Clinical Application of Aripiprazole Monohydrate Long-Acting Injectables for the Treatment of Schizophrenia:

A Consensus Panel Report

Christoph U. Correll, MD; Eric D. Achtyes, MD, MS; Martha Sajatovic, MD; Stephen R. Saklad, PharmD, BCPP; and Joseph F. Goldberg, MD

This Academic Highlights section of *The Journal of Clinical Psychiatry* presents the highlights of the virtual consensus panel meeting "Clinical Application of Aripiprazole Monohydrate Long-Acting Injectables for the Treatment of Schizophrenia: A Consensus Panel Report," which was held September 9, 2024.

The meeting was chaired by **Joseph F. Goldberg, MD**, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York. The faculty were **Eric D. Achtyes, MD, MS**, Department of Psychiatry, Western Michigan University Homer Stryker M.D. School of Medicine, Kalamazoo, Michigan; **Christoph U. Correll, MD**, Department of Psychiatry, Zucker Hillside Hospital, Glen Oaks, New York; Department of Psychiatry and Molecular Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York; Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin, Germany; German Center for Mental Health (DZPG), partner site Berlin, Berlin, Germany; **Martha Sajatovic, MD**, Department of Psychiatry and Department of Neurology, Case Western Reserve University School of Medicine, Cleveland, Ohio; and **Stephen R. Saklad, PharmD, BCPP**, Division of Pharmacotherapy, College of Pharmacy, The University of Texas at Austin, San Antonio, Texas.

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Schizophrenia is a severe neuroprogressive mental disorder characterized by high relapse rates, with most patients experiencing multiple relapses after recovering from a first psychotic episode.[1,2] These relapse episodes hold potentially serious consequences, including loss of autonomy, diminished employment and educational opportunities, the risk of harm to oneself or others, disruption of personal relationships, and increased stigmatization.[3,4] In addition to these psychosocial consequences, there is compelling evidence of biological harm, as some previously responsive patients may develop treatment resistance following each subsequent relapse episode, a phenomenon referred to as neurotoxicity or "neuroprogression."[5] Despite the availability of numerous pharmacological options for schizophrenia, poor adherence to prescribed antipsychotic medication is a major contributor to relapse, as impaired insight and cognitive dysfunction can interfere with a patient's ability to maintain consistent medication use.[6] Indeed, treatment nonadherence has been consistently identified as the strongest predictor of relapse and poor illness outcomes,[7] with studies showing that patients who discontinue medication are 2 to 5 times more likely to relapse compared to those who maintain adherence with their medication regimen.[3,5,8]

Due to the vast array of potential presenting symptoms, treatment of schizophrenia is complex and requires a comprehensive care plan integrating psychosocial interventions with effective pharmacological treatment.[9,10] Long-acting injectable (LAI) formulations of second-generation antipsychotics, such as aripiprazole, olanzapine, paliperidone, and risperidone, offer a promising strategy to mitigate nonadherence by reducing the frequency of dosing and ensuring consistent drug delivery over an extended period.[11,12] As a result, LAIs have been associated with lower relapse rates and improved clinical outcomes in patients diagnosed with schizophrenia, underscoring their clinical utility in preventing exacerbations and maintaining long-term stability.[13] Although LAI antipsychotic medications have generally been viewed as options to be tried only after failure of multiple oral medications, they have demonstrated favorable tolerability and consistent efficacy both in treating both acute episodes and in the maintenance phase of schizophrenia,[13,14] warranting consideration of their use earlier in the schizophrenia treatment algorithm.[15–20] Compared with oral medications, LAIs are associated with increased medication

adherence, prolonged time to first hospitalization, improved patient functionality, and reduced mortality and may be more beneficial when given earlier rather than later in the course of the disease.[21–28] LAIs are also associated with improved disease insight, which can be beneficial for many patients with schizophrenia as lack of insight is a driver of medication nonadherence.[29,30]

Aripiprazole is a second-generation partial dopamine D2 receptor agonist antipsychotic, which is available as an LAI in 2 different molecular versions, aripiprazole monohydrate and aripiprazole lauroxil, a prodrug of aripiprazole that we will not cover in this review, as it has been reviewed comprehensively very recently.[31] Aripiprazole monohydrate is available in 2 different LAI formulations, aripiprazole once-monthly 400 mg (AOM 400), which is an extended-release LAI formulation of aripiprazole monohydrate for administration every 28 days via deltoid or gluteal intramuscular injection, and aripiprazole 2-month ready-to-use 960 mg (Ari 2MRTU 960), which is the newest LAI formulation approved containing 960 mg of aripiprazole monohydrate that is administered by gluteal injection once every 2 months. Both formulations are approved in the US, Europe, and Canada for the treatment of schizophrenia in adults.[32–36] In the US and Canada, the aripiprazole monohydrate LAIs are also indicated for maintenance monotherapy treatment of bipolar I disorder in adults.[32–36] Among available LAI antipsychotics, aripiprazole is differentiated by its dopamine partial agonism.[37] Aripiprazole exhibits a high affinity for both dopamine and serotonin receptors, acting as a partial D_2, D_3, and $5\text{-}HT_{1A}$ agonist, as well as a $5\text{-}HT_{2A}$ antagonist.[38]

In a recent consensus panel meeting, a group of psychiatric experts was convened to evaluate the clinical utility of LAI antipsychotics, with a focus on aripiprazole monohydrate, as a viable treatment option for patients diagnosed with schizophrenia that can be administered early in the course of the disease. The panel reviewed the pharmacological advantages associated with partial dopamine agonists, the potential benefits of initiating LAI treatment early in the disease course, and the common misperceptions that contribute to underutilization of these formulations. Additional discussions addressed the role of non-prescribing healthcare professionals, the importance of patient-centered care, systemic barriers to access, and the need to prioritize holistic and functional recovery. This Academic Highlights article provides a summary of the panel's discussion and presents their key conclusions.

METHODS

In October 2024, a panel of experts in psychopharmacology, the clinical treatment of schizophrenia, and antipsychotic prescribing convened to develop clinical recommendations on the use of aripiprazole monohydrate LAIs for adults diagnosed with schizophrenia. The panel was chaired by Joseph F. Goldberg, MD, and included panelists Eric D. Achtyes, MD, Christoph U. Correll, MD, Martha Sajatovic, MD, and Stephen R. Saklad, PharmD. The consensus panel meeting was held virtually with facilitated discussion. The panel analyzed publicly available clinical trial data and shared their perspectives to reach a consensus on utilization of aripiprazole monohydrate LAIs in treatment considerations for schizophrenia. This article presents the consensus findings from the panel discussion.

ARIPIPRAZOLE MONOHYDRATE LONG-ACTING INJECTABLE: MYTHS AND MISPERCEPTIONS

Antipsychotics remain the cornerstone of schizophrenia treatment, with first-generation antipsychotics (FGAs), such as haloperidol and chlorpromazine, historically serving as the primary therapeutic agents.[39] These antipsychotics exert their effects through potent dopamine D_2 receptor antagonism, effectively reducing positive symptoms, such as hallucinations and delusions.[40] However, FGAs are associated with a high incidence of extrapyramidal symptoms (EPS), including drug-induced parkinsonism (DIP), dystonia, akathisia, and tardive dyskinesia, as well as limited efficacy in treating negative and cognitive symptoms.[41] These limitations led to the development of second-generation antipsychotics (SGAs), which retain D_2 receptor antagonism but incorporate additional serotonergic activity, particularly $5\text{-}HT_{2A}$ antagonism. This broader pharmacologic profile is believed to reduce EPS and provide greater efficacy across multiple symptom domains.[41,42] Despite these therapeutic advances, SGAs introduced new safety concerns, most notably increased risks of cardiometabolic side effects such as weight gain, insulin resistance, and dyslipidemia, which can negatively affect long-term health and treatment adherence.[14,41,43–45] Consequently, the use of SGAs requires individualized risk-benefit assessment and ongoing monitoring.[46,47]

To further address the persistent challenge of nonadherence, long-acting injectable (LAI) formulations of antipsychotics were introduced over 50 years ago to extend dosing intervals and reduce the need for daily oral medication. Although FGA LAIs offered the potential for improved adherence and clinical outcomes, their initial reception was mixed. Both clinicians and patients expressed concerns about increased adverse effects, questionable efficacy, and a perception that LAIs compromised patient autonomy by enforcing treatment.[41,42,48] Moreover, FGA LAIs were typically formulated in oil-based vehicles, which were associated with a higher incidence of injection site adverse events. The development of SGA LAIs aimed to overcome many of these challenges by offering improved tolerability, reduced EPS, and greater efficacy. Importantly, SGA

Table 1.
Common Myths vs Evidence About Aripiprazole LAI[a]

Misperception	Evidence
Partial D2 receptor agonists are less effective than D2 receptor antagonists in controlling positive symptoms of schizophrenia.	Partial dopamine agonist LAIs have proven efficacy for treating schizophrenia in multiple clinical trials. Studies have shown that partial dopamine agonist LAIs exhibit similar efficacy as dopamine antagonists in treating positive symptoms of schizophrenia and may even have greater efficacy in reducing negative symptoms and improving functional outcomes.[75,80]
LAIs have intolerable adverse effects.	Adverse effect frequency and adverse event–related discontinuations are generally the same or lower in patients taking LAIs, once tolerance to the oral medication has been established.[48]
LAIs are not helpful for addressing medication adherence.	Adherence rates are higher and discontinuation rates are lower in patients taking LAIs compared to patients taking oral antipsychotics.[13] Additionally, nonadherent patients are readily identified when prescribed an LAI.
LAI initiation may be difficult for patients.	In most cases, a short trial with an oral antipsychotic should be utilized to assess efficacy and tolerability, after which the patient can be transitioned directly to the LAI formulation of the same medication.[51,132]
Early recommendation and initiation of LAI treatment hinder patient autonomy and may impact the patient-provider relationship.	Patient surveys have found that patients feel better about their relationship with their provider when taking an LAI because of increased interactions with their healthcare team (due to injection administration visits and regular checkups).[62,63] Early treatment success with LAIs correlates to patient acceptance of treatment and improved adherence.[145] LAI injection clinics can provide an opportunity/setting to promote adherence and additional psychosocial support.[146]
LAIs should only be used as a last resort when patients have proven nonadherence to oral antipsychotics.	Early LAI treatment is associated with a longer time to relapse and reduced hospitalizations compared to long-term oral maintenance therapy and late initiation of LAI therapy,[21] especially in high-quality studies and those emulating clinical LAI use.[26]

[a]Adapted from Kane et al.[42]

LAIs use aqueous or polymer-based vehicles,[49] which are associated with fewer injection site reactions, further enhancing their acceptability and potential to support sustained treatment adherence.[14,42,50]

There are currently 10 LAI antipsychotics approved in the US for the treatment of schizophrenia, offering clinicians multiple options for tailoring therapy to patient needs.[51] Notably, aripiprazole is the only partial dopamine agonist available in LAI formulation, combining dopaminergic and serotonergic modulation with the adherence benefits of extended-release delivery.[52,53]

Despite their advantages over oral therapies, LAI antipsychotics are underutilized; fewer than 20% of patients diagnosed with schizophrenia have been prescribed LAIs worldwide.[54,55] Patient and clinician perceptions, including a lack of familiarity, perceived additional workload, and stigma, contribute to the relegation of LAIs as nonpreferred treatment options.[56] One survey, which included mental health nurses and physicians, found that three-fourths of physicians did not utilize LAIs as an early treatment option, even if they were aware of the clinical benefits of LAI antipsychotics. The most commonly cited reason by physicians for delaying LAI use was concerns about patient perception of LAIs.[42,57] Common patient concerns about LAI antipsychotic use include having to go to the clinic frequently for injections, lack of autonomy in medication administration, and stigma related to the perception that injectable antipsychotics are for patients with severe mental disorders.[42,56] Beyond barriers to LAI use, misunderstandings regarding partial agonist pharmacology and aripiprazole's mechanism of action may also contribute to underuse of the LAI formulations of aripiprazole (**Table 1**). Expanding clinician understanding of the aripiprazole monohydrate LAI mechanism of action, efficacy, and safety profile will allow prescribers to better facilitate conversations with patients and their caregivers about its early use as an effective and well-tolerated treatment for schizophrenia.

OVERCOMING BARRIERS TO LAI TREATMENT

Because LAI antipsychotic medications require administration by a healthcare professional, access to care may be limited in some areas. Transportation to a healthcare site may be a barrier due to a lack of personal or public transportation or a lack of a facility near the patient's home. Leveraging non-physician healthcare providers, such as nurses and pharmacists, to administer these injections creates more opportunities to access care and helps reduce or eliminate this barrier. Currently, almost all states in the US allow pharmacists to administer LAI antipsychotic medications, expanding LAI treatment access and convenience.[58] As a result, studies have shown that when pharmacists administer LAI antipsychotic medications it positively improves medication adherence and patient satisfaction.[59]

Stigma is an additional barrier that can play a role in LAI antipsychotic underutilization. A survey of 350 psychiatrists found that less than 36% of the providers' patients had been offered an LAI antipsychotic due to physician concerns about efficacy, adverse events, and medication cost.[19] Additional surveys have found that patients may be hesitant about loss of autonomy

Table 2.
Aripiprazole Receptor Binding Affinity[a]

Receptor and activity	Affinity	K_i (nmol/L)
D_2 (partial agonist)	Very high	0.34
D_3 (partial agonist)	Very high	0.8
5-HT_{1A} (partial agonist)	High	1.7
5-HT_{2A} (antagonist)	Moderate	3.4
5-HT_{2C} (partial agonist)	Limited	15
5-HT_7 (partial agonist)	High	39
α_{1A} (antagonist)	Moderate	57
α_{2C} (antagonist)	Moderate	38
α_{2A} (antagonist)	Moderate	74
H_1 (antagonist)	Moderate	61

[a]Adapted from Stelmach et al.[75]
Abbreviation: K_i=inhibitory constant (lower values representing higher affinity).

with LAI antipsychotic use as well as injection site pain, both of which are concerns that can be improved through a patient-centered discussion with a healthcare provider.[60] Of note, the recently published INTEGRATE international guidelines for the algorithmic treatment of schizophrenia[61] state that "the initial choice of antipsychotic should be made collaboratively with the patient and based on the side effect and efficacy profile. Dose scheduling, convenience, and the availability of a long-acting formulation of medication might also be factors to consider." Consistent with these guidelines, data indicated that when patients are fully informed about LAI therapy, it often becomes the patient's preference. A survey of French patients who had taken multiple dosage forms of antipsychotics found that LAIs were the patients' preferred dosage form, with interviewees reporting that they felt LAIs were more effective than other forms of medication and that they felt more supported in their illness through increased contact with their comprehensive care team. In the same survey, 49% of patients reported that LAI therapy could positively impact their future plans, particularly in finding a stable job.[62] Additional studies have shown that when presented with information about multiple hypothetical antipsychotic medication formulations, both patients and providers generally demonstrated a preference for LAIs over oral treatment.[63] The use of LAI drug formulation is not unique to psychiatry; similar formulations are employed in other areas of medicine, such as HIV treatment, low-density lipoprotein cholesterol treatment, diabetes management, and hormonal contraception, and have been demonstrated to improve adherence and clinical outcomes. These examples may help normalize the use of LAIs in mental health by framing them as part of a broader movement toward patient-centered, long-acting pharmacotherapy. Because the majority of patients in study samples will try LAI antipsychotic therapy when the option is fully explained and offered early in disease progression, there is a need to address stigma through provider and patient education and shared decision-making.[64,65]

Panel Consensus Statement #1

Reducing Stigma and Barriers: "Addressing stigma associated with LAIs is crucial. Leveraging the entire healthcare team surrounding the patient is likewise imperative for optimal results. The panel advocates for reframing LAIs as a viable first-line option rather than a punitive, last-resort measure, thus encouraging patient and clinician consideration and choice."

ARIPIPRAZOLE MONOHYDRATE: MECHANISM AND MEDICATION PROFILE

The multiple symptom domains of schizophrenia present a significant challenge in adequately treating schizophrenia. First-generation antipsychotics primarily target positive symptoms, while negative and cognitive symptoms have remained elusive to control and may even worsen with FGAs. Even low levels of negative symptoms are correlated with difficulties in aspects of everyday functioning and are closely linked with functional decline in patients living with schizophrenia.[66,67] Dopamine receptor partial agonists, such as aripiprazole, have proven to be effective in controlling multiple symptom domains in schizophrenia, including both positive and negative symptoms,[68–70] offering patients and providers the potential for better symptom control with a single medication.[71]

Aripiprazole has a multifaceted pharmacological mechanism, most notably via partial agonist activity at dopaminergic D_2 and D_3 and serotonergic 5-HT_{1A} receptors and antagonist activity at serotonergic 5-HT_{2A} receptors. Aripiprazole exhibits a higher affinity for the D_2 and D_3 receptors than for the serotonin receptors, so its proposed mechanism of action is predominantly a dopamine-system stabilizer (**Table 2**).[52,72] Aripiprazole's partial agonist activity allows it to bind to D_2 and D_3 receptors with a higher affinity than endogenous dopamine, therefore blocking dopamine from activating the receptors and modulating dopamine neurotransmission in the mesolimbic, striatal, and mesocortical pathways. It is hypothesized that positive symptoms of schizophrenia are related to hyperdopaminergic transmission in the striatal brain regions,[73,74] while cognitive and negative symptoms stem from impairment of dopamine transmission in the mesocortical and mesolimbic pathway, so modulating dopamine transmission in these areas may help mitigate positive, as well as negative, and cognitive symptoms of schizophrenia.[75,45,71]

Aripiprazole's special pharmacological profile allows it to be an effective treatment for schizophrenia with a lower risk of concerning adverse effects when compared with many other antipsychotics. First-generation D_2 dopamine receptor antagonism results in a dose-dependent blockade of most to all dopamine mediated

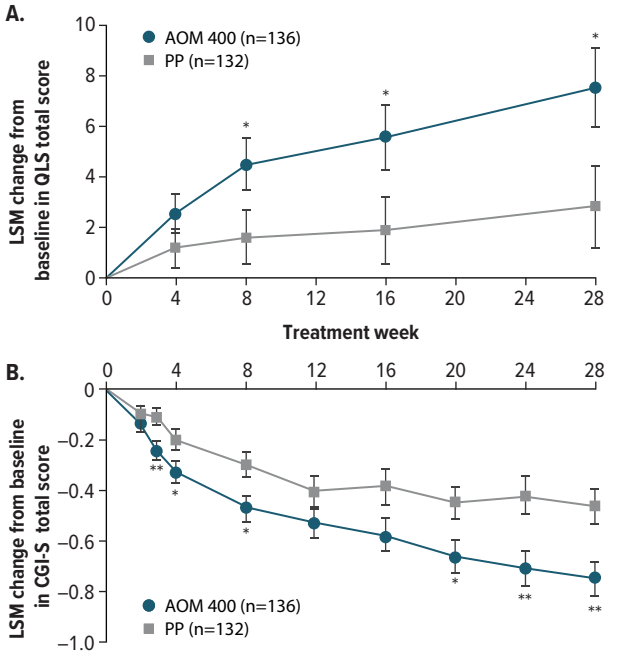
neurotransmission, which is associated with significant adverse effects, such as extrapyramidal symptoms (EPS), including akathisia and tardive dyskinesia.[41,76,77] Strong dopamine D_2 receptor antagonism may also cause dose-related elevations in prolactin levels, which are associated with infertility, osteoporosis, decreased libido, dysmenorrhea, galactorrhea, gynecomastia, and erectile dysfunction.[68,78] Aripiprazole's partial agonism at dopamine receptors regulates dopamine receptor-mediated neurotransmission, resulting in a lower risk of EPS and hyperprolactinemia than with most other antipsychotics. Additionally, due to aripiprazole's low affinity for histamine and muscarinic receptors, aripiprazole carries a lower risk of cardiometabolic adverse effects than most other second-generation antipsychotics.[43–45,68,78]

EFFICACY OF ARIPIPRAZOLE MONOHYDRATE LAIS FOR SCHIZOPHRENIA

Aripiprazole monohydrate LAIs have been rigorously studied for the treatment of schizophrenia. Efficacy was initially established for AOM 400 in a double-blind, placebo-controlled, 52-week trial, which evaluated the safety and efficacy of AOM 400 compared to placebo in patients with schizophrenia. The study found that treatment with AOM 400 significantly delayed the time to relapse in both the interim and final analyses ($P < .0001$) and demonstrated overall lower relapse rates than placebo (10.0% compared to 36.9%, respectively).[79] Due to the demonstrated efficacy of AOM 400 at interim analysis, the trial was terminated early, and its results supported the FDA approval of AOM 400 as a treatment for schizophrenia.[79] A subsequent 38-week double-blind, active controlled, study compared AOM 400 to oral aripiprazole (10 – 30 mg) over 38 weeks in patients with schizophrenia. AOM 400 was demonstrated to be non-inferior to oral aripiprazole in the Kaplan-Meier estimated impending relapse rates at week 26 (7.12% for AOM 400 and 7.76% for oral aripiprazole), the study's predefined primary efficacy endpoint. Adverse events were similar between the two groups, and no new safety findings were reported.[53] AOM 400 was also found to be non-inferior to oral aripiprazole in the secondary efficacy measure, time to all-cause discontinuation.[53] The QUAlity of Life with AbiliFY Maintena (QUALIFY) study compared AOM 400 to paliperidone palmitate once-monthly (PP1M) in patients diagnosed with schizophrenia, utilizing improvement in the Heinrichs-Carpenter Quality of Life Scale (QLS) as a primary endpoint. Participants in a pre-defined subgroup ≤35 years old taking AOM 400 revealed significant improvement in QLS total score compared to those taking PP1M, with improvement becoming significant at 8 weeks of treatment and continuing through follow-up at week 28 (**Figure 1A**). Additionally, Clinical Global Impression-Severity (CGI-S) scores were assessed as a secondary endpoint, with the AOM 400 treatment group demonstrating significantly reduced scores compared to the PP1M treatment group, with the difference becoming significant at week 3 with continued divergence from PP1M through to the end of the study (**Figure 1B**).[80]

Figure 1.

Change From Baseline in QLS and CGI-S Score in the QUALIFY Study[a]



[a]Reprinted from Naber et al.[80] Effects of AOM 400 and PP treatment in subjects ≤35 years on QLS total scores (A) and CGI-S scores (B). Least squares mean (LSM) changes from baseline were analyzed using a mixed model for repeated measures. Error bars indicate the standard error of the LSM.
*$P < .05$, **$P < .01$ indicate significant differences between treatments (AOM 400 vs PP).
Abbreviations: AOM = aripiprazole once-monthly 400 mg, CGI-S = Clinical Global Impression-Severity scale, PP = paliperidone palmitate once-monthly, QLS = Heinrichs–Carpenter Quality-of-Life Scale.

In a naturalistic, open-label, mirror-image study conducted in North America, patients diagnosed with schizophrenia who were taking oral antipsychotics were switched to AOM 400 and followed prospectively for 6 months. Hospitalization data from the 6 months prior to screening were collected retrospectively and compared with hospitalization rates during the prospective period. The primary analysis compared psychiatric hospitalization rates in the 3 months before switching to the 3 months after. Hospitalization was significantly reduced, with only 2.7% of patients hospitalized during the 3 months on AOM 400 compared to 27.1% in the 3 months prior while on oral antipsychotics ($P < .0001$). A secondary analysis comparing the full 6-month periods before and after the switch also showed a substantial reduction in hospitalizations (8.8% vs. 38.1%, $P < .0001$).[81]

The most recently developed aripiprazole monohydrate LAI, Ari 2MRTU 960, was approved based on a 32-week, open-label, bridging noninferiority study, which primarily evaluated its pharmacokinetics, safety, and tolerability and secondarily assessed its additional pharmacokinetic parameters and clinical efficacy compared with AOM 400 in clinically stable patients diagnosed with schizophrenia or bipolar I disorder. Ari 2MRTU 960 was designed to ensure that plasma concentrations remained similar and comparable to AOM 400 plasma concentrations after multiple doses.[82] It was shown that following 4 administrations, Ari 2MRTU 960 delivered mean aripiprazole plasma concentrations that remained above the minimum therapeutic concentration of aripiprazole over the full 2-month dosing interval.[36,83] In a secondary analysis that included only patients diagnosed with schizophrenia, the Positive and Negative Syndrome Scale (PANSS) score, CGI-S score, and Subjective Well-being under Neuroleptic Treatment–Short Form (SWN-S) score were monitored and found to be similar between the two treatment groups, with subjects remaining clinically stable throughout the course of the study (**Figure 2**).[84]

SAFETY OF ARIPIPRAZOLE MONOHYDRATE LAIS

While antipsychotic medication efficacy is vital to treatment success, adverse events from antipsychotic medication are also significant factors in patient quality of life and medication adherence.[85] One study found that most adverse events associated with antipsychotic medications, including EPS, cognitive adverse events, prolactin or endocrine-related effects, and cardiometabolic effects, significantly reduced the likelihood of adherence.[86] Therefore, prescribing a medication with a favorable tolerability profile is critical to allow patients the best chance to stay on antipsychotic treatment long-term. Aripiprazole monohydrate LAIs provide an effective treatment option with relatively minimal potential adverse events.

The safety profile of aripiprazole monohydrate LAIs has been established in numerous controlled trials against placebo, oral aripiprazole, and other LAI antipsychotics. In a large placebo-controlled trial, AOM demonstrated low levels of EPS symptoms, metabolic disturbances, and weight gain.[79] When compared to oral aripiprazole, patients taking AOM experienced similar rates of metabolic changes, weight gain, and EPS symptoms.[53] In the previously described QUALIFY study, patients receiving AOM were less likely to report increased weight, psychotic disorder, and insomnia than patients assigned to take PP1M, with a low incidence of EPS symptoms observed in both groups. Further, clinically significant weight gain, defined as an increase ≥7% from baseline were similar, but numerically lower for AOM 400 than PP1M, reported in 11.1% and 14.6% of trial participants, respectively.[80] Further, in an open-label, multiple-dose, randomized, parallel-arm, multicenter trial comparing AOM 400 with Ari 2MRTU 960 in patients diagnosed with schizophrenia, the incidence of treatment-related and serious adverse events was similar between AOM 400 and Ari 2MRTU 960, with increased weight, mild and transient injection site pain, akathisia, and insomnia as the most frequently reported adverse events for both dosage forms. All adverse events were consistent with the previously reported safety profile, and there were no discontinuations due to adverse events.[84] The majority of adverse events in either treatment group were mild to moderate in nature and occurred following the first injection, with a lower incidence of adverse events reported with subsequent injections of either AOM 400 or Ari 2MRTU 960.

CLINICAL APPLICATION OF ARIPIPRAZOLE MONOHYDRATE LAIS FOR SCHIZOPHRENIA TREATMENT

A vital component of schizophrenia treatment is medication adherence, as it is critical for symptom stability and relapse prevention. Rates of nonadherence in serious mental illnesses, including schizophrenia, can be as high as 40%-50%.[87,88] The consequences of nonadherence are severe; medication nonadherence may result in hospitalization following treatment gaps as short as 1–10 days due to breakthrough symptoms, which can lead to relapse, requiring acute medical care.[89] Medication nonadherence has also been associated with emergency services usage, poor social and occupational functioning, violence, arrests, increased suicide risk, lower quality of life, and treatment resistance.[29,90] Additionally, gaps in treatment due to medication nonadherence have been reported to be associated with longer durations of relapse, which are associated with a significant decrease in total brain, frontal lobe, and white matter volumes.[91]

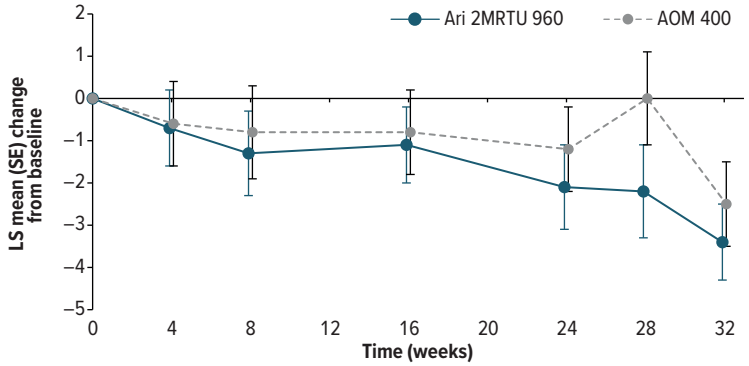
A systematic review by Velligan and colleagues identified 11 categories for medication nonadherence in serious mental illnesses. These included poor disease insight, negative attitude toward taking prescribed medications, distressing medication adverse effects, poor therapeutic alliance, stigma, substance abuse, cognitive impairment, depression, lack of family/social support, limited access to mental health care, and poor social functioning. Intentional nonadherence due to reduced disease insight was a significant factor in medication nonadherence in 55.6% of the studies analyzed.[29] A separate meta-analysis and systematic review confirmed these findings, reporting that patient lack of insight into their disease was a common factor associated with medication nonadherence in multiple studies.[87]

Early intervention with LAIs can improve medication adherence and patient insight, thereby preventing relapses and possibly reducing neuroprogression associated with multiple episodes of psychosis.[92–95] A study evaluating

Figure 2.

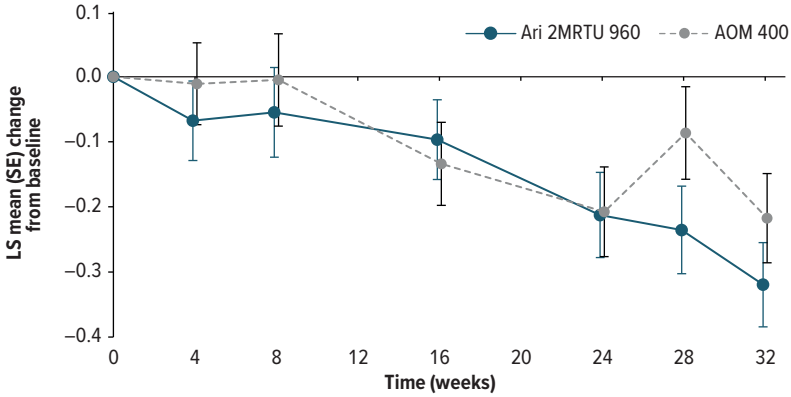
Mean Change From Baseline Through Week 32 in Key Efficacy Measures[a]

A. LS mean (SE) change from baseline through to week 32 in PANSS total score



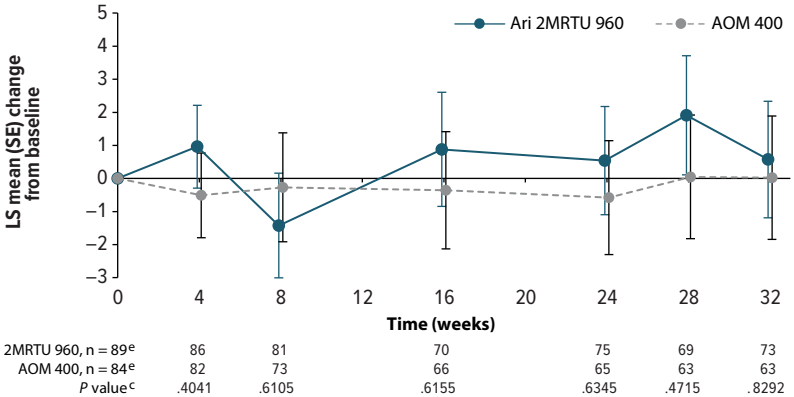
Ari 2MRTU 960, n = 89[b]	88	82	79	76	74	73
AOM 400, n = 85[b]	85	77	72	67	64	64
P value[c]	.9171	.7195	.8343	.5397	.1496	.5154

B. LS mean (SE) change from baseline through to week 32 in CGI-S score



Ari 2MRTU 960, n = 89[d]	88	82	79	76	74	73
AOM 400, n = 85[d]	85	77	72	67	64	64
P value[c]	.5115	.6119	.6699	.9591	.1263	.2767

C. LS mean (SE) change from baseline through to week 32 in SWN-S score



Ari 2MRTU 960, n = 89[e]	86	81	70	75	69	73
AOM 400, n = 84[e]	82	73	66	65	63	63
P value[c]	.4041	.6105	.6155	.6345	.4715	.8292

[a]Reprinted with permission from Citrome et al.[84] Data shown are from the efficacy analysis sample.
[b]Mean (SD) PANSS total score at baseline was 62.2 (13.7) in the Ari 2MRTU 960 group and 61.6 (13.3) in the AOM 400 group.
[c]P values for between-group comparisons were derived from an MMRM analysis with fixed effects of treatment, pharmacokinetic sampling schedule for determining the concentration of aripiprazole in patients' plasma, week, treatment-by-week interaction, and baseline-score-by-week interaction as covariates.
[d]Mean (SD) CGI-S score at baseline was 3.3 (0.9) in the Ari 2MRTU 960 group and 3.1 (0.9) in the AOM 400 group.
[e]Mean (SD) SWN-S total score at baseline was 94.1 (16.6) in the Ari 2MRTU 960 group and 95.9 (15.4) in the AOM 400 group.
Abbreviations: AOM 400 = aripiprazole once-monthly 400 mg, Ari 2MRTU 960 = aripiprazole 2-month ready-to-use 960 mg, CGI-S = Clinical Global Impression-Severity scale, LS = least squares, MMRM = mixed model for repeated measures, PANSS = Positive and Negative Syndrome Scale, SD = standard deviation, SE = standard error, SWN-S = Subjective Well-being under Neuroleptic Treatment – Short Form.

patients taking LAI risperidone for 50 weeks found that 26.4% of patients experienced a significant improvement in PANSS insight scores from "impaired" at baseline to "normal" or "near normal" by the end of the trial period. Patients who experienced improvement in insight scores also demonstrated improvement in negative symptoms, anxiety/depression, and overall quality of life.[16] Patients experiencing their first episode of psychosis are most likely to stop medications,[15] generally due to a lack of disease insight, which again highlights the utility of early intervention with an effective treatment regimen. The increased adherence associated with LAIs is likely the driver of improvements in patient insight and can be a useful strategy to keep patients engaged with their prescribing practitioner and healthcare team.[15]

In a retrospective study evaluating strategies for initiating LAI antipsychotics, patients who received an LAI proactively, before demonstrating nonadherence to oral medications or requiring emergency department (ED) visits or hospitalization due to relapse, experienced more favorable outcomes.[96] These included reduced rates of hospital admissions, shorter lengths of stay, and fewer ED visits. In contrast, patients who were initiated on an LAI only after signs of nonadherence, or following an ED visit or hospitalization, demonstrated poorer outcomes across these same measures. The poorest outcomes were observed in patients who received an LAI only after experiencing multiple episodes of psychosis. These findings support the clinical value of early intervention with LAI treatment as a preferred strategy in the management of schizophrenia.[96] Further, functional recovery, by early use of LAIs, is an important treatment goal in first episode and early phase patients.[97] A 2019 meta-analysis found that SGA LAIs were significantly better at improving psychosocial function, in short or long-term trials, compared to placebo or oral antipsychotics.[98] Early intervention has also been shown to increase employment and independent living and decrease disability and hospital admissions when compared with patients taking oral antipsychotic therapy.[11,99] Additionally, in a nationwide Swedish database study, the risk of work disability was lower during use versus nonuse of any antipsychotic, but the lowest risk was observed for LAI antipsychotics, followed by oral aripiprazole and oral olanzapine. Adjusted hazard ratios were similar for early illness periods of <2 years, 2–5 years, and later illness periods of >5 years since diagnosis.[100] Due to these benefits and the real-world challenges related to oral antipsychotic treatment, especially in terms of adherence, LAI antipsychotic medications may be a more prudent choice than oral therapies. This benefit of LAIs is greatest when offered proactively prior to evidence of nonadherence and the downstream complications that occur with relapse.[96,101]

In addition to improved patient outcomes, there is a significant economic impact associated with LAI use, including potential cost savings from reduced hospitalizations and lower healthcare utilization. LAI treatment can provide functional stability and reduce the need for frequent physician visits while facilitating more comprehensive care. In particular, LAI use in conjunction with psychosocial support may translate to cost savings by preventing severe relapses and preserving patient independence and productivity.[20,102]

Based on this evidence, the expert panel recommended a tiered approach to treating schizophrenia, favoring early use of LAIs. The panel recommended psychosocial treatments without pharmacotherapy in the prodromal phase of the disorder due to nonspecific symptoms and low conversion rates to psychosis.[103,104] When considering patients for whom pharmacotherapy is indicated, the panel recommended LAIs to be considered after the first episode of psychosis in conjunction with psychosocial treatments over starting an LAI after multiple relapses have occurred due to improved medication adherence, evidence of increased patient insight, reduced relapse recurrence, improved functional outcomes, and reduced mortality risk in patients treated with LAIs.[21,25,96,105–107]

Current practice guidelines from the American Psychiatric Association (APA)[108] and other international organizations[109] on the treatment of patients diagnosed with schizophrenia recommend that medication selection should be guided by shared decision-making and involve a discussion about targeted symptoms, potential medication adverse effects, and patient-specific risk factors.[110,111] Discussions should also include caregivers, such as family members, partners, or other significant individuals, when possible.[112,113] A recent qualitative interview study showed that treatment selection of a specific LAI should acknowledge individual patient and caregiver preferences regarding formulation and frequency, to ensure that targeted disease management goals are met.[114] The same study showed that patients, caregivers, and prescribers expressed overall positive views and general acceptance of an LAI administered once every 2 months for the treatment of schizophrenia given the perceived advantages of greater freedom and less treatment burden.[114] The 2020 APA guideline update highlights that LAI antipsychotics should be utilized when preferred by the patient and when clinically appropriate based on available evidence.[109, 115] One way to apply the LAI treatment paradigm in usual care settings is the GAIN approach, which consists of four steps (Goal setting, Action planning, Initiating treatment, and Nurturing motivation) to provide a structured conversation regarding LAI antipsychotic treatments, which can be utilized to gauge interest in eligible candidates for LAI antipsychotic therapy.[116] These recommendations underscore the importance of discussing LAI antipsychotics with patients and utilization of LAIs early in the disease progression.[117,118]

Despite the incorporation of LAIs into these guidelines, the expert panel highlighted the need for clearer, evidence-based guidelines that prioritize LAIs in the schizophrenia treatment algorithm. The panel highlighted potential gaps in evidence related to the sequencing of antipsychotic

therapies, particularly for patients who fail initial antipsychotic treatment. The expert panel discussed a recent meta-analysis that reviewed 11 randomized controlled trials assessing LAI efficacy for preventing hospitalization and relapse in patients with first-episode or early-phase schizophrenia. While the meta-analysis concluded that LAIs were not more effective than oral antipsychotics in preventing relapse or hospitalization, the expert panel noted that in 9 subgroup analyses that had a more pragmatic design or use of LAIs or had high-quality ratings, LAI treatment showed superior efficacy compared to oral antipsychotic therapy in patients with first-episode or early-phase schizophrenia.[26] As these designs are more applicable in the real-world setting, the expert panel concluded that the breakdown of these sub-analyses offers credence for LAI efficacy over oral medications even early in the illness phase in clinical practice where LAIs are still used too sparsely. The panel also reviewed the open-label European Long-Acting Antipsychotics in Schizophrenia Trial (EULAST), evaluating the effects of paliperidone LAI, aripiprazole monohydrate LAI, oral paliperidone, and oral aripiprazole on medication adherence in patients with early-phase schizophrenia.[119] Although the study found no difference in medication adherence between LAI and oral antipsychotics, the expert panel noted that the study results were affected by adherence bias because patients are more likely to take their oral medication when adherence is being actively monitored in a controlled clinical trial.[120] Even more importantly, the study randomized patients from the start to the oral or LAI formulation of aripiprazole or paliperidone, instead of randomizing patients who had been on the oral medication first to either stay on the oral formulation or continue on the LAI version. Not employing the usual sequence of treatment initiation for LAIs biased the results toward all-cause treatment failure, the primary outcome of the study.[120] Considering the real-world adherence advantage of LAIs over oral antipsychotics, the panel recommended early use of LAIs for schizophrenia.

Panel Consensus Statement #2

Importance of Early LAI Intervention: "The panel recommends that initiating LAI treatment early, especially directly after the first episode of schizophrenia, if possible, but at least in the first few years of the illness, can prevent relapses, enhance adherence, and improve symptomatic as well as functional outcomes. Functional recovery, by early use of LAIs, is an important treatment goal in patients with first-episode and early phase schizophrenia.[97] Early LAI use is recommended before considering clozapine, in part to assure the absence of pseudo–treatment resistance in the setting of poor adherence to oral medications,[121] which should be reserved for patients with true treatment resistance.[61,122,123]"

CANDIDATES FOR TREATMENT WITH ARIPIPRAZOLE MONOHYDRATE LAIS

It is important to consider all patient characteristics when evaluating if AOM 400 or Ari 2MRTU 960 is an appropriate treatment option for an individual diagnosed with schizophrenia. In many practices, LAI prescriptions are utilized for patients who are identified as nonadherent to medications. However, studies have shown that physicians often overestimate their patients' medication adherence rates.[124,125] The ideal patient profile for LAI therapy is someone with recent-onset schizophrenia and risk factors for nonadherence, including history of nonadherence to other medications, more severe psychotic symptoms, comorbid substance use, cognitive impairment, poor disease insight, and ambivalence or a negative attitude to diagnosis and medications. Patients on multiple medications are also an ideal target population, as LAI antipsychotic treatment has been shown to reduce overall chlorpromazine equivalent dose, which is a standardized method for comparing antipsychotics. LAI use has also been shown to reduce the overall number of mental health–related medications patients are prescribed.[126–129] Other specific patient populations who may benefit from an LAI include patients with a history of multiple hospitalizations or relapses, violent behavior, suicide attempts, or substance abuse; patients with cognitive impairment; or younger patients between the ages of 18 and 35.[20,130]

Aripiprazole monohydrate LAIs can be an optimal treatment for many patients diagnosed with schizophrenia due to aripiprazole's mechanism of action, efficacy, and tolerable adverse effect profile. As a dopamine partial agonist, aripiprazole monohydrate is the only LAI option for patients that does not come with a high risk of EPS, hyperprolactinemia, or cardiometabolic adverse effects.[78] It has evidence of improved efficacy compared to other LAI medications such as PP1M.[80] Additionally, Ari 2MRTU 960 may be administered using a 2-month dosing interval, allowing patients to go to a clinic for injections less frequently, only 6 times a year compared with 12 injections if prescribed for monthly administration. This addresses two common patient concerns and barriers to LAI use: stigma and frequent visits to a healthcare facility for LAI administration.[56]

Shared decision-making should be utilized for patients who are clinically stable on oral antipsychotics but wish to switch to an LAI formulation. Clinicians and patients should discuss disease stability versus functional recovery and the potential risks and benefits of transitioning to an LAI. Some patients may be clinically stable but have tolerability issues or have residual problematic symptoms that can be expected to improve. These residual issues may prevent achieving components of functional recovery that facilitate autonomy, such as engaging in social relationships or independently completing activities of daily living. Moreover, nonadherence is likely to increase

Table 3.
Dosing Strategies for Aripiprazole Monohydrate LAI[32-36,42,51]

Generic medication name/brand name	Initial dose	Maintenance dose and frequency	Oral supplementation
Aripiprazole/Abilify Maintena Traditional start strategy	400 mg with standard oral supplementation	400 mg monthly May down titrate to 300 mg monthly if tolerability issues arise	Continue oral aripiprazole or current oral antipsychotic for 14 days after initial injection†
Aripiprazole/Abilify Maintena Two-injection start/1-day initiation regimen	Two 400 mg doses, at different injection sites, deltoid or gluteal, with one 20 mg dose of oral aripiprazole[136,a]	May down titrate to 300 mg monthly if tolerability issues arise	No additional oral aripiprazole or other oral antipsychotic supplementation required
Aripiprazole/Abilify Asimtufii	960 mg	960 mg once every 2 months	Continue oral aripiprazole or current oral antipsychotic for 14 days after initial injection†
Aripiprazole/Abilify Asimtufii Two-injection start/1-day initiation regimen	One 960 mg in the gluteal muscle and one 400 mg doses, at different injection sites, deltoid or gluteal, with one 20 mg dose of oral aripiprazole[136,a]	May down titrate to 720 mg once every 2 months if tolerability issues arise	No additional oral aripiprazole or other antipsychotic supplementation required

[a]European HCPs reported that the AOM 400 two injection start strategy was easy to administer, well tolerated, and was associated improved treatment outcomes. Barriers to its use included patient reluctance and perceived safety concerns.[147]
†Transition guidance varies by region. In Europe, Abilify Maintena[34] prescribing information specifies to transition from oral aripiprazole. In the United States and Canada, either aripiprazole LAI may be initiated following oral aripiprazole or current oral antipsychotic.[32,33,35,36]

over time within even stable patients, and a meta-analysis found that while stopping antipsychotics posed the highest risk for relapse, followed by lowering the previously effective antipsychotic dose, switching and continuing antipsychotics had similarly protective value in the maintenance treatment of schizophrenia.[131] The expert panel recommended that LAIs may be considered as part of a shared-decision making process for patients who are clinically stable on oral antipsychotics, if potential benefits outweigh potential risks. The panel advised that if changes are made, they should be made slowly and carefully to ensure clinical stability is not interrupted.[132–134]

STARTING ARIPIPRAZOLE MONOHYDRATE LAIS

There are multiple strategies for initiating or switching to either of the aripiprazole monohydrate LAI formulations, which have been well characterized in the literature.[51,135] The choice of initiation strategy depends on the clinical context and the needs of both the patient and the prescribing clinician. According to the prescribing information in the United States,[32,33] Europe,[34] and Canada,[35,36] in patients naïve to aripiprazole, tolerability should be first established with oral aripiprazole and may take up to 14 days to fully assess prior to initiating either LAI formulation. Once tolerability has been assessed, two recommended start strategies are available, as summarized in **Table 3**. For AOM 400, the standard initiation approach includes a 14-day oral overlap to maintain therapeutic plasma concentrations while the LAI reaches steady state. In comparison, Ari 2MRTU 960 allows for transition from AOM 400 or from oral aripiprazole after establishing tolerability through various oral dosing regimens.

An alternative to the oral overlap is the two-injection start strategy, which is available for either aripiprazole monohydrate LAI formulation(s). For AOM 400, two injections of AOM 400 mg are administered at separate anatomical sites, deltoid or gluteal, along with a single 20 mg dose of oral aripiprazole.[136] For Ari 2MRTU 960, one injection of Ari 2MRTU 960 in the gluteal muscle and one injection of AOM 400 are administered at separate anatomical sites, deltoid or gluteal, along with a single oral dose of aripiprazole 20 mg. Each of these approaches achieves therapeutic plasma concentrations more rapidly and may be particularly useful in settings where immediate and sustained drug exposure is desired, such as acute care or when adherence to oral supplementation is uncertain. Regardless of the approach, both formulations aim to maintain sustained therapeutic drug levels while offering flexibility in treatment planning and the potential to improve adherence through less frequent dosing.[136–138]

MULTIDISCIPLINARY AND MULTIMODAL APPROACH TO CARE

Utilizing aripiprazole monohydrate LAIs as a treatment for schizophrenia symptoms and an aid for functional recovery requires team-based care and appropriate education to support the patient in managing injection administration, missed doses, and potential adverse events.[139] The 2020 APA guidelines indicate that psychosocial interventions, such as psychoeducation, cognitive behavioral therapy, social skills training, and lifestyle interventions, are an integral part of clinical care for patients with schizophrenia.[108] Utilizing LAIs to minimize symptoms and facilitate medication adherence, in combination with psychosocial interventions to provide the necessary skills for social integration and autonomous

daily living, allows patients to manage their condition more fully.[140–142] One survey found that patients taking LAIs were able to use psychosocial interventions to work toward functional goals, such as improving relationships, their ability to work, and socialization skills.[143] This effect may be due to increased disease insight as a result of assured adherence in patients taking LAIs or reduced medication administration burden. These findings highlight the utility of LAIs as part of a multidisciplinary care plan emphasizing functional recovery.[143]

Utilizing the care team to its fullest capabilities also improves the clinician-patient relationship and optimizes time spent with the patient to work on additional tools of functional recovery. As time constraints in patient visits and perceived workload increases may prevent prescribers from discussing LAIs as a potential treatment option, empowering non-prescriber care team members to aid in these conversations can be crucial.[42,56] Non-prescribers, such as social workers, therapists, nurses, and pharmacists, can play a crucial role in supporting patients treated with LAIs by providing medication education, communicating with patients and prescribers, helping coordinate the treatment plan, and administering LAI doses. Patients often have deep trust in their therapists, which makes them well-suited to discuss treatment satisfaction, review potential medication changes, and advocate for LAIs as a method of self-care. Using a multidisciplinary care approach that integrates LAI antipsychotics allows prescribers to focus on optimizing the patient's overall medication regimen and the patient's treatment plan during their visits.[144]

Panel Consensus Statement #3

Holistic Recovery Approach: "LAIs are seen as enablers of broader recovery goals beyond symptom control. Combining LAI treatment with psychosocial interventions fosters functional recovery,[100] allowing patients to achieve better quality of life through improved relationships, employment, and social integration."

CONCLUSION

The expert panel concluded that aripiprazole monohydrate LAIs offer a well-established efficacy and tolerability profile for patients with schizophrenia and that aripiprazole is distinguished as the only LAI formulation with a partial dopamine agonist mechanism of action. Its special mechanism of action supports its utility as a frontline option rather than a treatment of last resort. Early introduction of LAIs, paired with clinician and patient education, can shift longstanding misconceptions and reduce stigma surrounding LAI use. A pragmatic approach to treatment suggests the need for ongoing, collaborative efforts with non-physician healthcare providers to introduce aripiprazole monohydrate LAIs as a viable treatment option and provide comprehensive care focused on functional recovery. Integrating aripiprazole monohydrate LAIs earlier in the treatment continuum, through shared decision-making, may facilitate broader adoption and promote sustained symptom control, improved adherence, and functional recovery.

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REFERENCES

1. GBD 2021 Diseases and Injuries Collaborators*Lancet*. May 18 2024;403(10440):2133–2161.
2. American Psychiatric Association. Schizophrenia spectrum and other psychotic disorders. *Diagnostic and Statistical Manual of Mental Disorders*. 2022.
3. Kane JM. *J Clin Psychiatry*. 2007;68 Suppl 14:27–30.
4. Novick D, Montgomery W, Treuer T, et al. *BMC Psychiatry*. Aug 5 2015;15:189.
5. Emsley R, Chiliza B, Asmal L, et al. *BMC Psychiatry*. Feb 8 2013;13:50.
6. Kane JM, Kishimoto T, Correll CU.*World Psychiatry*. Oct 2013;12(3):216–26.
7. Carbon M, Correll CU. *Dialogues Clin Neurosci*. Dec 2014;16(4):505–24.
8. Robinson D, Woerner MG, Alvir JM, et al. *Arch Gen Psychiatry*. Mar 1999;56(3):241–7.
9. Barlati S, Nibbio G, Vita A.*Curr Opin Psychiatry*. May 1 2024;37(3):131–139.
10. Correll CU. *J Clin Psychiatry*. Apr 14 2020;81(3)doi:10.4088/JCP.MS19053BR2C
11. Correll CU, Citrome L, Haddad PM, et al. *J Clin Psychiatry*. 2016;77(suppl 3):1–24.

12. Haddad PM, Correll CU. *Expert Opin Pharmacother*. Mar 2023;24(4):473–493.
13. Kishimoto T, Hagi K, Kurokawa S, et al. *Lancet Psychiatry*. May 2021;8(5):387–404.
14. Vita G, Pollini D, Canozzi A, et al. *Psychiatry Research*. 2024/10/01/ 2024;340:116124.
15. Rubio JM, Taipale H, Tanskanen A, Correll CU, Kane JM, Tiihonen J. *Schizophr Bull*. Oct 21 2021;47(6):1611–1620.
16. Gharabawi GM, Lasser RA, Bossie CA, et al. *International Clinical Psychopharmacology*. 2006;21(4):233–240.
17. Yen CF, Chen CS, Ko CH, et al. *Psychiatry Clin Neurosci*. Aug 2005;59(4):403–9.
18. Cipolla S, Catapano P, D'Amico D, et al. *Brain Sci*. Apr 26 2024;14(5) doi:10.3390/brainsci14050433
19. Heres S, Hamann J, Kissling W, Leucht S. *J Clin Psychiatry*. Dec 2006;67(12):1948–53.
20. Kane JM, Rubio JM. *Ther Adv Psychopharmacol*. 2023;13:20451253231157219.
21. Kane JM, Schooler NR, Marcy P, et al. *JAMA Psychiatry*. Dec 1 2020;77(12):1217–1224.
22. Correll CU, Solmi M, Croatto G, et al. *World Psychiatry*. Jun 2022;21(2):248–271.
23. Alphs L, Brown B, Turkoz I, et al. *Schizophr Res*. May 2022;243:86–97.
24. Aymerich C, Salazar de Pablo G, Pacho M, et al. *Mol Psychiatry*. Jan 2025;30(1):263–271.
25. Alphs L, Baker P, Brown B, Fu DJ, et al. *Schizophr Res*. Oct 2022;248:58–63.
26. Vita G, Tavella A, Ostuzzi G, et al. *Ther Adv Psychopharmacol*. 2024;14:20451253241257062.
27. Wei Y, Yan VKC, Kang W, et al. *JAMA Netw Open*. Jul 1 2022;5(7):e2224163.
28. Arango C, Fagiolini A, Gorwood P, et al. *BMC Psychiatry*. Jun 21 2023;23(1):453.
29. Velligan DI, Sajatovic M, Hatch A, et al. *Patient Prefer Adherence*. 2017;11:449–468.
30. Guo J, Lv X, Liu Y, Kong L, et al. *Schizophrenia (Heidelb)*. May 15 2023;9(1):31.
31. Citrome L, Correll CU, Cutler AJ, et al. *Neuropsychiatr Dis Treat*. 2025;21:575–596.
32. ABILIFY MAINTENA (aripiprazole) for extended-release injectable suspension, for intramuscular use [package insert]. Otsuka America Pharmaceutical, Inc.2025.
33. ABILIFY ASIMTUFII (aripiprazole) extended-release injectable suspension, for intramuscular use [package insert]. Otsuka America Pharmaceutical, Inc.2025.
34. European Medicines Agency. Abilify Maintena. European Medicines Agency. Updated April 7, 2024. Accessed March 28, 2025. https://www.ema.europa.eu/en/medicines/human/EPAR/abilify-maintena
35. ABILIFY MAINTENA (aripiprazole) for extended-release injectable suspension 300 and 400 mg per vial, intramuscular use [product monograph]. Otsuka Canada Pharmaceutical, Inc; 2025.
36. ABILIFY ASIMTUFII (aripiprazole) prolonged release injectable suspension 720 mg/2.4 mL and 960 mg/3.2 mL, intramuscular injection [product monograph]. Otsuka Canada Pharmaceutical, Inc; 2025.
37. Mailman RB, Murthy V. *Curr Pharm Des*. 2010;16(5):488–501.
38. de Bartolomeis A, Tomasetti C, Iasevoli F. *CNS Drugs*. Sep 2015;29(9):773–99.
39. Kane JM, Correll CU. *J Clin Psychiatry*. Sep 2010;71(9):1115–24.
40. Solmi M, Seitidis G, Mavridis D, et al. *Mol Psychiatry*. Dec 2023;28(12):5319–5327.
41. Solmi M, Murru A, Pacchiarotti I, et al. *Ther Clin Risk Manag*. 2017;13:757–777.
42. Kane JM, McEvoy JP, Correll CU, et al. *CNS Drugs*. 2021;35(11):1189–1205.
43. Burschinski A, Schneider-Thoma J, Chiocchia V, et al. *World Psychiatry*. Feb 2023;22(1):116–128.
44. Pillinger T, McCutcheon RA, Vano L, et al. *Lancet Psychiatry*. Jan 2020;7(1):64–77.
45. Yonezawa K, Kanegae S, Ozawa H. Antipsychotics/neuroleptics: pharmacology and biochemistry. 2021:1–10.
46. Pillinger T, Howes OD, Correll CU, et al. *Lancet Psychiatry*. Nov 2023;10(11):860–876.
47. Firth J, Siddiqi N, Koyanagi A, et al. *Lancet Psychiatry*. Aug 2019;6(8):675–712.
48. Misawa F, Kishimoto T, Hagi K, et al. *Schizophr Res*. Oct 2016;176(2–3):220–230.
49. Correll CU, Kim E, Sliwa JK, et al. *CNS Drugs*. 2021;35(1):39–59.
50. Bloch Y, Mendlovic S, Strupinsky S, et al. Nov 2001;62(11):855–9.
51. Højlund M, Correll CU. *Expert Opinion on Pharmacotherapy*. 2023;24(13):1463–1489.
52. Shapiro DA, Renock S, Arrington E, et al. *Neuropsychopharmacology*. Aug 2003;28(8):1400–11.
53. Fleischhacker WW, Sanchez R, Perry PP, et al. *Br J Psychiatry*. Aug 2014;205(2):135–44.
54. Nasrallah HA. T*Acta Psychiatr Scand*. Apr 2007;115(4):260–7.
55. Arango C, Baeza I, Bernardo M, et al. *Rev Psiquiatr Salud Ment (Engl Ed)*. Apr-Jun 2019;12(2):92–105. Antipsicoticos inyectables de liberacion prolongada para el tratamiento de la esquizofrenia en Espana.
56. Parellada E, Bioque M. *CNS Drugs*. Aug 2016;30(8):689–701.
57. Cahling L, Berntsson A, Bröms G, et al. *BJPsych Bull*. Oct 2017;41(5):254–259.
58. National Alliance of State Pharmacy Associations. Pharmacist Administration of Long-Acting Injectable Antipsychotics. Updated June 3, 2024. Accessed January 14, 2025, https://naspa.us/blog/resource/med-admin-resources/
59. Murphy AL, Suh S, Gillis L, et al. *Pharmacy (Basel)*. Feb 27 2023;11(2) doi:10.3390/pharmacy11020045
60. Jaeger M, Rossler W. *Psychiatry Res*. Jan 30 2010;175(1-2):58–62.
61. McCutcheon RA, Pillinger T, Varvari I, et al. *Lancet Psychiatry*. Mar 31 2025;doi:10.1016/S2215-0366(25)00031-8
62. Caroli F, Raymondet P, Izard I, et al. *Patient Prefer Adherence*. Mar 21 2011;5:165–71.
63. Katz EG, Hauber B, Gopal S, et al. *Patient Prefer Adherence*. 2016;10:2127–2139.
64. Kane JM, Schooler NR, Marcy P, et al. *J Clin Psychiatry*. Apr 23 2019;80(3) doi:10.4088/JCP.18m12546
65. Correll CU, Rubio JM, Citrome L, et al. *Neuropsychiatr Dis Treat*. 2024;20:1995–2010.
66. Strassnig M, Bowie C, Pinkham AE, et al. Sep 2018;104:124–129.
67. Correll CU, Schooler NR. *Neuropsychiatr Dis Treat*. 2020;16:519–534.
68. Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. *Lancet*. Sep 14 2019;394(10202):939–951.
69. Ostuzzi G, Bertolini F, Tedeschi F, et al. *World Psychiatry*. Jun 2022;21(2):295–307.
70. Ostuzzi G, Bertolini F, Del Giovane C, et al. *Am J Psychiatry*. May 1 2021;178(5):424–436.
71. Kantrowitz JT. *Expert Opin Pharmacother*. Oct 2021;22(14):1811–1813.
72. Tamminga CA. *J Neural Transm (Vienna)*. Mar 2002;109(3):411–20.
73. Correll CU, Abi-Dargham A, Howes O. *J Clin Psychiatry*. Feb 15 2022;83(1) doi:10.4088/JCP.SU21024IP1
74. McCutcheon R, Beck K, Jauhar S, Howes OD. *Schizophr Bull*. Oct 17 2018;44(6):1301–1311.
75. Stelmach A, Guzek K, Rożnowska A, et al. *Pharmacological Reports*. 2023/02/01 2023;75(1):19–31.
76. Carbon M, Hsieh CH, Kane JM, et al. *J Clin Psychiatry*. Mar 2017;78(3):e264-e278.
77. Carbon M, Kane JM, Leucht S, et al. *World Psychiatry*. Oct 2018;17(3):330–340.
78. Di Sciascio G, Riva MA. *Neuropsychiatr Dis Treat*. 2015;11:2635–47.
79. Kane JM, Sanchez R, Perry PP, et al. *J Clin Psychiatry*. May 2012;73(5):617–24.
80. Naber D, Hansen K, Forray C, et al. *Schizophr Res*. Oct 2015;168(1–2):498–504.
81. Kane JM, Zhao C, Johnson BR, et al. *J Med Econ*. Feb 2015;18(2):145–54.
82. Harlin M, Yildirim M, Such P, et al. *CNS Drugs*. Apr 2023;37(4):337–350.
83. Harlin M, Chepke C, Larsen F, et al. *Neuropsychiatr Dis Treat*. 2023;19:1409–1416.
84. Citrome L, Such P, Yildirim M, et al. *J Clin Psychiatry*. Sep 4 2023;84(5) doi:10.4088/JCP.23m14873
85. Tandon R, Lenderking WR, Weiss C, et al. *Ann Gen Psychiatry*. 2020;19:42.
86. Dibonaventura M, Gabriel S, Dupclay L, et al. *BMC Psychiatry*. Mar 20 2012;12:20.
87. Semahegn A, Torpey K, Manu A, et al. *Systematic Reviews*. 2020/01/16 2020;9(1):17.
88. World Health Organization. Adherence to long-term therapies : evidence for action. Geneva, Switzerland: World Health Organization; 2003.
89. Weiden PJ, Kozma C, Grogg A, et al. *Psychiatr Serv*. Aug 2004;55(8):886–91.
90. Takeuchi H, Siu C, Remington G, et al. *Neuropsychopharmacology*. May 2019;44(6):1036–1042.
91. Andreasen NC, Liu D, Ziebell S, et al. *American Journal of Psychiatry*. 2013;170(6):609–615.
92. Tishler TA, Ellingson BM, Salvadore G, et al. *Schizophr Res*. May 2023;255:195–202.
93. Basu A, Patel C, Fu AZ, et al. *J Manag Care Spec Pharm*. Mar 2023;29(3):293–302.
94. Williamson DJ, Nuechterlein KH, Tishler T, et al. *Schizophr Res Cogn*. Dec 2022;30:100270.
95. Bartzokis G, Lu PH, Stewart SB, et al. *Schizophr Res*. Sep 2009;113(2-3):322–31.
96. Correll CU, Benson C, Emond B, et al. *Schizophrenia (Heidelb)*. Feb 11 2023;9(1):9.
97. Gorwood P, Yildirim M, Madera-McDonough J, et al. *BMC Psychiatry*. Apr 17 2025;25(1):398.

98. Olagunju AT, Clark SR, Baune BT. *Aust N Z J Psychiatry*. Jun 2019;53(6):509–527.
99. Correll CU, Galling B, Pawar A, et al. *JAMA Psychiatry*. Jun 1 2018;75(6):555–565.
100. Solmi M, Taipale H, Holm M, et al. *Am J Psychiatry*. Dec 1 2022;179(12):938–946.
101. Takács P, Czobor P, Fehér L, et al. *PLoS One*. 2019;14(6):e0218071.
102. Basu A, Benson C, Turkoz I, et al. *J Manag Care Spec Pharm*. Oct 2022;28(10):1086–1095.
103. Fusar-Poli P, Salazar de Pablo G, Correll CU, et al. *JAMA Psychiatry*. Jul 1 2020;77(7):755–765.
104. Salazar de Pablo G, Besana F, Arienti V, et al. *EClinicalMedicine*. Jun 2021;36:100909.
105. Kane JM, Robinson DG, Schooler NR, et al. *Am J Psychiatry*. Apr 1 2016;173(4):362–72.
106. Lopena OJ, Alphs LD, Sajatovic M, et al. *J Clin Psychiatry*. Sep 25 2023;84(6) doi:10.4088/JCP.23m14788
107. Subotnik KL, Casaus LR, Ventura J, et al. *JAMA Psychiatry*. 2015;72(8):822–829.
108. Keepers GA, Fochtmann LJ, Anzia JM, et al. *Am J Psychiatry*. Sep 1 2020;177(9):868–872.
109. Correll CU, Martin A, Patel C, et al. *Schizophrenia (Heidelb)*. Feb 24 2022;8(1):5.
110. Hamann J, Heres S. *Psychiatr Serv*. Dec 1 2014;65(12):1483–6.
111. Hamann J, Mendel R, Cohen R, et al. *Psychiatr Serv*. Aug 2009;60(8):1107–12.
112. Schuster F, Holzhüter F, Heres S, et al. *Health Expect*. Apr 2021;24(2):507–515.
113. Hamann J, Heres S. *Psychiatr Serv*. May 1 2019;70(5):418–421.
114. Pappa S, Yildirim M, Loomer S, et al. *Patient Prefer Adherence*. 2025;19:1179–1195.
115. Keepers GA, Fochtmann LJ, Anzia JM, et al. *American Journal of Psychiatry*. 2020;177(9):868–872.
116. Lasser RA, Schooler NR, Kujawa M, et al. *Psychiatry (Edgmont)*. Apr 2009;6(4):22–7.
117. Sajatovic M, Ross R, Legacy SN, et al. *Neuropsychiatr Dis Treat*. 2018;14:1475–1492.
118. Sajatovic M, Ross R, Legacy SN, et al. *Neuropsychiatr Dis Treat*. 2018;14:1463–1474.
119. Winter-van Rossum I, Weiser M, Galderisi S, et al. *Lancet Psychiatry*. Mar 2023;10(3):197–208.
120. Kane JM, Kishimoto T, Achtyes E, et al. *Lancet Psychiatry*. Jul 2023;10(7):480–481.
121. Howes OD, McCutcheon R, Agid O, et al. *American Journal of Psychiatry*. 2017;174(3):216–229.
122. Wagner E, Siskind D, Falkai P, et al. *Schizophr Bull*. Jul 4 2023;49(4):962–972.
123. Diniz E, Fonseca L, Rocha D, et al. *Braz J Psychiatry*. Sep-Oct 2023;45(5):448–458.
124. Martin KB. *Cureus*. Dec 2 2020;12(12):e11847.
125. Velligan DI, Wang M, Diamond P, et al. *Psychiatr Serv*. Sep 2007;58(9):1187–92.
126. Lee J, Oh S, Moon SY, et al. *Int Clin Psychopharmacol*. Jul 1 2024;39(4):250–256.
127. Moon J, Yang H, Jung S, et al. *Prog Neuropsychopharmacol Biol Psychiatry*. Dec 20 2024;135:111115.
128. Pae CU, Han C, Bahk WM, et al. *Clin Psychopharmacol Neurosci*. May 31 2021;19(2):233–242.
129. Bell Lynum K, Awasthi S, Huang S, et al. The Impact of Aripiprazole Once-Monthly Initiation and Persistence on Concomitant Psychiatric Medications in Adults: Diagnosed With Bipolar I Disorder: A Retrospective Analysis of Claims Data from the United States. Poster presented at: Psych Congress; October 29 – November 2024; Boston, Massachusetts.
130. Groenendaal E, Lynch S, Dornbush R, et al. *J Psychiatr Res*. Feb 2023;158:273–280.
131. Ostuzzi G, Vita G, Bertolini F, et al. *Lancet Psychiatry*. Aug 2022;9(8):614–624.
132. Weiden PJ, Du Y, Liu C-C, et al. *CNS Spectrums*. 2019;24(4):419–425.
133. Kim E, Kim S, Kim SW, et al. *Schizophr Res*. Jul 2025;281:180–190.
134. Milz R, Benson C, Knight K, et al. *Neuropsychiatric Disease and Treatment*. 2023;Volume 19:531–545.
135. Goldberg JF, Achtyes ED, Correll CU, et al. *J Clin Psychiatry*. Jun 13 2025;86(2)doi:10.4088/JCP.plunlai2424ah1
136. Wang Y, Wang X, Harlin M, et al. *Curr Med Res Opin*. Nov 2021;37(11):1961–1972.
137. Wang X, Raoufinia A, Bihorel S, et al. *Clin Pharmacol Drug Dev*. Feb 2022;11(2):150–164.
138. Wang Y, Harlin M, Larsen F, et al. *Clin Pharmacol Drug Dev*. Jun 2024;13(6):631–643.
139. Hu A. A practical review of long-acting injectable antipsychotics. U.S. Pharmacist. Updated May 14, 2024. Accessed Jan 10, 2025. https://www.uspharmacist.com/article/a-practical-review-of-longacting-injectable-antipsychotics
140. Correll CU, Ismail Z, McIntyre RS, Rafeyan R, Thase ME. *J Clin Psychiatry*. Aug 17 2022;83(5)doi:10.4088/JCP.LU21112AH2
141. Correll CU, Ismail Z, McIntyre RS, Rafeyan R, Thase ME. *J Clin Psychiatry*. Aug 3 2022;83(4)doi:10.4088/JCP.LU21112AH1
142. Correll CU, Brieden A, Janetzky W. *Schizophrenia (Heidelb)*. Nov 8 2023;9(1):80.
143. Bridges JF, Beusterien K, Heres S, et al. *Patient Prefer Adherence*. 2018;12:63–70.
144. Fernández-Miranda JJ, Díaz-Fernández S, López-Muñoz F. *Journal of Personalized Medicine*. 2022;12(7):1101.
145. Stanga V, Turrina C, Valsecchi P, et al. *Compr Psychiatry*. May 2019;91:1–5.
146. Lambert T. 311The management of a specialist clinic for long-acting injectable antipsychotics. In: Haddad P, Lambert T, Lauriello J, eds. *Antipsychotic Long-acting Injections*. Oxford University Press; 2016:0.
147. Fagiolini A, Leopold K, Pappa S, et al. *Adv Ther*. Apr 2025;42(4):1935–1949.