requiring Hp % Hps # Hp days Length of stay All cause discontinuation	NR	NR	Patients started LAI during Hp and later were transferred to ambulant treatment	FPZ decanoate (58) NR (58)	40/2 wk as a general rule, (range, 20–60 mg) NR	Significant reduction in relapse frequency after switching from oral APs FPZ decanoate ($P < .005$) Patients also had fewer Hps and shorter duration of stay after switching

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Supplementary eTable 1 (continued). Summary of Mirror-Image Studies

Study/ Country	N[a]	Data Source	LAI Phase	Follow-Up Duration, mo Oral AP/LAI	Inclusion Criteria	Reported Outcome	Age, y (mean ± SD)	% Male	Chronicity	Medication LAI (n)[b] / Oral AP (n)[b]	Medication Dose, mg (mean ± SD)	Key O utcomes
Morritt[69] 1974/UK	33	Single center	Retrospective, dropouts excluded	12/12	SCZ, administered FPZ decanoate and with 1 y record pre/post FPZ depot	# Hps % Hps # Hp days	NR	42.4	NR	FPZ decanoate (33) NR (33)	NR NR	Among 33 patients, the total number of Hp admissions was 60 before FPZ decanoate vs 12 after FPZ decanoate. Total number of days Hp decreased from 2,379 to 801.
Johnson and Freeman[70] 1972/UK	126[y]	Single center	Retrospective, dropouts excluded	12/12	SCZ, administered FPZ depot and with follow-up record of 1 or 2 y	% Hp Hp days	NR	NR	NR	FPZ enanthate or decanoate (126) NR (126)	12.5/5 wk to 25/10 d NR	After 1 y, FPZ was associated with a 57% decrease in Hp admissions and a 48% decrease in length of stay After 2 y, Hp admissions decreased 74%, and length of stay decreased 48%
Denham and Adamson[71] 1971/UK	103	Single center	Retrospective, dropouts excluded	24.8/24.8 (mean)	SCZ, receiving FPZ depot, ≥12-mo follow-up record after injection, with completely documented previous history	# Hps % Hps # Hp days # Hps due to specific reasons # Hp days due to specific reasons	38.5	55.3	Chronic	FPZ (103) NR (103)	FPZ enanthate (6.25–50 mg/ 2 wk) or decanoate (12.5–37.5 mg/ 2 wk) NR	Reduction in Hp admission rate and inpatient time after transition to depot agent
Malm[72] 1971/Denmark	44	Single center	Retrospective, dropouts excluded	36/36	SCZ, chronic, known to have difficulty with adherence to AP oral medication	# Hps # Hp days	NR	100	Chronic	FGA mix (44) NR (44)	NR NR	Lower number of Hps during LAI than during oral AP (rate ratio = 0.294, $P < .0001$)

[a]Original study sample size. [b]Number of patients analyzed. [c]Obtained directly from author. [d]Majority (60.3%) were from 36–55 years old. [e]Based on patients who received at least 4 doses of RLAI (n = 96). [f]Analyzed pre- vs post-LAI phase (6 months each), but study had 18-month extension follow-up phase. [g]Dose at 12 months. [h]Majority (65.2%) were between 25–44 years old. [i]Half of the participants were assessed in a mirror-image setting.

Abbreviations: AE = adverse event, AP = antipsychotic, ARI = aripiprazole, BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, CLO = clozapine, DOI = duration of illness, *DSM-IV = Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, ER = emergency room, FGA = first-generation antipsychotic, FPZ = fluphenazine, GAF = Global Assessment of Functioning, HAL = haloperidol, Hp = hospital/hospitalization, *ICD = International Classification of Diseases*, Int. = international, LAI = long-acting injectable, NR = not reported, PANSS = Positive and Negative Syndrome Scale, OLA = olanzapine, QUE = quetiapine, RIS = risperidone, RLAI = risperidone long-acting injectable, SCZ = schizophrenia, SzAD = schizoaffective disorder, SGA = second-generation antipsychotic, TEAE = treatment-emergent adverse event, UK = United Kingdom, USA = United States of America, VA = Department of Veterans Affairs, ZIP = ziprasidone. Symbol: # = number/number of.

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Supplementary eTable 2. Comparison by Antipsychotic of Number Needed to Harm for Weight Gain ≥ 7%, Somnolence, or Akathisia[a]

	Number Needed to Harm[b]		
Antipsychotic	Weight Gain ≥ 7%	Somnolence Adverse Event	Akathisia Adverse Event
Risperidone	18	13	15
Olanzapine	**6**	**7**	25
Quetiapine IR	**6**	10	ND
Quetiapine XR	22	**7**	188
Ziprasidone	16	15	100
Aripiprazole	20	20	25
Paliperidone	35	42	39
Iloperidone	10	16	ND
Asenapine	35	17	34
Lurasidone	67	11	10
Brexpiprazole	17	50	112
Cariprazine	34	100	15

[a]Updated from Citrome L. *CNS Drugs*. 2013;27:879–911 and Citrome L. *Int J Clin Pract*. 2015;69:978–997.

[b]Number needed to harm values < 10 are bolded in the table. For example, 1 additional outcome of weight gain ≥ 7% is observed every 6 patients treated with olanzapine or quetiapine IR versus placebo; somnolence is observed every 7 patients treated with olanzapine or quetiapine XR versus placebo; and 1 additional patient with complaint of akathisia can be expected every 10 patients treated with lurasidone versus placebo.

Abbreviations: IR = immediate release, ND = no difference from placebo, XR = extended release.

Supplementary eTable 3. Adverse Events (%) Occurring in at Least 5% of Patients Treated With Long-Acting Injectable Antipsychotics (LAIs)[a]

	Risperidone LAI (Risperdal Consta)		Olanzapine Pamoate (Zyprexa Relprevv)			Paliperidone Palmitate LAI (Invega Sustenna)						Paliperidone Palmitate LAI (Invega Trinza)	Aripiprazole LAI (Abilify Maintena)	Aripiprazole Lauroxil (Aristada)		Haloperidol Decanoate (Haldol)
Adverse Event	25 mg	50 mg	405/ 4 wk	210/ 2 wk	300/ 2 wk	39 mg	78 mg	156 mg	234/ 39 mg	234/ 156 mg	234/ 234 mg	273–819 mg	400 (300) mg	441 mg	882 mg	
Gastrointestinal disorders																
Constipation	5	7	…	…	…	…	…	…	…	…	…	…	10	…	…	2
Diarrhea	…	…	2	7	5	0	3	2	1	2	2	…	3	…	…	…
Dry mouth	0	7	2	6	4	3	1	0	1	1	1	…	4	…	…	3.4
Dyspepsia	6	6	…	…	…	…	…	…	…	…	…	…	…	…	…	…
Nausea	3	4	5	5	4	4	4	3	2	2	2	…	—	…	…	…
Vomiting	…	…	6	1	2	5	4	2	3	2	2	…	3	…	…	…
General disorders and administration site conditions																
Fatigue	3	9	4	2	3	1	2	2	1	2	1	…	…	…	…	…
Injection-site reaction	…	…	…	…	…	0	4	6	9	7	10	3	…	…	…	1.2
Injection-site pain	…	…	2	3	2	…	…	…	…	…	…	…	5	3	4	…
Infections and infestations																
Nasopharyngitis	…	…	3	6	1	0	2	2	4	2	2	…	…	…	…	…
Upper respiratory tract infection	2	0	3	1	4	2	2	2	1	2	4	10	4	…	…	…
Investigations																
Weight increased	5	4	5	6	7	4	4	1	1	1	2	9	17	2	2	2.9
Metabolism and nutrition disorders																
Increased appetite	…	…	1	4	6	…	…	…	…	…	…	…	…	…	…	…
Musculoskeletal and connective tissue disorders																
Pain in extremity	6	2	…	…	…	0	2	2	2	3	0	…	…	…	…	…
Back pain	…	…	4	3	5	2	1	3	1	1	1	…	4	…	…	…
Muscle rigidity	…	…	1	4	4	1	<1	<1	1	1	2	…	…	…	…	6.1
Nervous system disorders																
Headache	15	21	13	15	18	11	11	15	11	7	6	9	…	3	5	…
Parkinsonism	8	15	8	14	20	12	10	6	…	…	…	4	…	3	4	7.3
Dizziness	7	11	4	4	1	6	2	4	1	4	2	…	4	…	…	…
Akathisia	4	11	5	11	10	5	6	5	…	5	6	5	11	11	11	3.4
Sedation/somnolence	5	6	13	8	13	5	7	4	1	5	5	…	5	…	…	4.9
Extrapyramidal disorder	…	…	…	…	…	5	2	3	1	0	0	…	…	…	…	13.6
Dyskinesia	…	…	0	2	1	4	6	4	…	…	…	3	…	…	…	<1
Tremor	0	3	3	0	1	…	…	…	…	…	…	…	3	…	…	8
Psychiatric system disorders																
Agitation	…	…	…	…	…	10	5	9	8	5	4	…	…	…	…	…
Anxiety	…	…	…	…	…	8	5	3	5	6	6	…	…	…	…	…
Respiratory, thoracic, and mediastinal disorders																
Cough	4	2	…	5	9	2	3	1	0	1	1	…	…	…	…	…
Nasal congestion	2	0	2	1	7	…	…	…	…	…	…	…	2	…	…	…

[a]These data are derived from product labeling and not from randomized, head-to-head clinical studies comparing LAI antipsychotics. Comparisons must be made with caution, as they reflect different methods of assessment and adverse event definitions across studies.* Rates with placebo, which differ from label to label, are not shown.

*Hamer S, Haddad PM. Adverse effects of antipsychotics as outcome measures. *Br J Psychiatry Suppl.* 2007;191(50):s64–s70.

Symbol: … =event not reported.

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